Antenatal care

routine care for the healthy pregnant woman

2nd edition (2008 update)

National Collaborating Centre for Women's and Children's Health

Commissioned by the National Institute for Health and Clinical Excellence

This is the consultation draft of a partial update of the 2003 guideline. New or amended sections are indicated by a green bar in the right-hand side of the page.

Key recommendations have been selected from the new or amended recommendations.

Please comment on **new or amended** sections only. Sections that are unchanged from the original guideline are not being consulted on.

A separate consultation will take place on the proposed assessment tool (see Section 14) between 9 October and 3 December 2007. At this point, further information will be made available on the NICE website.

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Stakeholder organisations

- Action on Pre-Eclampsia (APEC)
- Antenatal Results and Choices
- Association for Continence Advice (ACA)
- Association for Improvements in Maternity Services (AIMS)

- Association of Radical Midwives
- Association of the British Pharmaceuticals Industry(ABPI)
- Aventis Pasteur MSD
- Brighton Healthcare NHS Trust
- British Association of Paediatric Surgeons
- British Association of Perinatal Medicine
- British Dietetic Association
- British Maternal and Fetal Medicine Society
- British Medical Association
- British National Formulary
- British Psychological Society
- BUPA
- Chartered Society of Physiotherapy
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- Royal College of Psychiatrists
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- Royal Pharmaceutical Society of Great Britain
- Royal Society of Medicine
- Scottish Intercollegiate Guidelines Network (SIGN)
- Sickle Cell Society
- Society and College of Radiographers
- STEPS
- Survivors Trust
- Twins and Multiple Births Association (TAMBA)
- UK Coalition of People Living with HIV and AIDS
- UK National Screening Committee
- UK Pain Society
- United Kingdom Association of Sonographers
- Victim Support
- Welsh Assembly Government (formerly National Assembly for Wales)
- West Gloucestershire Primary Care Trust
- Young Minds

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2008 update

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Stakeholder organisations

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All Wales Birth Centre Group
Antenatal Screening Wales
Association for Psychoanalytic Psychotherapy in the NHS
Association for Spina Bifida & Hydrocephalus (ASBAH)
Association of Breastfeeding Mothers
Association of British Clinical Diabetologists
Association of Chartered Physiotherapists in Women's Health
Association of Medical Microbiologists
Association of the British Pharmaceuticals Industry (ABPI)
Baby Lifeline
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Barnsley PCT
BDF Newlife (Birth Defects Foundation)
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Bedfordshire PCT
Berkshire Healthcare NHS Trust
Birmingham Women's Healthcare Trust
Birth Trauma Association
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Bradford Teaching Hospitals NHS Foundation Trust
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Bristol Health Services Plan
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British HIV Association (BHIVA)
British Hypertension Society
British Maternal and Fetal Medicine Society
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Calderdale PCT
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CEMACH
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Gloucestershire Acute Trust
Group B Strep Support
Group B Strep Support
Guys and St Thomas NHS Foundation Trust
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Huntleigh Healthcare
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Liverpool PCT
Liverpool Women's Hospital NHS Trust
Luton and Dunstable Hospital NHS Trust
Mast Diagnostics
Medicines and Healthcare Products Regulatory Agency (MHRA)
Mid and West Regional MSLC
Milton Keynes PCT
Monica Healthcare Ltd
MRC Centre of Epidemiology for Child Health
National Childbirth Trust
National Chlamydia Screening Programme
National Patient Safety Agency
National Public Health Service - Wales
NHS Direct
NHS Health and Social Care Information Centre
NHS Quality Improvement Scotland
NHS Sickle Cell and Thalassemia Screening Programme
North Tees and Hartlepool NHS Trust
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Nutrition Society
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PNI ORG UK
Positively Women
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Primary Care Pharmacists' Association
PRIMIS+
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Regional Maternity Survey Office
Regional Public Health Group - London
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Royal College of Nursing
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Royal College of Paediatrics and Child Health
Royal College of Pathologists
Royal College of Psychiatrists
Royal College of Radiologists

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Royal Society of Medicine
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Sandwell and West Birmingham NHS Trust
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Sheffield South West PCT
Sheffield Teaching Hospitals NHS Trust
Sickle Cell & Thalassaemia Association of Counsellors
Sickle Cell Society
Society and College of Radiographers
Survivors Trust, The
The British Psychological Society
TIPS Limited
University College London Hospitals NHS Foundation Trust
UK Coalition of People Living with HIV & AIDS
UK Forum on Haemoglobin Disorders
UK National Screening Committee
UK Newborn Screening Programme Centre
UK Thalassaemia Society
UNICEF Baby Friendly Initiative
United Lincolnshire Hospitals NHS Trust
University College London Hospitals NHS Trust
University Hospitals of Leicester
Victim Support
Welsh Assembly Government
Welsh Scientific Advisory Committee (WSAC)
West Middlesex University Hospital NHS Trust
Western Cheshire PCT
Wiltshire PCT
Wirral University Hospital Teaching NHS Trust
Women's Health Research Group
Worcestershire Acute NHS Trust
Worthing and Southlands Hospital NHS Trust
Worthing Hospital
Wyre Forest PCT
York NHS Trust
Yorkshire and Humber Local Supervisory Authority

Abbreviations

AC	Abdominal circumference
ACOG	American College of Obstetricians and Gynecologists
ACTH	adrenocorticotrophic hormone
AFI	amniotic fluid volume
AFP	alphafetoprotein
AIDS	acquired immunodeficiency syndrome
ANC	antenatal care
APEC	Action on Pre-eclampsia
ASB	asymptomatic bacteriuria
BERR	Department for Business, Enterprise and Regulatory Reform
□ hCG	beta human chorionic gonadotrophin
BMI	body mass index
BP	blood pressure
BPD	biparietal diameter
BV	bacterial vaginosis
BW	birth weight
CAMP	Christie, Atkinson, Munch, Peterson test
CDSC	Communicable Disease Surveillance Centre
CFGC	customised fetal growth chart
cfu/ml	colony-forming units per millilitre
CHO	carbohydrate
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMV	cytomegalovirus
CNS	central nervous system
CRL	crown rump length
CS	caesarean section
CTG	cardiotocography
DA	direct agglutination test
DARE	Database of Abstracts and Reviews of Effectiveness
DNA	deoxyribonucleic acid
DR	detection rate
DS	Down's syndrome
D_x	Diagnosis
eAg	hepatitis e antigen
ECV	external cephalic version
EEA	European Economic Area
EIA	enzyme immunoassay
EFW	estimated fetal weight
EL	evidence level
ELISA	enzyme-linked immunosorbent assay
EOGBS	early-onset group B streptococcus
EPDS	Edinburgh Postnatal Depression Scale
EPIC	external intermittent pneumatic compression
EU	European Union
FBG	fasting plasma glucose
FFN	fetal fibronectin
FGM	female genital mutilation
FL	femur length
FPG	fasting plasma glucose
FPR	false positive rate
FTA-abs	fluorescent treponemal antibody – absorbed test

GA	gestational age
GBS	group B streptococcus
GCT	glucose challenge test
GD	Gestational diabetes
GDG	Guideline Development Group
GDM	gestational diabetes mellitus
GPP	good practice point
GTT	glucose tolerance test
Hb	haemoglobin
HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HC	head circumference
hCG	human chorionic gonadotrophin (can be total or free beta)
HCV	hepatitis C virus
HDN	haemolytic disease of the newborn
HEED	Health Economic Evaluations Database
HELLP	haemolysis, elevated liver enzymes and low platelet count
HIV	human immunodeficiency virus
HPA	Health Protection Agency
HPLC	high-performance liquid chromatography
HTA	Health Technology Assessment
ICD-9	International Classification of Diseases, 9th edition
IPC	intrapartum care
IU	international units
IUGR	intrauterine growth restriction
LA	latex agglutination test
LE	leucocyte esterase
LGA	large for gestational age
LMP	last menstrual period
LR	Likelihood ratio
+LR	positive likelihood ratio
-LR	negative likelihood ratio
LSHTM	London School of Hygiene and Tropical Medicine
MCH	mean corpuscular haemoglobin
MeSH	medical subject headings
MIDIRS	Midwives Information and Resource Service
MoM	multiples of the median
MSAFP	maternal serum alpha feto-protein levels
MSHCG	maternal erum beta-human chorionic gonadotrophin levels
MTCT	mother-to-child transmission
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NCRSP	National Congenital Rubella Surveillance Programme
NHS	National Health Service
NHS EED	NHS Economic Evaluations Database
NICE	National Institute for Health and Clinical Excellence
NICU	neonatal intensive care unit
NNT	number needed to treat
NPV	negative predictive value
NS	not significant
NSC	(UK) National Screening Committee
NSF	National Service Framework
NT	nuchal translucency
OGTT	Oral glucose tolerance test
ONS	Office for National Statistics
OR	odds ratio
OTC	over-the-counter

PAPP-A	plasma protein A
PCR	polymerase chain reaction
PCT	primary care trust
PE	pre-eclampsia
PHLS	Public Health Laboratory Service
PIH	pregnancy-induced hypertension
1PPI	proton pump inhibitor
PPV	positive predictive value
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised controlled trial
RhD	rhesus D
RIBA	recombinant immunoblot assay
RNA	ribonucleic acid
RPG	random plasma glucose
RPR	rapid plasmin reagin test
RR	relative risk
RST	reagent strip testing
SD	standard deviation
SFH	symphysio-fundal height
SGA	small for gestational age
SIGN	Scottish Intercollegiate Guidelines Network
SP	specificity
SPD	symphysis pubis dysfunction
SPTB	spontaneous preterm birth
ST	sensitivity
T 18/13	trisomy 18 or 13
TPHA	*Treponema pallidum* haemagglutination assay
TVS	transvaginal sonography
uE3	unconjugated oestriol
UK	United Kingdom
US CDC	United States Centers for Disease Control and Prevention
US	ultrasound
USS	ultrasound scan
UTI	urinary tract infection
VDRL	Venereal Disease Research Laboratory (test for syphilis)
VE	vaginal examination
WHO	World Health Organization
WMD	weighted mean difference

Glossary of terms

Bias	Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually doesn't. Bias can occur by chance or as a result of systematic errors in the design and execution of a study. Bias can occur at different stages in the research process, e.g. in the collection, analysis, interpretation, publication or review of research data.
Blinding or masking	The practice of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned. For example, a clinical trial in which the participating patients or their doctors are unaware of whether they (the patients) are taking the experimental drug or a placebo (dummy treatment). The purpose of 'blinding' or 'masking' is to protect against bias. See also **Double blind study**.
Case—control study	A study that starts with the identification of a group of individuals sharing the same characteristics (e.g. people with a particular disease) and a suitable comparison (control) group (e.g. people without the disease). All subjects are then assessed with respect to things that happened to them in the past, e.g. things that might be related to getting the disease under investigation. Such studies are also called **retrospective** as they look back in time from the outcome to the possible causes.
Case report (or case study)	Detailed report on one patient (or case), usually covering the course of that person's disease and their response to treatment.
Case series	Description of several cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical trial	A research study conducted with patients which tests out a drug or other intervention to assess its effectiveness and safety. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease. This general term encompasses **controlled clinical trials** and **randomised controlled trials**.
Cohort	A group of people sharing some common characteristic (e.g. patients with the same disease), followed up in a research study for a specified period of time.
Cohort study	An observational study that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that patients received. Thus within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, e.g. comparing mortality between one group that received a specific treatment and one group which did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or 'prospective' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or 'retrospective' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.
Confidence interval	A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that is consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which we are 95% confident that the true effect lies.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment), in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Controlled clinical trial (CCT)	A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a **randomised controlled trial**.

Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost effectiveness	A type of economic evaluation that assesses the additional costs and benefits of doing something different. In cost effectiveness analysis, the costs and benefits of different treatments are compared. When a new treatment is compared with current care, its additional costs divided by its additional benefits is called the cost effectiveness ratio. Benefits are measured in natural units, for example, cost per additional heart attack prevented.
Cost utility analysis	A special form of **cost effectiveness** analysis where benefit is measured in quality adjusted life years. A treatment is assessed in terms of its ability to extend or improve the quality of life.
Crossover study design	A study comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another. For example, for a comparison of treatments A and B, half the participants are randomly allocated to receive them in the order A, B and half to receive them in the order B, A. A problem with this study design is that the effects of the first treatment may carry over into the period when the second is given. Therefore a crossover study should include an adequate 'wash-out' period, which means allowing sufficient time between stopping one treatment and starting another so that the first treatment has time to wash out of the patient's system.
Cross-sectional study	The observation of a defined set of people at a single point in time or time period – a snapshot. (This type of study contrasts with a **longitudinal study**, which follows a set of people over a period of time.)
Double blind study	A study in which neither the subject (patient) nor the observer (investigator or clinician) is aware of which treatment or intervention the subject is receiving. The purpose of blinding is to protect against bias.
Evidence based	The process of systematically finding, appraising and using research findings as the basis for clinical decisions.
Evidence-based clinical practice	Evidence-based clinical practice involves making decisions about the care of individual patients based on the best research evidence available rather than basing decisions on personal opinions or common practice (which may not always be evidence based). Evidence-based clinical practice therefore involves integrating individual clinical expertise and patient preferences with the best available evidence from research.
Evidence table	A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.
Exclusion criteria	See **Selection criteria**.
Experimental study	A research study designed to test whether a treatment or intervention has an effect on the course or outcome of a condition or disease, where the conditions of testing are to some extent under the control of the investigator. **Controlled clinical trial** and **randomised controlled trial** are examples of experimental studies.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available.
Gravid	Pregnant.
Health economics	A field of conventional economics which examines the benefits of healthcare interventions (e.g. medicines) compared with their financial costs.
Heterogeneity	Or lack of **homogeneity**. The term is used in **meta-analyses** and **systematic reviews** when the results or estimates of effects of treatment from separate studies seem to be very different, in terms of the size of treatment effects, or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow up.
Homogeneity	This means that the results of studies included in a **systematic review** or **meta-analysis** are similar and there is no evidence of **heterogeneity**. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance. See also **Consistency**.
Inclusion criteria	See **Selection criteria**.
Intervention	Healthcare action intended to benefit the patient, e.g. drug treatment, surgical procedure, psychological therapy.
Likelihood ratio	See **negative likelihood ratio** and **positive likelihood ratio**. For a full explanation, see Appendix E.
Longitudinal study	A study of the same group of people at more than one point in time. (This type of study contrasts with a **cross-sectional study**, which observes a defined set of people at a single point in time.)
Masking	See **Blinding**.

Meta-analysis	Results from a collection of independent studies (investigating the same treatment) are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. Where studies are not compatible, e.g. because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to statistically pool results in this way. See also **Systematic review** and **Heterogeneity**.
Multiparous	Having carried more than one pregnancy to a viable stage.
Negative likelihood ratio	The negative likelihood ratio describes the probability of having a negative test result in the diseased population compared with that of a non-diseased population and corresponds to the ratio of the false negative rate divided by the true negative rate (1 – sensitivity/specificity).
Non-experimental study	A study based on subjects selected on the basis of their availability, with no attempt having been made to avoid problems of bias.
Nulliparous	Having never given birth to a viable infant.
Number needed to treat (NNT)	This measures the impact of a treatment or intervention. It states how many patients need to be treated with the treatment in question in order to prevent an event that would otherwise occur; e.g. if the NNT = 4, then four patients would have to be treated to prevent one bad outcome. The closer the NNT is to one, the better the treatment is. Analogous to the NNT is the number needed to harm (NNH), which is the number of patients that would need to receive a treatment to cause one additional adverse event. e.g. if the NNH = 4, then four patients would have to be treated for one bad outcome to occur.
Observational study	In research about diseases or treatments, this refers to a study in which nature is allowed to take its course. Changes or differences in one characteristic (e.g. whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (e.g. whether or not they died), without the intervention of the investigator. There is a greater risk of selection bias than in **experimental studies**.
Odds ratio	Odds are a way of representing probability, especially familiar from betting. In recent years odds ratios have become widely used in reports of clinical studies. They provide an estimate (usually with a **confidence interval**) for the effect of a treatment. Odds are used to convey the idea of 'risk' and an odds ratio of one between two treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the **relative risk** (which uses actual risks and not odds) will be very similar. See also **Relative risk**, **Risk ratio**.
Parous	Having borne at least one viable offspring (usually more than 24 weeks of gestation).
Peer review	Review of a study, service or recommendations by those with similar interests and expertise to the people who produced the study findings or recommendations. Peer reviewers can include professional, patient and carer representatives.
Pilot study	A small-scale 'test' of the research instrument. For example, testing out (piloting) a new questionnaire with people who are similar to the population of the study, in order to highlight any problems or areas of concern, which can then be addressed before the full-scale study begins.
Placebo	Placebos are fake or inactive treatments received by participants allocated to the **control group** in a clinical trial, which are indistinguishable from the active treatments being given in the experimental group. They are used so that participants are ignorant of their treatment allocation in order to be able to quantify the effect of the experimental treatment over and above any **placebo effect** due to receiving care or attention.
Placebo effect	A beneficial (or adverse) effect produced by a **placebo** and not due to any property of the placebo itself.
Positive Likelihood ratio	The positive likelihood ratio describes the probability of having a positive test result in the diseased population compared with that of a non-diseased population and corresponds to the ratio of the true positive rate divided by the false positive rate (sensitivity/(1 – specificity)).
Power	See **Statistical power**.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are **retrospective**.
p value	If a study is done to compare two treatments then the p value is the probability of obtaining the results of that study, or something more extreme, if there really was no difference between treatments. (The assumption that there really is no difference between treatments is called the 'null hypothesis'.) Suppose the p-value was 0.03. What this means is that, if there really was no difference between treatments, there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of p is below 0.05 (i.e. less than 5%) the result is seen as statistically significant. Where the value of p

	is 0.001 or less, the result is seen as highly significant. p values just tell us whether an effect can be regarded as statistically significant or not. In no way do they relate to how big the effect might be, for which we need the **confidence interval**.
Qualitative research	Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions. It generates non-numerical data, e.g. a patient's description of their pain rather than a measure of pain. In health care, qualitative techniques have been commonly used in research documenting the experience of chronic illness and in studies about the functioning of organisations. Qualitative research techniques such as focus groups and in-depth interviews have been used in one-off projects commissioned by guideline development groups to find out more about the views and experiences of patients and carers.
Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the National Census, which counts people and households.
Random allocation or randomisation	A method that uses the play of chance to assign participants to comparison groups in a research study; for example, by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual (or each unit in the case of cluster randomisation) being entered into a study has the same chance of receiving each of the possible interventions.
Randomised controlled trial	A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. (Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.)
Relative risk	A summary measure which represents the ratio of the risk of a given event or outcome (e.g. an adverse reaction to the drug being tested) in one group of subjects compared with another group. When the 'risk' of the event is the same in the two groups the relative risk is 1. In a study comparing two treatments, a relative risk of 2 would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment. Relative risk is sometimes used as a synonym for **risk ratio**.
Reliability	Reliability refers to a method of measurement that consistently gives the same results. For example, someone who has a high score on one occasion tends to have a high score if measured on another occasion very soon afterwards. With physical assessments it is possible for different clinicians to make independent assessments in quick succession and if their assessments tend to agree then the method of assessment is said to be reliable.
Retrospective study	A retrospective study deals with the present and past and does not involve studying future events. This contrasts with studies that are **prospective**.
Risk ratio	Ratio of the risk of an undesirable event or outcome occurring in a group of patients receiving experimental treatment compared with a comparison (control) group. The term **relative risk** is sometimes used as a synonym of risk ratio.
Sample	A part of the study's target population from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole.
Screening	The presumptive identification of an unrecognised disease or defect by means of tests, examinations or other procedures that can be applied rapidly. Screening tests differentiate apparently well persons who may have a disease from those who probably have not. A screening test is not intended to be diagnostic but should be sufficiently **sensitive** and **specific** to reduce the proportion of false results, positive or negative, to acceptable levels. Persons with positive or suspicious findings must be referred to the appropriate healthcare provider for diagnosis and necessary treatment.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Sensitivity	In diagnostic testing, this refers to the chance of having a positive test result given that you have the disease. 100% sensitivity means that all those with the disease will test positive, but this is not the same the other way around. A patient could have a positive test result but not have the disease — this is called a 'false positive'. The sensitivity of a test is also related to its 'negative predictive value' (true negatives) – a test with a sensitivity of 100% means that all those who get a negative test result do not have the disease. To fully judge the accuracy of a test, its **specificity** must also be considered.
Specificity	In diagnostic testing, this refers to the chance of having a negative test result given that you do not have the disease. 100% specificity means that all those without the disease will test negative, but this is not the same the other way around. A patient could have a negative test result yet still have the disease – this is called a 'false negative'. The specificity of a test is also related to its 'positive predictive value' (true positives) – a test with a specificity of 100%

	means that all those who get a positive test result definitely have the disease. To fully judge the accuracy of a test, its **sensitivity** must also be considered.
Statistical power	The ability of a study to demonstrate an association or causal relationship between two **variables**, given that an association exists. For example, 80% power in a clinical trial means that the study has a 80% chance of ending up with a *P* value of less than 5% in a statistical test (i.e. a statistically significant treatment effect) if there really was an important difference (e.g. 10% versus 5% mortality) between treatments. If the statistical power of a study is low, the study results will be questionable (the study might have been too small to detect any differences). By convention, 80% is an acceptable level of power. See also **p value**.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a **meta-analysis**.
Validity	Assessment of how well a tool or instrument measures what it is intended to measure.
Variable	A measurement that can vary within a study, e.g. the age of participants. Variability is present when differences can be seen between different people or within the same person over time, with respect to any characteristic or feature that can be assessed or measured.

1
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1 Introduction

1.0 Introduction

The original antenatal care guideline was published by NICE in 2003. Since then a number of important pieces of evidence have become available, particularly concerning gestational diabetes, haemoglobinopathy and ultrasound, so that the update has been initiated earlier than planned. This early update has also provided an opportunity to look at a number of aspects of antenatal care and these include:

- the development of a method to assess women for whom additional care is necessary (the 'assessment tool')
- information giving to women
- lifestyle:
  - vitamin D supplementation
  - alcohol use
- screening for the baby:
  - use of ultrasound for gestational age assessment and screening for fetal abnormalities
  - methods for determining normal fetal growth
  - haemoglobinopathy screening
- screening for the mother:
  - gestational diabetes
  - pre-eclampsia and preterm labour
  - chlamydia.

1.1 Aim of the guideline

The ethos of this guideline is that pregnancy is a normal physiological process and that, as such, any interventions offered should have known benefits and be acceptable to pregnant women. The guideline has been developed with the following aims: to offer information on best practice for baseline clinical care of all pregnancies and comprehensive information on the antenatal care of the healthy woman with an uncomplicated singleton pregnancy. It provides evidence-based information for clinicians and pregnant women to make decisions about appropriate treatment in specific circumstances. The guideline will complement the Children's National Service Frameworks (England and Wales), which is in development and which will produce standards for service configuration, with emphasis on how care is delivered and by whom, including issues of ensuring equity of access to care for disadvantaged women and women's views about service provision (For more information, see www.dh.gov.uk/en/Policyandguidance/Healthandsocialcaretopics/ChildrenServices/Childrenservicesinformation/index.htm for England and www.wales.nhs.uk/sites/page.cfm?orgid=334&pid=934 for Wales). The guideline has also drawn on the evidence-based recommendations of the UK National Screening Committee (NSC).

The *Changing Childbirth* report explicitly confirmed that women should be the focus of maternity care.[1] Care during pregnancy should enable a woman to make informed decisions, based on her needs, having discussed matters fully with the professionals involved.

Reviews of women's views on antenatal care suggest that key aspects of care valued by women are respect, competence, communication, support and convenience.[2] Access to information and provision of care by the same small group of people are also key aspects of care that lend themselves to a pregnant woman feeling valued as an individual and more in control.[3]

Current models of antenatal care originated in the early decades of the 20th century. The pattern of visits recommended at that time (monthly until 30 weeks, then fortnightly to 36 weeks and then

weekly until delivery) is still recognisable today. It has been said that antenatal care has escaped critical assessment.[4] Both the individual components and composite package of antenatal care should conform to the criteria for a successful screening programme, namely that:

- the condition being screened for is an important health problem
- the screening test (further diagnostic test and treatment) is safe and acceptable
- the natural history of the condition is understood
- early detection and treatment has benefit over later detection and treatment
- the screening test is valid and reliable
- there are adequate facilities for confirming the test results and resources for treatment
- the objectives of screening justify the costs.

A complete list of the NSC criteria for screening can be found in the NSC online library (www.nsc.nhs.uk/library/lib_ind.htm) under the title, *The UK National Screening Committee's criteria for appraising the viability, effectiveness and appropriateness of a screening programme*.

1.2 Areas outside the remit of the guideline

The guideline will not produce standards for service configuration, which are being addressed by the Children's National Service Frameworks (England and Wales), nor will it address quality standard issues (such as laboratory standards), which are addressed by the National Screening Committee.[5]

Although the guideline addresses screening for many of the complications of pregnancy, it does not include information on the investigation and appropriate ongoing management of these complications if they arise in pregnancy (for example, the management of pre-eclampsia, fetal anomalies and multiple pregnancies).

Any aspect of intrapartum and postpartum care has not been included in this guideline. This includes preparation for birth and parenthood, risk factor assessment for intrapartum care, breastfeeding and postnatal depression. These topics will be addressed in future National Institute for Clinical Excellence (NICE) guidelines on intrapartum and postpartum care.

The guideline offers recommendations on baseline clinical care for all pregnant women but it does not offer information on the additional care that some women will require. Pregnant women with the following conditions usually require care additional to that detailed in this guideline:

- cardiac disease, including hypertension
- renal disease
- endocrine disorder or diabetes requiring insulin
- psychiatric disorder (on medication)
- haematological disorder, including thromboembolic disease, autoimmune diseases such as antiphospholipid syndrome
- epilepsy requiring anticonvulsant drugs
- malignant disease
- severe asthma
- drug use such as heroin, cocaine (including crack cocaine) and ecstasy
- HIV or hepatitis B virus (HBV) infected
- autoimmune disorders
- obesity (body mass index, BMI, 35 or more at first contact) or underweight (BMI less than 18 at first contact)
- women who may be at higher risk of developing complications e.g. women 40 years and older and women who smoke
- women who are particularly vulnerable (e.g. teenagers) or who lack social support
- women who have experienced any of the following in previous pregnancies:
  - recurrent miscarriage (three or more consecutive pregnancy losses) or a mid-trimester loss
  - severe pre-eclampsia, HELLP syndrome or eclampsia
  - rhesus isoimmunisation or other significant blood group antibodies
  - uterine surgery including caesarean section, myomectomy or cone biopsy

- antenatal or postpartum haemorrhage on two occasions
- retained placenta on two occasions
- puerperal psychosis
- grand multiparity (more than six pregnancies)
- a stillbirth or neonatal death
- a small-for-gestational-age infant (less than fifth centile)
- a large-for-gestational-age infant (greater than 95th centile)
- a baby weighing less than 2500 g or more than 4500 g
- a baby with a congenital anomaly (structural or chromosomal).

1.3 For whom is the guideline intended?

This guideline is of relevance to those who work in or use the National Health Service (NHS) in England and Wales:

- professional groups who share in caring for pregnant women, such as obstetricians, midwives, radiographers, physiotherapists, anaesthetists, general practitioners, paediatricians and others
- those with responsibilities for commissioning and planning maternity services, such as primary care trusts in England, Health Commission Wales, public health and trust managers
- pregnant women.

A version of this guideline for pregnant women, their partners and the public is available, entitled *Routine antenatal care for healthy pregnant women. Understanding NICE guidance: information for pregnant women, their families and the public*. It can be downloaded from the NICE website (www.nice.org.uk) or ordered via the NHS Response Line (0870 1555 455; quote reference number N0310 for an English version and N0311 for an English and Welsh version).

1.4 Who has developed the guideline?

The Guideline was developed by a multi-professional and lay working group (the Guideline Development Group) convened by the National Collaborating Centre for Women's and Children's Health (NCC-WCH). Membership included:

- two consumers
- two general practitioners
- two midwives
- two obstetricians
- a radiographer
- a neonatologist
- a representative from the Confidential Enquiry into Maternal Deaths (CEMD).

Staff from NCC-WCH provided methodological support for the guideline development process, undertook the systematic searches, retrieval and appraisal of the evidence and wrote successive drafts of the document.

In accordance with the NICE guideline development process,[6] all guideline development group members have made and updated any declarations of interest.

1.5 Who has developed the guideline update?

The guideline update was developed by a multi-professional and lay working group (the Guideline Development Group) convened by the National Collaborating Centre for Women's and Children's Health (NCC-WCH). Membership included:

- two service user representatives
- two midwives
- two obstetricians
- a general practitioner
- an ultrasonographer

- an MRC-funded research fellow.

Staff from NCC-WCH provided methodological support for the guideline development process, undertook the systematic searches, retrieval and appraisal of the evidence and wrote successive drafts of the document.

In accordance with the NICE guideline development process,[6] all guideline development group members have made and updated any declarations of interest (Appendix A).

1.6 Guideline methodology

The development of the guideline was commissioned by the National Institute for Clinical Excellence (NICE) and developed in accordance with the guideline development process outlined in *The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups*, available from the NICE website (www.nice.org.uk).[6]

Update methodology

The guideline update was developed in accordance with the NICE guideline development process outlined in thee 2006 and 2007 editions of the guidelines manual[632],[633]. Table 1.1 summarises the key stages of the guideline development process and which version of the process was followed at each stage.

Table 1.1 Stages in the NICE guideline development process and the versions followed at each stage

Stage	2006 version	2008 version
Scoping the guideline (determining what the guideline would and would not cover)	✓	
Preparing the work plan (agreeing timelines, milestones, guideline development group constitution etc)	✓	
Forming and running the guideline development group	✓	
Developing clinical questions	✓	
Identifying the evidence	✓	
Reviewing and grading the evidence	✓	✓
Incorporating health economics	✓	✓
Making group decisions and reaching consensus		✓
Linking guidance to other NICE guidance		✓
Creating guideline recommendations		✓
Developing clinical audit criteria		✓
Writing the guideline		✓
Validation (stakeholder consultation on the draft guideline)		✓
Declaration of interests[a]	✓	✓

[a] The process for declaring interests was extended in November 2006 to cover NCC-WCH staff and to include personal family interests

Literature search strategy

The aim of the literature review was to identify and synthesise relevant evidence within the published literature, in order to answer the specific clinical questions. Searches were performed using generic and specially developed filters, relevant MeSH (medical subject headings) terms and free-text terms. Details of all literature searches are available upon application to the NCC-WCH.

Guidelines by other development groups were searched for on the National Guidelines Clearinghouse database, the TRIP database and OMNI service on the Internet. The reference lists in these guidelines were checked against the searches to identify any missing evidence.

Searches were carried out for each topic of interest. The Cochrane Database of Systematic Reviews, up to Issue 3, 2003, was searched to identify systematic reviews of randomised controlled trials, with or without meta-analyses and randomised controlled trials. The electronic database, MEDLINE (Ovid version for the period January 1966 to April 2003), EMBASE (Ovid version from January 1980 to April 2003), MIDIRS (Midwives Information and Resource Service), CINAHL (Cumulative Index to Nursing and Allied Health Literature), the British Nursing Index (BNI) and PsychInfo were also searched.

The Database of Abstracts and Reviews of Effectiveness (DARE) was searched. Reference lists of non-systematic review articles and studies obtained from the initial search were reviewed and journals in the RCOG library were hand-searched to identify articles not yet indexed. There was no systematic attempt to search the 'grey literature' (conferences, abstracts, theses and unpublished trials).

A preliminary scrutiny of titles and abstracts was undertaken and full papers were obtained if they appeared to address the Guideline Development Group's (GDG) question relevant to the topic. Following a critical review of the full version of the study, articles not relevant to the subject in question were excluded. Studies that did not report on relevant outcomes were also excluded. Submitted evidence from stakeholders was included where the evidence was relevant to the GDG clinical question and when it was either better or equivalent in quality to the research identified in the literature searches.

The economic evaluation included a search of:

- NHS Economic Evaluations Database (NHS EED)
- www.ohe-heed.com http://nhscrd.york.ac.uk/nhsdhp.htm
- Cochrane Database of Systematic Reviews, Issue 3, 2003
- MEDLINE January 1966 to April 2003
- EMBASE 1980 to April 2003.

Relevant experts in the field were contacted for further information.

The search strategies were designed to find any economic study related to specific antenatal screening programmes. Abstracts and database reviews of papers found were reviewed by the health economist and were discarded if they appeared not to contain any economic data or if the focus of the paper did not relate to the precise topic or question being considered (i.e. to screening strategy alternatives that were not relevant to this guideline). Relevant references in the bibliographies of reviewed papers were also identified and reviewed. These were assessed by the health economists against standard criteria.

Literature search strategy for the 2008 update

Relevant published evidence to inform the guideline development process and answer the clinical questions was identified by systematic search strategies. Additionally, stakeholder organisations were invited to submit evidence for consideration by the GDG provided it was relevant to the clinical questions and of equivalent or better quality than evidence identified by the search strategies.

Systematic searches to answer the clinical questions formulated and agreed by the GDG were executed using the following databases via the 'Ovid' platform: Medline (1966 onwards), Embase (1980 onwards), Cumulative Index to Nursing and Allied Health Literature (1982 onwards) and

PsycINFO (1967 onwards). The most recent search conducted for the three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects) was during Quarter 1, 2007. Searches to identify economic studies were undertaken using the above databases, and the NHS Economic Evaluations Database (NHS EED).

Search strategies combined relevant controlled vocabulary and natural language in an effort to balance sensitivity and specificity. Unless advised by the GDG, searches were not date specific. Language restrictions were not applied to searches. Both generic and specially developed methodological search filters were used appropriately.

There was no systematic attempt to search grey literature (conferences, abstracts, theses and unpublished trials). Hand searching of journals not indexed on the databases was not undertaken.

Towards the end of the guideline development process searches were re-executed, thereby including evidence published and included in the databases up to 8 June 2007. Any evidence published after this date was not included. This date should be considered the starting point for searching for new evidence for future updates to this guideline.

Further details of the search strategies, including the methodological filters employed, are available on an accompanying disc.

Clinical effectiveness

For all the subject areas, evidence from the study designs least subject to sources of bias was included. Where possible, the highest levels of evidence were used, but all papers were reviewed using established guides (see below). Published systematic reviews or meta-analyses were used if available. For subject areas where neither was available, other appropriate experimental or observational studies were sought.

Identified articles were assessed methodologically and the best available evidence was used to form and support the recommendations. The highest level of evidence was selected for each clinical question. Using the evidence-level structure shown in Table 1.1, the retrieved evidence was graded accordingly.

Hierarchy of evidence

The clinical question dictates the highest level of evidence that should be sought. For issues of therapy or treatment, the highest level of evidence is meta-analyses of randomised controlled trials or randomised controlled trials themselves. This would equate to a grade A recommendation.

For issues of prognosis, a cohort study is the best level of evidence available. The best possible level of evidence would equate to a grade B recommendation. It should not be interpreted as an inferior grade of recommendation, as it represents the highest level of evidence attainable for that type of clinical question.

Table 1.1 Structure of evidence levels

Level	Definition
1a	Systematic review and meta-analysis of randomised controlled trials
1b	At least one randomised controlled trial
2a	At least one well-designed controlled study without randomisation
2b	At least one other type of well-designed quasi-experimental study
3	Well-designed non-experimental descriptive studies, such as comparative studies, correlation studies or case studies
4	Expert committee reports or opinions and/or clinical experience of respected authorities

For diagnostic tests, test evaluation studies examining the performance of the test were used if the efficacy of the test was required. Where an evaluation of the effectiveness of the test on

management and outcome was required, evidence from randomised controlled trials or cohort studies was sought.

All retrieved articles have been appraised methodologically using established guides. Where appropriate, if a systematic review, meta-analysis or randomised controlled trial existed in relation to a topic, studies of a weaker design were not sought.

The evidence was synthesised using qualitative methods. These involved summarising the content of identified papers in the form of evidence tables and agreeing brief statements that accurately reflect the relevant evidence. Quantitative techniques (meta-analyses) were performed if appropriate and necessary.

For the purposes of this guideline, data are presented as relative risk (RR) where relevant (i.e. in RCTs and cohort studies) or as odds ratios (OR) where relevant (i.e. in systematic reviews of RCTs). Where these data are statistically significant they are also presented as numbers needed to treat (NNT), if relevant.

Health economics

In antenatal care, there is a relatively large body of economic literature that has considered the economic costs and consequences of different screening programmes and considered the organisation of antenatal care. The purpose of including economic evidence in a clinical guideline is to allow recommendations to be made not just on the clinical effectiveness of different forms of care, but on the cost effectiveness as well. The aim is to produce guidance that uses scarce health service resources efficiently; that is, providing the best possible care within resource constraints.

The economic evidence is focused around the different methods of screening, although some work has been undertaken to examine the cost effectiveness of different patterns of antenatal care (the number of antenatal appointments) and to explore women's preferences for different aspects of their antenatal care. The economic evidence presented in this guideline is not a systematic review of all the economic evidence around antenatal care. It was decided that the health economic input into the guideline should focus on specific topics where the guideline development group thought that economic evidence would help them to inform their decisions. This approach was made on pragmatic grounds (not all the economic evidence could be reviewed with the resources available) and on the basis that economic evidence should not be based only on the economic literature, but should be consistent with the clinical effectiveness evidence presented in the guideline. Some of the economic evaluation studies did not address the specific alternatives (say, for screening) that were addressed in the guideline. Therefore, for each of the specific topic areas where the economic evidence was reviewed, a simple economic model was developed in order to present the guideline development group with a coherent picture of the costs and consequences of the decisions based on the clinical and economic evidence. The role of the health economist in this guideline was to review the literature in these specific areas and obtain cost data considered to be the closest to current UK opportunity cost (the value of the resources used, rather than the price or charge).

The approach adopted for this guideline was for the health economic analysis to focus on specific areas. Topics for economic analysis were selected on the following basis by the guideline development group.

- Does the proposed topic have major resource implications?
- Is there a change of policy involved?
- Are there sufficient data of adequate quality to allow useful review or modelling?
- Is there a lack of consensus among clinicians?
- Is there a particular area with a large amount of uncertainty?

Where the above answers were 'yes', this indicated that further economic analysis including modelling is more likely to be useful.

The Guideline Development Group identified six areas where the potential impact of alternative strategies could be substantial and where the health economics evidence should focus. These were: screening for asymptomatic bacteriuria, screening for group B streptococcus, screening for syphilis, screening for sickle cell and thalassaemia, ultrasound screening for structural abnormalities and Down's syndrome screening.

For all these topics, a review of the economic evidence was undertaken, followed by simple economic modelling of the cost effectiveness in England and Wales of different strategies.

The review of the economic evaluation studies included cost-effectiveness studies (only those where an incremental cost-effectiveness ratio had been determined or could be determined from the data presented). The topic had to focus on the appropriate alternatives (the appropriate clinical question), preferably able to be generalised to the England and Wales setting, and therefore be useful in constructing a simple decision model. The review of the evidence included cost-effectiveness studies, cost-consequence studies (cost of present and future costs only) and high-quality systematic reviews of the evidence. A narrative review of all the evidence is not presented in the main guideline. Appendix B shows the way the models have been constructed, the economic and clinical parameters incorporated into each model, the sources of data that have been used (cost data and clinical data), the results of the baseline model and the sensitivity analysis.

Evidence on the cost consequences associated with alternative screening strategies was obtained from various published sources that addressed these issues. The purpose was to obtain good quality cost data judged by the health economist to be as close as possible to the true opportunity cost of the intervention (screening programme).

The key cost variables considered were:

- the cost of a screening programme (the cost of different screening interventions and the cost of expanding and contracting a screening programme)
- the cost of treatment of women found to be carriers of a disease
- the cost of any adverse or non-therapeutic effects of screening or treatment to the woman
- the cost of the consequences of screening and not screening to the fetus and infant, including fetal loss, ending pregnancy, and the lifetime costs of caring for infants born with disabilities.

Cost data not available from published sources were obtained from the most up-to-date NHS reference cost price list. Some cost data could not be obtained from published sources or from NHS reference costs and therefore consensus methods were used in the Guideline Development Group to obtain an indicative estimate of the likely costs. The range of sources of cost data are set out in the appendix that explains the methodology adopted to construct each of the economic models created for this guideline.

In some cases (i.e., for screening for asymptomatic bacteriuria and for haemoglobinopathies), the economic modelling work began and had to be abandoned due to lack of data of the effectiveness of the different screening options. Appendix B provides some discussion of these models that could not be completed in the guideline and areas for future research.

Limitations of the economic evidence in this guideline

Economic analyses have been undertaken alongside a wide range of antenatal screening procedures. A systematic review of antenatal screening was undertaken in 2001.[7] This review found that many of the studies identified were of poor quality, since they did not consider the effects of screening on future health (of mother and baby) but only costs averted by a screening programme.

In this guideline, the costs of screening and the costs of the benefits or harm of screening have been considered simultaneously where possible (i.e. where the data exist). It has not been possible to include many of the consequences of a screening programme because the data do not exist on these less straightforward or measurable outcomes (such as the benefit foregone from ending pregnancy).

The economic analysis of screening methods in the guideline has not been able to consider the following:

- the value to the woman of being given information about the health of her future child
- the value of being able to plan appropriate services for children who are born with disabilities
- the value of a life of a child born with disability, to the child, to the family and to society in general
- the value to a woman of being able to choose whether to end a pregnancy

- the value of a life foregone as a consequence of screening.

The cost-effectiveness studies reviewed for this guideline had narrowly defined endpoints; for example, a case of birth defect detected and subsequently averted as a result of a screening test. Some of the studies have considered the cost consequences of avoiding the birth of an infant with severe disabilities and their long-term care costs. The value of future life foregone (of a healthy or a disabled infant's life) due to screening has not been explicitly considered in any of the economic evidence of antenatal screening. Since economic evaluation should always consider the costs and benefits of an intervention in the widest possible sense, this could be seen as a limitation of the analysis presented in this guideline. The consequences of this are discussed in Appendix B.

Health Economics for the 2008 update

The aim of the economic input into the guideline was to inform the GDG of potential economic issues relating to antenatal care. The health economist helped the GDG by identifying topics within the guideline that might benefit from economic analysis, reviewing the available economic evidence and, where necessary, conducting (or commissioning) economic analysis. Reviews of published health economic evidence are presented alongside the reviews of clinical evidence and are incorporated within the relevant evidence statement and recommendations. For some questions, no published evidence was identified, and decision analytic modelling was undertaken. Results of this modelling are presented in the guideline text where appropriate, with full details in Appendix B.

Economic evaluations in this guideline have been conducted in the form of a cost-effectiveness analysis, with the health effects measured in an appropriate non-monetary outcome indicator. The NICE technology appraisal programme measures outcomes in terms of quality adjusted life years (QALYs). Where possible, this approach has been used in the development of this guideline. However, where it has not been possible to estimate QALYs gained as a result of an intervention, an alternative measure of effectiveness has been used.

Cost-effectiveness analysis, with the units of effectiveness expressed in QALYs (known as cost-utility analysis) is widely recognised as a useful approach for measuring and comparing the efficiency of different health interventions. The QALY is a measure of health outcome which assigns to each period of time (generally one year) a weight, ranging from 0 to 1, corresponding to health related quality of life during that period. It is one of the most commonly used outcome measures in health economics. A score of one corresponds to full health and a score of zero corresponds to a health state equivalent to death. Negative valuations, implying a health state worse then death, are possible. Health outcomes using this method are measured by the number of years of life in a given health state multiplied by the value of being in that health state.

Forming and grading the recommendations

The Guideline Development Group was presented with the summaries (text and evidence tables) of the best available research evidence to answer their questions. Recommendations were based on, and explicitly linked to, the evidence that supported them. A recommendation's grade may not necessarily reflect the importance attached to the recommendation. For example the Guideline Development Group felt that the principles of woman-centred care that underpin this guideline (Chapter 3) are particularly important but some of these recommendations receive only a D grade or good practice point (GPP).

The Group worked where possible on an informal consensus basis. Formal consensus methods (modified Delphi techniques or nominal group technique) were employed if required (e.g. grading recommendations or agreeing audit criteria).

The recommendations were then graded according to the level of evidence upon which they were based. The strength of the evidence on which each recommendation is based is shown in Table 1.2. The grading of recommendations will follow that outlined in the Health Technology Assessment (HTA) review *How to develop cost conscious guidelines*.

Limited results or data are presented in the text. More comprehensive results and data are available in the relevant evidence tables.

External review

The guideline has been developed in accordance with the NICE guideline development process.[6] This has included the opportunity for registered stakeholders to comment on the scope of the guideline, the first draft of the full and summary guidelines and the second draft of all versions of the guideline. In addition, the first draft was reviewed by nominated individuals with an interest in antenatal care. All drafts, comments and responses were also reviewed by the independent Guideline Review Panel established by NICE.

The comments made by the stakeholders, peer reviewers and the NICE Guideline Review Panel were collated and presented anonymously for consideration by the Guideline Development Group. All comments were considered systematically by the Group and the resulting actions and responses were recorded.

Table 1.2 Strength of the evidence upon which each recommendation is based

Grade	Definition
A	Directly based on level I evidence
B	Directly based on level II evidence or extrapolated recommendation from level I evidence
C	Directly based on level III evidence or extrapolated recommendation from either level I or II evidence
D	Directly based on level IV evidence or extrapolated recommendation from either level I, II or III evidence
Good practice point (GPP)	The view of the Guideline Development Group
NICE Technology Appraisal	Recommendation taken from the NICE Technology Appraisal

2 Summary of recommendations and practice algorithm

2.1 Key priorities for implementation

Lifestyle considerations

Oral vitamin D supplement of 10 micrograms per day should be offered to healthy pregnant women at risk of vitamin D deficiency, for example women with dark skin, women who usually cover their skin, women who eat a vegan diet and women in age group 19-24 years.

Screening for haematological conditions

Screening for haemoglobinopathies should be carried out as soon as possible in pregnancy, in the context of either primary or secondary care.

Screening for fetal anomalies

Participation in regional congenital anomaly registers is strongly recommended to facilitate the audit of detection rates.

The screening test for Down's syndrome offered should be the 'combined test' (nuchal translucency, beta-human chorionic gonadotrophin, pregnancy-associated plasma protein-A) between 11 weeks and 13 weeks and 6 days. Between 15 and 20 weeks the most clinically and cost effective serum screening test should be offered (triple or quadruple test).

Screening for clinical conditions

Screening for gestational diabetes using risk factors is recommended in a normal healthy population. Risk factors which should be used are:

- body mass index $>$ 30 kg/m^2
- previous macrosomic baby $\geq$4.5 kg
- previous gestational diabetes (see the Diabetes in pregnancy guideline, currently in development)
- family history of diabetes (first degree relative with type 1 or type 2 diabetes)
- women from a high-risk ethnic group, which would include:
  - South Asian (Indian, Pakistani, Bangladeshi)
  - Black Caribbean
  - Chinese.

2.2 Summary of recommendations

Chapter 3 Woman-centred care and informed decision making

3.2 Antenatal education

2008 Recommendations

The following schedule should be used when providing information antenatally:

1. At first contact with a healthcare professional:

- All antenatal screening
- Signs of miscarriage
- Nutrition and diet, including folic acid supplementation
- Food hygiene, including avoidance of mould-ripened cheese and pate
- How the baby develops during pregnancy
- Exercise, including pelvic floor exercises
- Lifestyle advice including smoking cessation; recreational drug use and alcohol consumption

2. At booking:

- Place of birth (for further information on this topic, please refer to the Intrapartum care guideline, due to be published in September 2007 [634])
- Care pathway
- Breastfeeding
- Further discussion of all antenatal screening including the anomaly scan and screening for Down's Syndrome

3. Before or at 36 weeks:

- Breastfeeding technique
- Preparation for labour and birth
- Recognition of active labour
- Care of new baby
- Postnatal self-care
- Awareness of baby blues and postnatal depression

4. At 38-40 weeks:

- Options for management of post-dates pregnancy.

This can be achieved by providing a pregnancy book such as 'The Pregnancy Book' (Department of Health, 2007).

Communication and information should be provided in a form that is accessible to pregnant women who have additional needs, such as those with physical, cognitive or sensory disabilities and those who do not speak or read English. [635].

Information can also be provided using media such as video or touch screen technology and should be supported by written information.

Pregnant women should be offered evidence-based information and support to enable them to make informed decisions regarding their care. Information should include details of where they will be seen and who will undertake their care. [635]

At each antenatal appointment, midwives and doctors should offer consistent information and clear explanations and should provide pregnant women with an opportunity to discuss issues and ask questions.

Pregnant women should be offered opportunities to attend participant-led antenatal classes, including breastfeeding workshops.

Women's decisions should be respected, even when this is contrary to the views of the health care provider.

Pregnant women should be informed about the purpose of any screening test before it is performed. The health care professional should ensure the woman has understood this information and has sufficient time to make an informed decision. The right of a woman to accept or decline a test should be made clear. [635]

Information about antenatal screening should be provided in a setting where discussion can take place; this may be in a group setting or on a one-to-one basis. This should be carried out before booking.

Any information about screening should include balanced and accurate information about the condition being screened for.

Research recommendation

Alternative ways of helping healthcare professionals to support pregnant women in making informed decisions should be investigated.

Chapter 4 Provision and organisation of care

4.1 Who provides care?

Midwife and GP-led models of care should be offered to women with an uncomplicated pregnancy. Routine involvement of obstetricians in the care of women with an uncomplicated pregnancy at scheduled times does not appear to improve perinatal outcomes compared with involving obstetricians when complications arise. [A]

4.2 Continuity of care

Antenatal care should be provided by a small group of carers with whom the woman feels comfortable. There should be continuity of care throughout the antenatal period. [A]

A system of clear referral paths should be established so that pregnant women who require additional care are managed and treated by the appropriate specialist teams when problems are identified. [D]

4.3 Where should antenatal appointments take place?

Antenatal care should be readily and easily accessible to all women and should be sensitive to the needs of individual women and the local community. [C]

The environment in which antenatal appointments take place should enable women to discuss sensitive issues such as domestic violence, sexual abuse, psychiatric illness and illicit drug use. [Good practice point]

4.4 Documentation of care

Structured maternity records should be used for antenatal care. [A]

Maternity services should have a system in place whereby women carry their own case notes. [A]

A standardised, national maternity record with an agreed minimum data set should be developed and used. This will help carers to provide the recommended evidence-based care to pregnant women. [Good practice point]

4.5 Frequency of antenatal appointments

A schedule of antenatal appointments should be determined by the function of the appointments. For a woman who is nulliparous with an uncomplicated pregnancy, a schedule of ten appointments should be adequate. For a woman who is parous with an uncomplicated pregnancy, a schedule of seven appointments should be adequate. [B]

Early in pregnancy, all women should receive appropriate written information about the likely number, timing and content of antenatal appointments associated with different options of care and be given an opportunity to discuss this schedule with their midwife or doctor. [D]

Each antenatal appointment should be structured and have focused content. Longer appointments are needed early in pregnancy to allow comprehensive assessment and discussion. Wherever possible, appointments should incorporate routine tests and investigations to minimise inconvenience to women. [D]

4.6 Gestational age assessment: LMP and ultrasound

2008 Recommendations

Pregnant women should be offered an early ultrasound scan to determine gestational age and to detect multiple pregnancies. This will ensure consistency of gestational age assessment, and reduce the incidence of induction of labour for post-date pregnancies.

Ideally, the early ultrasound scan should be undertaken between 10 and 13 weeks 6 days and use crown – rump length (CRL) measurement to determine gestational age. If the CRL is greater than 84 mm, gestational age should be estimated using head circumference.

4.7 What should happen at antenatal appointments?

The assessment of women who may or may not need additional clinical care during pregnancy is based on identifying those in whom there are any maternal or fetal conditions associated with an excess of maternal or perinatal death or morbidity. While this approach may not identify many of the women who go on to require extra care and will also categorise many women who go on to have normal uneventful births as 'high risk',[58,59] ascertainment of risk in pregnancy remains important as it may facilitate early detection to allow time to plan for appropriate management.

The needs of each pregnant woman should be assessed at the first appointment and reassessed at each appointment throughout pregnancy because new problems can arise at any time. Additional appointments should be determined by the needs of the pregnant woman, as assessed by her and her care givers, and the environment in which appointments take place should enable women to discuss sensitive issues. Reducing the number of routine appointments will enable more time per appointment for care, information giving and support for pregnant women.

The schedule below, which has been determined by the purpose of each appointment, presents the recommended number of antenatal care appointments for women who are healthy and whose pregnancies remain uncomplicated in the antenatal period; ten appointments for nulliparous women and seven for parous women.

First appointment

The first appointment needs to be earlier in pregnancy (prior to 12 weeks) than may have traditionally occurred and, because of the large volume of information needs in early pregnancy, two appointments may be required. At the first (and second) antenatal appointment:

- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by written information (on topics such as diet and lifestyle considerations, pregnancy care services available, maternity benefits and sufficient information to enable informed decision making about screening tests)
- identify women who may need additional care (see Algorithm and Section 1.2) and plan pattern of care for the pregnancy
- check blood group and rhesus D (RhD) status
- offer screening for anaemia, red-cell alloantibodies, hepatitis B virus, HIV, rubella susceptibility and syphilis
- offer screening for asymptomatic bacteriuria (ASB)
- offering screening for Down's syndrome
- offer early ultrasound scan for gestational age assessment
- offer ultrasound screening for structural anomalies (20 weeks)
- measure BMI and blood pressure (BP) and test urine for proteinuria.

After the first (and possibly second) appointment, for women who choose to have screening, the following test should be arranged before 16 weeks of gestation (except serum screening for Down's syndrome, which may occur up to 20 weeks of gestation):

- blood tests (for checking blood group and RhD status and screening for anaemia, red-cell alloantibodies, hepatitis B virus, HIV, rubella susceptibility and syphilis)
- urine tests (to check for proteinuria and screen for ASB)
- ultrasound scan to determine gestational age using:
  - crown–rump measurement if performed at 10 to 13 weeks
  - biparietal diameter or head circumference at or beyond 14 weeks
- Down's syndrome screening using:
  - nuchal translucency at 11 to 14 weeks
  - serum screening at 14 to 20 weeks.

16 weeks

The next appointment should be scheduled at 16 weeks to:

- review, discuss and record the results of all screening tests undertaken; reassess planned pattern of care for the pregnancy and identify women who need additional care (see Algorithm and Section 1.2)
- investigate a haemoglobin level of less than 11g/dl and consider iron supplementation if indicated
- measure BP and test urine for proteinuria
- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.

18–20 weeks

At 18–20 weeks, if the woman chooses, an ultrasound scan should be performed for the detection of structural anomalies. For a woman whose placenta is found to extend across the internal cervical os at this time, another scan at 36 weeks should be offered and the results of this scan reviewed at the 36-week appointment.

25 weeks

At 25 weeks of gestation, another appointment should be scheduled for nulliparous women. At this appointment:

- measure and plot symphysis–fundal height
- measure BP and test urine for proteinuria
- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.

28 weeks

The next appointment for all pregnant women should occur at 28 weeks. At this appointment:

- offer a second screening for anaemia and atypical red-cell alloantibodies
- investigate a haemoglobin level of less than 10.5 g/dl and consider iron supplementation, if indicated
- offer anti-D to rhesus-negative women
- measure BP and test urine for proteinuria
- measure and plot symphysis–fundal height
- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.

31 weeks

Nulliparous women should have an appointment scheduled at 31 weeks to:

- measure BP and test urine for proteinuria
- measure and plot symphysis–fundal height
- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information
- review, discuss and record the results of screening tests undertaken at 28 weeks; reassess planned pattern of care for the pregnancy and identify women who need additional care (see Algorithm and Section 1.2).

34 weeks

At 34 weeks, all pregnant women should be seen in order to:

- offer a second dose of anti-D to rhesus-negative women
- measure BP and test urine for proteinuria
- measure and plot symphysis–fundal height
- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information

- review, discuss and record the results of screening tests undertaken at 28 weeks; reassess planned pattern of care for the pregnancy and identify women who need additional care (see Algorithm and Section 1.2).

36 weeks

At 36 weeks, all pregnant women should be seen again to:

- measure BP and test urine for proteinuria
- measure and plot symphysis–fundal height
- check position of baby
- for women whose babies are in the breech presentation, offer external cephalic version (ECV)
- review ultrasound scan report if placenta extended over the internal cervical os at previous scan
- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.

38 weeks

Another appointment at 38 weeks will allow for:

- measurement of BP and urine testing for proteinuria
- measurement and plotting of symphysis–fundal height
- information giving, with an opportunity to discuss issues and ask questions; verbal information supported by antenatal classes and written information.

40 weeks

For nulliparous women, an appointment at 40 weeks should be scheduled to:

- measure BP and test urine for proteinuria
- measure and plot symphysis–fundal height
- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.

41 weeks

For women who have not given birth by 41 weeks:

- a membrane sweep should be offered
- induction of labour should be offered
- BP should be measured and urine tested for proteinuria
- symphysis–fundal height should be measured and plotted
- information should be given, with an opportunity to discuss issues and ask questions; verbal information supported by written information.

General

Throughout the entire antenatal period, healthcare providers should remain alert to signs or symptoms of conditions which affect the health of the mother and fetus, such as domestic violence, pre-eclampsia and diabetes.

For an outline of care at each appointment see the Algorithm (Section 2.4).

Chapter 5 Lifestyle considerations

5.3 Working during pregnancy

Pregnant women should be informed of their maternity rights and benefits. [C]

The majority of women can be reassured that it is safe to continue working during pregnancy. Further information about possible occupational hazards during pregnancy is available from the Health and Safety Executive. [D]

A woman's occupation during pregnancy should be ascertained to identify those at increased risk through occupational exposure. [Good practice point]

5.5 Nutritional supplements

Pregnant women (and those intending to become pregnant) should be informed that dietary supplementation with folic acid, before conception and up to 12 weeks of gestation, reduces the risk of having a baby with neural tube defects (anencephaly, spina bifida). The recommended dose is 400 micrograms per day. [A]

Iron supplementation should not be offered routinely to all pregnant women. It does not benefit the mother's or the fetus's health and may have unpleasant maternal side effects. [A]

Pregnant women should be informed that vitamin A supplementation (intake greater than 700 micrograms) might be teratogenic and therefore it should be avoided. Pregnant women should be informed that as liver and liver products may also contain high levels of vitamin A, consumption of these products should also be avoided. [C]

2008 Recommendations

Normal healthy women should not be routinely offered vitamin D supplementation during pregnancy.

Oral vitamin D supplement of 10 micrograms per day should be offered to healthy pregnant women at risk of vitamin D deficiency, for example women with dark skin, women who usually cover their skin, women who eat a vegan diet and women in age group 19-24 years.

Research recommendation

There is need for future research into the effectiveness of routine Vitamin D supplementation for pregnant and breastfeeding women.

5.6 Food-acquired infections

Pregnant women should be offered information on how to reduce the risk of listeriosis by:

- drinking only pasteurised or UHT milk
- not eating ripened soft cheese such as Camembert, Brie and blue-veined cheese (there is no risk with hard cheeses, such as Cheddar, or cottage cheese and processed cheese)
- not eating pâté (of any sort, including vegetable)
- not eating uncooked or undercooked ready-prepared meals. [D]

Pregnant women should be offered information on how to reduce the risk of salmonella infection by:

- avoiding raw or partially cooked eggs or food that may contain them (such as mayonnaise)
- avoiding raw or partially cooked meat, especially poultry. [D]

5.7 Prescribed medicines

Few medicines have been established as safe to use in pregnancy. Prescription medicines should be used as little as possible during pregnancy and should be limited to circumstances where the benefit outweighs the risk. [D]

5.8 Over-the-counter medicines

Pregnant women should be informed that few over-the-counter (OTC) medicines have been established as being safe to take in pregnancy. OTC medicines should be used as little as possible during pregnancy. [D]

5.9 Complementary therapies

Pregnant women should be informed that few complementary therapies have been established as being safe and effective during pregnancy. Women should not assume that such therapies are safe and they should be used as little as possible during pregnancy. [D]

5.10 Exercise in pregnancy

Pregnant women should be informed that beginning or continuing a moderate course of exercise during pregnancy is not associated with adverse outcomes. [A]

Pregnant women should be informed of the potential dangers of certain activities during pregnancy, for example, contact sports, high-impact sports and vigorous racquet sports that may involve the risk of abdominal trauma, falls or excessive joint stress, and scuba diving, which may result in fetal birth defects and fetal decompression disease. [D]

5.11 Sexual intercourse in pregnancy

Pregnant woman should be informed that sexual intercourse in pregnancy is not known to be associated with any adverse outcomes. [B]

5.12 Alcohol and smoking in pregnancy

2008 Recommendations

Pregnant women should limit their alcohol intake to less than one standard drink (1.5 UK units or 12g of alcohol) per day and if possible avoid alcohol in the first 3 months of pregnancy.

Women should be informed that binge drinking (defined as more than 5 standard drinks on a single occasion) may be particularly harmful during pregnancy.

Research recommendation

More research is required into the level and frequency of binge-drinking that constitutes a risk.

Pregnant women should be informed about the specific risks of smoking during pregnancy (such as the risk of having a baby with low birthweight and preterm). The benefits of quitting at any stage should be emphasised. [A]

Women who smoke or who have recently stopped should be offered smoking cessation interventions. Interventions that appear to be effective in reducing smoking include advice by physician, group sessions and behavioural therapy (based on self-help manuals). [A]

Women who are unable to quit smoking during pregnancy should be encouraged to reduce smoking. [B]

5.13 Cannabis use in pregnancy

The direct effects of cannabis on the fetus are uncertain but may be harmful. Cannabis use is associated with smoking, which is known to be harmful; therefore women should be discouraged from using cannabis during pregnancy. [C]

5.14 Air travel during pregnancy

Pregnant women should be informed that long-haul air travel is associated with an increased risk of venous thrombosis, although whether or not there is additional risk during pregnancy is unclear. In the general population, wearing correctly fitted compression stockings is effective at reducing the risk. [B]

5.15 Car travel during pregnancy

Pregnant women should be informed about the correct use of seatbelts (that is, three-point seatbelts 'above and below the bump, not over it'). [B]

5.16 Travelling abroad during pregnancy

Pregnant women should be informed that, if they are planning to travel abroad, they should discuss considerations such as flying, vaccinations and travel insurance with their midwife or doctor. [Good practice point]

Chapter 6 Management of common symptoms of pregnancy

6.1 Nausea and vomiting in early pregnancy

Women should be informed that most cases of nausea and vomiting in pregnancy will resolve spontaneously within 16 to 20 weeks of gestation and that nausea and vomiting are not usually

associated with a poor pregnancy outcome. If a woman requests or would like to consider treatment, the following interventions appear to be effective in reducing symptoms [A]:

- nonpharmacological:
  - ginger
  - P6 acupressure
- pharmacological:
  - antihistamines.

Information about all forms of self-help and nonpharmacological treatments should be made available for pregnant women who have nausea and vomiting. [Good practice point]

6.2 Heartburn

Women who present with symptoms of heartburn in pregnancy should be offered information regarding lifestyle and diet modification. [Good practice point]

Antacids may be offered to women whose heartburn remains troublesome despite lifestyle and diet modification. [A]

6.3 Constipation

Women who present with constipation in pregnancy should be offered information regarding diet modification, such as bran or wheat fibre supplementation. [A]

6.4 Haemorrhoids

In the absence of evidence of the effectiveness of treatments for haemorrhoids in pregnancy, women should be offered information concerning diet modification. If clinical symptoms remain troublesome, standard haemorrhoid creams should be considered. [Good practice point]

6.5 Varicose veins

Women should be informed that varicose veins are a common symptom of pregnancy that will not cause harm and that compression stockings can improve the symptoms but will not prevent varicose veins from emerging. [A]

6.6 Vaginal discharge

Women should be informed that an increase in vaginal discharge is a common physiological change that occurs during pregnancy. If this is associated with itch, soreness, offensive smell or pain on passing urine there may be an infective cause and investigation should be considered. [Good practice point]

A 1-week course of a topical imidazole is an effective treatment and should be considered for vaginal candidiasis infections in pregnant women. [A]

The effectiveness and safety of oral treatments for vaginal candidiasis in pregnancy is uncertain and these should not be offered. [Good practice point]

6.7 Backache

Women should be informed that exercising in water, massage therapy and group or individual back care classes might help to ease backache during pregnancy. [A]

Chapter 7 Clinical examination of pregnant women

7.1 Measurement of weight and body mass index

Maternal weight and height should be measured at the first antenatal appointment, and the woman's body mass index (BMI) calculated (weight [kg]/height[m]^2). [B]

Repeated weighing during pregnancy should be confined to circumstances where clinical management is likely to be influenced. [C]

7.2 Breast examination

Routine breast examination during antenatal care is not recommended for the promotion of postnatal breastfeeding. [A]

7.3 Pelvic examination

Routine antenatal pelvic examination does not accurately assess gestational age, nor does it accurately predict preterm birth or cephalopelvic disproportion. It is not recommended. [B]

7.4 Female genital mutilation

Pregnant women who have had female genital mutilation should be identified early in antenatal care through sensitive enquiry. Antenatal examination will then allow planning of intrapartum care. [C]

7.5 Domestic violence

Health care professionals need to be alert to the symptoms or signs of domestic violence and women should be given the opportunity to disclose domestic violence in an environment in which they feel secure. [D]

7.6 Psychiatric screening

Women should be asked early in pregnancy if they have had any previous psychiatric illnesses. Women who have had a past history of serious psychiatric disorder should be referred for a psychiatric assessment during the antenatal period. [B]

Pregnant women should not be offered routine screening, such as with the Edinburgh Postnatal Depression Scale, in the antenatal period to predict the development of postnatal depression. [A]

Pregnant women should not be offered antenatal education interventions to reduce perinatal or postnatal depression, as these interventions have not been shown to be effective. [A]

Chapter 8 Screening for haematological conditions

8.1 Anaemia

Pregnant women should be offered screening for anaemia. Screening should take place early in pregnancy (at the first appointment) and at 28 weeks when other blood screening tests are being performed. This allows enough time for treatment if anaemia is detected. [B]

Haemoglobin levels outside the normal UK range for pregnancy (that is, 11 g/dl at first contact and 10.5 g/dl at 28 weeks) should be investigated and iron supplementation considered if indicated. [A]

8.3 Blood grouping and red cell alloantibodies

Women should be offered testing for blood group and RhD status in early pregnancy. [B]

It is recommended that routine antenatal anti-D prophylaxis is offered to all non-sensitised pregnant women who are RhD negative. (See 'Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women' [NICE technology appraisal 41], currently being updated.)

Women should be screened for atypical red cell alloantibodies in early pregnancy and again at 28 weeks regardless of their RhD status. [B]

Pregnant women with clinically significant atypical red cell alloantibodies should be offered referral to a specialist centre for further investigation and advice on subsequent antenatal management.[D]

If a pregnant woman is RhD-negative, consideration should be given to offering partner testing to determine whether the administration of anti-D prophylaxis is necessary. [Good practice point]

2008 Recommendations

Pre-conceptual counselling and carrier testing should be available to all women who are identified as being at higher risk of haemoglobinopathies using the Family Origin Questionnaire (NHS Antenatal and Newborn Screening Programmes) See Appendix F

Screening for haemoglobinopathies should be carried out as soon as possible in pregnancy, in the context of either primary or secondary care.

Prior to screening, women should be provided with information about sickle cell disorders and thalassaemias, including carrier status, and the implications of each.

Screening for sickle cell disorders and thalassaemias should be offered to all pregnant women (ideally by 10 weeks), and be preceded by counselling. The type of screening depends upon the prevalence.

In high prevalence areas (more than 1.5 cases per 10 000 pregnancies) screening using high performance liquid chromatography should be offered to all women to identify carriers of both sickle cell disease and thalassaemia.

In low prevalence areas (less than or equal to 1.5 cases per 10 000 pregnancies) all women should be offered screening for haemoglobinopathies using the Family Origins Questionnaire (NHS Antenatal and Newborn Screening Programmes). See Appendix F.

- If the Family Origins Questionnaire (NHS Antenatal and Newborn Screening Programmes) indicates high risk of sickle cell disorders, screening using high performance liquid chromatography should be offered.
- If the Family Origins Questionnaire (NHS Antenatal and Newborn Screening Programmes) indicates high risk of thalassaemia and mean corpuscular haemoglobin less than 27pg screening using high performance liquid chromatography should be offered).

All partners of identified carriers of haemoglobinopathies should be offered counselling and screening.

Chapter 9 Screening for fetal anomalies

9.1 Screening for structural anomalies

2008 Recommendations

Ultrasound screening for fetal abnormalities should be routinely offered between 18 and 20 weeks.

Women should be given information regarding the purpose and implications of the anomaly scan in order to enable them make an informed choice as to whether or not to have the scan. The purpose of the scan is:

To identify fetal abnormalities and allow:

reproductive choice (Termination of pregnancy: TOP)
intrauterine therapy
managed delivery in specialist centre
parents to prepare (for TOP/palliative care/Rx/disability).

Women should be informed of the limitations of routine ultrasound screening including the fact that detection rates vary by the type of fetal abnormality.

Following the anomaly scan women should be given information of the findings to enable them to make an informed choice as to whether they wish to continue with the pregnancy or have a termination of pregnancy.

Participation in regional congenital anomaly registers is strongly recommended to facilitate the audit of detection rates.

Fetal echocardiography involving four chamber and outflow tract view is recommended as part of the routine ultrasound scan at 18-20 weeks for fetal abnormalities.

Routine screening for cardiac anomaly by nuchal translucency is not recommended.

When routine ultrasound screening is performed at 18-20 weeks for neural tube defects, alpha-feto protein testing is not required.

Research recommendation:

Research should be undertaken to elucidate the relationship between increased nuchal translucency and cardiac defects.

9.2 Screening for Down's syndrome

2008 Recommendations

All pregnant women should be offered screening for Down's syndrome. Women should understand that it is their choice to embark on screening for Down's syndrome.

Screening for Down's syndrome should be performed by the end of first trimester (13 weeks and 6 days gestation), but provision should be made to allow later screening (up to 20 weeks gestation) for women booking later in the pregnancy

The screening test for Down's syndrome offered should be the 'combined test' (nuchal translucency, beta-human chorionic gonadotrophin, pregnancy-associated plasma protein-A) between 11 weeks and 13 weeks and 6 days. Between 15 and 20 weeks the most clinically and cost effective serum screening test should be offered (triple or quadruple test).

The integrated test should not be routinely used as a screening test for Down's syndrome.

Information about the screening options for Down's syndrome which can be understood by all women, including those whose first language is not English, should be given to women as early as possible and ideally before the booking visit, allowing the opportunity for further discussion before embarking on screening.

It should include:

a) the screening pathway for both screen positive and screen negative
b) the decisions needing to be made at each point along the pathway and their consequences
c) the fact that screening does not provide a definitive diagnosis
d) information about chorionic villus sampling and amniocentesis
e) balanced and accurate information about Down's syndrome

If a woman receives a screen positive result, she should have rapid access to appropriate counselling by trained staff.

The second trimester ultrasound scan (at 18-20 weeks) should not be routinely used for Down's syndrome screening using soft markers

The presence of an isolated soft marker with an exception of increased nuchal fold noted on the routine anomaly scan (at 18-20weeks gestation), should not be used to adjust the a priori risk for Down's syndrome.

The presence of an increased nuchal fold or two or more soft markers should prompt the offer of fetal medicine referral.

Research recommendations

There should be multicentred studies to evaluate the practicality and acceptability of the integrated test for Down's syndrome

Further studies should be undertaken to establish the feasibility of the measurement of inhibin, including quality control, in routine laboratory use.

Chapter 10 Screening for infections

10.1 Asymptomatic bacteriuria

Pregnant women should be offered routine screening for asymptomatic bacteriuria by midstream urine culture early in pregnancy. Identification and treatment of asymptomatic bacteriuria reduces the risk of preterm birth. [A]

10.2 Asymptomatic bacterial vaginosis

Pregnant women should not be offered routine screening for bacterial vaginosis because the evidence suggests that the identification and treatment of asymptomatic bacterial vaginosis does not lower the risk for preterm birth and other adverse reproductive outcomes. [A]

10.3 Chlamydia trachomatis

2008 Recommendations

Chlamydia screening should not be offered as part of routine antenatal care.

Health care professionals need to inform pregnant women under the age of 25 about the high prevalence of chlamydia infection in their age group, and give details of their local National Chlamydia Screening Programme provision.

Research recommendation

Further research needs to be undertaken to assess the effectiveness, practicality and acceptability of chlamydia screening in an antenatal setting.

10.4 Cytomegalovirus

The available evidence does not support routine cytomegalovirus screening in pregnant women and it should not be offered. [B]

10.5 Hepatitis B virus

Serological screening for hepatitis B virus should be offered to pregnant women so that effective postnatal intervention can be offered to infected women to decrease the risk of mother-to-child transmission. [A]

10.6 Hepatitis C virus

Pregnant women should not be offered routine screening for hepatitis C virus because there is insufficient evidence on its effectiveness and cost effectiveness.[C]

10.7 HIV

Pregnant women should be offered screening for HIV infection early in antenatal care because appropriate antenatal interventions can reduce mother-to-child transmission of HIV infection. [A]

A system of clear referral paths should be established in each unit or department so that pregnant women who are diagnosed with an HIV infection are managed and treated by the appropriate specialist teams. [D]

10.8 Rubella

Rubella susceptibility screening should be offered early in antenatal care to identify women at risk of contracting rubella infection and to enable vaccination in the postnatal period for the protection of future pregnancies. [B]

10.9 Streptococcus Group B

Pregnant women should not be offered routine antenatal screening for group B streptococcus (GBS) because evidence of its clinical effectiveness and cost effectiveness remains uncertain. [C]

10.10 Syphilis

Screening for syphilis should be offered to all pregnant women at an early stage in antenatal care because treatment of syphilis is beneficial to the mother and fetus. [B]

Because syphilis is a rare condition in the UK and a positive result does not necessarily mean that a woman has syphilis, clear paths of referral for the management of women testing positive for syphilis should be established. [Good practice point]

10.11 Toxoplasmosis

Routine antenatal serological screening for toxoplasmosis should not be offered because the harms of screening may outweigh the potential benefits. [B]

Pregnant women should be informed of primary prevention measures to avoid toxoplasmosis infection such as:

- washing hands before handling food
- thoroughly washing all fruit and vegetables, including ready-prepared salads, before eating
- thoroughly cooking raw meats and ready-prepared chilled meals
- wearing gloves and thoroughly washing hands after handling soil and gardening
- avoiding cat faeces in cat litter or in soil. [C]

Chapter 11 Screening for clinical conditions

11.1 Gestational diabetes mellitus

2008 Recommendations

Screening for gestational diabetes using risk factors is recommended in a normal healthy population. Risk factors which should be used are:

- body mass index $>$ 30 kg/m^2
- previous macrosomic baby $\geq$4.5 kg
- previous gestational diabetes (see the Diabetes in pregnancy guideline, currently in development) [636]
- family history of diabetes (first degree relative with type 1 or type 2 diabetes)
- women from a high-risk ethnic group, which would include:
  - South Asian (Indian, Pakistani, Bangladeshi)
  - Black Caribbean
  - Chinese.

Screening via fasting plasma glucose, random blood glucose, glucose challenge test and urinalysis for glucose should not be undertaken.

Diagnosis of gestational diabetes should be made using a 75g 2hr oral glucose tolerance test at 24-28 weeks of gestation using the World Health Organization (WHO) criteria (see the Diabetes in pregnancy guideline, currently in development[636])

In order to make an informed decision about gestational diabetes (GD) screening and testing, women should be informed that:

- in most women GD will respond to changes in diet and exercise
- a small number of women may need insulin therapy or tablets if diet and exercise is not effective in controlling GD
- if GD is not controlled there is a small risk of birth complications such as shoulder dystocia
- a diagnosis of GD may lead to increased monitoring during both pregnancy and labour.

11.2 Pre-eclampsia

2008 Recommendations

Pregnant women should be made aware of the need to seek immediate advice from a health care professional if they experience symptoms of pre-eclampsia. Symptoms include: severe headache;

problems with vision, such as blurring or flashing before the eyes; severe pain just below the ribs; vomiting and sudden swelling of face, hands or feet.

The presence of significant hypertension and/or proteinuria should alert the healthcare professional of the need for increased surveillance

At the first antenatal appointment the following risk factors should be determined:

- age 40 or over
- nulliparity
- pregnancy interval of more than 10 years
- family history of pre-eclampsia
- previous history of pre-eclampsia
- body mass index of 35 kg/m^2 or over
- pre-existing vascular disease such as hypertension
- pre-existing renal disease
- multiple pregnancy.

More frequent blood pressure measurements should be considered for women who have any of the above factors.

Blood pressure measurement and urinalysis for protein should be carried out at each antenatal visit to screen for pre-eclampsia.

Blood pressure should be measured by standard mercury sphygmomanometer or semi automatic device as outlined below:

- Remove tight clothing, ensure arm is relaxed and supported at heart level
- Use cuff of appropriate size
- Inflate cuff to 20-30 mmHg above palpated systolic blood pressure
- Lower column slowly, by 2 mm per second or per beat

} Only devices using auscultation (mercury/hybrid)

- Read blood pressure to the nearest 2 mmHg
- Measure diastolic as disappearance of sounds (phase V)

Hypertension in which there is a single diastolic blood pressure of 110 mmHg or two consecutive readings of 90mmHg at least 4 hours apart and/or significant proteinuria (1+) should prompt increased surveillance.

Although there is a great deal published on alternative screening methods for pre eclampsia, none has satisfactory sensitivity and specificity, and therefore are not recommended.

Research recommendations

Further research using large prospective studies may produce useful findings particularly into alpha feto protein, beta human chorionic gonadotrophin, fetal DNA in maternal blood and uterine artery dopplers or potentially a combination of these.

11.3 Preterm birth

2008 Recommendation

Routine screening of low risk women for preterm labour should not be offered.

Research recommendation

There is need for future research investigating the value of transvaginal ultrasound to measure cervical length and funnelling to identify women at risk of preterm labor.

11.4 Placenta praevia

Because most low-lying placentas detected at a 20-week anomaly scan will resolve by the time the baby is born, only a woman whose placenta extends over the internal cervical os should be offered another transabdominal scan at 36 weeks. If the transabdominal scan is unclear, a transvaginal scan should be offered. [C]

Chapter 12 Fetal growth and wellbeing

2008 Recommendations

Symphysio-fundal height should be measured and recorded at each antenatal appointment from 24 weeks gestation.

A fetal growth scan to detect small-for-gestational-age unborn babies should be offered to women if the symphysio-fundal height measurement is 3 centimetres greater or less than the gestational age in weeks.

Ultrasound estimation of fetal size for suspected large-for-gestational-age unborn babies should not be undertaken in a low-risk population.

Doppler ultrasound should not be used to monitor fetal growth during pregnancy.

Customized fetal growth charts should not be used for screening for small-for-gestational-age babies.

Research recommendations

Further prospective research is required to evaluate the diagnostic value and effectiveness (both clinical and cost-effectiveness) of:

1.customized fetal growth charts,
2.Symphysio-fundal height measurement
3. routine ultrasound in the third trimester in predicting small or large for gestational age babies.

Chapter 13 Management of specific clinical conditions

13.1 Pregnancy after 41 weeks (see also Chapter 4.6 Gestational age assessment)

Prior to formal induction of labour, women should be offered a vaginal examination for membrane sweeping. [A]

Women with uncomplicated pregnancies should be offered induction of labour beyond 41 weeks. [A]

From 42 weeks, women who decline induction of labour should be offered increased antenatal monitoring consisting of at least twice-weekly cardiotocography and ultrasound estimation of maximum amniotic pool depth. [Good practice point]

13.2 Breech presentation at term

All women who have an uncomplicated singleton breech pregnancy at 36 weeks of gestation should be offered external cephalic version (ECV). Exceptions include women in labour and women with a uterine scar or abnormality, fetal compromise, ruptured membranes, vaginal bleeding and medical conditions. [A]

Where it is not possible to schedule an appointment for ECV at 37 weeks of gestation, it should be scheduled at 36 weeks. [Good practice point]

Chapter 14 The development of an assessment tool

Research recommendation

Multi-centred validation studies are required in the UK to assess the use of the Antenatal care assessment tool. Using structured questions the tool aims to support the routine antenatal care of all women by identifying women who may require additional care. The tool identifies women who:

- can remain within or return to the routine antenatal pathway of care
- may need additional obstetric care for medical reasons
- may need social support and/or medical care for a variety of socially complex reasons.

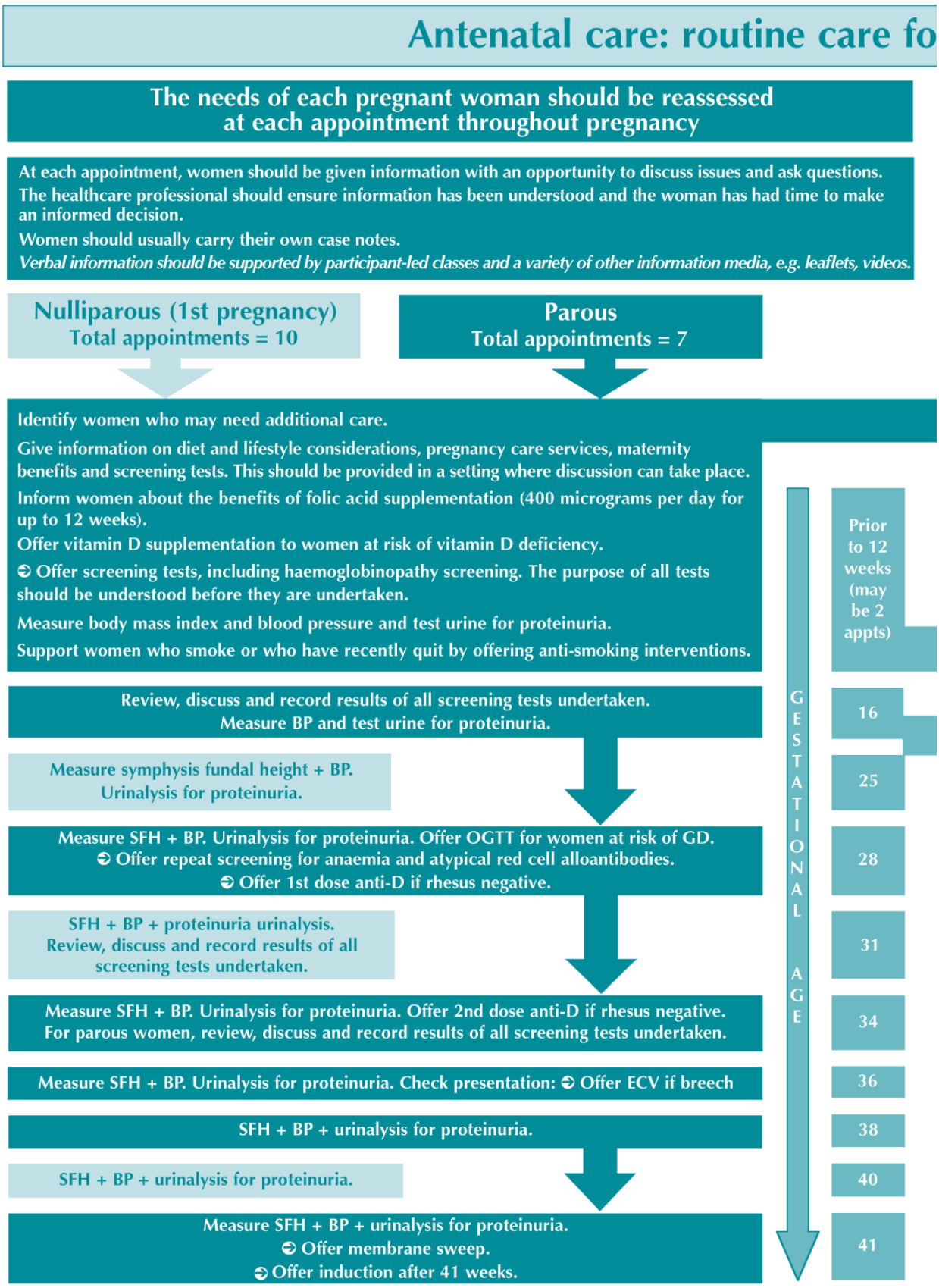
2.3 Future research recommendations

Antenatal care is fortunate to have some areas where research evidence can clearly underpin clinical practice. However, it is noticeable that there are key areas within care where the research evidence is limited. For some of these areas, such as screening for gestational diabetes and first-trimester screening for anomalies, research is under way and results are awaited but for others there is an urgent need to address the gaps in the evidence.

- Effective ways of helping health professionals to support pregnant women in making informed decisions should be investigated. (Chapter 3)
- There is a lack of qualitative research on women's views regarding who provides care during pregnancy. (4.1)
- Alternative methods of providing antenatal information and support, such as drop in services, should be explored. (4.5)
- Research that explores how to ensure women's satisfaction and low morbidity and mortality with a reduced schedule of appointments should be conducted. (4.5)
- Further research to quantify the risk of air travel and to assess the effectiveness of interventions to prevent venous thromboembolism in pregnancy is needed. (5.14)
- More information on maternal and fetal safety for all interventions for nausea and vomiting in pregnancy (except antihistamines) is needed. (6.1)
- Further research into other nonpharmacological treatments for nausea and vomiting in pregnancy is recommended. (6.1)
- Although many treatments exist for backache in pregnancy, there is a lack of research evaluating their safety and effectiveness. (6.7)
- More research on effective treatments for symphysis pubis dysfunction is needed. (6.8)
- There is a lack of research evaluating effective interventions for carpal tunnel syndrome. (6.9)
- Although there are effective screening tools and screening for domestic violence has been shown to be acceptable to women, there is insufficient evidence on the effectiveness of interventions in improving health outcomes for women who have been identified. Therefore evaluation of interventions for domestic violence is urgently needed. (7.5)
- The effectiveness and costs of an ethnic question for antenatal screening for sickle cell and thalassaemia is needed. (8.2)
- The effectiveness and costs of laboratory methods for antenatal screening for sickle cell and thalassaemia is needed. (8.2)
- Up-to-date randomised controlled trials are needed to confirm the beneficial effect of screening for asymptomatic bacteriuria. (10.1)
- Further investigation into the benefits of screening for chlamydia in pregnancy is needed. (10.3)
- Further research into the effectiveness and cost effectiveness of antenatal screening for streptococcus group B are needed. (10.9)
- Research is needed to determine the optimal frequency and timing of blood pressure measurement and on the role of screening for proteinuria. (11.2)
- Further research on more effective ways to detect and manage small- and large-for-gestational-age fetuses is needed. (12.2)
- Further research is necessary to determine if tocolysis improves the success rate of external cephalic version. (13.2)

2.4 Algorithm: Antenatal care: routine care for the healthy pregnant woman

Antenatal care: routine care fo



Key: β-hCG = beta human chorionic gonadotrophin • 'combined test' = nuchal translucency + β-hCG + PAPP-A serum HELLP = haemolysis, elevated liver liver enzymes and low platelet count • LGA = large for gestational age • OGTT = SGA = small for gestational age • USS = ultrasound scan • VE = vaginal examination

r the healthy pregnant woman

Antenatal care should be provided by a small group of carers with whom the woman feels comfortable. There should be continuity of care throughout the antenatal period.

Healthcare professionals should be alert to the symptoms or signs of domestic violence and women should be given the opportunity to disclose domestic violence.

Women who may need additional care

Planning care: assessment

Are any of the following present?

- Conditions such as hypertension, cardiac, hepatic or renal disease, endocrine, psychiatric or haematological disorders, epilepsy, diabetes, asthma, cystic fibrosis, autoimmune diseases, cancer, HIV
- Factors that make the woman vulnerable such as those who lack social support
- Age 40 years and older or 18 years and younger
- BMI greater than or equal to 35 or less than 18
- Previous caesarean section
- Severe pre-eclampsia, HELLP or eclampsia
- Previous pre-eclampsia or eclampsia
- 3 or more miscarriages
- Previous preterm birth or mid trimester loss
- Previous psychiatric illness or puerperal psychosis
- Previous neonatal death or stillbirth
- Previous baby with congenital abnormality
- Previous SGA or LGA infant
- Family history of genetic disorder
- Multiple pregnancy

These women are likely to need additional care which is outside the scope of this guideline. The care outlined here is the '*baseline care*'.

Pregnant women should be informed about the purpose of any screening test before it is performed. The right of a woman to accept or decline a test should be made clear.

To be arranged early in pregnancy (before 16 weeks of gestation)

Blood tests to screen for:

- blood group, rhesus status and red cell antibodies
- haemoglobin (to screen for anaemia)
- hepatitis B virus
- HIV
- rubella susceptibility
- syphilis serology.

Urine test to screen for asymptomatic bacteriuria.

Ultrasound scan to determine gestational age.

Down's syndrome screening:

- 'Combined test' at 11–14 weeks
- Serum screening at 15–20 weeks.

To be arranged between 18 to 20 weeks of gestation

Ultrasound scan for detection of structural anomalies.

If the placenta is found to extend across the internal cervical os at this time, another scan at 32 weeks and again at 36 weeks if placenta within 2 cm of cervical os. If trans-abdominal scan unclear a transvaginal scan should be offered.

The following interventions are *NOT* recommended components of routine antenatal care:

- Repeated maternal weighing
- Breast examination
- Pelvic examination
- Screening for post natal depression using EPDS
- Iron supplementation
- Screening for the following infections
  - *Chlamydia trachomatis*
  - cytomegalovirus
  - hepatitis C virus
  - group B streptococcus
  - toxoplasmosis
  - bacterial vaginosis
- Screening for preterm birth by assessment of cervical length (either by USS or VE) or using fetal fibronectin
- Formal fetal movement counting
- Antenatal electronic cardiotocography
- Ultrasound scanning after 24 weeks
- Umbilical artery Doppler USS
- Uterine artery Doppler USS to predict pre-eclampsia

This algorithm should, where necessary, be interpreted with reference to the full guideline.

screening • ECV = external cephalic version • EPDS = Edinburgh Postnatal Depression Scale • GD = gestational diabetes
oral glucose tolerance test • PAPPA-A = pregnancy-associated plasma protein A • SFH = symphysio-fundal height

3 Woman-centred care and informed decision making

3.1 Provision of information

Clinical question

What, how and when information should be offered during the antenatal period to inform women's decisions about care during pregnancy, labour, birth and the postnatal period?

Previous NICE guidance (for the updated recommendations see below)

Pregnant women should offered opportunities to attend antenatal classes and have written information about antenatal care. [A]

Pregnant women should be offered evidence-based information and support to enable them to make informed decisions regarding their care. Information should include details of where they will be seen and who will undertake their care. Addressing women's choices should be recognised as being integral to the decision-making process. [C]

At the first contact, pregnant women should be offered information about pregnancy care services and options available, lifestyle considerations, including dietary information, and screening tests. [C]

Pregnant women should be informed about the purpose of any screening test before it is performed. The right of a woman to accept or decline a test should be made clear. [D]

At each antenatal appointment, midwives and doctors should offer consistent information and clear explanations and should provide pregnant women with an opportunity to discuss issues and ask questions. [D]

Communication and information should be provided in a form that is accessible to pregnant women who have additional needs, such as those with physical, cognitive or sensory disabilities and those who do not speak or read English. [GPP]

Research recommendation:

Effective ways of helping health professionals to support pregnant women in making informed decisions should be investigated.

3.1.1 Introduction and background

Informed decision-making involves making reasoned choice based on relevant information about the advantages and disadvantages of all the possible courses of action (including taking no action).[8] It requires that the individual has understood both the information provided and the full implications of all the alternative courses of action available. In providing information for women antenatally it is important that health care professionals are aware of what informed choice entails and that they provide information in order to facilitate this. The provision of clear information, time for women to consider decisions and seek additional information, as well as the need for care to be provided in an individualised, woman-focussed way are key components of Standard 3 of the National Service Framework for Maternity Care (September 2004 www.dh.gov.uk/).

3.1.2 Effectiveness of information giving

Description of included studies

Common areas were chosen to search for evidence regarding the effectiveness of information giving. These were chosen either because of their relevance to this guideline update, or because they are areas where a body of evidence was known to exist that could be drawn on to illustrate general principles that could inform the clinical question. The areas chosen were: breastfeeding information; dietary information; smoking cessation and travel safety. The section on breastfeeding information includes: a Cochrane systematic review and a Health Technology Assessment, an RCT, 2 cluster RCTs, 2 controlled trials, a prospective cohort study and 2 descriptive studies. The section on dietary information comprises 5 studies: a Cochrane systematic review, an RCT, a prospective cohort study, a qualitative study and a retrospective study.

3.1.3 Breastfeeding information/preparation

Findings

A Cochrane systematic review (2005) [637] examined the interventions that aim to encourage women to breastfeed, to evaluate their effectiveness in terms of changes in the number of women who initiate breastfeeding and to report any other effects of such interventions. [EL 1+] The review included 7 randomized controlled trials with or without blinding of any breastfeeding promotion intervention among healthy low risk pregnant women with healthy infants. There was no limitation of study by country of origin or language. The outcome measure studied was initiation rate of breastfeeding. The 7 studies suffered from a high overall risk of bias due to unclear or inadequate allocation concealment. Regarding attrition bias, 3 of 7 studies reported breastfeeding initiation for all participants. The remaining 4 studies had up to 25% losses to follow up between recruitment and breastfeeding initiation. A total of 1388 women were included. These 7 studies were classified and analyzed under three types of intervention: health education, breastfeeding promotion packs, and early mother-infant contact. 5 trials involving 582 women showed that breastfeeding education had a significant effect on increasing initiation rates compared to routine care RR 1.53, 95% CI 1.25-1.88. These trials evaluated programmes delivered in the USA to low income women. It was concluded that the forms of intervention evaluated were effective at increasing breastfeeding initiation rates among women on low incomes in the USA.

A Health Technology Assessment (2000) [638] evaluated the existing evidence to identify which promotion programmes are effective at increasing the number of women who start to breastfeed. [EL 1+] The review also assessed the impact of such programmes on the duration and exclusivity of breastfeeding. Randomized controlled trials, non randomized controlled trials with concurrent controls, and before-after studies (cohort and cross-sectional) were included in the review. The study participants included pregnant women, mothers in the immediate postpartum period before the first breastfeed, any participant linked to pregnant women or new mothers, or any participant who may breastfeed in the future, or be linked to a breastfeeding woman in the future. The review included any type of intervention designed to promote the uptake of breastfeeding and the control groups could receive an alternative breastfeeding promotion programme or standard care. A total of 59 studies met the selection criteria out of which 14 were RCTs, 16 non-RCTs and 29 before-after studies. Intervention were grouped into categories: health education; health sector initiatives (HSI) – general; HSI Baby Friendly Hospital Initiative (BFHI); HSI-training of health professionals; HSI – US Department of Agriculture's Special Supplemental Nutrition Program for Women, Infants, and Children (WIC); HSI – social support from health professionals; peer support; media campaigns; and multifaceted interventions. The health education intervention was covered in 9 RCTs, 7 non RCTs and 3 before-after studies. The result of this intervention showed that there is limited impact on initiation rates of breastfeeding by giving breastfeeding literature alone, or combined with a more formal, non-interactive method of health education. Small, informal, group health education classes, delivered in the antenatal period, can be an effective intervention to increase initiation rates, and in some cases the duration of breastfeeding, among women from different income or ethnic groups. 2 RCTs, 3 non RCTs and 5 before-after studies were included in relation to HIS: WIC. It was found that effective WIC interventions included one-to-one health education in the antenatal period, peer counselling in the ante- and postnatal periods, or a combination of one-to-one health education and peer counselling in the ante and postnatal periods. WIC programs were

effective at increasing both the initiation and duration of breastfeeding among women of low-income groups in USA. Regarding HIS: training of health professionals, 5 before and after studies were included. Although there is limited evidence but it suggests that these programmes may be useful in improving the knowledge of midwives and nurses. There were no favourable results shown in terms of changes in attitudes of health professionals, or changes in breastfeeding rates. There was one RCT on social support intervention and it did not significantly increase rates of initiation compared with standard care. 2 non-RCTs were included related to peer support and showed that peer support programmes, when delivered as a stand-alone intervention to women in low-income groups, to be an effective intervention at increasing initiation rates (and duration) among women who had expressed a wish to breastfeed. 2 before after studies were found related to media campaigns which suggested that a media campaign as a stand-alone intervention, and particularly television commercials, may improve attitudes towards, and increase initiation rates of breastfeeding. There was 1 RCT and 10 before and after studies related to multifaceted interventions that found multifaceted interventions comprising of a media campaign and/or a peer support programme combined with structural changes to the health sector (HSI) or, in fewer cases, combined with health education activities are effective in increasing initiation rates (and duration and exclusivity of breastfeeding). It was concluded that there is sufficient evidence of effectiveness to increase the availability of good practice health education programmes.

A cluster randomised controlled trial in a teaching hospital in North West of England (2005) [639] [EL 1-] assessed the effectiveness of an antenatal educational breastfeeding intervention which attempted to enable woman to achieve their own target for breastfeeding duration. It was delivered by a lactation consultant to both pregnant women and their attendant midwife. The primary outcome was the proportion that fulfilled their antenatal breastfeeding expectation and the secondary outcomes were the number of women breastfeeding on discharge and at four months. Women who expressed a desire to breast-feed at the start of their pregnancy were allocated to either routine antenatal education or an additional single educational group session supervised by a lactation specialist and attended by midwives from their locality. Data were collected using a series of questionnaires and diaries. 1312 women were randomized but 1249 (95%) women were available for analysis. The study results found no difference between the groups in the proportion of women who attained their expected duration of breastfeeding (OR 1.2; 95% CI 0.89-1.6). There were no differences between the groups in the uptake of breastfeeding on discharge (OR = 1.2; 95% CI 0.8-1.7) or exclusively at four months (OR = 1.1; 95% CI 0.6-1.8). The intervention was only available antenatally, and it failed to address the emotional and physical needs of women in the postnatal period. The study included women who expressed a desire to breastfeed so the results cannot be generalized to all women. It was not possible to conceal the study group allocation from the recruiting midwife or to blind the women or the attending midwives from the treatment allocation.

A randomized controlled trial conducted in Singapore (2007) [640] aimed to address the impact of simple antenatal educational interventions on breastfeeding practice. [EL 1-] Low risk antenatal women were randomly assigned to one of the 3 groups. Group A received breastfeeding educational material and individual coaching from a lactation counsellor. Group B received breastfeeding educational material with no counselling. Group C received routine antenatal care only. A total of 401 women were recruited. The results showed that women who received simple antenatal instruction with a short, single, individual counselling session combined with educational material were practiced exclusive and predominant breastfeeding more often than women receiving routine care alone at 3 months (odds ratio [OR] 2.6, 95% confidence interval [CI] 1.2-5.4) and 6 months (OR 2.4, 95% CI 1.0-5.7) postpartum. More women practiced exclusive and predominant breastfeeding at 6 months among women receiving individual counselling compared with women exposed to educational material alone (OR 2.5, 95% CI 1.0-6.3). A number of limitations were noted for this trial. There was contamination between the groups and women in the control group came to know about the interventions offered to the other groups simply by speaking to women in those groups. There was insufficient sample size to fulfil power calculations. The most useful breastfeeding intervention includes demonstration of breastfeeding techniques (educational video) one-to-one teaching by a trained lactation counsellor, and a breastfeeding education booklet.

A Canadian randomized controlled trial (2006) [641] sought to determine the effects of an antenatal breastfeeding workshop on maternal breastfeeding self-efficacy and breastfeeding duration. [EL 1-] 101 nulliparous women, expecting a single child, an uncomplicated birth, and planning to breastfeed were randomized into either the intervention group or the control group. Both groups received standard care and in addition the intervention group attended a 2.5-hour prenatal breastfeeding workshop (based on Bandura's theory of self-efficacy and adult learning principles). The main outcome measures were maternal breastfeeding self-efficacy (measured with a revised breastfeeding self-efficacy scale) and breastfeeding duration (measured at 4 weeks and 8 weeks postpartum). The study suffered from participation bias because the participants were self-selecting. Overall both the groups had higher breastfeeding rates at 8 weeks postpartum when compared with the national statistics. This indicates that due to the participation bias the participants may have started out more committed to or more confident about breastfeeding than the general population. Higher self-efficacy scores and a higher proportion of exclusively breastfeeding women were seen in the group who attended the workshop as compared to women who did not attend the workshop, although by 8 weeks postpartum this difference was no longer statistically significant (Intervention 61.70 (5.8) vs control 58.91 (9.1); t= -1.60 [95% CI -6.28 to -0.70]; p=0.115).

A USA based non-randomized controlled trial (1997) [642] examined the effect of specific antenatal breastfeeding information on postpartum rates of breastfeeding among WIC participants. [EL 1-] This information was provided in group classes by nurse practitioners. A total of 14 women in the experimental group and 17 in the control group received prenatal nutrition education through the WIC program. The experimental group received at least one breastfeeding education class and a follow-up class was offered but not required. The control group received the standard prenatal education class which included content on the appropriate diet for pregnancy and they were taught that breastfeeding is the preferred method of infant feeding rather than the 'how-to's' of breastfeeding. All participants were interviewed at 1 month postpartum WIC visit. The study suffered from a small sample size and wide variance in the duration of breastfeeding that lead to a low statistical power. The results showed no significant difference in breastfeeding incidence between the two groups, however, there was a significantly higher percentage of women still breastfeeding at 3 and 4 months postpartum in the experimental versus the control group. The control group breastfed for 29.5 +/- 43.6 days, while the experimental group breastfed for 76 days +/- 104.3 (p =0.05). It was found that multiparous women who had bottle-fed previous children, breastfed for a shorter duration (18 +/- 22 days) than primiparous women (60 +/- 87 days) though not statistically significant.

A US based quasi-randomized controlled trial (1984) [643] was used to determine the effect of prenatal breastfeeding education on maternal reports of success in breastfeeding and maternal perception of the infant [EL 1-]. All subjects were enrolled to attend childbirth education classes and vaginally delivered full-term, healthy infants without complication. 40 nulliparous women who desired to breastfeed were randomly assigned to control and experimental groups according to the childbirth class in which they were enrolled. 20 women attended a prenatal breastfeeding education class and 20 were in the control group. The independent variable used in this study was prenatal breastfeeding education class. The two dependent variables were maternal report of success in breastfeeding and maternal perception of the infant. The maternal perception of the infant variable was measured using the Neonatal Perception Inventory (NPI). The NPI I was administered 1-2 days postpartum and the NPI II was administered at 1 month postpartum. The results showed that there was a significantly higher frequency of success in breastfeeding among primiparous women who received prenatal breastfeeding education as compared to those who did not. There was a significant difference in the NPI I scores in both experimental and control subjects at 1-2 days postpartum. The NPI II scores of the experimental mothers were significantly more positive at 1 month postpartum. Primiparous women in the experimental group reported significantly more positive NPI II scores than the control group.

A quasi-experimental design with pre- and post-intervention groups was carried out in Chile (1996) [644] to assess the impact of five interventions on breastfeeding patterns and duration. [EL 2] The five interventions were training the health team in breastfeeding; implementing activities at the prenatal clinic; implementing activities at the hospital; creating an outpatient lactation clinic; and offering the Lactational Amenorrhea Method (LAM) as an initial form of family planning. During the intervention phase, a sixth intervention (prenatal breastfeeding skills group education (PBSGE) was

added for a subset of the women in the intervention group. A subset of 59 women (for the sixth intervention) was drawn from 123 mother/child pairs of the intervention group. The women in the sixth intervention group attended the prenatal breastfeeding skills group education sessions (conducted by a trained nurse-midwife at the outpatient prenatal clinic) during the third trimester of pregnancy. Each session lasted about 20 minutes and the topics covered were; breast care, breastfeeding advantages for the infant and for the mother, breastfeeding technique, anatomy and physiology of the mammary gland, prevention of breastfeeding problems, rooming-in, and immediate contact. The five interventions demonstrated a significant increase in full breastfeeding at six months (32% to 67%). A significantly higher percentage of the sixth intervention women were fully breastfeeding at six months compared to those who received only the five basic interventions (80% vs. 65%). The effect was greater among nulliparous women.

An Australian qualitative study (2003) [645] explored the physical, social and emotional experiences influencing women's baby-feeding decisions by investigating women's own decision-making processes. [EL 3] The study was undertaken with 29 women using face-to-face in depth interviews that were audio-tape recorded and transcribed verbatim. Data was analyzed using thematic analysis. A number of themes were identified in this study that appeared to influence the baby-feeding decision. One of the most dominant themes was the embodied expression of breast feeding. Another dominant theme was that breast feeding could be difficult and problematic. It was found that the women observed and sought information from a variety of sources as well as exploring their own understandings of themselves and their breasts. Based on this knowledge the women made their antenatal baby-feeding decisions. These baby-feeding decisions grouped into four thematic groups, 'assuming I'll breast feed'; 'definitely going to breast feed'; 'playing it by ear' and 'definitely going to bottle feed'. Each of these standpoints was associated with, and precipitated a number of behaviors and strategies. It was concluded that there is need for antenatal educators and midwives who provide care in pregnancy to acknowledge a range of experiences and expectations of women and to provide diverse educational opportunities to meet a range of needs.

A USA based descriptive study carried out in 1982 [646] sought to determine the relationship between nulliparous women's information on breast-feeding and success in breast-feeding. [EL 3] The study hypothesis was that pregnant women having relatively more information on breast-feeding would breast-feed their infants beyond 4 weeks, as compared to pregnant women with relatively little information on breastfeeding would breastfeed their infants for less than 4 weeks. A multiple-choice questionnaire of 26-items was developed to measure the pregnant women's knowledge about breastfeeding. The questionnaire was tested for its validity and was pilot tested on 30 nulliparous women who were not a part of the main study which yielded a two-week test-retest reliability of 0.87. A post delivery mail questionnaire on breastfeeding outcome was completed 5-6 weeks following delivery and the results of the two questionnaires were correlated. The anonymity of the participants was ensured by assigning code numbers to all questionnaires. The results showed that women who breastfed beyond 4 weeks after delivery had high overall breastfeeding information scores than mothers who breastfed less than 4 weeks. The decision to breastfeed made early in pregnancy was associated with successful breastfeeding whereas the decision to breastfeed made late in pregnancy was associated with unsuccessful breastfeeding. There was a positive correlation between breastfeeding information scores and the number of breastfeeding information sources used by nulliparous women.

Evidence summary

There is evidence from randomised controlled trials that breastfeeding initiation rates and, in some instances breastfeeding duration, can be improved by antenatal breastfeeding education, particularly if this is interactive and takes place in small informal groups. One-to-one counselling and peer support antenatally are also effective.

3.1.4 Nutrition-related pregnancy interventions

A Cochrane systematic review (1999)[65] assessed the effects of advising pregnant women to increase their energy and protein intakes on those intakes, on gestational weight gain, and on outcome of pregnancy. [EL 1+] The studies included made controlled comparisons of nutritional advice, whether administered on a one-to-one basis or to groups of women. The interventions included

specific advice to increase dietary energy and protein intake. Dietary intake and pregnancy outcome were the main outcome measures. A total of 4 trials including 1108 women were included. The results showed that advice to increase energy and protein intakes seems to be successful in achieving those goals, but the increases are lower than those reported in trials of actual protein/energy supplementation. The evidence regarding the effects on pregnancy outcome are not truly representative as available only from one trial with very narrow confidence intervals. None of the trials reported any potential adverse effects that might accompany increased fetal size, such as an increased risk of prolonged labour or caesarean section. It was concluded that nutritional advice appears effective in increasing pregnant women's energy and protein intakes, but the effects on fetal, infant, or maternal outcomes remain uncertain, and seem likely to be minimal.

A USA based randomized controlled trial (2004) [647] developed and evaluated a tailored nutrition education CD-ROM program for participants in the Special Supplemental Nutrition Program for Women, Infants and Children (WIC). [EL 1+] Eligible participants were computer-randomized into either the intervention or the control group. The intervention group completed a baseline survey (lasting approx 15 minutes), received the intervention program (soap opera and interactive feedback lasting 20-25 minutes), and answered immediate postpartum questions. The control group completed the surveys but did not receive the intervention until after follow-up. Both groups were asked to return in 1 month for follow-up. At follow-up, intervention participants answered the survey questions, whereas control participants completed the survey and receives the tailored intervention. The study sample comprised a total of 307 respondents to the follow-up survey (response rate 74.8%). 96% participants were females, 20% were pregnant, and 50% were minorities (African American and other). The main outcome measures included total fat and fruit and vegetable intake, knowledge of low-fat and infant feeding choices, self-efficacy, and stages of change. The results showed that the intervention group members significantly increased self-efficacy and scored significantly higher on both low-fat and infant feeding knowledge compared with controls.

A USA based prospective cohort study (2004) [648] aimed to evaluate the efficacy of an intervention directed at preventing excessive gestational weight gain. [EL 2+] The study used a historical control group. The intervention group constituted women with normal and overweight pregnancy BMI. The control group consisted of women with normal and overweight BMI from an earlier observational study of postpartum weight retention. 179 women in the intervention group had their gestational weight gain monitored by health care providers and also received postal patient education. The intervention was designed to encourage pregnant women to gain an amount of weight during pregnancy that is within the range recommended by Institute of Medicine. It had 2 major components: a clinical component (that includes guidance about and monitor gestational weight gain by health care providers using new tools in the obstetric charts) and a by-mail patient education program. 381 women formed an historical control group. At one year postpartum 158 women in the intervention group and 359 women in the control group were available for analysis. The study population was monitored from early pregnancy until 1-year postpartum. The results showed that low-income women who received the intervention had a significantly reduced risk of excessive gestational weight gain (OR, 95% CI 0.41, 0.20-0.81). There was a significantly reduced risk of retaining more than 2.27 kg in low income overweight women (OR, 95% CI 0.24, 0.07-0.89).

A Netherlands based retrospective qualitative study by Szwajcer et al., 2005[649] (EL 2-) aimed to explore the use of nutrition-related information sources (mass media, social environment and health professionals) nutrition related information-seeking behaviours and motives before and throughout pregnancy. In-depth face-to-face interviews of 1 h with 5 groups of 12 women (a total of 60 women) from different parts of Netherlands were conducted at conference rooms or at the respondent's home and women were mainly selected via midwifery practices. The 5 groups included women who wanted a child, women in their first, second and third trimester of the first pregnancy and women in their first trimester of the second pregnancy. All pregnant women seek or are confronted with at least some pregnancy-specific nutrition information. 3 groups of women could be distinguished in relation to the manifestation of nutrition-related information-seeking behaviours during first-time pregnancies; women who feel like a mother from the moment they know that they are pregnant, women who feel like a mother later in pregnancy and, women who do not feel like a mother yet. Each group had its own specific information-seeking behaviour.

Women in the first trimester mainly sought nutrition information in the media, such as the internet, books, magazines, 9-month calendars and brochures. In the second trimester, nutrition information was sought from the 9-month calendar (fun and tips) and friends (experienced). Women in the third trimester sought information from friends (information on breastfeeding). Information sources of the second group of women were mainly brochures provided by the midwife and the midwife herself. The third group of women mainly relied on their own common sense. Second-time pregnant women relied on their experience, the midwife and books for specific questions.

A USA based retrospective study (1985) [650] evaluated the effect of intensive nutrition counselling on weight gain of pregnant women and birth weight of their infants.[EL 2-] Data were collected through retrospective review of medical records. The test group consisted of 114 women who were admitted to the clinic before the 35th week of pregnancy, attended a 30-minute prenatal nutrition class given by the clinic dietician and counselled by the clinic dietician at each visit. This group was sampled between the years 1979 and 1981. The control group consisted of 86 women who were admitted to the prenatal clinic before 35th week of pregnancy and attended a 20-minute prenatal nutrition class, and was sampled for the years 1975 to 1977. 2 different dietitians worked with the 2 groups. The results showed that the women in the test group gained 2.5 kg more weight than in the control group. The test group women vs control group women had fewer low birthweight infants, 4% vs. 13%, although this difference is not statistically significant. They also had infants weighing 100 gm more at birth than infants born to women in the control group. It should be noted that women in the intervention group attended antenatal clinic significantly earlier in pregnancy than women in the control group, and had significantly more antenatal consultations.

3.1.5 Smoking cessation

Findings

A Cochrane systematic review, 2004[651] [EL 1+] assessed the effects of smoking cessation programs during pregnancy on the health of the foetus, infant, mother, and family. A total of 64 trials were included (51 RCT s with 20,931 women and 6 cluster-randomised trials with 7,500 women). A significant reduction in smoking in the intervention groups of 48 trials was noted (RR 0.94, 95% CI 0.93 to 0.95). Smoking cessation interventions reduced low birth weight (RR 0.81, 95% CI 0.70 to 0.94) and preterm birth (RR 0.84, 95% CI 0.72 to 0.98), and there was a 33 g (95% CI 11 g to 55 g) increase in mean birth weight. The results with very low birth weight, stillbirths, perinatal or neonatal mortality were statistically insignificant. One intervention strategy, rewards plus social support (two trials), resulted in a significantly greater smoking reduction than other strategies (RR 0.77, 95% CI 0.72 to 0.82). Five trials of smoking relapse prevention (over 800 women) showed no statistically significant reduction in relapse.

A UK based prospective study, 2002[652] [EL 2+] evaluated the impact of the current antismoking advice in the UK on smoking habits of women with planned pregnancies. 2 hospitals in North London were included whose policy is to provide all women at the first trimester booking visit with leaflets and direct counseling for those who admit to smoking. Information was collected over a 6-month period at random from women booking for routine antenatal care. The study population included 117 (65%) women who did not currently smoke (non-smokers) and 63 (35%) who were active smokers at the beginning of their pregnancy. Thirty-nine non-smokers were found to be passive smokers. Three women took up smoking during pregnancy. 84.1% smokers made no change in their smoking behaviour during pregnancy, 11.1% reduced their cigarette consumption and only 4.8% gave up smoking during the first half of pregnancy. None of the partners changed their smoking habits. All women were aware that smoking in pregnancy could be deleterious to their health and that of their fetus.

A USA based randomized controlled trial, 2006[653] [EL 1+] tested the efficacy of a pregnancy tailored telephone counseling intervention for pregnant smokers. The intervention used a motivational interviewing style. The study hypothesized that telephone counseling would increase smoking cessation rates at the end of pregnancy and 3 months post partum compared with a control group that was given a brief counseling. Pregnant women included in the study were identified as current cigarette smokers if they had smoked at least 1 cigarette in the past 7 days. The study population of 442 pregnant smokers referred by prenatal providers and a managed care plan

were ≥18 years of age and at ≤ 26 weeks of gestation. Trained counselors using cognitive-behavioral and motivational interviewing methods called intervention subjects throughout pregnancy and for 2 months postpartum (a mean of 5 calls and a mean total contact of 68 minutes). Controls received just one 5-minute counseling call. The results showed that 7 day tobacco abstinence rates in the intervention vs control groups were 10.0% vs 7.5% at end of pregnancy (OR 1.37, 95% CI 0.69–2.70) and 6.7% vs 7.1% at 3 months postpartum (OR 0.93, 95% CI 0.44–1.99). The end-of-pregnancy cessation rates increased among 201 light smokers (< 10 cigarettes/day at study enrollment) in the intervention group (intervention 19.1% versus control 8.4% (OR 2.58, 95% CI 1.1–6.1) and among 193 smokers who attempted to quit in pregnancy before enrollment (intervention 18.1% versus control 6.8%; OR 3.02, CI 1.15–7.94).

A USA based randomized controlled study, 1993[654] [EL 1+] evaluated a brief contact smoking cessation program among 57 pregnant women at two urban clinics. All the subjects were given a specially created videotape or a booklet related to smoking. After this the subjects were randomly assigned to receive either a nurse counseling message or usual care at the clinic. There was no statistically significant difference in smoking status among the two groups. 12% reported smoking cessation at one month after entry in the study, 18% reported in the ninth month of pregnancy, and 9% at one month post-partum. Over half of the patients attempted to quit smoking in the first month and 68% made at least one quit attempt during the entire study period.

A cluster randomized controlled trial in New Zealand, 2004[655] [EL 1+] tested the hypothesis that in a usual primary maternity care setting appropriate interventions delivered by midwives can help women to stop/ reduce smoking and facilitate longer duration of breast feeding. The midwives were stratified by locality and randomly allocated into a control group which provided usual care and three intervention groups. In the first intervention group, a programme of education and support for smoking cessation or reduction was given. In the second one, a programme of education and support for breast feeding was given. In the third one both programmes were given. A total of 297 women were recruited by 61 midwives. The women who received only the smoking cessation or reduction programme were significantly more likely to have reduced, stopped smoking or maintained smoking changes than women in the control group, at 28 weeks and 36 weeks gestation. Women who received both the smoking cessation and breast-feeding education and support programmes were significantly more likely to have changed their smoking behaviour at 36 weeks gestation than the control group. The post natal period showed no difference in rates of cessation or reduction between the groups. Also there was no difference in rates of full breast feeding between the control and intervention groups for women who planned to breast feed.

3.1.6 Travel safety information

Findings

A USA based prospective trial, 1985[656] [EL 1-] administered a special 30-minute curriculum consisting of a lecture, a motion picture demonstrating the consequences of not using child car safety seats, and a question-and-answer session to couples attending prenatal classes. All parents were telephone interviewed at 4-6 months postpartum. The results showed that 96% of parents who received the special curriculum reported they used a crash-tested child car safety seat, as compared to 78% of those who had not received the curriculum. The compliance significantly rose from 60% before curriculum to 94% after curriculum at a hospital where parents were associated with low compliance (e.g., lower income, low use of seat belts, lower educational level).

A prospective study, 1982[657] [EL 2-] in USA investigated the influence of an in-hospital prenatal and postpartum educational program on the prenatal use of infant car restraints. The participants were given demonstrations and talks on automobile crash statistics in the prenatal course; and a car safety film on the hospital television, a pamphlet given to each mother, and instructions to nurses to encourage parents' purchase and use of car restraints in the postpartum period. The results showed that the actual use of infant restraints on the trip home was highest in the pre- plus postnatal education group although it was statistically insignificant. There was higher restraint shown in the group given counseling in any period than no counseling.

3.1.7 Alcohol

Findings

Two trials were conducted in UK, 1990[658] [EL 1+] that compared three methods of imparting basic information and advice regarding the risks of alcohol in pregnancy at the first visit to the antenatal clinic. The effects on drinking patterns were assessed by written information alone, written information coupled with personalized advice and written information with personalized advice reinforced by a specially produced video. The written information was in the form of a special edition of the leaflet 'Pregnancy. What you need to know' published by the Health Education Council available commonly in antenatal clinics during 90s. The personalized advice was given by the interviewing doctor. The 4 min video was designed to encourage mothers to reduce their drinking and gave suggestions how to do so. Trial I had Group 1 (written information) and Group 2 (written information + verbal reinforcement). Trial II had Group 3 (written information) and Group 4 (written information + verbal reinforcement + video). 3 questionnaires were given to the women: 1st at their first visit to the clinic, 2nd at about 28 weeks of gestation and 3rd given in the week immediately prior to delivery. The results showed no significant differences within or between trials in terms of behavioural change. Significantly more mothers in both arms of the second trial recommended one unit or less a day as the safe level of drinking during pregnancy.

3.1.8 Gestational diabetes

Findings

A descriptive study with a retrospective analysis, 1995[659] [EL 2-] in USA compared two treatment approaches designed to help gestational diabetic women manage their pregnancies: a hospital, outpatient-based, nursing intervention and a traditional, office-based care provided by obstetricians. A research model was constructed after a literature review that used three variables: input variables (risk factors prior to gestation), moderating variables (conditions that occur during pregnancy), and outcome variables (normal vs abnormal outcomes for mother and infant). The two treatment approaches were compared using this research model. In treatment 1 (nursing intervention) all patients completed the hospital GD outpatient education program regardless of referral source or subsequent treatments by other professionals. In treatment 2 (obstetricians only) all patients treated by an obstetrician only (i.e. who did not participate in the nursing intervention and not seen by an endocrinologist, a specialist in internal medicine, or a registered dietician). The study results showed that there was no statistically significant reduction in the risk of abnormal outcomes for mother or infant in either of the treatment approaches.

Evidence summary for Sections 3.1.4 to 3.1.8

There is some evidence of a fair quality from the field of nutritional support that intensive antenatal dietary counselling and support is effective in increasing women's knowledge about healthy eating and can impact upon eating behaviours. There is no evidence linking this with improved pregnancy outcomes however.

There is good quality evidence to show that smoking cessation interventions help women reduce smoking and decrease adverse neonatal outcomes.

3.1.9 How information is given to women antenatally

A total of 9 studies - 7 RCTs, 1 cluster controlled trial, and 1 prospective cohort study, have been included in this section. All these studies have compared different methods of providing information during antenatal period in terms of uptake of screening tests, anxiety levels, knowledge, and other outcomes. The methodological quality of the included trials is generally good but no two studies have compared similar methods of providing information. The review is further subdivided by the type of information provided, that is, general information about pregnancy/screening tests or specific information about a disease/complication.

General information about pregnancy / screening tests (3 studies)

Description of included studies

A randomized trial comparing three methods of giving information for prenatal testing was conducted in UK (1995)[12] – routine information given in antenatal clinics at booking visit by the doctor or midwife (control group), extra information given individually before 16 weeks or at an extra hospital visit by a research midwife (individual group), and extra information given to a group of 4 to12 women separate from the routine antenatal clinics (class group). [EL 1+]. The study population comprised of pregnant women less than 15 weeks gestational age and they were allocated to the three groups by simple randomization using sealed opaque envelopes. Main outcome measures evaluated were attendance at the extra information sessions, uptake rates of prenatal screening tests (ultrasound, Down's syndrome, cystic fibrosis, haemoglobinopathy), levels of anxiety, understanding, and satisfaction with decisions. Questions on level of anxiety were administered at 16-18 weeks, 20 weeks, 30 weeks and 6 weeks post delivery to assess anxiety at different times. Questions on information were administered at 16-18 weeks, and satisfaction questions at 30 and 46 weeks. All analysis was by intention-to-treat analysis but blinding has not been specified and sample size calculations not performed.

A second RCT (2000) [660] was conducted in five antenatal clinics in a university teaching hospital in UK to compare the effectiveness of touch screen method with information leaflets for providing women with information about prenatal tests [EL 1+]. The study population comprised of both low and high risk pregnant women booking appointment for antenatal care. After recruitment, baseline information was collected and women were randomly allocated to the intervention (touch screen and information leaflet) or control group (leaflet only) using consecutive, sealed, opaque envelopes. Use of touch screen was limited to the intervention group by means of a password. Primary outcome measured was women's informed decision making on prenatal testing as measured by their uptake and understanding of the purpose of 5 screening tests (ultrasound scan at booking, serum screening, detailed anomaly scan, amniocentesis and chorionic villus sampling). Secondary outcomes included woman's satisfaction with the information and their anxiety levels. Primary outcomes were assessed by a self completed postal questionnaire (developed from a validated instrument) at around 16 and then 20 weeks, and anxiety by the Spielberg state-anxiety inventory. Quality control checks were conducted on random sample of 10% of questionnaires, statistical analysis done on intention-to-treat basis, and power and sample size calculations were performed.

A cluster RCT (2002)[13] was conducted in Wales, UK to investigate the effect of leaflets on promoting informed choice in women using maternity services. [EL 1-] 12 maternity units each having more than 1000 deliveries annually were grouped into 10 clusters (some units shared management or consultants) and randomly assigned to the intervention units (5 units receiving set of leaflets) or control units (5 units continue with normal care) by tossing a coin. A set of 10 leaflets summarizing the evidence on 10 decisions that women face during pregnancy and childbirth, and encouraging them to make informed decisions were used as the intervention. In the intervention units some relevant leaflets were given at 10-12 weeks and the rest at 34-36 weeks. Participants included an antenatal sample (women reaching 28 weeks during the six-week study period) and a postnatal sample (delivering during the study period) of women both prior to introduction of the leaflets and nine months after they were introduced; thus four groups of participants were identified. Primary outcome measured was the change in proportion of women who reported exercising informed choice, while secondary outcomes were women's levels of knowledge, satisfaction with information, and possible consequences of informed choice. Outcomes were assessed using a postal questionnaire (piloted before use) sent at 28 weeks gestation for the antenatal sample and 8 weeks post-delivery for the postnatal sample. Power and sample size calculations were performed, analyses done on intention-to-treat basis and confounding variables were adjusted, but blinding of outcome investigators is not achieved. Moreover there was selection bias (poor response rate) and the study had low power.

Findings

A total of 1691 women consented to participate in the UK RCT [12], 567 in the control group, 563 in the individual group, and 561 in the class group. The baseline demographic features of the three groups were comparable. Attendance at the extra sessions was low (overall 52%) and was lower at

classes than at individual appointments (adj. OR 0.45; 95%CI 0.35 to 0.58). Uptake of ultrasound at 18 weeks was almost universal (99%) and not affected by either intervention. Low uptake of Down's syndrome screening in the control group improved slightly after the intervention in the individual group (OR 1.45; 95% CI 1.04-2.02) but was not affected by extra information given in classes. High uptake of cystic fibrosis screening at the baseline was lowered both in the individual group (OR 0.44; 95%CI 0.20-0.97) and the class group (OR 0.39; 95%CI 0.18-0.86). Women in the individual group were found to have significantly reduced levels of anxiety at 20 weeks ($p=0.02$) compared to the control group, and thereafter anxiety was reduced but not significantly. Pregnant women given extra information either at individual level or in classes felt that they had received more relevant information and understood it better. They were also more satisfied with the information received.

In the second RCT [660] of the 1050 women randomized to the intervention group ($n=524$) and control group ($n=526$), only 64% returned all the three questionnaires and the sample sizes for measuring uptake and understanding were 358 and 376 respectively. There were no significant differences between the intervention and the control groups for the baseline characteristics and reasons or rate of loss up. More women in the intervention group underwent detailed anomaly scan compared to the control group (94% versus 87%, $p=0.01$), but for rest of the screening tests uptake rates were similar. All women in the trial had good baseline knowledge of the screening tests and this increased significantly in both the groups after the intervention, but no apparent greater gain in knowledge was seen among women in the intervention arm compared to the control arm. Levels of anxiety declined significantly among the nulliparous women in the intervention group ($p<0.001$). Both groups reported high level of satisfaction with the information leaflets ($>95\%$), and a similar proportion of women in the intervention group reported that they would recommend the touch screen to other women. The authors concluded that touch screen method conferred no additional benefit to that provided by the more traditional method of information leaflet but seemed to reduce anxiety and may be most effective for information provision to selected women, that is those with relevant adverse history or abnormal results.

In the Welsh cluster RCT[13] the overall response rate was 64% with a rate of 65% (3164/4835) for the antenatal sample and 63% (3288/5235) for the postnatal one. Socio-demographic characteristics of women in the intervention and control units were similar in the antenatal sample, while in postnatal sample respondents after the intervention were an average 7 months younger. Proportion of women who reported exercising informed choice increased slightly after the intervention in both the units, but there was no significant difference in the change between the two groups for either the antenatal or the postnatal sample. A small increase in satisfaction with information was observed in the antenatal sample of the population in the intervention units compared to the control units (OR 1.40; 95%CI 1.05 to 1.88). However due to operational difficulties, just 75% of the women in the intervention units reported receiving at least one of the information leaflets. It was concluded that evidence based information leaflets were not effective in promoting informed choice in women using maternity services.

Specific information

Down's syndrome screening (4 studies)

Description of included studies

An RCT was conducted in Canada (1997) [661] to investigate to what extent a newly revised educational pamphlet on triple screening (developed using consumer consultation and providers perception & suggestions) improves patient knowledge and to identify subgroups not benefiting from these materials. [EL 1+] The study population of women with singleton pregnancies less than 18 weeks gestational age was recruited from 6 different sites in both urban and rural areas. Participants were randomly allocated (computer-generated random list in block-randomization sequence for each site) to receive the pamphlet on triple-marker screening in the intervention group, or similar appearing pamphlet on daily activities during pregnancy in the control group. The method of allocation was concealed till the time of enrolment. The primary outcome measure was the Maternal Serum Screening Knowledge Questionnaire (a validated 14-item scale). Blinding of outcome investigators has not been specified. Power and sample size calculations were performed.

A second RCT (2004) [662] conducted in a prenatal diagnosis clinic in UK to evaluate decision analysis as a technique to facilitate women's decision making about prenatal diagnosis for Down's syndrome using measures of effective decision making. [EL 1+] Pregnant women receiving a screen positive maternal serum screening (MSS) test for Down's syndrome (risk $\geq$ 1 in 250) were randomly allocated to the intervention or the control group using sealed, opaque envelopes. Routine consultation based on the MSS result sheet was provided to the control group subjects, while in the intervention group a decision analysis consultation using three prompts was employed - a decision tree representing test options and consequences, a utility elicitation question prompting women to choose between the burden of having a child with Down's syndrome and that of pregnancy termination, and a threshold graph identifying the alternatives. All the consultations were audio tape-recorded, transcribed and coded. Participants also completed a questionnaire after the consultation and one month later after the receipt of their test results. Main outcomes measured were risk perception, test decision, subjective expected utilities, knowledge, informed decision making, conflict in decision making, anxiety, and perceived usefulness of consultation. All the consultations in the two groups were provided by a single professional and calculations for power and sample size performed. Blinding of outcome investigator and intention-to-treat analysis has not been carried out.

Another RCT conducted in Hong Kong, China (2004) compared an interactive multimedia decision aid (IMDA) with a leaflet and a video to give information about prenatal screening for Down syndrome, and to determine women's acceptance of IMDA [663]. [EL 1+] All Chinese women attending a prenatal clinic in a tertiary hospital before 20 weeks of gestation were invited to participate and offered either an integrated screening test (presenting before 15 weeks) or a serum screening test (presenting after 15 weeks). After informed consent eligible women were randomized into the intervention group (information leaflet, 30-minute video and then browsing IMDA) or the control group (information leaflet and watching 30-minute video only) by consecutive, sealed, opaque envelopes. Apart from giving information contained in the leaflet and/or video, the IMDA prompted women to choose their option with information about its implication, and followed it with a frequently asked question and answer session. IMDA could only be accessed in a closed room by women in the intervention group. The primary outcome evaluated was uptake of the screening test, and secondary outcomes measured were women's initial decision, understanding, and satisfaction with the information that they received. The instrument used for measuring outcome was a questionnaire given to both the groups after watching the video, and another one given to the intervention group after the IMDA session. Analysis was done on intention-to-treat basis, and confounding variables were controlled in evaluating women's acceptance of the decision aid. Sample size was calculated prior to study.

Another UK RCT (2001) [664] was carried out to assess the effect of a Down syndrome screening video (specifically produced fulfilling all RCOG recommendations) on the test uptake, knowledge, anxiety and worry. [EL 1-] The study population made of consecutive pregnant women referred for antenatal care was allocated either to the intervention group (sent video at home before the hospital booking visit) or the control group who received usual care by quazi-randomization technique. This method of allocation (odd or even unit number) was not subject to bias as it was carried out by the staff unconnected with the trial. All women also received screening information in the form of a leaflet before booking and from a midwife at the time of booking. Outcomes evaluated were test uptake (using record linkage), knowledge (multiple-choice questionnaire with 12 items), worries (multiple-choice questionnaire with 16 items), and anxiety (Hospital Anxiety and Depression scale). Baseline characteristics of the intervention and the control group have not been compared. Blinding of outcome investigator has not been specified and calculations for sample size and analysis on intention-to-treat basis not performed.

Findings

Findings from the Canadian RCT [661] showed the success rate of the recruitment process among eligible women to be 94.7% (198/209). Baseline demographic, obstetric and medical factors were similar between the intervention/triple marker screening group (n = 133) and the control/daily activity group (n = 65). The mean overall knowledge score was significantly higher in the intervention group (0.89 versus 0.52 on a scale from -2 to +2, $p < 0.001$) compared to the control group. Also women receiving pamphlet on triple screening had higher scores for the domains of test characteristics, ancillary tests, and target conditions ($p < 0.001$) but not for the domains of

indication and timing of tests. These results remained the same even after controlling for potential confounding variables. Subgroups not benefiting from the triple marker screening pamphlet were women aged 25 years and younger and those not speaking English at home. Those who had completed university or postgraduate education had high levels of knowledge with and without the pamphlet.

Findings from the second RCT [662] showed no differences in the socio-demographic characteristics (apart from gestation), risk assessed by MSS test, and return rates of the questionnaires between the two groups. Similar proportion of women chose to have a diagnostic test – 47/58 (81%) in the control group versus 48/59 (81%) in the intervention group. Choice of test did not differ by group allocation, but decision analysis women evaluated more information during their consultation both positively and negatively than those in the control group (positive evaluation - mean score 3.18 versus 2.55, $F=6.30$, $p=0.01$; negative evaluation - mean score 3.00 versus 2.37, $F=5.98$, $p=0.02$). These women also perceived the risk more realistic ($p=0.05$) and had a lower decisional conflict over time. Decision analysis consultations lasted about 6 minutes longer but women did not perceive consultations to be any more or less directive, useful or anxiety provoking than the routine ones. No significant differences were observed for the other outcomes.

In the third RCT [663] a total of 201 women were randomized to the intervention ($n=100$) and the control group ($n=101$), and the questionnaire was completed by 90% women in the intervention group and 99% in the control group. The baseline characteristics of the two groups were similar. There were no significant differences in the initial decision for and the final uptake of the screening test between the intervention and the control group (p value for all the tests > 0.05). After watching the video 54.1% women in the control group and 55.1% in the intervention group reported that they had no more questions. After browsing the IMDA the proportion of women having no more questions increased to 77.0% ($p<0.001$), and 86.6% women agreed that IMDA was user-friendly and 78.9% that it was acceptable. A higher proportion of younger women (age < 35 years) accepted IMDA compared to those over 35 years of age ($p=0.03$), but the difference was not significant after adjusting for confounding variables.

For the UK quasi-RCT a total of 993 women were allocated to the video group and 1007 to the control group [664]. No statistically significant difference was observed in the screening uptake rate between the two groups (64.2% versus 64.7%). Questionnaires were sent at 17-19 weeks only to the first 1200 women randomized in the two groups, and after exclusions the sample size was 499 (video group) and 552 (control group). Rate of questionnaire completion was similar between the two groups. Knowledge about screening was increased in the video group with a mean score of 7.3 compared with 6.7 in the controls ($p=0.0005$), but there was no difference between the two groups in specific worries about abnormalities in the baby, and general anxiety. The outcomes were also evaluated in relation to baseline demographic characteristics of housing tenure and age. Knowledge was found to be significantly higher in owner occupiers and older age groups, anxiety scores lower in owner occupiers, and worry scores higher in older age groups. The authors concluded that knowledge of prenatal testing can be increased by using a video, and moreover this can be done without making women more anxious or worried about fetal abnormalities.

Preterm delivery (1 study)

Description of included study

Patient education was included as an integral part of a multi-faceted programme aimed at reducing preterm birth deliveries in a province in New York (USA), and this cohort study (1989) examined specifically the effectiveness of patient education to preterm birth prevention [665]. [EL 2-] All women beginning antenatal care by 36 weeks and not at high risk for preterm delivery were enrolled for the study and offered a class about recognizing the signs and symptoms of preterm labour. The class consisted of a 15-minute videotape presentation followed by a 15-minute discussion led by a registered nurse staff member where several printed educational materials were also given. Outcome evaluated were the rates of preterm delivery and low birth weight. Blinding of outcome investigators has not been specified and confounding variables have not been controlled.

Findings

The study population was 2326 women and of these 487 attended the class with most participating between 24 and 32 weeks of gestational age. There were no significant differences between the class attendees and non-attendees for the baseline demographic and obstetric variables. Women attending classes had babies with a higher mean birth weight ($p=0.03$) and gestational age ($p=0.12$), but improvement in gestational age did not reach statistical significance. The preterm birth rate was reduced by 17% and low birth weight rate by 27% among women attending the classes compared to the non-attendees, but these differences were statistically not significant.

HIV (1 study)

Description of included study

This UK (Scottish) RCT (1998) aimed to determine whether different methods of offering voluntary HIV test to all pregnant women would lead to significantly different uptake rates, and to assess the impact of these methods on women's satisfaction, anxiety and knowledge [666]. [EL 1+] All pregnant women booked in a tertiary hospital in UK were invited to participate in the trial. Four different combinations of providing information using a leaflet sent with booking information package ('all blood tests information' or 'HIV specific test information') and discussion with a midwife ('Minimal' or 'Comprehensive') were compared. After recruitment the subjects were computer randomized into five groups – Group 1 was the control group with no leaflet or discussion, Group 2 given 'all blood tests' leaflet and 'minimal discussion' by midwife, Group 3 given 'all blood tests' leaflet and 'comprehensive discussion' by midwife, Group 4 given 'HIV specific test' leaflet and 'minimal discussion' by midwife, and Group 5 given 'HIV specific test' leaflet and 'comprehensive discussion' by midwife. Except Group 1 which was offered HIV testing on request, all the other four groups were directly offered the test by the midwife, that is, the policy of universal testing was followed. The key outcomes were uptake of testing and women's knowledge of HIV, satisfaction with consultation, and anxiety. Hospital records along with a questionnaire given to women after discussion with a midwife were used to assess the outcomes. Analysis was done on intention-to-treat basis and regression used to determine independent predictors of uptake.

Findings

Of the 3505 women randomized at booking, 3024 participated in the study over a 10 month period. Baseline demographic characteristics of the five groups were similar. Uptake rates were 6% for the control group and each of the methods of directly offering the test resulted in a higher uptake than in the control group (chi-square test, $df = 4$, $p<0.0001$). However there was no significant difference between the four groups where the test was offered directly (chi-square test, $df = 3$, $p=0.37$). The best independent predictor of uptake was being directly offered the test. General knowledge of HIV was good and did not differ significantly by the method of offering testing, but specific knowledge about HIV and benefits of testing increased with the amount of information given (chi-square test of linear trend, $df = 4$, $p<0.001$). No significant difference was found regarding anxiety and satisfaction.

Evidence summary

Evidence from a single trial [EL 1+) indicates that extra information about screening tests given individually or in a group leads to higher level of satisfaction and understanding among pregnant women, but might decrease uptake of some screening tests.

There is high quality evidence that informational leaflets are effective in increasing the knowledge of pregnant women about screening tests (general and for Down's syndrome), and the use of touch screen method does not improve uptake rate of screening tests compared to the leaflets.

Evidence from a good quality trial shows that decision-aid techniques are helpful to pregnant women in making informed choices about the screening tests for Down's syndrome.

Results from a good quality trial show that using interactive multimedia decision aid does not improve uptake of screening test for Down's syndrome compared to the information provided by leaflets and video.

There is limited evidence on effectiveness of informational material for reducing preterm deliveries. Results from a single cohort study show that educating women using a video film followed by a discussion are ineffective in preventing preterm births.

Evidence from a single good quality trial indicates that both written and verbal information leads to a higher uptake of HIV screening tests in pregnant women without increasing their anxiety.

3.1.10 Perspectives of clinicians and women regarding information giving

Three good quality descriptive studies have been included under this section. The first study explored and compared the perceptions of clinicians and patients regarding screening tests, the second evaluated information provided for Down's syndrome from the perspective of health care practitioners only, and the last one looked at the social context in respect to introduction of a new informational leaflet for prenatal care.

Description of included studies

A qualitative descriptive study was conducted in USA (2005) to explore the interaction between the contrasting perspectives of clinicians and the patients, and consider how differences in their primary orientations might effect efforts to assure patients are making informed decisions about prenatal genetic testing [667]. [EL 3] This study combined data from a series of related studies and altogether a convenience sample of 40 patients and a convenience snowball sample of 50 clinicians were interviewed along with observations of 101 genetic counselling sessions. Women interviewed were those offered amniocentesis following an abnormal AFP while the clinicians interviewed included 25 physicians, 20 clinical staff and 5 genetic counsellors. Patients and clinicians were interviewed from the same clinics and who had interacted with each other in order to capture their contrasting perspectives. The interviews averaging about 2 hours were tape-recorded and transcribed, and followed a standardized set of open-ended questions. Information and knowledge content scores were generated from the interviews based on eight informational elements considered important by the clinicians when offering amniocentesis. All phases of data processing and analysis were cross-checked during conference sessions and any discrepancy was addressed.

A qualitative study in UK (2002) explored the information given to pregnant women and their partners about Down's syndrome from the perspective of health care practitioners, and looked at some ways in which this information could be constructed [668]. [EL 3] Health practitioners whose work was related directly or indirectly to perinatal care were recruited (n = 70) using 'snowballing' technique, and their informed consent was taken. Individual interviews lasting between one and two hours were conducted in the form of semi-structured 'guided conversations'. Most of the interviewees (56/70) then participated in group discussions with an average group size of 9 (6 participants, 2 sociologists, 1 group leader). Groups were of mixed disciplines and seniority and their discussions were tape recorded, fully transcribed, analyzed by content for emergent themes and then coded. Each session lasted approximately two hours. Findings of this study are based on the 11 group discussions that took place and do not include data from the interviews held earlier.

Qualitative research was conducted independently but alongside the cluster-randomized trial[13] to understand the social context in which the leaflets (10 pairs of informed choice) were used.[14] [EL 3] The study involved non-participant observation and in-depth interviews with health professionals and pregnant women in both the intervention (5 units receiving the leaflets) and the control units (5 units continuing normal care). Consultations were observed to identify how the leaflets were used and how informed choice and decision making occurred in practice. Face to face interviews were conducted using a semi-structured format to discuss various aspects of information giving (availability, quality, and understanding), the meaning of informed choice, and the role of child-bearing women in decision making. Sampling was initially 'opportunistic' depending on the availability and willingness to participate, but later became 'selective' to ensure uniform representation of both the health professionals and pregnant women. Towards the end of the intervention period, women who had questioned or declined the choices offered to them and staff who offered information withheld by their colleagues were selectively interviewed to identify the interplay between hierarchy, power and trust.

Findings

One-third of the patients interviewed were 25-30 years of age, more than half were married and three-quarters had decided to go for amniocentesis. Almost half of the clinicians interviewed were working in private genetics speciality clinics, 22% were MD with genetics speciality and 10% genetic counsellors. Of the 101 genetic counselling sessions, women were observed in two-third cases while in the rest she was both observed and interviewed. Broadly both the clinicians and patients shared the obvious goal of prenatal care that is to ensure a healthy pregnancy, but their understanding and orientations to this undertaking were quite different. For the clinicians, consultations were a routine part of their everyday work of trying to identify, prevent and control problems. In contrast, patients considered consultations as disruption of their routine of nurturing and protecting their pregnancy. While moving through the process of prenatal genetic diagnosis, each defined the shared goal of promoting a healthy pregnancy in strikingly different ways:

- *Meaning of an abnormal screening test* – In the genetic counselling sessions, clinicians usually began by noting that the abnormal screening test only indicates that there might be a problem (specifying a percent 'risk') and explaining that further testing was required for the diagnosis. Most of the patients (87%) felt anxious with the news and many began crying, while 63% said that they were told nothing about the reason for referral to a genetics specialist and they thought it was a routine prenatal visit.
- *Ultrasound to confirm dates* – For the clinicians, it was a mundane step to verify whether further testing was required and usually occurred without discussion with the patient. The patient on the other hand was primarily concerned with getting information about the well-being of the baby.
- *Offer of amniocentesis* – Clinicians were primarily concerned with finding and responding to a problem and 96% described acceptance of testing by the patients as being based on their desire to know the well being of the baby. All the patients accepting the offer of amniocentesis said they had wanted reassurance about the baby's health after the positive screening tests results, while 90% women declining the offer did it for not willing to risk a miscarriage.

Clinicians discussed all the essential elements of information giving in only 59% of the consultations. Elements most consistently covered were that the test is optional, risks of procedure, and risks for the anomaly, while the least covered elements were the nature of anomaly and alternatives to amniocentesis. Patients overall knowledge score averaged about 53% and the elements for which they showed most complete knowledge included reasons for doing amniocentesis, test is optional, nature of the invasive procedure, and what information can this test give. The elements least completely discussed included risk of anomaly, alternatives to amniocentesis, and nature of the anomaly.

But there was no statistical correlation between the completeness of information included in consultant's consultations and the level of knowledge exhibited by the patients during the interviews (Pearson correlation = 0.204, p = 0.289).

In the UK qualitative study [668] of the 56 health practitioners who participated in the group discussions, there were 20 midwives, 20 doctors, and 16 from a variety of other disciplines. The principal findings from the study:

- *What women were thought to know about Down's syndrome* – Practitioners felt that more time was spent explaining the complexities of the actual screening process rather than the condition being screened. Moreover many women did not have adequate knowledge about some of the basic features of Down syndrome. This was ascribed to fewer births of infants with DS and medical innovations shifting people's perception of normality.
- *How information about Down's syndrome is presented* – Though many practitioners felt that their way of providing information influenced decision-making by pregnant women, they seldom made any positive and realistic statement about the condition. Leaflets distributed to the pregnant women at the time of booking visit were frequently used to provide information. These leaflets contained little information about DS itself and devoted most of its space to the screening process. Many staff members were also reluctant to provide positive aspects of information as they felt that it might not present a realistic picture to the prospective parents.
- *From where do practitioners obtain their knowledge* – Most practitioners themselves had little time and practical experience of dealing with DS cases. They relied on medical textbooks,

leaflets and articles for knowledge and these sources usually focussed on the potential problems of the syndrome and its management strategies.

- *Ways in which information about DS was negatively constructed* – The authors explained that lack of access to adequate health care (denial of treatment for common ailments, decreased probability of affected children attending mass screening) along with the difficulty in distinguishing visual/hearing problems from learning disabilities leads to the development of a negative picture about DS.

A total of 886 episodes of consultations with pregnant women were observed - 653 held by midwives, 167 by obstetricians and 66 by the obstetric ultrasonographers. 383 face-to-face interviews were conducted (173 childbearing women, 177 midwives, 28 obstetricians, 12 obstetric ultrasonographers, and 3 obstetric anaesthetists). Though the health professionals were positive about the leaflet and their potential in helping women make informed choices, they were seldom used to maximum effect in clinical practice. The various reasons observed were the time constraint, unavailability of choice in regular practice, disagreement of staff with its content or an option given in it, and their distribution usually in a concealed manner or 'wrapped' up with other advertising material. Health professionals were also observed to influence decision making in pregnant women towards technological intervention by conveying information which either minimized the risk of the intervention or emphasized the potential for harm without the intervention. They reinforced notions of 'right' and 'wrong' choices instead of 'informed choices' and this was promoted by their fear of litigation. A strong hierarchy was observed within the maternity services with the obstetricians at the top, midwives and health professionals other than doctors in the middle, and pregnant women at the bottom. This led to concern in midwives about the consequences of recommending options that contradicted obstetrically defined clinical norms. Because of their trust in health professionals, women seldom questioned them or made alternative requests, and this ensured 'informed compliance' rather than 'informed decision making'.

Evidence summary

There is evidence from a well conducted qualitative study which shows that the process of informed decision-making for prenatal screening tests is hampered by inadequate information provided to pregnant women during consultations, and the divergent approaches taken by the information provider (clinicians) and information taker (patients).

Though the health care providers intend to provide complete information about DS screening and its subsequent path way to prospective parents, their ability to do so is limited by time constraint, their limited experience of the condition after birth and lack of factual information given in the sources they used to acquire knowledge about DS.

Time constraints, fear of litigation, power hierarchies, and imperativeness of current technological interventions act as barriers in promoting leaflets for informed decision making in maternity care. Women were found to merely comply with the information provided by health professionals and were unable to make an 'informed choice'.

3.1.11 Women's preference for source of information

Description of included study

A retrospective cohort study (2004) was carried out using data from an earlier study to find out i) whom women perceive as influencing their decision about prenatal screening and diagnosis for birth defects ii) who they would have liked to talk more to, and iii) what sources of information they preferred [669]. [EL 2+] The sample population comprised of pregnant women from eighteen hospitals in Australia at approximately 24 weeks gestational age and over 37 years of age at the estimated date of delivery. Questionnaires seeking women's choices and preferences for the above mentioned three objectives were developed through a process of piloting, and differences between women who did and who did not undergo prenatal testing were examined for each of the objective.

Findings

The sample population for the final analysis included 724 women with 539 undergoing prenatal testing (tested group) and 185 not going for prenatal testing (untested group). The baseline socio-demographic characteristics of the two groups were similar. More than 90% women in both the groups reported that they themselves had a strong influence on their decision to be tested or not, and 70% reported their partner as strongly influencing their decision. Statistically no significant difference was observed between the two groups for the above parameters, but significantly higher proportion of women in the tested group were influenced by their doctor or genetic counsellor ($p < 0.001$ for both) and a friend or a nurse ($p < 0.01$ for both). 35.7% of women in the tested group were more likely to talk to other women who have had the tests as compared to 21% women in the untested group ($p < 0.001$). Higher proportion of tested women would have preferred to talk to a genetic counsellor (9.5% versus 8.6%, $p = 0.002$), while women in the untested group were more likely to talk to a pastoral carer (2.5% versus 10.6%, $p < 0.001$). There were no significant differences between the groups with respect to a specialist, general practitioner, friend, nurse/midwife or other pregnant women. In both the tested and the untested groups, the preferred source of getting information was face-to-face discussion or counselling (69.1% tested group, 47.4% untested group), and the difference between the two groups was statistically significant ($p < 0.001$). The second preferred choice was pamphlet (48.7% tested group, 42.8% untested group, $p = 0.18$) followed by video (35.2% tested group, 24.9% untested group, $p = 0.01$). Untested women were significantly more likely to say that they were not interested in any information than the tested women. The authors concluded that since a high proportion of women were responsible for their own decisions about prenatal testing, it is unlikely that universal acceptance and uptake will occur even in this group of women with advanced age. Moreover there continues to be a need for face-to-face sessions with a doctor or a counsellor in combination with printed information material.

Evidence summary

Evidence shows that the decision whether or not to undergo a prenatal screening test is usually made by the woman herself. However, those choosing to undergo testing report that healthcare professionals also have a strong influence on their decision. Women prefer getting information from face-to-face discussion or counselling rather than other methods.

3.1.12 Women's views of general antenatal information provision

Description of included studies

7 descriptive studies are included in this section, 4 conducted in the UK, 2 in the US and 1 from New Zealand.

An English retrospective cross-sectional questionnaire survey (2005) was identified for review that investigated women's views of information-giving during the antenatal period [670] [EL 3]. All women giving birth in the study area during a 3 month period were invited to participate in the survey ($n = 700$). 329 women returned a completed questionnaire (response rate 47%).

A longitudinal questionnaire survey conducted in England 1998-1999 investigated women's views of information-giving in maternity care [671].[EL 3] Invitations to participate in the survey and the first questionnaire were posted to all women booked for a first appointment in a randomly selected month. Sixty women completed a questionnaire at 5 times points during their maternity care: before booking; following the 20 week ultrasound scan; after 34 weeks; on the postnatal ward; time of community discharge (14-28 days after birth), representing a final response rate of 60/475.

A local English longitudinal, prospective survey (1997) of antenatal classes conducted in one large teaching hospital and National Childbirth Trust classes in the neighbouring area sought men and women's views concerning class content [672] (1997) [EL 3]. Three questionnaires were distributed to couples (separate questionnaires for men and women), one prior to the commencement of classes, one at the end of the course of antenatal classes, and one after the birth of the baby. The first questionnaire was posted (details of its return are unclear), the second was handed out and returned to the antenatal educator at the end of the final session. It is unclear how the third questionnaire was distributed and returned. The overall response rate for all 3 questionnaires was

159/400. One open-ended question on each questionnaire asked for respondents' views of class content. The response rates for this question on each questionnaire were 31.5%, 22% and 71% respectively.

A retrospective, national survey was conducted with a randomly selected sample of women giving birth during a particular month in 1984 [673]. [EL 3] The sample was drawn from 10 regions of England stratified by county on a north to south basis. 1920 women were included in the survey and 1508 returned a completed questionnaire (response rate 79%). Women were asked what had been their main sources of information during pregnancy and how useful these had been. (Information received during labour and postpartum was also asked about but will not be reported here.)

A USA concurrent mixed methods study [674] conducted in 2003-4 (Bennet et al, 2006) involved 202 (response rate 90%) low-income African-American women in face to face interviews to ask their views and experiences of pregnancy and antenatal care [EL 3]. The study aimed to investigate differences between women with low literacy skills and those with higher literacy skills. A randomly selected sub-group of participants (n = 40) carried out a free-list task where participants were asked to list up to 10 words or short phrases for 'things you think about when going to the doctor when you are pregnant'. Responses from the free-list task were then subject to cultural consensus analysis (or cultural domain analysis). This technique is used to define how members of group make sense of or understand a particular aspect of life (cognitive domain). Four focus groups were conducted to confirm and explore the items/themes identified through the free-list task. These involved 8 women with low literacy skills (defined as $<= 6^{th}$ grade) and 10 women with higher literacy skills ($>= 9^{th}$ grade), matched by age and postpartum month. Findings from the focus groups were analysed using a grounded theory approach in order to confirm factor items identified through cultural consensus analysis and to look for meaning in and relationships between items.

A USA cross-sectional interview-based descriptive study was conducted in order to identify differences between the health promotion content women wanted to discuss during antenatal consultations and issues actually discussed, and to compare health promotion content of consultations between African-American women and Mexican-American women [675] [EL 3]. Interviews were conducted with 159 African-American or Mexican-American women with low income recruited from a 'low risk' antenatal clinic affiliated to a tertiary care hospital (response rate 91%). Within the research interview women were read a list of 27 health promotion topics and asked 'did you want or need information about [topic]' and then they were asked 'did you talk about [topic]?'.

A cross-sectional questionnaire survey carried out in New Zealand (1999) investigated women's information needs and sources [676] [EL 3]. Recruitment was carried out using posters placed in public places where pregnant and postnatal women were expected to see them. The sample is thus a volunteer sample and it is not possible to compare the sample of respondents with non-respondents. Respondents included women planning a pregnancy (n = 7), pregnant women (n = 30) and women who had given birth in the previous 3 months (n = 13).

Findings

The UK retrospective survey asked women how they preferred information to be provided [670]. 70% of women stated a preference for one to one discussion, and a similar proportion cited leaflets as their preferred method. Only 20% indicated that taught classes or discussion groups was the preferred method of receiving information. Whilst the majority of women reported that they understood the written information provided during pregnancy, sub-group analysis revealed an important difference. Whilst 72% of women from professional/semi-professional groups reported that they understood all written materials, only 45.5% of women from non-professional/non-working groups reported this high level of understanding. Over 90% of women expressed that they had been given enough information and an opportunity to make decisions about screening tests. However, women's responses regarding diet, alcohol intake, exercise and smoking indicated that the information received had little or no effect on their attitude or behaviour. When asked whether information they had received influenced their decision about where to give birth, 70% said it had

little or no influence. However, the only choices available in the study area were birth in the local hospital or home birth.

The English longitudinal study of women's views of information-giving [671] identified a number of areas where women reported they would have liked more information. For all women these included pregnancy complications and caesarean section. A quarter of nulliparous women indicated that they wanted more information about baby development. Open responses suggested that the timing of information was important to women eg. preferring pregnancy-related information to be given as early as possible (ie. before booking appointment), and the high value placed on information that was individually tailored.

Findings from the UK local survey of men and women's views of the content of antenatal classes suggested that both men and women would have preferred more information about the postnatal period to be provided by antenatal classes. This need was apparent at all phases of the survey but most prominent in the postnatal questionnaire where 95/111 (86%) participants included this topic in their response to an open-ended question. The major category within this theme was information about caring for the new baby.

Findings from the English national survey carried out in 1984 were reported separately for nulliparous and multiparous women [673] [EL 3]. Almost three-quarters of nulliparous women had attended antenatal classes, however only 6% cited these as the most helpful source of information. Non-professional sources of information (own mother, husband, friends and relatives) were considered the most useful sources of information by 43% of nulliparous women, compared with 24% who reported professional sources (midwife, GP, obstetrician, health visitor) as the most useful. When asked about the amount of information given during pregnancy, 59% of all women said they felt it had been the right amount of information, 20% reported it had been too much and 20% that it had not been enough. A quarter of women felt that they had not been able to discuss all the things they had wanted to during antenatal consultations. Women who were not married, those whose social class was manual and those who did not own their own homes were more likely to report dissatisfaction in this.

Findings from the UK local survey of men and women's views of the content of antenatal classes suggested that both men and women would have preferred more information about the postnatal period to be provided by antenatal classes. This need was apparent at all phases of the survey but most prominent in the postnatal questionnaire where 95/111 (86%) of the participants included this topic in their response to an open-ended question. The major category within this theme was information about caring for the new baby.

Cultural consensus analysis of findings from the US concurrent mixed methods study (n = 9 women with low literacy level; n = 31 women with higher literacy) [674] revealed the following items as most salient when women were asked what they thought about when considering an antenatal appointment (from most to least salient): finding out if everything is okay; long wait; questions (communication with carer); needles (blood tests); woman's weight and hearing the baby's heartbeat [EL 3]. Items associated with communication between women and their carers were identified as making up an organising theme when women were discussing obstacles to care. This was common across all 4 focus groups. Women in all groups described ideal communication as communication where each person makes statements that are accurately understood and completely responded to by the other person. Women in all groups valued carers who provided information in a way they could understand, eg. where complex concepts or words were 'broken down' in order to make them more easily understood. It was important to women that they were able to tell their carer when they hadn't understood something so that the carer could explain further.

The USA cross-sectional descriptive study [675] involved interviews with 112 African-American women and 47 Mexican-American women. 72% of the women were younger than 24 years, and 65% were multiparous. 39% of women in the sample had less than 12 years education and 45% had household incomes of less than $1000 per month. Bivariate analysis revealed statistically significant differences ($p < 0.001$) between topics women wanted to discuss and topics actually discussed. Statistical analysis was performed using the Sign test for paired data. Although p values are given values for the Sign statistic are not reported. Significantly more women wanted or needed information but did not discuss using seatbelts safely, dealing with stress and conflict, family

planning, and caring for the new baby. Women did not want or feel they needed information but discussed taking vitamin/mineral supplements, eating specific food groups, drinking adequate amounts of water, stopping specific substance use. More differences were reported between information wanted or needed and information discussed for African-American women compared with Mexican-American women (adjusted regression analysis $R^2 = 0.39$, $p < 0.001$).

Findings from the New Zealand cross-sectional survey showed that the sources pregnant women most often used for information were their midwife (37%), friends (23%) and the GP (13%) [676]. Advice from midwives was thought to be useful because it tended to be practical and reassuring. The theme of reassurance was prominent amongst women's responses. Topics that pregnant women wanted information about included: knowing what is normal; how to prepare for birth; coping with labour and birth; how to look after the baby; what to expect after birth. Multiparous women identified some different information needs including: coping with morning sickness; self care during pregnancy; birth after caesarean section; and financial needs and options. The educational background of women did not appear to be related to the kind of information needs they reported.

Evidence summary

Most women preferred information to be provided on a fae to face basis. The extent to which there was an understanding of what was said was dependent upon their working background.

A wide range of information was required, for example, details about screening in pregnancy, advice about smoking cessation, alcohol use and vitamin supplementation to place of birth and breast feeding

3.1.13 Women's views of specific antenatal information interventions

Description of included studies

A further 3 descriptive studies were identified for inclusion in this section of the review, one international study and 2 from the US.

A web-based cross-sectional survey has been conducted to identify perceived barriers to, and benefits of, attending a smoking cessation course [677] [EL 3]. The questionnaire targeted pregnant smokers and pregnant recent ex-smokers. Due to the nature of the sample selection details of non-respondents are not available. The survey comprised a 20-item decisional-balance measure, a method devised to help understand why people do or do not change behaviour. Items were based upon emergent themes from a UK focus group (n = 10 pregnant women who smoked).

A focus group study conducted in USA aimed to evaluate women's responses to educational messages concerning the risks and prevention of listeriosis, and to identify preferred delivery methods for such information [678] [EL 3]. Eight focus groups were carried out involving a total of 63 pregnant women. 64% of participants were multiparous and 87% were caucasian. 2 focus groups were conducted in 4 cities selected to provide geographical diversity. In each city one focus group was conducted with women educated to high-school level and one with women educated to college level. Focus groups were videotaped and audiorecorded. Common themes were identified within and across groups.

An older American study published in 1979 interviewed women to discover their perceptions of dietary information and advice provided during pregnancy [679] [EL 3]. Women were interviewed during an antenatal appointment between 34 and 38 weeks of pregnancy. All women with an estimated date of delivery falling within a specified 2-month period were invited to take part in the study, 92 agreed and were interviewed, a response rate of 86%.

Findings

The web-based survey of smoking cessation advice was completed by 443 women who were pregnant smokers or recent (within previous month) ex-smokers [677] [EL 3]. Most respondents were from the UK or the US. The most frequently endorsed barriers to attending a smoking cessation course were 'I am afraid I would disappoint myself' (54.2%), 'I do not tend to seek help for this sort

of thing' (40.6%), 'I do not have access to such a course' (40.5%) and 'I do not have time to attend the appointments' (39.8%). The latter 2 barriers were significantly more frequently identified by respondents from the US compared with those from the UK. The 2 statements with the least agreement were 'People that are close to me would not support me attending such a course' (9.8%) and 'Stopping smoking is not particularly important to me' (7.6%). The most frequently endorsed benefits of attending a smoking cessation course were: 'Advice about managing my cigarette cravings would be useful' (74.2%); 'Praise and encouragement with stopping smoking would be helpful' (70.7%); 'Advice about safe medications to help me stop smoking would be useful' (69.2%) and 'Someone checking my progress would be helpful' (64.5%). Approximately half of all respondents agreed with all the benefits statements. Respondents who agreed with the benefits of attending a smoking cessation course were significantly more likely to express an interest in receiving help of this kind (ANOVA, all at $p < 0.01$).

Findings from the USA focus group study [678] revealed that most participants were not aware that pregnant women are highly susceptible to food-borne illness. Few women reported receiving information about food safety from health care professionals contacted during pregnancy, and none remembered receiving information specifically about listeriosis. Commonly cited sources of information about food safety included books and magazines on antenatal care. Women suggested that written information on listeriosis be provided as part of the antenatal booking information package. Some women felt this written information should be backed up with specific advice from a health care professional, either during consultations or antenatal classes. Most participants reported using books and magazines as a main source of information. College educated women also reported using the internet as a source of information. Participants also felt that knowledge of listeriosis should be improved amongst the general population and suggested using the media to deliver public health food safety messages.

Findings from the 1979 USA interview-based survey showed that whilst 75% women felt pregnant women in general needed dietary advice, only half said that they personally needed such advice [679] [EL 3]. The most common reasons for this response was that advice was remembered from a previous pregnancy (39%) or that the woman already had a good knowledge of dietary requirements (35%). Only 11% women reported that they had acquired dietary information from other sources (eg. books/leaflets). One third of respondents reported that complying with dietary advice worried them 'a lot', with the most common concern being excessive weight gain during pregnancy. A similar proportion of women reported difficulty complying with dietary advice, especially that relating to dietary restrictions. When asked about their satisfaction with dietary information only 3 women reported any shortfall. Dietary information did not appear to be well recalled by women. When asked what was the most useful dietary advice they had received only 36 women (39%) could recall specific dietary information.

Evidence summary

There is poor quality evidence to show that most women considered information given during pregnancy as being adequate. Most women reported using books and magazines as the main source of information although the evidence is of poor quality.

Advice about smoking cessation and dietary issues do not seem in general to be effective. Dietary advice seemed to be obtained from sources other than the antenatal clinic.

3.2 Antenatal classes

3.2.1 Effectiveness of antenatal classes

Introduction

Antenatal classes are often used to give information regarding pregnancy, birth, infant feeding and parenting. However, antenatal education can encompass a broader concept of educational and supportive measures that help women and their partners to understand and explore their own social, emotional, psychological and physical needs during this time. It is often the aim of classes that through providing this opportunity in a supportive group environment prospective parents will

be able to develop self-awareness and confidence in their abilities, experience birth more positively and adjust more successfully to the changes that parenthood brings.

Description of included studies

This review was conducted to investigate the effectiveness of antenatal classes ie. their impact on specified outcomes. The review comprises 1 systematic review reporting findings from 5 RCTs plus 4 before and after studies and 2 retrospective cross-sectional studies. Most of the included studies are from the US and Australia.

A systematic review of six RCTs involving 1443 women was identified for inclusion in this review[27] [EL 1+]. One of these trials (n = 1275) was an evaluation of an intervention aimed specifically at increasing rates of vaginal birth following caesarean section and so will be excluded from this analysis. This leaves 5 small trials for inclusion here (total n = 168). All trials were conducted in either the US or Canada and published between 1981 and 1999. The intervention included was any structured educational programme, offered to individuals or groups, relating to preparation for childbirth, caring for a baby and adjustment to parenthood, compared with 'usual care' (not always described). Outcome measures included: knowledge acquisition; anxiety; woman's sense of control/active decision-making; pain and pain relief; obstetric interventions; breastfeeding; and psychological adjustment to parenthood.

A UK retrospective survey conducted in 1994 investigated the reported usefulness of coping strategies taught in antenatal classes [680] [EL 3]. Antenatal classes aimed to provide women with a range of 3 coping strategies from which to choose to help them cope with labour: change of position; relaxation and 'sighing out slowly' breathing. All 3 strategies were practised during the antenatal sessions and women were encouraged to practise further at home. Women who had attended at least 4 of the 5 antenatal sessions were interviewed 72 hours after the birth of their baby (n = 121).

A USA descriptive study (2003) investigated the effects of antenatal classes on women's beliefs and perceptions of childbirth [681] [EL 3]. The study used a validated 64-item questionnaire, the Utah Test for the Childbearing Year, to assess 4 areas of women's beliefs and attitudes about childbirth: fear of childbirth; childbearing locus of control; passive compliance vs. active participation in childbirth; personal values about childbearing and child rearing. The scale was administered to women before and after attendance at a series of antenatal classes which focussed on building women's capacity to be active participants in their labour. 57 women from 10 sets of antenatal classes completed the pre-test questionnaire, 42 of whom also completed the post-test questionnaire.

A USA questionnaire-based survey conducted in 1994 compared couples' (n = 119) self-care agency before and after attendance at a series of antenatal classes [682] [EL 3]. Self-care agency was measured using the Appraisal of Self-care Agency Scale developed by Evers (1986).

An Australian before and after questionnaire-based study conducted in 2000 compared a course of 4 participant-led classes with 4 traditional classes [683] [EL 3]. The participant-led classes were designed to identify and address couples' fears and concerns regarding childbirth and parenting. The 4 traditional classes focussed on breathing and relaxation techniques and preparation for labour. Couples registering for classes at the study hospital were alternately allocated to either the participant-led classes (n = 36 couples) or the traditional classes (n = 34 couples).

A second Australian questionnaire-based survey (1991) investigated nulliparous women's reasons for non-attendance at antenatal classes, knowledge acquired at classes and satisfaction with the antenatal programme [684] [EL 3]. In the first phase of the study all nulliparous women giving birth in a large teaching hospital in a 4 month period were invited to complete a questionnaire within 3 days of giving birth. A final sample of 325 women (response rate 91%) completed this phase of the study. In the second phase of the study, aimed at assessing levels of acquired knowledge and satisfaction following attendance at classes, all women and their partners attending classes over a 3 month period were invited to participate. A pre-test questionnaire was distributed for completion prior to attending the first class and a post-test questionnaire was distributed, completed and

collected during the fourth and final session. Both questionnaires were completed by 117 women (response rate 82%) and 82 men (response rate (58%).

An Australian retrospective cross-sectional study (2002) compared Sample n = 59 expecting their first baby who had attended an expanded course of antenatal classes aimed at preparing couples for parenting and early lifestyle changes following childbirth (n = 19 couples) with those of couples attending standard classes (n = 14 couples) [685] [EL 3]. The classes provided in the intervention group utilised adult learning principles, including needs identification and shared knowledge and experiences facilitated through same-sex discussion groups. Participants comprised a convenience sample with final response rates of 64% for the intervention group and 47% for the comparison group.

Findings

Due to heterogeneity of included studies in the systematic review meta-analysis of study findings could not be conducted[27] [EL 1+]. Amongst the 5 RCTs no consistent results were seen. No trials reported on labour and birth outcomes, anxiety, or breastfeeding. Knowledge acquisition and baby care competencies were investigated. One small study (n = 10) showed greater frequency of maternal attachment behaviours when specific maternal attachment preparation was included in the classes compared with standard classes without this component (WMD 52.60 points, CI 21.82 to 83.38). Two other studies showed greater knowledge acquisition, one in relation to father's parenting knowledge preparation (n = 28; WMD 9.55, CI 1.25 to 17.85), the other compared expanded childbirth education classes with standard/usual classes (n = 48; WMD 1.62, CI 0.49 to 2.75). There is concern over selection bias in the latter study however, since some exclusion criteria were applied post randomisation, and reported baseline differences were not controlled for in the analysis.

The 1994 UK retrospective interview-based study found that 88% women (n = 106) used 'sighing out slowly' breathing, 51% (n = 61) used change of position and 40% (n = 48) used a relaxation technique. Almost all women (98%) were accompanied by a birth partner during labour. The most common effects reported for 'sighing out slowly' breathing was that of relaxation/calming (36%) and distraction (34%). Relaxation techniques were reported by 33% of the women who used it as being effective in providing relaxation. Only 12% women who used this technique reported that it provided a distraction. Change of position was reported by 14% women as providing a distraction, whilst only 6% found it relaxing. Change in position was the most effective in terms of pain relief with 22% of women reporting that it provided some pain relief. 19% of women who used 'sighing out slowly' breathing and 12% of those who used relaxation techniques reported that they provided some pain relief. A minority of women found the coping strategy (strategies) used of minimal or no benefit ('sighing out slowly' breathing 7%; change of position 9%; relaxation 12%).

The 2003 USA before and after study found that women's mean scores for fear of childbirth and passive compliance vs. active participation decreased significantly after participation in the antenatal classes (fear (n = 37) 9.68 vs. 8.32, $p < 0.05$; compliance vs. active participation (n = 38) 3.84 vs. 2.89, $p < 0.02$). This shift suggests a decrease in fear of childbirth and a shift from passive compliance towards active participation. There was no significant change in scores for locus of control (n = 41; x = 1.98 vs. 1.49) and personal values about childbearing (n = 39; x = 4.03 vs. 3.97). It is not known whether or not these changes in questionnaire scores relate to changes in women's experience of childbirth.

The second USA before and after study [682] found that self-care agency was very high in women and men both before and after attendance at a series of antenatal classes. For women there was no significant difference between scores obtained before and after antenatal classes (mean score pre-class 97.1; post class 97.5). Men did show a significant increase following class attendance (mean scores 91.3 and 94.7). It is unclear whether or how this increase may have impacted on self-care behaviour.

Findings from the first Australian study [683] showed that women who attended participant-led antenatal classes reported significantly higher levels of increased knowledge relating to childbirth, baby care and becoming a parent than women attending traditional classes ($F(1, 59) = 11.89$, $p < 0.01$). This difference was not evident for men attending the classes ($F(1, 57) = 2.59$, NS). Women in the intervention group also reported higher level of preparedness for the experience of

pregnancy ($t = 3.05$, $p < 0.01$) and for self-care following birth ($t = 3.12$, $p < 0.01$). No differences were found for preparedness for labour, birth, mood and lifestyle changes following birth, or caring for the baby. Again no differences were found for men's reported preparedness for any of the factors investigated. Both men and women in the intervention group were significantly more satisfied with the way classes were presented and the topics included in the classes compared with couples in the traditional classes.

The second Australian questionnaire-based survey (1991) [684] found that 82% of nulliparous women attended antenatal classes, the majority of whom (83%) attended classes provided by the hospital where they were booked to give birth. Women who chose to attend classes were older, of a higher educational level, more likely to be married or living as married, and more likely to have private health insurance than women who chose not to attend. The most common reasons for not attending antenatal classes were that women felt they knew all that they wanted to know about pregnancy and giving birth (18% of non-attenders) or did not have time to attend classes (15%). Stepwise logistic regression analysis was used to investigate the possible effects of attendance at classes on 3 health-related behaviours (breastfeeding, cigarette smoking and knowledge of community services); 5 aspects of satisfaction with childbirth and 3 intrapartum interventions (use of pethidine, epidural and forceps birth). This analysis revealed that demographic factors had greater association with these outcomes than attendance at antenatal classes. Women's and men's knowledge of issues relating to pregnancy and childbirth increased significantly following attendance at antenatal classes across all topic areas measured. Most of the course components were rated as either 'very' or 'quite' useful by the majority of respondents. Of the 24 items included, 17 were rated as very or quite useful by at least 70% of participants. Items relating to labour were rated as very or quite useful by over 90% of participants. Items with fewer ratings of very or quite useful were: family planning; baby health centres; and nutrition and weight gain.

Findings from the Australian retrospective study [685] showed no significant differences between the intervention and control groups in the type of antenatal care chosen nor place of birth (no figures reported). Significantly more women in the intervention group stated that their labour had been 'managed as [they] liked' (84% vs. 43%; $\chi^2 = 5.4$, $p < 0.05$). No significant differences were found between the 2 groups regarding women's experience of pain or views of pain relief used during labour (again figures not given). Women in the intervention group were also more likely to rate their parenting experience more highly than women in the control group (mean score on parenting rating scale $x = 89.4$ vs. $x = 83.6$; $t(31) = 2.06$, $p < 0.05$). No significant difference was seen between the 2 groups regarding adjustment to life change following birth (mean score $x = 38.0$ vs. 37.0; $t(31) = 0.36$, NS). Open-ended responses to the questionnaire indicated that 70% of the women and 85% of the men in the intervention group felt as prepared as they could have been for parenting compared with 25% of the women and 40% of the men in the comparison group (numbers of participants not given).

3.2.2 Women's experiences and views of antenatal classes

Whilst a number of studies were identified which addressed women's views of antenatal classes the majority were of very poor methodological quality. As a result only 7 descriptive studies were included in the final review, 4 from the UK, 2 from Australia and one conducted in Canada.

Description of included studies

A longitudinal questionnaire survey has been conducted in England (2000) to investigate women's views of information-giving in maternity care [671]. [EL 3] Invitations to participate in the survey and the first questionnaire were posted to all women booked for a first appointment in a randomly selected month. Sixty women completed a questionnaire at 5 times points during their maternity care: before booking; following the 20 week ultrasound scan; after 34 weeks; on the postnatal ward; time of community discharge (14-28 days after birth), representing a final response rate of 60/475.

A UK retrospective cross-sectional questionnaire survey (2005) was also identified for review that investigated women's views of information-giving during the antenatal period [670]. [EL 3] All women

giving birth in the study area during a 3 month period were invited to participate in the survey (n = 700). 329 women returned a completed questionnaire (response rate 47%).

A local English longitudinal, prospective survey (1997) of antenatal classes conducted in one large teaching hospital and National Childbirth Trust classes in the neighbouring area sought men and women's views concerning class content [672]. [EL 3] Three questionnaires were distributed to couples (separate questionnaires for men and women), one prior to the commencement of classes, one at the end of the course of antenatal classes, and one after the birth of the baby. The first questionnaire was posted (details of its return are unclear), the second was handed out and returned to the antenatal educator at the end of the final session. It is unclear how the third questionnaire was distributed and returned. The overall response rate for all 3 questionnaires was 159/400. One open-ended question on each questionnaire asked for respondents' views of class content. The response rates for this question on each questionnaire were 31.5%, 22% and 71% respectively.

A rigorous Australian qualitative study conducted in 1998 -1999 used a grounded theory approach to describe and understand women's experience of antenatal classes, what they considered to be important and how useful they found the information provided [686]. [EL 3] Four participant-guided interviews were undertaken, 3 during pregnancy and one post birth. The sample size of 13 was decided when saturation of the collected data was reached. The findings reported here relate to 2 of the interviews – the third trimester interview and the postnatal interview (10 -14 days following birth). All interviews lasted about one hour and were conducted in the woman's own home. A detailed description is given of how the grounded theory analysis was carried out and how credibility, fittingness and auditability of the analysis was achieved. This process included returning full transcripts of each interview to the woman involved a few days after the interview for her to review and comment upon, asking her to check its accuracy and make corrections where necessary.

A retrospective, national survey was conducted with a randomly selected sample of women giving birth during a particular month in 1984 [673] [EL 3]. The sample was drawn from 10 regions of England stratified by county on a north to south basis. 1920 women were included in the survey and 1508 returned a completed questionnaire (response rate 79%). Women were asked what had been their main sources of information during pregnancy and how useful these had been. (Information received during labour and postpartum was also asked about but will not be reported here.)

A retrospective cross-sectional questionnaire survey conducted in Australia sought women's reasons for attending classes, expectations of classes and whether expectations were being met [687] [EL 3]. A self-reported questionnaire was distributed to all women giving birth at the 2 study hospitals in a 1 month period in 1997. The questionnaire was handed to women whilst they were on the postnatal ward and returned via a collection box prior to the woman going home. 143 completed questionnaires were returned, a response rate of 62% (56%of the target population). Of the respondents, 50 had attended antenatal classes (35%), 33 of whom had attended all sessions.

A Canadian cross-sectional questionnaire survey included investigation of women's reasons for not attending early (first trimester) antenatal classes and women's interest in attending early classes [688] [EL 3]. The questionnaire was distributed to all women attending antenatal classes in the study area during one specified week in 1990. Classes included community-based and hospital-based classes, some of which charged a registration fee. All courses included early pregnancy classes which focussed on pregnancy and healthy lifestyle issues, although women could choose when to join the course. At the time the survey was undertaken 46% of the classes were in the early pregnancy section of the course. The questionnaire was distributed, completed and returned during the antenatal class, and women were encouraged to complete the survey with their partner if he was present. 437 women agreed to complete the survey, a response rate of 98.9%.

Findings

The English longitudinal study of women's views of information-giving [671] identified a number of areas where women reported they would have liked more information. For all women these included pregnancy complications and caesarean section. A quarter of nulliparous women indicated that they wanted more information about baby development. Open responses suggested

that the timing of information was important to women eg. preferring pregnancy-related information to be given as early as possible (ie. before booking appointment), and the high value placed on information that was individually tailored.

The UK retrospective survey asked women how they preferred information to be provided [670]. 70% of women stated a preference for one to one discussion, and a similar proportion cited leaflets as their preferred method. Only 20% indicated that taught classes or discussion groups was the preferred method of receiving information. Whilst the majority of women reported that they understood the written information provided during pregnancy, sub-group analysis revealed an important difference. Whilst 72% of women from professional/semi-professional groups reported that they understood all written materials, only 45.5% of women from non-professional/non-working groups reported this high level of understanding. Over 90% of women expressed that they had been given enough information and an opportunity to make decisions about screening tests. However, women's responses regarding diet, alcohol intake, exercise and smoking indicated that the information received had little or no effect on their attitude or behaviour. When asked whether information they had received influenced their decision about where to give birth, 70% said it had little or no influence. However, the only choices available in the study area were birth in the local hospital or home birth.

Findings from the UK local survey of men and women's views of the content of antenatal classes suggested that both men and women would have preferred more information about the postnatal period to be provided by antenatal classes. This need was apparent at all phases of the survey but most prominent in the postnatal questionnaire where 95/111 (86%) participants included this topic in their response to an open-ended question. The major category within this theme was information about caring for the new baby.

Women in the Australian qualitative study [686;689] were well educated (12/13 had a degree or diploma) and 11 were in full-time employment. 12 of the women were Caucasian and 1 was Australian-Chinese. All were booked for a hospital birth. When asked about their experience of antenatal classes in the third trimester, most women were satisfied with the amount of information provided about labour and pain relief. However, for some women the emphasis some antenatal teachers placed on labouring without drugs was a cause of some concern. Women were less pleased with the amount of information provided concerning breastfeeding and care of the new baby, and they contrasted this lack of information with the large amount of information given about labour and birth. Women's responses indicated that more practical advice, including practical advice on breastfeeding and what to expect when feeding, would have been welcome. During the post-birth interview women were asked to reflect on the information they had received during antenatal classes and how well they felt the classes prepared them for labour, birth and the postnatal period. The women felt classes had not prepared them for labour, with all women expressing the sentiment that nothing could prepare you for labour and birth. The preference for more practical information and advice about infant feeding (not just breastfeeding), how to handle and communicate with your baby and general baby care (eg. bathing, playing with your baby) was also commonly expressed. Lack of information about discomfort following birth was also noted. [EL 3+]

Findings from the English national survey carried out in 1984 are reported separately for nulliparous and multiparous women [673] [EL 3]. Almost three-quarters of nulliparous women had attended antenatal classes, however only 6% cited these as the most helpful source of information. Non-professional sources of information (own mother, husband, friends and relatives) were considered the most useful sources of information by 43% of nulliparous women, compared with 24% who reported professional sources (midwife, GP, obstetrician, health visitor) as the most useful. When asked about the amount of information given during pregnancy, 59% of all women said they felt it had been the right amount of information, 20% reported it had been too much and 20% that it had not been enough. A quarter of women felt that they had not been able to discuss all the things they had wanted to during antenatal consultations. Women who were not married, those whose social class was manual and those who did not own their own homes were more likely to report dissatisfaction in this.

Findings from the Australian retrospective questionnaire survey are based upon data collected from the 33 women who attended a full course of antenatal classes [687]. All women stated that they attended classes in order to gain information. Other important reasons for attending classes were: 'to reduce anxiety or increase confidence' (94%), 'to have partner present and involved' (85%); and 'to have a more positive emotional experience' (76%). Women were also asked to rate how well the classes had met their expectations in relation to the factors listed as influencing their decision to attend classes. Findings showed that expectations had been met for the majority of women. Women were also asked to rate the level of appropriateness of the amount of information given on a range of topics. Most women reported that they felt the amount of information was right regarding normal labour (97%), pain relief in labour (91%), choices in decision-making during childbirth (88%), and complications/interventions during labour and birth (91%). There were 3 areas where a fair proportion of women reported that the amount of information proved was too little: relaxation and breathing for labour (33%), nutrition/diet (27%), and infant care (21%).

The Canadian survey [688] investigating early pregnancy classes found that the 3 most common reasons women gave for not attending early pregnancy classes were: insufficient knowledge about the classes (69%); early classes were not considered useful (29%); and early classes not convenient (18%) (women were invited to give multiple responses if appropriate). An open-ended question asking for ideas on how to encourage women to attend early classes elicited the following responses: encourage doctors to promote early classes and using a public awareness programme to advertise the content and availability of the classes. Women reported that they would like information in early classes on how the baby develops, signs and symptoms of miscarriage, nutrition and exercise. [EL 3]

Evidence summary for Section 3.2

The available evidence shows that for women and their partners, knowledge regarding pregnancy, birth and parenting issues is increased following attendance at antenatal classes, and that the wish to receive this information is a strong motivator for attending classes. There is little evidence that attendance impacts on any birth outcomes (such as mode of birth or use of analgesia) although there is some evidence from qualitative research that women's experience of birth and parenting may be improved if they attend client-led classes compared with more traditional classes.

Evidence from well-conducted qualitative research shows that women generally view antenatal classes positively. Whilst most women appear satisfied with the content of classes in terms of pregnancy, labour and birth information there is an expressed wish for more information regarding postnatal issues including general baby-care.

GDG interpretation

There is some evidence that breastfeeding initiation rates and breastfeeding duration can be improved by interactive antenatal breastfeeding education. One-to-one counselling and peer support antenatally are also effective.

There is some evidence that intensive antenatal dietary counselling and support is effective in increasing women's knowledge about healthy eating and can impact upon eating behaviours. There is no evidence linking this with improved pregnancy outcomes however.

There is good quality evidence to show that smoking cessation interventions help women reduce smoking and decrease adverse neonatal outcomes.

There is high quality evidence that informational leaflets are effective in increasing the knowledge of pregnant women about screening tests (in general and for Down's syndrome), and that the use of a touch screen method does not improve uptake rate of screening tests compared to the leaflets but may reduce anxiety and be particularly useful for women with abnormal results. Videos can increase knowledge of prenatal diagnosis without increasing anxiety. Decision analysis techniques can also be useful.

There is evidence from a well conducted qualitative study showing that the process of informed decision-making for prenatal screening tests is hampered by inadequate information provided to pregnant women during consultations, and the divergent approaches taken by clinicians and patients.

Evidence shows that the decision whether or not to undergo a prenatal screening test is usually made by the woman herself. However, those choosing to undergo testing report that healthcare professionals also have a strong influence on their decision. Women prefer getting information from face-to-face discussion or counselling rather than other methods.

There is evidence that both written and verbal information leads to a higher uptake of HIV screening tests in pregnant women without increasing their anxiety.

The available evidence shows that for women and their partners, knowledge regarding pregnancy, birth and parenting issues is increased following attendance at antenatal classes, and that the wish to receive this information is a strong motivator for attending classes. Women usually view these classes positively. There is little evidence that attendance impacts on any birth outcomes (such as mode of birth or use of analgesia) although there is some evidence from qualitative research that women's experience of birth and parenting may be improved if they attend client-led classes compared with more traditional classes.

Recommendations

The following schedule should be used when providing information antenatally:

1. At first contact with a healthcare professional:
   - All antenatal screening
   - Signs of miscarriage
   - Nutrition and diet, including folic acid supplementation
   - Food hygiene, including avoidance of mould-ripened cheese and pate
   - How the baby develops during pregnancy
   - Exercise, including pelvic floor exercises
   - Lifestyle advice including smoking cessation; recreational drug use and alcohol consumption
2. At booking:
   - Place of birth (for further information on this topic, please refer to the Intrapartum care guideline, due to be published in September 2007 [634])
   - Care pathway
   - Breastfeeding
   - Further discussion of all antenatal screening including the anomaly scan and screening for Down's Syndrome
3. Before or at 36 weeks:
   - Breastfeeding technique
   - Preparation for labour and birth
   - Recognition of active labour
   - Care of new baby
   - Postnatal self-care
   - Awareness of baby blues and postnatal depression
4. At 38-40 weeks:
   - Options for management of post-dates pregnancy.

This can be achieved by providing a pregnancy book such as 'The Pregnancy Book' (Department of Health, 2007).

Communication and information should be provided in a form that is accessible to pregnant women who have additional needs, such as those with physical, cognitive or sensory disabilities and those who do not speak or read English. [635].

Information can also be provided using media such as video or touch screen technology and should be supported by written information.

Pregnant women should be offered evidence-based information and support to enable them to make informed decisions regarding their care. Information should include details of where they will be seen and who will undertake their care. [635]

At each antenatal appointment, midwives and doctors should offer consistent information and clear explanations and should provide pregnant women with an opportunity to discuss issues and ask questions.

Pregnant women should be offered opportunities to attend participant-led antenatal classes, including breastfeeding workshops.

Women's decisions should be respected, even when this is contrary to the views of the health care provider.

Pregnant women should be informed about the purpose of any screening test before it is performed. The health care professional should ensure the woman has understood this information and has sufficient time to make an informed decision. The right of a woman to accept or decline a test should be made clear. [635]

Information about antenatal screening should be provided in a setting where discussion can take place; this may be in a group setting or on a one-to-one basis. This should be carried out before booking.

Any information about screening should include balanced and accurate information about the condition being screened for.

Research recommendation

Alternative ways of helping healthcare professionals to support pregnant women in making informed decisions should be investigated.

4 Provision and organisation of care

4.1 Who provides care?

One systematic review assessed the clinical effectiveness and perception of antenatal care by type of antenatal care provider, i.e. midwife and general practitioner-led managed care was compared with obstetrician and gynaecologist-led shared care.[32] Three trials were included in the study, randomising 3041 women who were considered to be low risk (i.e. no medical or obstetrical complications). The two largest trials were set in Scotland (n = 2952). Of these, one assessed midwifery-led care and the other assessed care led by midwives and GPs.

No differences were observed between the midwife and GP-managed care and the obstetrician and gynaecologist-led shared care for preterm birth, caesarean section, anaemia, urinary tract infections, antepartum haemorrhage and perinatal mortality. However, the midwife and GP-managed care group had a statistically significant lower rate of pregnancy-induced hypertension (Peto OR 0.56, 95% CI 0.45 to 0.70) and pre-eclampsia (Peto OR 0.37, 95% CI 0.22 to 0.64) than the standard care group. This could result from either a decreased incidence or decreased detection. [Evidence level 1a]

There was no significant difference in the levels of satisfaction with the types of care provided between the two groups.

Based on this meta-analysis of 3041 women from three trials, midwife-managed or midwife and GP-managed antenatal care programmes for women at 'low risk' did not increase the risk of adverse maternal or perinatal outcomes.

Recommendation

Midwife and GP-led models of care should be offered to women with an uncomplicated pregnancy. Routine involvement of obstetricians in the care of women with an uncomplicated pregnancy at scheduled times does not appear to improve perinatal outcomes compared with involving obstetricians when complications arise. [A]

Future research

There is a lack of qualitative research on women's views regarding who provides care during pregnancy.

4.2 Continuity of care

The care of women during pregnancy, labour, and the postnatal period is often provided by many caregivers. Women may have caregivers who only work in particular settings, such as the antenatal clinic or the labour ward, and who cannot provide them with continuity of care. For the purposes of this guideline, continuity of care is defined as the provision of care by the same small team of caregivers throughout pregnancy. However, no trials investigated continuity of care solely in the antenatal period and therefore it is not possible to separate the results associated with continuity of care in the antenatal and intrapartum periods.

Two systematic reviews analysed the effects of continuous care during pregnancy and childbirth.[33,34]

One systematic review assessed the clinical effectiveness of continuity of care during pregnancy and childbirth and the postnatal period with routine care by multiple caregivers.[33] [Evidence level 1a] Two trials, one set in the UK, the other in Australia, were included in the review. They

randomised 1815 women to continuity of care by a small group of midwives as well as consultation with an obstetrician compared with routine care provided by physicians and midwives. Women who had continuity of care by a team of midwives were less likely to:

- experience clinic waiting times greater than 15 minutes (Peto OR 0.14, 95% CI 0.10 to 0.19)
- be admitted to hospital antenatally (Peto OR 0.79, 95% CI 0.64 to 0.97)
- fail to attend antenatal classes (Peto OR 0.58, 95% CI 0.41 to 0.81)
- be unable to discuss worries in pregnancy (Peto OR 0.72, 95% CI 0.56 to 0.92)
- not feel well-prepared for labour (Peto OR 0.64, 95% CI 0.48 to 0.86).

There was no significant difference in the rates of caesarean section, induction of labour, stillbirth and neonatal death, preterm birth, admission to the neonatal unit, or birthweight less than 2500 g. Further outcomes are reported in the corresponding evidence table.

One other systematic review compared continuity of midwifery care with standard maternity services.[34] This review included seven RCTs, which randomised 9148 women. The women randomised to continuous care had significantly lower rates of many outcomes related to the intrapartum period, such as induction of labour, augmentation of labour and electronic fetal monitoring. There were no significant differences in the rates of caesarean section, admission to the neonatal unit, postnatal haemorrhage, antenatal admission to hospital or duration of labour. No maternal deaths were reported. Satisfaction with care was reported by six of the seven trials but not included in the meta-analysis due to lack of consistency between measures. However, women with continuous care were more satisfied with care during all phases of pregnancy and differences were statistically significant for each study separately. Women in the continuous care group were more pleased with information giving and communication with the caregivers and felt more involved in the decision making and more in control. [Evidence level 1a]

Four more recent RCTs that were not included in either of the above reviews were also located.[35–38]

Another RCT in England which compared caseload midwifery care with traditional shared care.[35] Caseload midwifery care refers to a group of midwives caring for a specific number of women where a midwife has her own group of women, with back-up support provided by another midwife when needed. This study found that although there was a significant difference between caseload and traditional care groups in terms of level of 'known carer at delivery', there were no significant differences in terms of rates of normal vaginal deliveries, operative deliveries or neonatal outcome. [Evidence level 1b]

An Australian RCT compared continuity of midwifery care in a community-based setting with standard care in a hospital-based antenatal clinic.[36] The latter was characterised by a lack of continuity of care as a large number of clinicians provided care. No differences in any clinical outcomes were reported except a significantly lower caesarean section rate in the midwife-led community-based care group (OR 0.6, 95% CI 0.4 to 0.9). [Evidence level 1b] The women in the community-based continuity of care group also reported significantly less waiting time and easier access to care and a higher perceived quality of care than the hospital-based control group.[37] [Evidence level 1b]

Another Australian RCT compared continuity of care provided by midwives with standard care provided by a variety of midwives and obstetric staff.[38] The women assigned to the intervention group experienced less augmentation of labour, less use of epidural analgesia and fewer episiotomies; no differences in perinatal mortality between the two groups was observed. [Evidence level 1b]

An RCT on satisfaction with continuity of care found that continuity of care provided by team midwifery was associated with increased satisfaction compared with standard care attended by various doctors.[39] A woman from the intervention group was twice as likely to agree with the statement, 'Overall, care during pregnancy was very good' (OR 2.22, 95% CI 1.66 to 2.95). The intervention appeared to have greatest impact on satisfaction with care during the antenatal period compared with the intrapartum and postnatal period. [Evidence level 1b]

In most cases, the evidence demonstrates an association between continuity of care and lower intervention rates compared with standard maternity or hospital-based care as well as beneficial effects upon various psychosocial outcomes.

Recommendation

Antenatal care should be provided by a small group of carers with whom the woman feels comfortable. There should be continuity of care throughout the antenatal period. [A]

A system of clear referral paths should be established so that pregnant women who require additional care are managed and treated by the appropriate specialist teams when problems are identified. [D]

4.3 Where should antenatal appointments take place?

A meta-analysis of three RCTs examined whether a policy of home visits for antenatal care reduced the amount of antenatal care provided by nine hospital maternity units in France; 1410 women with pregnancy complications were assessed.[40] In the control group, women received the usual care provided by the maternity units with visits to the outpatient clinics as necessary. In the intervention group, the women received one or two home visits a week by a midwife in addition to the usual care. No difference in the rate of hospital admissions was found (pooled OR 0.9, 95% CI 0.7 to 1.2) but the average number of visits to the outpatient clinic was significantly lower in the two trials in which it was measured. [Evidence level 1a] Maternity care must be readily and easily accessible to all women. They should be sensitive to the needs of the local population and based primarily in the community.[9] [Evidence level 4]

RECOMMENDATION

Antenatal care should be readily and easily accessible to all women and should be sensitive to the needs of individual women and the local community. [C]

The environment in which antenatal appointments take place should enable women to discuss sensitive issues such as domestic violence, sexual abuse, psychiatric illness and illicit drug use. [Good practice point]

4.4 Documentation of care

The information in antenatal records is collected for two main purposes:

- administration
- identification of maternal risk, fetal risk, and special requirements so that further management can be planned.

Beyond the management of patient care, however, antenatal records also serve as vehicles for quality assurance, legal documentation, communication and epidemiological research for deciding future public health measures.

In an RCT of three methods of taking an antenatal history, unstructured histories taken on paper by midwives, structured paper histories (incorporating a checklist) and an interactive computerised questionnaire in an antenatal clinic in England were compared.[41] The number of clinical responses to factors arising from the antenatal histories were measured and each response was weighted for clinical importance. The structured questionnaires were reported to provide more and better information and their use improved clinical response to risk factors compared with unstructured paper histories. Computerised systems offered no further advantage over structured paper histories. [Evidence level 1b]

Women carrying their own case notes

Three RCTs have examined the effect of giving women their own maternity case notes to carry during pregnancy.[42–44] The impact on quality of care and maternal and perinatal outcomes was assessed. In all three trials, women were randomised either to carry their own antenatal case notes or to the usual system of case notes remaining in the hospital. In the latter case, women usually carried a cooperation card.

The first study (n = 246) found that both the women and health professionals involved considered that giving a woman her own maternity case notes during pregnancy was a good idea and was a positive step towards improving the quality of care.[44] [Evidence level 1b] No reasons were found during the study to deny women carrying their own notes and no insurmountable problems arose.

In the second study (n = 290) specific outcomes and hypotheses were proposed.[42] [Evidence level 1b] The two groups of women were comparable in terms of sociodemographic characteristics. Results from the questionnaires showed that:

- women carrying their own notes were nearly 50% more likely to say they felt in control of their pregnancy (rate ratio 1.45, 95% CI 1.08 to 1.95)
- more than 70% were more likely to say they found it easier to talk to the doctors and midwives during pregnancy (rate ratio 1.73, 95% CI 1.16 to 2.59).
- there were no other significant differences between the groups in terms of any of the other outcomes predicted
- there was no difference in the availability of notes for clinic appointments but approximately 1 hour of hospital clerical time was saved per week because of not having to retrieve and refile notes.

The third study (n = 150) was conducted among English-speaking women in an Australian metropolitan area, using open-ended questions.[43] [Evidence level 1b] Parous women who carried their own notes were significantly more likely to report that the doctors and midwives explained everything in their records to them than parous women with cooperation cards or nulliparous women from either group.

- 89% of women carrying their own notes responded positively. They felt more in control, felt more informed, liked having access to their results and felt it gave them an opportunity to share information particularly with other family members and partners.
- 11% of women carrying their own notes responded negatively, as they thought the record was too bulky, the system inconvenient or were worried they would forget notes.
- No differences were noted in numbers of lost records in each group.
- 89% of women in the hand-held notes group wanted to carry their notes in a future pregnancy as well as 52% of the cooperation-card group.

Women like to carry their own maternity care records. This can lead to an increased feeling of control during pregnancy. It may facilitate communication between the pregnant woman and the health professionals involved with her care.

RECOMMENDATIONS

Structured maternity records should be used for antenatal care. [A]

Maternity services should have a system in place whereby women carry their own case notes. [A]

A standardised, national maternity record with an agreed minimum data set should be developed and used. This will help carers to provide the recommended evidence-based care to pregnant women. [Good practice point]

4.5 Frequency of antenatal appointments

Antenatal care programmes as currently practised originate from models developed in 1929. As advances in medicine and technology have occurred, new components have been added to antenatal care, mostly for screening purposes. However, the significance of the frequency of antenatal care appointments and the interval between appointments has not been tested scientifically.

An observational study explored the relationship between the number of antenatal visits made by 17,765 British women and adverse perinatal outcomes.[45] [Evidence level 3] No consistent relationship between admission to the neonatal unit or perinatal mortality and number of antenatal visits was found. A significant positive relationship between number of antenatal visits and caesarean section was found and low birthweight (less than 2500 g) was positively associated with number of visits for nulliparous but not for parous women.

Two systematic reviews of RCTs have evaluated the evidence of the effectiveness of different models of care based on a reduced number of antenatal care visits compared with the standard number of antenatal care visits.[32,46] [Evidence level 1a] Both reviews included the same seven trials.

Both systematic reviews assessed the clinical effectiveness and perception of care (by women) of different antenatal care programmes. Frequency of antenatal care visits was one of the components of care assessed by the reviews. Four of the trials were conducted in developed countries and three in less developed countries, with a total of 57,418 women randomised to receive either a reduced number of antenatal care visits (with or without 'goal-oriented' components) or the standard number of antenatal care visits.

Between the two reviews, outcomes assessed were: preterm delivery (less than 37 weeks), pre-eclampsia, caesarean section, induction of labour, antenatal haemorrhage, postnatal haemorrhage, low birthweight, small-for-gestational-age at birth, postpartum anaemia, admission to neonatal intensive care unit, perinatal mortality, maternal mortality, urinary tract infection and satisfaction of care. The results did not demonstrate a difference in any of the biological outcomes. Women from the developed-country trials reported less satisfaction with the frequency of visits in the reduced number group (3 RCTs, n = 3393, Peto OR 0.61, 95% CI 0.52 to 0.72). However, the women in these trials were being told that they had fewer visits and were therefore aware that other women had more visits than they did. It should also be noted that there was clinical and statistical heterogeneity among the three trials that looked at this outcome.

The objective of both these systematic reviews was to demonstrate equivalent efficacy of the intervention. A problem with equivalence trials is that when the two interventions are similar the outcomes are also likely to be similar. A limitation common to both of these reviews, highlighted by the authors, was protocol deviations that resulted in nonsignificant reductions in the number of visits in the intervention group. The average difference in number of visits between the two arms in the trials was approximately two in both reviews. In the context of routine antenatal care in developed countries (10–14 visits), a difference of two visits would be unlikely to demonstrate a measurable impact upon pregnancy outcomes. However, when analysing the two largest trials, which took place in less developed countries, the reduction in the number of visits is proportionately much larger (from six to four visits). Within these trials, no adverse impact on maternal or perinatal outcomes was associated with reduced visits.

A moderate reduction in the traditional number of antenatal visits is not associated with an increase in adverse maternal or perinatal outcomes. However, a reduced number of appointments may be associated with a reduction in women's satisfaction with their antenatal care. It is likely that routine antenatal care for women without risk or complications can be provided with fewer appointments. It is possible that the key issue is not more or less antenatal care, but the implementation of procedures that have been shown to be effective and which may increase women's satisfaction with care. The frequency of appointments can then be planned accordingly.

In a secondary analysis of data from an RCT comparing a traditional and a reduced schedule of antenatal appointments in London, England, women who were satisfied with reduced schedules were more likely to have a caregiver who both listened and encouraged them to ask questions than women who were not satisfied with reduced schedules.[47] [Evidence level 3] A survey of women's expectations on number of antenatal care appointments in Sweden found that preference for more or fewer appointments was associated with parity, marital status, age, education, obstetric history, previous birth experience and timing of pregnancy.[48] [Evidence level 3] Older women (over 35 years), parous women, less educated women and women with more than two children preferred fewer appointments, whereas younger women (under 25 years), single women and women with a prior adverse pregnancy history indicated a preference for more appointments than the standard schedule.

Economic considerations

The cost of antenatal appointments is determined by the number of appointments overall, and the type and grade of health care provider. The cost effectiveness of the antenatal appointment schedule is determined by the primary outcomes of the antenatal care (preterm birth, low birthweight babies, maternal or infant mortality, birth complications and intensive care) and also

secondary outcomes such as maternal and professional satisfaction with the package of care provided.

The evidence to date on the optimum number of antenatal appointments is inconclusive. The majority of studies have not focused on the cost effectiveness or cost benefit of the number of antenatal appointments. The World Health Organization (WHO) Antenatal Care Trial included an assessment of quality of care and an economic evaluation. The authors concluded that the provision of routine antenatal care by the new model did not affect maternal and perinatal outcomes and therefore was more cost effective. However, the study setting of the trial was developing countries.

Most of the existing research in industrialised countries is based on low-risk women as diagnosed at first contact. One UK based study compared a traditional antenatal appointment schedule with a reduced schedule of appointments.[49] The estimated total cost to the NHS of the traditional schedule (around 13 appointments) was £544, of which around £250 occurred antenatally. The estimated total costs for the reduced appointment schedule (six or seven appointments) were around £560, of which £255 occurred antenatally. The authors found that any reduced costs of fewer appointments were offset by the greater number of babies requiring special or intensive care, so that the total costs were not different. Sensitivity analyses varied the unit costs of care and length of postnatal stay and found substantial overlap between schedules, leading to inconclusive results. No difference was detected in the primary outcome (caesarean section) between the two groups. The authors reported differences in the secondary outcome (maternal satisfaction and psychological outcomes) that were significantly poorer for women receiving fewer appointments than for women receiving traditional care.

A study comparing pregnancy outcomes between England and Wales and France[50] demonstrated that, although the number of appointments is lower in France, there were no differences detected in pregnancy outcomes. This suggests that fewer appointments would be more cost effective if only these outcomes were considered.

Clearly, fewer routine antenatal appointments for low-risk pregnant women could release antenatal care resources for women who need additional support. The issue of 'satisfaction' is complex, since the long-term effects (and costs) of lower satisfaction and poorer psychosocial outcomes is not addressed in any of the studies.

Willingness-to-pay studies are one way of exploring whether one form of care is more highly valued by users of services (what they would be willing to sacrifice to have a particular form of care). This approach can incorporate the value of different forms of care and not only the final outcome. The value of information and reassurance to pregnant women is usually not included in economic evaluation.

Only one economic study has been undertaken to estimate women's valuation of antenatal care. This study did not address the number of appointments but did address the value of different providers of antenatal care. It suggested there was no significant difference in the monetary value women placed on alternatives forms of provision.[51]

Recommendations

A schedule of antenatal appointments should be determined by the function of the appointments. For a woman who is nulliparous with an uncomplicated pregnancy, a schedule of ten appointments should be adequate. For a woman who is parous with an uncomplicated pregnancy, a schedule of seven appointments should be adequate. [B]

Early in pregnancy, all women should receive appropriate written information about the likely number, timing and content of antenatal appointments associated with different options of care and be given an opportunity to discuss this schedule with their midwife or doctor. [D]

Each antenatal appointment should be structured and have focused content. Longer appointments are needed early in pregnancy to allow comprehensive assessment and discussion. Wherever possible, appointments should incorporate routine tests and investigations to minimise inconvenience to women. [D]

Future research

Alternative methods of providing antenatal information and support, such as drop in services, should be explored.

Research that explores how to ensure women's satisfaction and low morbidity and mortality with a reduced schedule of appointments should be conducted.

4.6 Gestational age assessment

Clinical question

What is the diagnostic value and effectiveness of screening methods in determining gestational age?

Previous NICE guidance (for the updated recommendations see below)

Pregnant women should be offered an early ultrasound scan to determine gestational age (in lieu of LMP for all cases) and to detect multiple pregnancies. This will ensure consistency of gestational age assessments, improve the performance of mid-trimester serum screening for Down's syndrome and reduce the need for induction of labour after 41 weeks. [A]

Ideally, scans should be performed between 10 and 13 weeks and use crown–rump length measurement to determine gestational age. Pregnant women who present at or beyond 14 weeks of gestation should be offered an ultrasound scan to estimate gestational age using head circumference or biparietal diameter. [Good practice point]

Introduction and background

All pregnant women should be offered an early ultrasound scan to determine the gestational age of the pregnancy (in lieu of LMP). An early ultrasound examination allows accurate dating, reduces the rate of induction in post term deliveries, allows identification of multiple pregnancies so the pregnancy can be managed appropriately, and of major fetal malformations such as anencephaly. It is also necessary so that Down's syndrome screening (either 1st or 2nd trimester) can be performed at the correct time.

Accuracy of screening tests

A total of 13 studies have been included in this section:

Description of included studies

A USA based retrospective study, 1995[690] [EL II] examined the comparability of the LMP-based and the clinical examination of gestational age as collected on one state (South Carolina's) vital records. They also investigated the concordance between these measures and explored whether sociodemographic or delivery hospital characteristics influenced their agreement. A sample size of 150,898 cases that contained both CE and LMP-based values with a range of 20 to 45 weeks were selected.

A Denmark based study, 2006[691] [EL II] compared the predicted date of delivery LMP, CRL and BPD with the actual date of delivery in a population of pregnant women divided into those with certain and those with uncertain LMP. 657 spontaneous deliveries were used for analysis, n = 339 and 318 in the certain and uncertain LMP groups, respectively. Healthy women who were enrolled at the first visit during their pregnancy underwent ultrasound examinations in the first and second trimesters.

A Finland based study, 2001[692] [EL II] compared different ultrasound measurements CRL, BPD, and FL, for predicting the day of delivery at 8–16 weeks' gestation. They also compared them to prediction by certain and uncertain LMP. 17,221 non-selected singleton pregnancies at 8–16 completed weeks were scanned by ultrasound. The last menstrual period (LMP) was considered certain in 13,541 and uncertain in 3680 cases.

A USA based prospective cohort study, 2002[53] [EL II] evaluated the accuracy of algorithms for the assignment of gestational age with the use of the last menstrual period and early ultrasound

information. 4 algorithms were compared: LMP only, ultrasound scans only, use of LMP except when there was a disparity of ≥7 days in the estimated date of confinement in which case ultrasound scanning was used and the use of LMP except when there was a disparity of ≥ 14 days in the estimated date of confinement in which case ultrasound scanning was used. The women were enrolled at 24 to 29 weeks of gestation. 3147 women had both LMP and early ultrasound scan and were recruited and interviewed in the comparisons of pregnancy dating. There was an evaluation of digit preference in the last menstrual period dates and a comparison of mean gestational age, preterm and post-term categories with the use of kappa statistics, difference between actual and expected delivery date, and birth weight among subgroups with discrepant assignments.

A longitudinal study, 2006[693] [EL II] in Mexico sought to determine the best method for gestational age estimation from four communities in rural Guatemala. Gestational age at birth was determined by an early second trimester measure of BPD, LMP, the Capurro neonatal examination and symphysio-fundal height (SFH) for 171 women-infant pairs. Regression modelling was used to determine which method provided the best estimate of gestational age using ultrasound as the reference.

A USA based retrospective study, 2001[694] [EL II] investigated the concordance between gestational age data obtained by clinical estimate with data calculated from the date of the last menstrual period (LMP) as recorded on birth certificates. 476,034 computerized birth records from 20-44 weeks of gestation were analyzed.

A prospective study in Norway, 2006[695] [EL II] tested whether the HC predicts the day of confinement better than BPD. 4179 consecutive women attending the second trimester routine ultrasound examination at 17–20 weeks of gestation were included. The difference between the time of delivery and the predicted date of delivery calculated with HC and BPD (based on pregnancy duration of 282 days) was noted.

A study in Denmark, 1999[696] [EL II] compared the error in the predicted date of delivery using BPD with the error using the LMP. 14,805 spontaneous deliveries with a reliable LMP were included and their predicted dates of delivery were calculated using two assumptions: average length of pregnancy of 280 and of 282 days.

A UK based prospective study, 1993[697] [EL II] aimed to determine the most accurate predictor of the date of delivery for pregnant women in a community-based population. The two methods compared were: a calculation based on LMP or a prediction based on the measurement by ultrasound scan. 106 women were included in the analysis.

A Nigerian study, 1989[698] [EL II] assessed the accuracy of gestational age using the locally produced normogram and compared with predictors based on menstrual dates. 84 Nigerian women who had no complications of pregnancy and delivered infants whose birth weights were appropriate for 40 weeks were assessed. The ultrasonographer was blinded to the clinical details of the study population.

A population study, 1985 in USA[699] [EL II] sought to determine if a single ultrasonic measurement performed in a technician oriented routine screening program was more accurately predictive of gestational age than menstrual history. In addition they determined whether a single BPD or CRL measurement was more predictive of gestational age and how the predictive accuracy of these measurements changed throughout pregnancy. 4257 consecutive pregnancies were scanned in 4246 patients as part of a routine antenatal two-tier ultrasonic screening program. The first-tier scans were performed before 20th week of gestation, whereas the second-tier scans were performed between 26 weeks and term. The estimated date of confinement based on ultrasound measurements was compared with menstrual history in its ability to predict the actual onset of spontaneous labor.

A USA based prospective study, 1983[700] [EL II] compared the relative accuracy of estimated dates of confinement predicted by first trimester CRL versus second trimester BPD measurements in 27 women. The actual delivery date was compared with the estimated date of confinement predicted by the CRL and the BPD.

A Swedish study, 1983[701] [EL II] evaluated the fetal CRL screening program. 53 women with regular, 28-day interval menstrual cycles were extracted consecutively from the register of the ultrasound laboratory.

Findings

The results of the USA study showed that LMP-based measure produced higher percentages of pre-term and post-term births. More than 60 percent of the last menstrual period-based preterm births were classified as preterm by the clinical estimate. The sensitivity of the clinical estimate was 27 percent for post-term births. The overall concordance (the percentage of cases with the same value for both measures) was 47 percent, but it varied considerably by gestational age. Between 30 and 35 weeks, the clinical estimate exceeded the last menstrual period-based value by 2 weeks or more for more than 40 percent of the cases. Concordance also varied by race of mother, hospital delivery size, trimester prenatal care began, and birth weight.

In the Danish study the median prediction errors (predicted - actual date of delivery) estimated by ultrasonography in the first and second trimesters and by corrected LMP according to cycle length were 2.32, 0.16, and 3.00 days, respectively, in women with certain LMP, and 1.71, 0.00, and 3.00 days, respectively, in women with uncertain LMP. The median gestational age at delivery estimated by ultrasonography in the first and second trimesters and by corrected LMP according to cycle length was 282, 280, and 283 days, respectively, in both groups.

The results of the Finland study showed that at all gestational ages, ultrasound was superior to certain LMP in predicting the day of delivery to at least 1.7 days. CRL of 15–60 mm was superior to BPD, but at a later gestation BPD (at least 21 mm) was more precise. Regression models using a combination of any two or three ultrasonic variables did not improve accuracy of prediction. When ultrasound was used instead of certain LMP, the number of post-term pregnancies decreased from 10.3% to 2.7% ($P < .001$).

The results of US study showed that last menstrual period reports showed digit preference, assign gestation 2.8 days longer on average than ultrasound scanning, yield substantially more post-term births (12.1% vs 3.4%), and predict delivery among term births less accurately. Misclassification of births as post-term was more common in younger women, those of non-optimal pre-pregnancy body weight, cigarette smokers, and women who reported last menstrual period using preferred dates of the month.

In the Mexican study gestational age estimated by LMP was within +/-14 days of the ultrasound estimate for 94% of the sample. LMP-estimated gestational age explained 46% of the variance in gestational age estimated by ultrasound whereas the neonatal examination explained only 20%.

The USA study showed the overall exact concordance of 46% between the two measurements. For +1 week it was 78%, and for +2 weeks it was 87%. The incidence of prematurity with menstrual gestational age was 16%, while it was 12% with the clinical estimate. About 47% of the LMP-based preterm births were classified as term by clinical estimate. 83% of clinically estimated preterm births were also preterm by LMP-based gestation. The authors concluded that agreement between menstrual and clinical estimates of gestational age occurs most often close to term, with significant disagreement in preterm and post-term births.

The Norwegian study showed that for the group of spontaneous onset of labour (n = 3336), 5.6% were post-term (≥ 296 days) according to HC and 5.7% according to BPD. Premature births (< 37 weeks) were 3.9% with HC measurement and 3.6% with BPD method. For the entire group, the median differences between actual and predicted delivery with HC and BPD were 0.9 and 1.2 days, respectively. In the spontaneous onset of labour group the corresponding differences were 0.9 and 1.4 days. The difference between the HC and BPD methods was significant ($P < 0.0001$).

In the Denmark study the average discrepancy between predicted date of delivery from BPD and LMP and date of spontaneous delivery was 7.96 and 8.63 days, respectively ($p < 0.0001$). Adding 282 instead of 280 days to the first day of the LMP reduced the error of the LMP method from 8.63 to 8.41 days, reduced the percentage of classified post-term deliveries from 7.9 to 5.2% and

increased the preterm births from 3.96 to 4.48%. It was found that none of the models of combined use of LMP and BPD were superior to the use of BPD alone.

The results of UK study showed that at an error of ±5 days, the scan prediction is accurate in 52% of cases and last menstrual period in 37%, a difference of 15% (95% confidence interval 4% to 23%). The scan accuracy is significantly better than LMP accuracy.

The Nigerian study showed that ultrasound dating was more accurate than menstrual dating as evident from the number of women who delivered on and within 1 or 2 weeks of predicted delivery dates. 12/84 (14.3%) women delivered on the days predicted by ultrasound whereas only 3/84 (3.6%) delivered on days estimated by LMP. 69/84 (82.1%) ultrasound predictions were correct to within 1 week of predicted dates as compared to 42/84 (50%) predictions based on LMP. The difference reached statistical significance $p < 0.05$.

In the American study 84.7% patients with optimal menstrual history delivered within ±2 weeks of the predicted date. Only 69.7% delivered within ±2 weeks of the estimate date of confinement based on suspect menstrual history. CRL measurements were as predictive (84.6%) as optimal menstrual history. BPD measurements done between 12 and 18 weeks' gestation were significantly more accurate in gestational predictions (89.4%) than those based on menstrual history ($P < .001$).

The results of the American study showed a statistically insignificant ($p > 0.9$) difference of mean error between predicting the actual date of delivery by CRL (7.73 days) and BPD (7.65 days). In both methods there was a greater tendency to overestimate the actual date of delivery.

The results of the Swedish study showed that 25% of pregnant women had a difference between menstrual age and gestational age estimated on the basis of CRL, exceeding 7 days. Regular menstrual cycles and reliable menstrual history reduced this to 19%. Post-mature deliveries > 294 days were reduced from 1 in 15 to 1 in 300 by using CRL.

Effectiveness of screening test

A total of 6 studies have been included in this section.

Description of included studies

A randomised controlled trial, 2004 in USA[702] [EL 1+] sought to determine whether application of a program of routine first trimester ultrasound screening to a low-risk population would result in a decreased rate of induction of labour for post-term pregnancy.

A randomised clinical trial, 1999 in Australia[52] [EL 1+] assessed the efficacy of an ultrasound scan at the first antenatal visit. Study population comprised 648 women attending for their first antenatal visit at less than 17 weeks of gestation with no previous ultrasound scan in the pregnancy, who were expected to give birth at the hospital, and for whom there was no indication for an ultrasound at their first visit. Eligible consenting women were enrolled by telephone randomisation into either the ultrasound at first visit group, who had an ultrasound at the time of their first antenatal visit, or the control group in whom no ultrasound assessment was done at their first antenatal visit.

A randomized controlled trial, 1988 in Sweden[703] [EL 1+] evaluated the effectiveness of one-stage screening in the second trimester in pregnant women with no clear indication for elective scanning. 4997 women were randomized into a screening group where women had an ultrasound scan at about 15 weeks and a control/non-screening group where women did not have a scan before 19 weeks. All women in the screening group had gestational age and expected date of delivery estimation from BPD with charts derived from a Swedish population. For the control group, last menstrual period with specialty calibrated calendars was used.

A Norway based randomized controlled trial, 2000[704] [EL 1+] evaluated the possible benefits of the routine use of ultrasound screening in pregnancy. 825 women were allocated to an ultrasound scan between 18-32 weeks of gestation in addition to receiving routine antenatal care. 803 women received standard antenatal care, but could only be referred for ultrasound examination on clinical indication.

A hospital based cohort study in Canada, 2005[705] [EL 2++] assessed the association between maternal and fetal characteristics, discrepancy between last normal menstrual period and early (<20 weeks) ultrasound-based gestational age and the association between discrepancies and

pregnancy outcomes. The study population comprised a total of 46,514 women with both menstrual and early ultrasound-based gestational age estimates.

A systematic review, 1998 [EL 1+] assessed whether routine early pregnancy ultrasound influences the diagnosis of fetal malformations and of multiple pregnancies, the rate of clinical interventions, and the incidence of adverse fetal outcome compared with its selective use. Nine good quality trials were included.

Findings

In the American study 5/104 women in the first trimester screening group and 12/92 women in the second trimester screening group had labour induced for post term pregnancy (P= 0.04, RR 0.37, 95% CI 0.14-0.96).

In the Australian study 9% of women in the ultrasound at first visit group needed adjustment of their expected date of delivery as a result of the 18 to 20 week ultrasound, compared with 18% of women in the control group (RR 0.52, 95% CI 0.34-0.79; P = 0.002). Fewer women in the ultrasound at first visit group reported feeling worried about their pregnancy (RR 0.80, 95% CI 0.65-0.99; P = 0.04) or not feeling relaxed about their pregnancy (RR 0.73, 95% CI 0.56-0.96; P = 0.02), compared with women in the control group.

The results of the Swedish study showed that labour was less often induced among screened women both for all reasons 5.9% *vs.* 9.1%, p< 0.0001 and for suspected post-term pregnancy 1.7% *vs.* 3.7%, p< 0.0001. Among babies born to screened women, fewer had a birth weight < 2500g (59 *vs.* 95, p=0.005) and mean birth weight was 42g higher (p=0.008).

In the Norwegian study the incidence of induced labor due to apparent post-term pregnancies was 70% lower in the ultrasound-screened group. Inductions from all causes were also less frequent among ultrasound-screened women. There were six perinatal deaths among the screened and seven among the controls after excluding three lethal malformations among the controls. The proportion of infants with Apgar score less than 8 after 5 min was lower among the screened group (P = 0.04). The need for positive pressure ventilation for more than 1 min was lower among the screened group (P = 0.02).

In the Canadian study positive discrepancies between LMP and early ultrasound scan were more likely in multiparous mothers and those with diabetes, small stature or high pre-pregnancy body mass index. The proportion of women with discrepancies $\geq +7$ days was significantly higher among chromosomally malformed and female fetuses. With increasingly positive differences between LMP and ultrasound scan, the mean birthweight declined and the risk of low birthweight increased. Associations with fetal growth measures were more plausible with early ultrasound estimates.

The results of systematic review showed that routine ultrasound examination significantly reduced the rates of induction of labour for post-term pregnancy (OR 0.61, 95% CI 0.52-0.72).

Evidence Summary

Evidence suggests that ultrasound is a more accurate predictor of gestational age than LMP. If only LMP is available EDD should be calculated as the first day of the LMP plus 282

The estimated date of delivery based on LMP is subject to significant rror and will be influenced by mothers age, parity, BMI and smoking

Routine ultrasound examination significantly reduces the rates of induction of labour for post dates.

CRL measurement should be used in first trimester for the estimation of gestational age. CRL > 90 mm is unreliable in estimating gestational age in second trimester and HC measurement, which appears more reliable than BPD, should be used instead when establishing an estimated date of confinement in 2nd trimester.

Recommendations

Pregnant women should be offered an early ultrasound scan to determine gestational age and to detect multiple pregnancies. This will ensure consistency of gestational age assessment, and reduce the incidence of induction of labour for post-date pregnancies.

Ideally, the early ultrasound scan should be undertaken between 10 and 13 weeks 6 days and use crown – rump length (CRL) measurement to determine gestational age. If the CRL is greater than 84 mm, gestational age should be estimated using head circumference.

4.7 What should happen at antenatal appointments?

Recommendations

The assessment of women who may or may not need additional clinical care during pregnancy is based on identifying those in whom there are any maternal or fetal conditions associated with an excess of maternal or perinatal death or morbidity. While this approach may not identify many of the women who go on to require extra care and will also categorise many women who go on to have normal uneventful births as 'high risk',58,59 ascertainment of risk in pregnancy remains important as it may facilitate early detection to allow time to plan for appropriate management.

The needs of each pregnant woman should be assessed at the first appointment and reassessed at each appointment throughout pregnancy because new problems can arise at any time. Additional appointments should be determined by the needs of each pregnant woman, as assessed by her and her care givers, and the environment in which appointments take place should enable women to discuss sensitive issues. Reducing the number of routine appointments will enable more time per appointment for care, information giving and support for pregnant women.

The schedule below, which has been determined by the purpose of each appointment, presents the recommended number of antenatal care appointments for women who are healthy and whose pregnancies remain uncomplicated in the antenatal period; ten appointments for nulliparous women and seven for parous women.

First appointment

The first appointment needs to be earlier in pregnancy (prior to 12 weeks) than may have traditionally occurred and, because of the large volume of information needs in early pregnancy, two appointments may be required. At the first (and second) antenatal appointment:

- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by written information (on topics such as diet and lifestyle considerations, pregnancy care services available, maternity benefits and sufficient information to enable informed decision making about screening tests)
- identify women who may need additional care (see Algorithm and Section 1.2) and plan pattern of care for the pregnancy
- check blood group and RhD status
- offer screening for anaemia, red-cell alloantibodies, hepatitis B virus, HIV, rubella susceptibility and syphilis
- offer screening for asymptomatic bacteriuria (ASB)
- offering screening for Down's syndrome
- offer early ultrasound scan for gestational age assessment
- offer ultrasound screening for structural anomalies (20 weeks)
- measure BMI and blood pressure (BP) and test urine for proteinuria.

After the first (and possibly second) appointment, for women who choose to have screening, the following test should be arranged before 16 weeks of gestation (except serum screening for Down's syndrome, which may occur up to 20 weeks of gestation):

- blood tests (for checking blood group and RhD status and screening for anaemia, red-cell alloantibodies, hepatitis B virus, HIV, rubella susceptibility and syphilis)
- urine tests (to check for proteinuria and screen for ASB)
- ultrasound scan to determine gestational age using:

– crown–rump measurement if performed at 10 to 13 weeks
– biparietal diameter or head circumference at or beyond 14 weeks
• Down's syndrome screening using:
– nuchal translucency at 11 to 14 weeks
– serum screening at 14 to 20 weeks.

16 weeks

The next appointment should be scheduled at 16 weeks to:

- review, discuss and record the results of all screening tests undertaken; reassess planned pattern of care for the pregnancy and identify women who need additional care (see Algorithm and Section 1.2)
- investigate a haemoglobin level of less than 11g/dl and consider iron supplementation if indicated
- measure BP and test urine for proteinuria
- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.

18–20 weeks

At 18–20 weeks, if the woman chooses, an ultrasound scan should be performed for the detection of structural anomalies. For a woman whose placenta is found to extend across the internal cervical os at this time, another scan at 36 weeks should be offered and the results of this scan reviewed at the 36-week appointment.

25 weeks

At 25 weeks of gestation, another appointment should be scheduled for nulliparous women. At this appointment:

- measure and plot symphysis–fundal height
- measure BP and test urine for proteinuria
- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.

28 weeks

The next appointment for all pregnant women should occur at 28 weeks. At this appointment:

- offer a second screening for anaemia and atypical red-cell alloantibodies
- investigate a haemoglobin level of less than 10.5 g/dl and consider iron supplementation, if indicated
- offer anti-D to rhesus-negative women
- measure BP and test urine for proteinuria
- measure and plot symphysis–fundal height
- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.

31 weeks

Nulliparous women should have an appointment scheduled at 31 weeks to:

- measure BP and test urine for proteinuria
- measure and plot symphysis–fundal height
- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information
- review, discuss and record the results of screening tests undertaken at 28 weeks; reassess planned pattern of care for the pregnancy and identify women who need additional care (see Algorithm and Section 1.2).

34 weeks

At 34 weeks, all pregnant women should be seen in order to:

- offer a second dose of anti-D to rhesus-negative women
- measure BP and test urine for proteinuria
- measure and plot symphysis–fundal height
- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information
- review, discuss and record the results of screening tests undertaken at 28 weeks; reassess planned pattern of care for the pregnancy and identify women who need additional care (see Algorithm and Section 1.2).

36 weeks

At 36 weeks, all pregnant women should be seen again to:

- measure BP and test urine for proteinuria
- measure and plot symphysis–fundal height
- check position of baby
- for women whose babies are in the breech presentation, offer external cephalic version (ECV)
- review ultrasound scan report if placenta extended over the internal cervical os at previous scan
- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information

38 weeks

Another appointment at 38 weeks will allow for:

- measurement of BP and urine testing for proteinuria
- measurement and plotting of symphysis–fundal height
- information giving, with an opportunity to discuss issues and ask questions; verbal information supported by antenatal classes and written information.

40 weeks

For nulliparous women, an appointment at 40 weeks should be scheduled to:

- measure BP and test urine for proteinuria
- measure and plot symphysis–fundal height
- give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.

41 weeks

For women who have not given birth by 41 weeks:

- a membrane sweep should be offered
- induction of labour should be offered
- BP should be measured and urine tested for proteinuria
- symphysis–fundal height should be measured and plotted
- information should be given, with an opportunity to discuss issues and ask questions; verbal information supported by written information.

General

Throughout the entire antenatal period, healthcare providers should remain alert to signs or symptoms of conditions which affect the health of the mother and fetus, such as domestic violence, pre-eclampsia and diabetes.

For an outline of care at each appointment see the Algorithm (Section 2.4).

5 Lifestyle considerations

5.1 Physiological, psychosocial and emotional changes in pregnancy

Many common physiological, psychosocial and emotional changes occur during pregnancy. Many of these changes may be due to the normal hormonal changes that are taking place in a pregnant woman's body or due to worries associated with pregnancy, such as concerns about the birth or the baby's wellbeing. *The pregnancy book*[23] has a chapter on feelings and relationships in pregnancy as well as a chapter on feelings that the father of the child may be encountering.

Some of the common changes that pregnant women might encounter include:

- bleeding gums or gingivitis (note that dental treatment is free during pregnancy and for a year after the birth of the baby) – see Section 5.2
- heartburn (indigestion) – see Section 6.2
- constipation – see Section 6.3
- vaginal discharge (thrush) – see Section 6.6
- varicose veins – see Section 6.5
- haemorrhoids (piles) – see Section 6.4
- backache – see Section 6.7
- swelling of the ankles, fingers, face and hands due to the body holding more fluid in pregnancy – a certain amount of swelling, or oedema, is normal later in pregnancy; however, more severe cases may indicate pre-eclampsia if present with other symptoms and signs (see Section 11.2).

Chapter 9 in *The Pregnancy Book*[23] addresses other common physiological problems encountered in pregnancy such as itching, feeling hot and skin and hair changes.

Not all women will experience all of the above symptoms but it is important for pregnant women to be aware that some of these changes are normal in pregnancy and to be alert to symptoms of potentially harmful complications. It is also important for pregnant women to be reassured that most symptoms of pregnancy are not putting them or their fetus in danger and to be made to feel comfortable about asking their healthcare provider about these changes.

5.2 Maternity health benefits

Prescriptions and dental treatment are free during pregnancy and for a year after the birth.

5.3 Working during pregnancy

Pregnant women want information about maternity benefits and rights. Healthcare professionals need to be aware of current UK legislation regarding employment. As of April 2007, women who work for an employer are entitled to 26 weeks of 'Ordinary Maternity Leave' and 26 weeks 'Additional Maternity Leave' – making one year in total. Provided you meet certain notification requirements, you can take this no matter how long you've been with your employer, how many hours you work or how much you're paid.

Pregnant employees also have special employment rights; for example, the right to take time off work for antenatal care. Under current UK legislation:

- a woman in employment is not allowed to continue working beyond 33 weeks of gestation, unless the woman's GP informs her employer that she may continue to do so
- it is unlawful for an employer to require or allow a woman in their employment to return to work in the two weeks following childbirth

- employers are required to assess risks which might be posed to the health and safety of pregnant women, those who are breastfeeding or who have given birth in the past six months. If a significant risk is identified, steps to avoid the risk should be taken, such as:
  - use of preventative or protective behaviours
  - altering working conditions or hours
  - arranging alternative work.

As this information often changes with time, antenatal healthcare providers and pregnant women are encouraged to visit the Working Families website (www.workingfamilies.org.uk) for more comprehensive and up-to-date information. Fact sheets on maternity benefits for students, single parents and young mothers can also be downloaded from this website. Up-to-date information on maternity benefits can also be accessed at the Department for Work and Pensions website (http://www.dwp.gov.uk/lifeevent/famchild/fc_expecting_a_baby.asp) or the Government's interactive guidance site (www.direct.gov.uk/en/Parents/index.htm). Further information may also be obtained from the Department for Business, Enterprise and Regulatory Reform (BERR) website

Exposure to radiation and chemicals

Some workers are occupationally exposed to potentially teratogenic or toxic substances or environments. For some of these, there is evidence to support an association between exposure and adverse maternal or neonatal outcomes, e.g. exposure to x-rays for healthcare workers. For other exposures, data are inconclusive, e.g. there are inconsistent data to support an association with miscarriage in workers exposed to vapours in the dry-cleaning and painting industries.[60–62] Further information on occupational hazards can be obtained from the Health and Safety Executive website: www.hse.gov.uk/mothers/index.htm.

Physical aspects of work

One meta-analysis of 29 observational studies analysed data on 160,988 women who worked during pregnancy.[63] The outcomes it considered were preterm birth, hypertension or pre-eclampsia and small-for-gestational-age babies. Physically demanding work and prolonged standing may be associated with poor outcomes but the evidence on prolonged hours and shift working is inconclusive. Employment per se has not been associated with increased risks in pregnancy.

One further cohort study from Poland that was not included in this review was located.[64] Although heavy physical work, as reported by the woman, was shown to be significantly associated with the birth of a small-for-gestational-age baby, no significant differences were reported when heavy physical work load was evaluated by level of energy expenditure. [Evidence level 2b]

RECOMMENDATIONS

Pregnant women should be informed of their maternity rights and benefits. [C]

The majority of women can be reassured that it is safe to continue working during pregnancy. Further information about possible occupational hazards during pregnancy is available from the Health and Safety Executive. [D]

A woman's occupation during pregnancy should be ascertained to identify those at increased risk through occupational exposure. [Good practice point]

5.4 Dietary information and education

In addition to the information contained in this guideline on what women should and should not eat during pregnancy, good sources of dietary information during pregnancy include *The Pregnancy Book*[23] and the publication *Eating While You Are Pregnant* from the Food Standards Agency, which may also be accessed online at: http://www.food.gov.uk/aboutus/publications/nutritionpublications/. Further information can also be found on the following site: http://www.eatwell.gov.uk/agesandstages/pregnancy/whenyrpregnant/

In general, women should be given information about the benefits of eating a variety of foods during pregnancy including:

- plenty of fruit and vegetables
- starchy foods such as bread, pasta, rice and potatoes
- protein, such as lean meat, fish, beans and lentils
- plenty of fibre, which can be found in wholegrain breads and fruits and vegetables
- dairy foods, such as milk, yoghurt and cheese.

Pregnant women should be informed of foods that may put them or their fetus at risk including:

- soft mould ripened cheeses, such as Camembert, Brie and blue-veined cheese
- pâté (including vegetable pâté)
- liver and liver products
- uncooked or undercooked ready-prepared meals
- uncooked or cured meat, such as salami
- raw shellfish, such as oysters
- fish containing relatively high levels of methylmercury, such as shark, swordfish and marlin, which might affect the nervous system of the fetus.

The Food Standards Agency has also recently announced that pregnant women should limit their consumption of:

- tuna to no more than two medium size cans or one fresh tuna steak per week
- caffeine to 300 milligrams a day. Caffeine is present in coffee, tea and colas.

One systematic review of RCTs was located that assessed whether or not the provision of dietary information leads to improved maternal and perinatal outcomes compared with no dietary information.[65] The review was last updated in 1996, however, and although there was evidence that dietary information increased energy and protein intake, data concerning the outcome of pregnancy were available from only one trial, which was not of high quality.

5.5 Nutritional supplements

Folic acid

Neural tube defects, which comprise open spina bifida, anencephaly and encephalocele, affect 1.5/1000 pregnancies in the UK.[66] These congenital malformations, which arise from neural tube defects, are preventable through public health measures.

The effect of increased consumption of multivitamins or folic acid consumption before conception on the prevalence of neural tube defects was assessed in a systematic review of four RCTs of 6425 women.[67] In all the RCTs, folic acid was taken before conception and up to 6–12 weeks of gestation. This periconceptional folate supplementation was found to substantially reduce the prevalence of neural tube defects (relative risk 0.28, 95% CI 0.13 to 0.58). There was a reduction both where the mother had not had a previously affected fetus or infant (relative risk 0.07, 95% CI 0.00 to 1.32) and when the mother had given birth to a previously affected infant (OR 0.31, 95% CI 0.14 to 0.66). There were no significant differences found in the rates of miscarriage, ectopic pregnancy or stillbirth with folate supplementation compared with no folate supplementation. [Evidence level 1a] The effect of starting folic in early pregnancy has not been evaluated.

A concern raised in this review was the possible adverse effect of folate supplementation on causing an increase in the rate of twin pregnancies, with an associated increase in the rate of perinatal mortality. However, results from a large cohort study in China (n = 242,015 women) found no association between consumption of folic acid supplements in pregnancy (400 micrograms per day) and multiple births (rate ratio 0.91, 95% CI 0.82 to 1.0).[68] [Evidence level 2a]

It is estimated that only one-third of women take folic acid supplements before conception. As folic acid is needed at the time of embryogenesis and many women do not plan a pregnancy, folic acid-fortified foods have been advocated in the UK.[69] Folic acid-fortified foods have been found to be effective in achieving beneficial levels of red-cell folate. However, increasing intake through foods naturally containing folates has not been found to be effective.[70] While other countries, such as the USA, Canada and Chile, have put the fortification of wheat flour into practice and observed

resultant decreases in the birth prevalence of neural tube defects, in May 2002, the UK Foods Standards Agency decided against recommending mandatory folic acid fortification.[69]

Current advice from an Expert Advisory Group report issued by the Department of Health[71] is that women who do not have a prior history of neural tube defects should take folic acid prior to conception and daily during the first 12 weeks of pregnancy. The recommended amount is 400 micrograms/day for women who have not had a previous baby with a neural tube defect. This report was largely based on evidence from a large multicentre RCT.[72] Although the size of effect for a given dose of folic acid has been quantified and modelling has indicated that a reduced risk is associated with higher doses (i.e., 500 micrograms in lieu of 400 micrograms), the practical application of an increased dose of folic acid has not yet been investigated in studies or trials and therefore cannot be recommended.[73]

RECOMMENDATION

Pregnant women (and those intending to become pregnant) should be informed that dietary supplementation with folic acid, before conception and up to 12 weeks of gestation, reduces the risk of having a baby with neural tube defects (anencephaly, spina bifida). The recommended dose is 400 micrograms/day. [A]

Iron supplementation

A systematic review of 20 randomised controlled trials compared iron supplementation with either placebo or no iron in pregnant women (n = 5552) with normal haemoglobin levels (greater than 10 g/dl) at less than 28 weeks of gestation.[74] Routine iron supplementation raised or maintained the serum ferritin level above 10 micrograms/litre and resulted in a substantial reduction in women with a haemoglobin level below 10 or 10.5g/dl in late pregnancy. There was no evidence of any beneficial or harmful effects on maternal or fetal outcomes. [Evidence level 1a]

The largest trial (n = 2682) of selective versus routine iron supplementation showed an increased likelihood of caesarean section and postpartum blood transfusion among those receiving selective supplementation, but fewer perinatal deaths.[75] [Evidence level 1b]

Another systematic review looked at the effects of routine iron and folate supplements on pregnant women with normal levels of haemoglobin.[76] Eight trials involving 5449 women were included. Routine supplementation with iron and folate raised or maintained the serum iron and ferritin levels and serum and red-cell folate levels. It also resulted in a substantial reduction of women with a haemoglobin level below 10 or 10.5 g/dl in late pregnancy. However, routine supplementation with iron and folate had no detectable effects, either beneficial or harmful, on any measures of maternal or fetal outcome. [Evidence level 1a]

Oral iron has also been associated with gastric irritation and altered bowel habit (i.e. constipation or diarrhoea).[77]

See also Section 8.1 on anaemia.

RECOMMENDATION

Iron supplementation should not be offered routinely to all pregnant women. It does not benefit the mother's or fetus's health and may have unpleasant maternal side effects. [A]

Vitamin A

In areas of the world where vitamin A deficiency is prevalent, supplementation may be beneficial for pregnant women.[78] [Evidence level 1a] Vitamin A deficiency is not prevalent among pregnant women in England and Wales and therefore the results of this review were not considered relevant to this guideline.

High levels of preformed vitamin A during pregnancy are considered to be teratogenic.[79–81] From the epidemiological evidence, it is not possible to establish a clear dose–response curve or threshold above which vitamin A intake may be harmful during the first trimester (considered to be the critical period for susceptibility). A dose between 10,000 and 25,000 iu of vitamin A may pose a teratogenic risk.

The intake of vitamin A during pregnancy should be limited to the recommended daily amount, which, in Europe, is 2310 iu, equivalent to 700 micrograms. As liver and liver products contain variable and sometimes very high amounts of vitamin A (10,000–38,000 mg per typical portion size of 100g), these foodstuffs should be avoided in pregnancy.

The consumption of liver and liver products by pregnant women (and moreover the intake of greater than 700 micrograms) is associated with an increase in the risk of certain congenital malformations.[81]

RECOMMENDATION

Pregnant women should be informed that vitamin A supplementation (intake greater than 700 micrograms) might be teratogenic and therefore it should be avoided. Pregnant women should be informed that, as liver and liver products may also contain high levels of vitamin A, consumption of these products should also be avoided. [C]

Vitamin D

Clinical Question

What is the effectiveness of Vitamin D supplementation during pregnancy?

The effectiveness of interventions to promote an optimal intake of Vitamin D to improve the nutrition of preconceptional, pregnant and post-partum women and children was undertaken by National collaborating centre for women's and children's health in 2006 as part of the maternal and child nutrition review by NICE. guidance.nice.org.uk/page.aspx?o=421763 (in press)

Previous NICE guidance (for the updated recommendations see below)

There is insufficient evidence to evaluate the effectiveness of vitamin D in pregnancy. In the absence of evidence of benefit, vitamin D supplementation should not be offered routinely to all pregnant women. [A]

Evidence statement

The evidence statements drawn from this review (unpublished) are as follows:

1. Evidence from ten studies (eight 1+ RCTs and two 2+ studies) show that antenatal vitamin D supplementation is effective in improving the vitamin D status of Asian and Caucasian women.

2. Evidence from two RCTs indicates that infants of mothers who received an antenatal vitamin D supplement achieved a higher body weight during the first year after birth than infants of mothers who received no antenatal vitamin D supplement.

3. A 2+ study found that breast-fed infants of supplemented (400 IU/day [10 ug/day]) and non-supplemented mothers had lower serum 25 hydroxy vitamin D concentrations than formula-fed infants six days after delivery.

4. There is 1+ evidence to suggest that supplemented breastfed infants (1000 IU/day [25 ug/day] during the 1st trimester) achieved a higher serum 25 hydroxy vitamin D levels than un-supplemented breastfed infants, at birth and at four days of age.

5. Evidence from a 1+ study indicates that the weights of supplemented (400 IU/day [10 ug/day]), un-supplemented breast-fed infants and formula-fed infants did not differ at six months.

6. Evidence from two 1+ RCTs indicates that the effect of vitamin D supplements on infant bone mineral content is uncertain. The results from two studies were found to be conflicting.

7. There is 1- and 2- evidence to suggest that health education programmes on the prevention of vitamin D deficiency had the potential to improve the knowledge base about vitamin D, increase the uptake of vitamin D supplements and reduce the number of hospital admissions with rickets and osteomalacia.

GDG interpretation of evidence

There is good evidence that vitamin D supplementation during pregnancy in low income groups improves vitamin D status and improves growth in the first year of life.

It can be extrapolated from this that incidence of rickets will decrease as a result of this.

The GDG identifies the following groups as vulnerable:

- Women in low income households
- Asian and Black women
- low intake of dietary source of vitamin D such as full fat dairy products, eggs, animal products.
- Women 19-24 years of age [706]

Recommendations

Normal healthy women should not be routinely offered vitamin D supplementation during pregnancy.

Oral vitamin D supplement of 10 micrograms per day should be offered to healthy pregnant women at risk of vitamin D deficiency, for example women with dark skin, women who usually cover their skin, women who eat a vegan diet and women in age group 19-24 years.

Research recommendation

There is need for future research into the effectiveness of routine Vitamin D supplementation for pregnant and breastfeeding women.

5.6 Food-acquired infections

Listeriosis

Listeriosis is an illness caused by a bacterium called *Listeria monocytogenes*, which may present with mild, flu-like symptoms. It is also associated with miscarriage, stillbirth and severe illness in the newborn baby. There is a higher incidence of listeriosis in the pregnant population (12/100,000) than in the general population 0.7/100,00).[83] Contaminated food is the usual source of infection.[83] Usual sources include unpasteurised milk, ripened soft cheeses and pâté. *L. monocytogenes* are also found in soil and in the faeces of domestic and wild animals.

RECOMMENDATION

Pregnant women should be offered information on how to reduce the risk of listeriosis by:

- drinking only pasteurised or UHT milk
- not eating ripened soft cheese such as Camembert, Brie and blue-veined cheese (there is no risk with hard cheeses, such as Cheddar, or cottage cheese and processed cheese)
- not eating pate (of any sort, including vegetable)
- not eating uncooked or undercooked ready-prepared meals. [D]

Salmonella

Salmonella is a bacterium which causes food poisoning. It is usually found in poultry, eggs, unprocessed milk and in raw or undercooked meat and water. It may also be carried by pets like turtles and birds. The incidence of *Salmonella* infection in England and Wales is at its lowest level since 1985.[84] While *Salmonella* has not been shown to affect an unborn baby, it can cause severe diarrhoea and vomiting. Current guidelines recommend that pregnant women should avoid eating raw eggs or food that contains eggs that are raw or partially cooked. Eggs should be cooked until solid. As chicken and raw meat can also be source of *Salmonella*, all meat should be thoroughly cooked and hands washed carefully after preparing chicken or other meat.[85]

RECOMMENDATION

Pregnant women should be offered information on how to reduce the risk of *Salmonella* infection by:

- avoiding raw or partially cooked eggs or food that may contain them (such as mayonnaise)
- avoiding raw or partially cooked meat, especially poultry. [D]

Toxoplasmosis

See Section 10.11.

5.7 Prescribed medicines

Prescribing during pregnancy involves the balance between benefit to the mother and potential harm to the fetus. There are only a small number of drugs that have well proven safety in pregnancy and a number of drugs that were initially thought to be safe in pregnancy and later withdrawn. General principles include prescribing only well-known and tested drugs at the smallest possible doses and only when the benefit to the mother outweighs the risk to the fetus.[77]

In addition, physiological changes of pregnancy need to be considered when prescribing drugs. Drug absorption is affected due to decreased gastric emptying and delayed gut motility. Drug distribution is affected by decreased albumin and increased plasma volume of pregnancy. Drug metabolism is also affected; in particular, lipid-soluble drugs and the excretion of drugs are altered by the increased renal clearance that occurs in pregnancy. The other physiological consideration is that all the drugs that cross the placenta will also be metabolised and excreted by the fetus.[86]

RECOMMENDATION

Few medicines have been established as safe to use in pregnancy. Prescription medicines should be used as little as possible during pregnancy and should be limited to circumstances where the benefit outweighs the risk. [D]

5.8 Over-the-counter medicines

As few conventional medicines have been established as safe to take during pregnancy, a general principle of use of drugs in pregnancy is that as few should be used as possible. However, pregnancy does result in a number of symptoms and over-the-counter (OTC) medication may be used for the relief of these symptoms. In particular, the treatment of common symptoms in pregnancy, nausea and vomiting, heartburn, constipation and haemorrhoids are covered in Chapter 6.

RECOMMENDATION

Pregnant women should be informed that few over-the-counter (OTC) medicines have been established as being safe to take in pregnancy. OTC medicines should be used as little as possible during pregnancy. [D]

5.9 Complementary therapies

There is an assumption that complementary and alternative therapies are natural and therefore safe. Just as with prescription and OTC medicines, however, complementary and alternative therapies cannot be assumed to be without risk. In fact, the safety and efficacy of most complementary therapies during pregnancy has not been established.[87,88] Nevertheless, their use among pregnant women in developed countries is common and also reported to be increasing.[89–92] Although it is important for women to inform their healthcare providers about the use of complementary medicines during pregnancy, one study reported that up to one-quarter of women failed to do so.[93]

Herbal medicines

The Medicines Control Agency has responded to concerns around the safety of herbal medicines and has compiled recommendations as to their use for pregnant women. Many herbal medicines are not licensed medicines and therefore fall outside of statutory provisions for safety, quality and

efficacy criteria.[94] [Evidence level 4] This raises the additional concern of under-reporting of adverse events.

Evidence as to the safety and efficacy of most herbal products is based on case reports, case series and retrospective surveys.[95] [Evidence level 4] There are few trials assessing clinical safety, notable exceptions being evening primrose oil[96] [Evidence level 2b], ginger (see Chapter 6, Section 6.1 on nausea and vomiting) and raspberry leaf.[97] [Evidence level Ib] While neither ginger nor raspberry leaf was associated with adverse outcomes for the mother or baby, raspberry leaf was not found to confer any benefit and the results of the primrose oil trial suggested associations with negative outcomes, such as an increase in the incidence of prolonged rupture of the membranes.

A recently completed study on the use of *Echinacea* during pregnancy reported no association with increased risk for major malformations.[98] [Evidence level 2a] A study on the reproductive safety of St John's wort (*Hypericum perforatum*) is currently underway in Canada.[99]

Acupuncture

Acupuncture is a Chinese system of treatment and diagnosis. It is based on stimulation of certain points on the surface of the body that is thought to affect the function of specific organs. During the antenatal period, acupressure has been used for nausea and vomiting (see Chapter 6, Section 6.1) and moxibustion for breech presentation of the fetus (see Chapter 13.2).

Massage therapy

Massage therapy has been found to be effective in the relief of backache during pregnancy (see Chapter 6, Section 6.7).

Hypnosis and aromatherapy

Although studies on hypnosis and aromatherapy during childbirth were located, no studies on their effectiveness or safety for use during pregnancy were found.

RECOMMENDATION

Pregnant women should be informed that few complementary therapies have been established as being safe and effective during pregnancy. Women should not assume that such therapies are safe and they should be used as little as possible during pregnancy. [D]

5.10 Exercise in pregnancy

Exercise includes a range of physical activities and not all sports have the same impact on pregnancy. The physiological and morphological changes that occur during pregnancy may interfere with a woman's ability to engage in some forms of physical activity safely. In the absence of any obstetric or medical complications, however, most women can begin or maintain a regular exercise regimen during pregnancy without causing harm to their fetus.

In an RCT that compared babies born to women who continued regular exercise during pregnancy with women who did not exercise regularly during pregnancy, no differences in neurodevelopmental outcomes at one year of age were reported.[100] [Evidence level 1b]

One systematic review assessed the effects of advising healthy pregnant women to engage in regular (at least two to three times per week) aerobic exercise on physical fitness, ease or difficulty of childbirth and delivery, and on the course and outcome of pregnancy.[101]. Ten trials randomising 688 women were included, all of which had methodological shortcomings. Five of the ten trials reported significant improvement in physical fitness in the exercise group; however, the measures used to assess fitness varied across the trials and were therefore not subject to meta-analysis. A conflicting result with no mean difference in gestational age (three RCTs, n = 416; WMD 0.02, 95% CI –0.4 to 0.4) and an increased risk of preterm birth in the exercise group was found (three RCTs, n = 421; RR 2.29, 95% CI 1.02 to 5.13). No other adverse outcomes were reported and one trial (n = 15) found improvement among exercising women in several aspects of self-reported body image, including muscle strength, energy level and body build.[101] [Evidence level 1a]

Pregnant women should avoid exercise that involves the risk of abdominal trauma, falls or excessive joint stress, as in high impact sports, contact sports and vigorous racquet sports. They are also recommended not to scuba dive, because the risk of birth defects seems to be greater among those who do, and there is a serious risk of fetal decompression disease.[102] [Evidence level 3]

Maternal exercise during pregnancy does not appear to have a negative effect on the fetus or on birth outcomes.

RECOMMENDATION

Pregnant women should be informed that beginning or continuing a moderate course of exercise during pregnancy is not associated with adverse outcomes. [A]

Pregnant women should be informed of the potential dangers of certain activities during pregnancy, for example, contact sports, high-impact sports and vigorous racquet sports that may involve the risk of abdominal trauma, falls or excessive joint stress, and scuba diving, which may result in fetal birth defects and fetal decompression disease. [D]

5.11 Sexual intercourse in pregnancy

Two American cohort studies of over 52,000 pregnant women reported an inverse association between the frequency of sexual intercourse at various times during pregnancy and the risk of preterm delivery.[103,104] [Evidence level 2a] No association between frequency of sexual intercourse and perinatal mortality was observed.[104] A study among women identified with bacterial vaginosis (BV) or *Trichomonas vaginalis* in the USA reported a similar decreased risk for preterm birth among women who reported more frequent intercourse than women who reported less frequent intercourse, but this finding applied only to women with BV and not to those with *T. vaginalis*.[105]

RECOMMENDATION

Pregnant woman should be informed that sexual intercourse in pregnancy is not known to be associated with any adverse outcomes. [B]

5.12 Alcohol and smoking in pregnancy

Alcohol consumption in pregnancy

Clinical question

What is the minimum level of alcohol intake associated with fetal alcohol syndrome and other baby outcomes?

Previous NICE guidance (for the updated recommendations see below)

A recent clinical guidance on antenatal care published in UK by NICE, 2003 stated that women should limit their alcohol consumption to no more than one standard unit per day, noting that alcohol has an adverse effect on the fetus.

Introduction and background

Alcohol passes freely across the placenta to the unborn baby and, while there is general agreement that women should not drink excessively during pregnancy, it remains unclear what level of drinking is harmful to a pregnant woman and her baby. Investigating the effects of maternal drinking during pregnancy on a child's development is difficult, due to confounding factors such as socio-economic status, smoking as well as accurately measuring alcohol consumption levels and patterns both before and after birth.

Different studies have raised concerns about a variety of pregnancy outcomes which may be affected by alcohol intake during pregnancy, including growth before and after birth, spontaneous miscarriage, stillbirth and preterm birth. A pregnancy outcome which has been linked to heavy

alcohol intake during pregnancy is fetal alcohol syndrome, which is characterized by reduced birthweight and length, including small head size, congenital and intellectual abnormalities and facial features. However, not all babies of women who drink heavily during pregnancy have fetal alcohol syndrome and diagnosing fetal alcohol syndrome can be difficult as it requires a reliable measure of maternal alcohol intake throughout pregnancy, as well as the exclusion of other congenital syndromes with similar features.

The Department of Health now recommends that pregnant women should not drink any alcohol during pregnancy (http://www.dh.gov.uk/en/News/DH_074968) but the evidence behind this statement is unclear. However binge-drinking, is more problematic. The Midwives' Information and Resource Service (2003) advises that light, infrequent drinking constitutes no risk to their baby. Although some women avoid alcohol during pregnancy, 25-50% of European women continue to drink alcohol and some drink at harmful levels for the baby (http://ec.europa.eu/health-eu/news_alcoholineurope_en.htm).

Description of included studies

A systematic review, 2005, National Perinatal Epidemiology Unit[707] [EL 2++] evaluated the fetal effects of low-to-moderate prenatal alcohol exposure and binge drinking. The review sought to determine whether an intake of up to six drinks a week was associated with more risk than total abstention and whether binge drinking by low-to-moderate drinkers is associated with harm. They also aimed to evaluate a 'safe level'. Two definitions were used in the review:

Low-to-moderate prenatal alcohol exposure - This was defined as less than one drink per day (equivalent to maximum 1.5 UK units or 12 grams of alcohol daily). This was compared to no alcohol consumption or very small amounts.

Binge drinking - Authors' definitions were used. These definitions varied between studies but a 'binge' was mainly defined as 5 or more drinks on any one occasion.

This review evaluated studies concerning two measures of consumption: (1) average alcohol intake of less than 7 drinks per week (or less than one drink per day) and (2) binge drinking. This review looked at a total of 10 outcomes with low-to-moderate consumption of alcohol. A total of 11 separate studies examined the effect of binge drinking on the 10 outcomes above.

One case control study in Spain[708], 2006 [EL 2+] analyzed the influence of alcohol drinking during pregnancy on low birth weight. The cases (n=552) were mothers delivering a single newborn weighing < 2500g and controls (n=1451) were selected randomly from all delivering women. Personal interviews, clinical charts, and prenatal care records were used for obtaining information.

A case control study in Italy[709], 2006 [EL 2+] analyzed the effect of alcohol intake on the risk of SGA birth, preterm or at term, and the potential interaction between alcohol consumption and risk factors for SGA birth. A total of 555 cases, women (mean age 31 years, range 16-43) who delivered SGA babies and 1966 controls, women (mean age 31 years, range 14-43) who gave birth at term (> or =37 weeks of gestation) to healthy infants of normal weight at the hospitals where cases had been identified were included in the study.

Findings

The outcomes from the systematic review were;

Spontaneous abortion: A total of 8 studies looked at the effects of low-to-moderate alcohol consumption on spontaneous abortion. 5 of these reported a significant effect: 2 had significant limitations, one had significant results among heavy smokers and the remaining 2 were of borderline statistical significance. The highest reported risk was a relative risk of 3.79 (95% CI 1.18 to 12.17) associated with consuming up to 10 units (equivalent to 6.7 drinks).

Stillbirth: 5 studies examined stillbirth as the outcome and only one study reported significantly increased rates of stillbirth in babies of women who drank up to 25-60g per week in pregnancy. Three studies reported higher rates of stillbirth in women who abstained but these were not statistically significant differences and were unadjusted for potential confounders.

APH: One study included antepartum haemorrhage (APH) as an outcome and found no increase in risk of APH with low-to-moderate level of alcohol consumption.

IUGR: 7 studies examined intrauterine growth restriction as an outcome and only one study found a significant association but it was unadjusted for potential confounders. Three studies found low-to-moderate alcohol consumption to be mildly protective but, although of borderline statistical significance, two may have been subject to recall bias.

Birthweight: 20 studies included birth weight as an outcome but only one reported a significant increase in the risk of low birth weight with consumption of <0.1 oz alcohol per day (adjusted RR 3.20, 95% CI 1.87 to 5.46). However, at 0.1 - 0.25 oz per day, the RR was lower at 1.36 (95% CI 0.48 to 3.88). This result was inconsistent as higher levels were not associated with increased risk. It appeared that small amounts of alcohol exerted a mildly protective effect.

Preterm birth: One out of a total of 16 studies that examined preterm birth as an outcome reported a significantly increased risk of preterm birth (RR of 2.11 and 2.15 in women consuming <0.1 oz and 0.1-0.25 oz respectively of absolute alcohol per day at 7 months gestation). This study suffered from residual confounding as it was unadjusted for socioeconomic status.

Malformation: None of the 6 studies that examined malformations as the outcome reported a significant association with low-to-moderate alcohol consumption although a trend in that direction was apparent in some studies.

HC and birth length: A total of 5 studies looked at head circumference and birth length as the outcome and only one found a higher proportion of low birth weight babies among those whose mothers drank low-to-moderate amounts in pregnancy. However, this study suffered from lack of adjustment for potential confounders. None of the other studies reported any differences at these levels of consumption.

Postnatal growth: 2 studies that examined the association between alcohol exposure and postnatal growth differed in their results. One of these studies, which followed children up to age 14, found that children of women who drank small amounts in pregnancy were consistently lighter. However, the other study found that children of abstainers tended to be lighter. Neither of the results was significant.

Neurodevelopmental outcome: 7 studies looked at neurodevelopmental outcomes; one was conducted at birth as compared to others that were later in childhood. 1 study found a statistically insignificant poorer result in children of low-to-moderate drinkers and this analysis was unadjusted for potential confounders.

Out of these 4 studies looked at neurodevelopmental outcomes and showed consistently poorer results in children exposed to binge drinking in pregnancy. The effects although quite small, included an increase in 'disinhibited behaviour', a reduction in verbal IQ and increase in delinquent behaviour, and more learning problems and poorer performance. The studies suffered from a possible overlap between binge drinkers who otherwise drink little and binge drinkers who generally drink substantial amounts. These studies represent the most consistent evidence suggesting that binge drinking in pregnancy may be associated with poor neurodevelopmental outcomes.

The results of the Spanish showed that alcohol consumption of less than 6 g/day decreased the risk for low birth weight (adjusted OR = 0.64; 95% CI, 0.46-0.88). A similar result was obtained for moderate drinkers (<12 g/day) on weekends only. The opposite relationship was observed between alcohol consumption on weekdays of 12 g/day or greater (adjusted OR = 2.67; 95% CI, 1.39-5.12), not observed in those drinking on weekends only.

The results of the Italian showed that there was no increase in the risk of SGA birth observed in women drinking one or two drinks/day in pregnancy. The Odds ratios of 3 or more drink per day were 3.2 (1.7-6.2) for ≥ 3 drinks during the first trimester, 2.7 (1.4-5.3) during the second and 2.9 (1.5-5.7) during the third.

Evidence summary

No threshold level of alcohol consumption during pregnancy, above which alcohol is harmful to the baby and below which it is safe, was identified clearly across all studies. A systematic review of low-to-moderate alcohol during pregnancy (less than one drink or 1.5 units per day) concluded that

'there was no consistent evidence of adverse effects from low-to-moderate prenatal alcohol consumption but the evidence is probably not strong enough to rule out any risk.'

Low-to-moderate alcohol intake:

There was possibly a slight increase in miscarriage

Studies of growth outcomes, including intrauterine growth, birthweight, head circumference and birth length, and postnatal growth are inconsistent and several report a protective effect of low-to-moderate alcohol intake compared with no alcohol during pregnancy.

Of seven studies, only one found neurodevelopmental outcomes to be poorer in babies of mothers with low-to-moderate alcohol intake and this was limited by confounding.

Most studies of preterm birth, stillbirth and spontaneous abortion found no association with low-to-moderate alcohol intake; those studies which reported increased risk had significant limitations.

No studies found any association between low-to-moderate alcohol intake and congenital malformation but the numbers needed to exclude this possibility would need to be very large.

Binge-drinking:

Binge-drinking was not associated with an increased risk of stillbirth, spontaneous abortion, preterm birth, congenital malformation, antepartum haemorrhage or prenatal and postnatal growth.

Four studies of neurodevelopmental outcomes reported poorer behavioural and intellectual results in children of mothers with low-to-moderate alcohol intake during pregnancy. However, measurement of the pattern and level of binge-drinking before and after birth was very variable and conclusions about safe or harmful threshold levels could not be made.

GDC interpretation of evidence

There is no evidence of a threshold level of alcohol consumption during pregnancy, above which alcohol is harmful to the baby.

In the absence of clear evidence of a threshold it would appear that drinking no more than 1.5 units/day is not associated with harm to the baby but there remains a possibility that there is an increased miscarriage rate in association with alcohol consumption although the evidence is limited and of poor quality.

There is limited poor quality evidence that binge drinking as defined by drinking 5 or more units in a single episode may be associated with neurodevelopmental harm to the baby.

Recommendations

Pregnant women should limit their alcohol intake to less than one standard drink (1.5 UK units or 12g of alcohol) per day and if possible avoid alcohol in the first 3 months of pregnancy.

Women should be informed that binge drinking (defined as more than 5 standard drinks on a single occasion) may be particularly harmful during pregnancy.

Research recommendation

More research is required into the level and frequency of binge-drinking that constitutes a risk.

Smoking in pregnancy

Although it is estimated that up to 25% of women who smoke stop before their first antenatal appointment,[112] 27% of pregnant women in the UK report that they are current smokers at the time of the birth of the baby.[113]

Smoking is a significant modifiable cause of adverse pregnancy outcome in women and its dangers have been widely established. Meta-analyses have shown significant associations between maternal cigarette smoking in pregnancy and increased risks of perinatal mortality,[114] sudden infant death syndrome,[114] placental abruption,[115,116] preterm premature rupture of membranes,[116] ectopic pregnancies,[116] placenta praevia,[116] preterm delivery,[117] miscarriage,[114] low birthweight[114] and the development of cleft lip and cleft palate in children.[118] [all studies: Evidence levels 2 and 3]

Smoking during pregnancy has also been reported to reduce the incidence of pre-eclampsia;[116,119] however, this association should be considered in context with the many negative risks associated with smoking during pregnancy. [Evidence levels 2 and 3]

Cohort studies have shown significant associations between maternal cigarette smoking in pregnancy and increased risks of small-for-gestational-age infant,[120] stillbirth[121] and fetal and infant mortality.[122] [Evidence level 2]

In addition, the link between maternal cigarette smoking and reduced birthweight has been established in over 100 publications based on studies of more than 500,000 births published between 1957 and 1986, with babies born to smokers being a consistent 175–200 g smaller than those born to similar non-smokers.[123] It has been estimated that if all pregnant women stopped smoking, a 10% reduction in infant and fetal deaths would be seen.[122] As smoking is a potentially preventable activity, it is an important public health issue in pregnancy.

Long-term effects on children born to mothers who smoked during pregnancy have been studied but report conflicting results.[124–126] [Evidence level 3] It is possible that effects of smoking in pregnancy resolve later in childhood.

One review of systematic reviews of RCTs found two systematic reviews and three additional RCTs that assessed the effects of smoking cessation programmes implemented during pregnancy.[127]

The first review (44 trials, n = 16,916 women) found a significant reduction in smoking in late pregnancy among women who attended smoking cessation programmes compared with no programme (Peto OR 0.53, 95% CI 0.47 to 0.60)[112] [Evidence level 1a] The trials in this review showed substantial clinical heterogeneity; however, the effect was still present when analysis was restricted to trials in which abstinence from smoking was confirmed by means other than self-report (Peto OR 0.53, 95% CI 0.44 to 0.63). A subset of ten trials that included information on fetal outcome showed a reduction in low birthweight (Peto OR 0.8, 95% CI 0.67 to 0.95), a reduction in preterm birth (Peto OR 0.83, 95% CI 0.69 to 0.99) and an increase in mean birthweight of 28 g (95% CI 9 g to 49 g) among women who attended anti-smoking programmes. However, no differences in very low birthweight or perinatal mortality were observed.

The second review (10 RCTs, n = 4815 pregnant women) included a trial of physician advice, a trial of advice from a health educator, a trial of group sessions, and seven trials on behavioural therapy based on self-help manuals.[128] Cessation rates ranged from 1.9% to 16.7% among those who did not receive an intervention and from 7.1% to 36.1% among those who participated in an intervention. The review found that cessation programmes significantly increased the rate of quitting (absolute risk increase with intervention versus no intervention 7.6%, 95% CI 4.3 to 10.8). [Evidence level 1a]

Three additional RCTs compared nicotine patches with placebo, a brief (10–15 minutes) smoking intervention delivered by a midwife compared with usual care (n = 1120 pregnant women), and motivational interviewing with usual care (n = 269 women in their 28th week of pregnancy). Nicotine patches were not significantly associated with a difference in quit rates.[129] [Evidence level 1b] Furthermore, the safety of nicotine replacement therapy in pregnancy has not been established. The intervention delivered by midwives was based on a 10–15 minute session in which verbal counselling was backed up with written information and arrangements for continuing self-help support were made, if necessary. This intervention found no difference in smoking behaviour when compared with the women who received usual care.[130] [Evidence level 1b] The motivational interviewing trial was based on intensified, late pregnancy counselling of 3 to 5 minutes plus the distribution of self-help booklets mailed weekly, and follow-up letters and telephone calls. This trial also reported no difference in cessation rates when compared with women in their 34th week of pregnancy or at 6 months postpartum.[131] [Evidence level 1b]

An RCT was conducted in three NHS trusts in England.[132] The intervention consisted of giving self-help booklets on quitting smoking to pregnant women at the first opportunity, together with a booklet for partners, family members and friends. Four more booklets were sent to the woman at weekly intervals. The intervention was reported to be ineffective at increasing smoking cessation. [Evidence level 1b]

Pregnant women who are unable to quit during pregnancy often reduce the number of cigarettes that they smoke. Data indicate this can significantly reduce nicotine concentrations and can offer some measure of protection for the fetus, with a 50% reduction being associated with a 92 g increase in birthweight.[133,134]

The NHS pregnancy smoking telephone help line is available at 0800 169 9 169.

RECOMMENDATIONS

Pregnant women should be informed about the specific risks of smoking during pregnancy (such as the risk of having a baby with low birthweight and preterm). The benefits of quitting at any stage should be emphasised. [A]

Women who smoke or who have recently stopped should be offered smoking cessation interventions. Interventions that appear to be effective in reducing smoking include advice by physician, group sessions and behavioural therapy (based on self-help manuals). [A]

Women who are unable to quit smoking during pregnancy should be encouraged to reduce smoking. [B]

5.13 Cannabis use in pregnancy

There is limited evidence on the impact of maternal cannabis consumption during pregnancy. Cannabis is often smoked as a mix with tobacco. One of the problems with research into cannabis consumption during pregnancy is accurately measuring the amount of cannabis consumed. Research can also be confounded by factors such as socio-economic status, alcohol use, smoking and the use of other drugs.

An estimated 5% of mothers reported smoking cannabis before and during pregnancy in England.[135] [Evidence level 3]

A meta-analysis of ten observational studies that were adjusted for cigarette smoking presented data on 32,483 live births.[136] Studies were examined where possible according to an arbitrarily defined dose response. Infrequent use was defined as no greater than once a week, and frequent use was defined as at least four times a week. Where possible, results were presented by gestational age at time of consumption. In the five studies that reported mean birthweight:

- any cannabis use during the first trimester of pregnancy reduced the mean birthweight by 48 g (95% CI –83 g to –14 g)
- any cannabis use during the second trimester of pregnancy reduced the mean birthweight by 39 g (95% CI –75 g to –3 g)
- any cannabis use during the third trimester of pregnancy reduced the mean birthweight by 35 g (95% CI –71g to 1 g)
- infrequent use of cannabis resulted in an increase in mean birthweight of 62 g (95% CI 8 g to 132 g)
- frequent use of cannabis resulted in a reduction in mean birthweight of 131 g (95% CI –209 g to –52 g).

In the five studies that reported the odds ratio for low birthweight (less than 2500 g), the pooled OR was 1.09 (95% CI 0.94 to 1.27) for any cannabis use during pregnancy.

A study of over 12,000 women in England found no association between any level of cannabis use (weekly, less than weekly, or no cannabis and before, during or after the first trimester) and perinatal death, preterm delivery and admission to the neonatal unit.[135] [Evidence level 3] After adjustment for confounding (youth, caffeine, alcohol and illicit drug use), no statistically significant association between cannabis use and birthweight was found.

There is insufficient evidence to conclude that maternal cannabis use at the levels reported causes low birthweight. However, a study on behavioural outcomes of children at three years of age found increased fearfulness and poorer motor skills among those who were born to mothers who used cannabis during pregnancy.[126] [Evidence level 3] Taking the precautionary principle based on the

positive associations between cannabis use and cigarette smoking, it is recommended that women should be discouraged from using cannabis in pregnancy.

Note

As women who use heroin, cocaine (including crack cocaine), ecstasy, ketamine, amphetamines or other drugs during pregnancy are likely to require additional care due to more adverse effects, these topics were deemed to be outside the remit of this guideline which is intended for healthy women with uncomplicated singleton pregnancies.

RECOMMENDATION

The direct effects of cannabis on the fetus are uncertain but may be harmful. Cannabis use is associated with smoking, which is known to be harmful; therefore women should be discouraged from using cannabis during pregnancy. [C]

5.14 Air travel during pregnancy

No direct estimates of the risk of travel-related venous thromboembolism in pregnancy were located. The overall incidence of symptomatic venous thrombosis after a long-haul flight has been estimated to be around 1/400 to 1/10,000. Asymptomatic venous thrombosis is estimated to be about ten times this figure.[137] [Evidence level 4] Venous thromboembolism is reported to complicate 0.13/1000 to 1/1000 pregnancies,[137–140] [Evidence level 3] and it has been suggested that this risk is increased in pregnant women during air travel.[137] [Evidence level 4]

The risk of venous thromboembolism is attributed predominantly to immobility during air travel. In a trial of 231 passengers randomised to wearing below-knee elastic stockings on both legs compared with passengers who did not wear such stockings, a decreased risk of deep vein thrombosis was observed in the intervention group (OR 0.07, 95% CI 0 to 0.46).[141] [Evidence level 1b] No evidence on the effectiveness of compression stockings specifically in pregnant women was located. Other precautionary measures for all travellers that pregnant women should be informed about include isometric calf exercises, walking around the aircraft cabin when possible and avoiding dehydration by drinking plenty of water and by minimising alcohol and caffeine intake.[137] [Evidence level 4]

Commercial flights are normally safe for a pregnant woman and her fetus. However, most airlines restrict the acceptance of pregnant women. In general, uncomplicated singleton pregnancies may fly long distances until the 36th week of gestation and a letter from a doctor or midwife confirming good health, normal pregnancy and the expected date of delivery should be carried after the 28th week of pregnancy.[142] Medical clearance is required by some airlines for pregnant women if delivery is expected less than 4 weeks after the departure date or if any complications in delivery may be expected. As different airlines may have different restrictions, specific airlines should be contacted directly for more information.

RECOMMENDATION

Pregnant women should be informed that long-haul air travel is associated with an increased risk of venous thrombosis, although whether or not there is additional risk during pregnancy is unclear. In the general population, wearing correctly fitted compression stockings is effective at reducing the risk. [B]

Future research

Further research to quantify the risk of air travel and to assess the effectiveness of interventions to prevent venous thromboembolism in pregnancy is needed.

5.15 Car travel during pregnancy

From 1997 to 1999, seven pregnant women were killed in road traffic accidents.[143] [Evidence level 3] Irrespective of where one is sitting in the car, it has been a legal requirement in the UK to wear a seatbelt since 1991 and this law applies to pregnant women.

A 1998 survey on pregnant women's knowledge and use of seatbelts showed that, while 98% of pregnant front-seat passengers wore a seatbelt, only 68% wore one in the back of the car.[144] The survey also found that only 48% of women correctly identified the correct way to use a seatbelt, with only 37% reporting that they had received information on the correct use of seatbelts while pregnant. The women who had received information while pregnant were more likely to correctly position their seatbelts than women who had received no information (OR 0.35, 95% CI 0.17 to 0.70). [Evidence level 3]

An American study investigating the education of pregnant women on the correct use of seatbelts found that, even with minimal information on wearing a seatbelt, seatbelt use increased from 19.4% to 28.6%.[145] [Evidence level 2a]

The correct use of seatbelts is particularly important in pregnant women, as incorrect use may cause harm to the fetus and fail to protect the woman in the case of an accident. A retrospective study of 43 pregnant women involved in road traffic accidents showed an increase in adverse fetal outcome, including fetal loss, with improper maternal restraint use compared with women who used seatbelts properly: in minor crashes 33% (2/6) versus 11% (2/18); moderate crashes 100% (1/1) versus 30% (3/10); severe crashes 100% (5/5) versus 100% (3/3).[146] [Evidence level 3]

In an older study comparing lap-belt restraint with no seatbelt use among 208 pregnant women who were involved in severe rural car accidents, maternal mortality was 3.6% among those wearing a lap belt compared with 7.8% among those not wearing a seatbelt.[147] Total maternal injuries, including death, was 10.7% among women wearing a lap belt compared with 21.1% among those not wearing a seatbelt. Fetal mortality was 16.7% among women wearing a lap belt compared with 14.4% among women not wearing a seatbelt. [Evidence level 3]

No human studies on the comparison of lap belts compared with three-point seatbelts in pregnant women were located; however, a study in pregnant baboons investigating the use of three-point restraints versus lap belts found a fetal death rate of 8.3 % among animals wearing with a three-point restraint on impact compared with a 50% fetal death rate among animals impacted with lap belts only.[148] [Evidence level 2a]

A study on pregnancy outcomes in pregnant women drivers found that women who were not wearing seatbelts were 1.9 times more likely to have a low birthweight baby (95% CI 1.2 to 2.9) and 2.3 times more likely to give birth within 48 hours after a motor vehicle crash (95% CI 1.1 to 4.9) when compared with women drivers who were wearing seatbelts (adjusted for age and gestational age at crash).[149] Fetal death was 0.5% (7/1349) in women who did not use seatbelts and 0.2% (2/1243) in women who did use seatbelts. [Evidence level 3]

The Confidential Enquiry into Maternal Deaths in the United Kingdom provides information on the correct use of seatbelts in pregnancy.[143]

- Above and below the bump, not over it.
- Use three-point seatbelts with the lap strap placed as low as possible beneath the 'bump', lying across the thighs with the diagonal shoulder strap above the bump lying between the breasts.
- Adjust the fit to be as snug as comfortably possible.

RECOMMENDATIONS

Pregnant women should be informed about the correct use of seatbelts (that is, three-point seatbelts 'above and below the bump, not over it'). [B]

5.16 Travelling abroad during pregnancy

Vaccinations

In the event that a pregnant woman is travelling abroad, care must be taken to ensure that any vaccines that are received are not contraindicated in pregnancy. In general, killed or inactivated vaccines, toxoids and polysaccharides can be given during pregnancy, as can oral polio vaccine. Live vaccines are generally contraindicated because of largely theoretical risks to the fetus. Measles, mumps, rubella, BCG and yellow fever vaccines should be avoided in pregnancy.[150]

The risks and benefits of specific vaccines should be examined in each individual case and the advice of a travel medicine doctor should be sought for women considering travel in pregnancy. Table 5.1 summarises the WHO-compiled information on the use of various vaccines in pregnancy.

Yellow fever

Vaccination against yellow fever may be considered after the sixth month of pregnancy when the risk from exposure is deemed greater than the risk to the fetus and pregnant women. Yellow fever is transmitted by mosquitoes and fatality from yellow fever in unimmunised adults is 50%.[151] Women should be informed about the risks of yellow fever and about areas where the risk of exposure to yellow fever is high.[150]

Malaria

Malaria in a pregnant woman increases the risk of maternal death, miscarriage, stillbirth and low birthweight with associated risk of neonatal death and preterm birth.[154,155] [Evidence level 2a] The risks associated with malaria infection in nonimmune pregnant women include miscarriage in up to 60% of cases and maternal mortality of up to 10%.[156]

As with all travellers, taking precautions against insect bites is an important preventive measure. This includes minimising skin exposure and the use of bed nets. As pregnant women appear to attract twice as many malaria-carrying mosquitoes as women who are not pregnant,[157] [Evidence level 3] pregnant women should be extra diligent in using measures to protect against mosquito bites, but should take care not to exceed the recommended dosage of insect repellents as the safety of DEET (N,N-diethyl-m-toluamide, now called N,N-diethyl-3-methylbenzamide) has not been established in pregnancy.[154] [Evidence level 3] One case report was found of a child who was born with mental disability, impaired sensorimotor coordination and craniofacial dysmorphology to a woman who had applied DEET on a daily basis throughout pregnancy in addition to using chloroquine.[158] [Evidence level 3] One study on the use of permethrin bed nets in pregnancy on the Thai–Burmese border reported no adverse effects on pregnancy or infant outcome but also reported a marginal effect of bed nets on the reduction of malaria compared with no bed nets (reduction seen in one of three test sites, RR 1.67, 95% CI 1.07 to 2.61).[159] [Evidence level 1b]

Table 5.1 Vaccination in pregnancy[150]

Vaccine	Use in pregnancy	Comments
BCG*	No	
Cholera	No[151]	Safety not determined
Hepatitis A	Yes, administer if indicated	Safety not determined
Hepatitis B	Yes, administer if indicated	
Influenza	Yes, administer if indicated	In some circumstances; consult a physician
Japanese encephalitis**	No	Safety not determined
Measles*	No***	
Meningococcal disease	Yes, administer if indicated	Only if significant risk of infection[151]
Mumps*	No***	
Oral poliomyelitis vaccine	Yes, administer if indicated	
Inactivated poliomyelitis vaccine	Yes, administer if indicated	Normally avoided
Rabies	Yes, administer if indicated	
Rubella*	No***	

Tetanus/diphtheria	Yes, administer if indicated	
Typhoid Ty21a		Safety not determined
Smallpox	No[152]	
Varicella*	No	
Yellow fever*	Yes, administer if indicated	Avoid unless at high risk

* live vaccine, to be avoided in pregnancy
** Contrary to the WHO, other reports indicate that the vaccine is both contraindicated in pregnancy and may be administered in pregnancy[152,153]
*** Pregnancy should be delayed for 3 months after vaccine given

The antimalarials chloroquine and proguanil may be given in usual doses in areas where *Plasmodium falciparum* strains of malaria are not resistant. In the case of proguanil, 5 mg of folic acid/day should be given. The manufacturer of mefloquine advises avoidance as a matter of principle but studies of mefloquine in pregnancy (including during the first trimester) have revealed no evidence of harm; it may therefore be considered for travel to chloroquine-resistant areas. Pyrimethamine with dapsone (Maloprim®, GSK) should not be used in pregnancy; the preparation has been discontinued in the UK. Doxycycline is contraindicated during pregnancy. Proguanil hydrochloride with atovaquone (Malarone®, GSK) should be avoided during pregnancy unless there is no suitable alternative.[77]

Travel insurance

Women who will be travelling while pregnant should obtain adequate medical and travel insurance, ensuring in advanced that complications relating to pregnancy are covered, as well as medical care in the case of birth overseas for both the mother and baby. Most insurance companies will cover up to 28 weeks and there are a few that cover to 32 weeks.[160] Insurance companies will generally cover pregnant women, providing that:

- the pregnant woman returns to this country by the time stated
- the pregnant woman has had no antenatal problems that have required treatment, especially if this has entailed a stay in hospital
- the pregnant woman is travelling with the consent of her doctor.160

Travel insurance agencies should be contacted directly for more comprehensive information. Pregnant women should compare various policies and read the exclusion clauses carefully before choosing. In some cases, insurance policies will terminate benefit if medical care is sought from medical facilities that are not approved[161] and some policies will cover the mother but will not extend to coverage of the baby if it is born while the woman is travelling.[162] Other policies will not cover medical expenses after a certain gestation date or for specific outcomes of pregnancy, such as miscarriage.[163]

If the pregnant woman is travelling within the European Economic Area (EEA), then she will need an E111 form. This will cover the cost of care in a hospital but it does not cover the cost of transport to get to the hospital or to bring the baby home. If the pregnant women is more than 36 weeks' pregnant or intends to have the baby within the EEA but outside the UK, she needs form E112. The Department of Health International Relations Unit can be contacted to obtain the leaflet *Health Advice for Travellers*, which gives more information. This leaflet may also be available from the local post office or health centre.[160]

RECOMMENDATION

Pregnant women should be informed that, if they are planning to travel abroad, they should discuss considerations such as flying, vaccinations and travel insurance with their midwife or doctor. [Good practice point]

6 Management of common symptoms of pregnancy

6.1 Nausea and vomiting in early pregnancy

The causes of nausea and vomiting in pregnancy are not known and, although the rise in human chorionic gonadotrophin (hCG) during pregnancy has been implicated, data about its association are conflicting.[164] Nausea and vomiting occurs more commonly in multiple pregnancies and molar pregnancies.[165] Nausea is the most common gastrointestinal symptom of pregnancy, occurring in 80–85% of all pregnancies during the first trimester, with vomiting an associated complaint in approximately 52% of women.[166,167] [Evidence level 3] Hyperemesis gravidarum refers to pregnant women in whom fluid and electrolyte disturbances or nutritional deficiency from intractable vomiting develops early in pregnancy. This condition is much less common with an average incidence of 3.5/1000 deliveries 168 and usually requires hospital admission.

The severity of nausea and vomiting varies greatly among pregnant women. The majority of women with nausea and vomiting report symptoms within 8 weeks of their last menstrual period (94%), with over one-third of women (34%) reporting symptoms within 4 weeks of their last menstrual period.[166,167] [Evidence level 3] Most women (87–91%) report cessation of symptoms by 16–20 weeks of gestation and only 11–18% of women report having nausea and vomiting confined to the mornings.[166,167] [Evidence level 3]

One systematic review of observational studies found a reduced risk associated with nausea and vomiting and miscarriage (OR 0.36, 95% CI 0.32 to 0.42) and conflicting data regarding reduced risk for perinatal mortality.[165] [Evidence level 3] No association with nausea and vomiting and teratogenicity has been reported.[169] [Evidence level 3]

Despite reassurance that nausea and vomiting does not have harmful effects on pregnancy outcomes, nausea and vomiting can severely impact on a pregnant woman's quality of life. Two observational studies have reported on the detrimental impact that nausea and vomiting may have on day-to-day activities, including interfering with household activities, restricting interaction with children, greater use of healthcare resources and time lost off work. [170,171] [Evidence level 3]

Interventions for nausea and vomiting that do not require prescription include ginger, acupressure and vitamin B. Prescribed treatments for nausea and vomiting include antihistamines and phenothiazines.

Ginger

One RCT of ginger treatment (250 mg four times daily) compared with placebo reported a significant reduction in the severity of nausea and vomiting ($p = 0.014$) and a reduction in episodes of vomiting ($p = 0.021$) after four days in the treatment group.[172] [Evidence level 1b] No difference in the rates of miscarriage, caesarean section or congenital anomalies was observed between the two groups.

Two systematic reviews on various treatments for nausea and vomiting in pregnancy reported on the results of one RCT of ginger which was a double-blind, placebo-controlled crossover trial of 27 women who were hospitalised for hyperemesis and used ginger (250 mg four times daily).[173,174] [Evidence level 1b] Both the degree of nausea and number of attacks of vomiting were reduced with the ginger treatment ($p = 0.035$).[174] [Evidence level 1b]

Another RCT assessed ginger syrup to alleviate nausea and vomiting in pregnancy.[175] The intervention included 1 tablespoon of ginger syrup or placebo in 4 to 8 fluid ounces of water four times daily. Higher improvement on a nausea scale was observed by women in the ginger group

and vomiting resolved in 67% of the women in this group by day 6 compared with only 20% in the control group. [Evidence level 1b]

P6 acupressure

The P6 point (Neiguan) point is located on the volar surface of the forearm approximately three fingerbreadths proximal to the wrist.

Three systematic reviews of RCTs on P6 acupressure for the relief of nausea and vomiting were found.[173,174,176] [Evidence level 1a] The reviews used different inclusion criteria and each included four or more of seven RCTs. Six out of the seven trials showed a positive effect for stimulation of the P6 pressure point. The seventh trial (n = 161) showed no difference between acupressure and sham acupressure or no treatment.[174,176] [Evidence level 1a] This trial did not present its data in a form that could be included in a meta-analysis.[173] [Evidence level 1a]

The review that excluded three of the seven trials did so because they were of crossover design without separate results from the first cross over period being available. A meta-analysis of dichotomised data from two of the trials reported evidence of benefit (Peto OR 0.35, 95% CI 0.23 to 0.54) but the continuous data from a third trial did not (in contrast to the finding in the reviews above).

More recent RCTs have also reported a reduction in symptoms of nausea and vomiting among women with acupressure wristbands compared with women with dummy bands or no treatment at all.[177–180] [Evidence level 1b] A possible placebo effect with sham acupressure was also reported in two of the studies.[178,180]

The risk of adverse effects of acupressure on pregnancy outcome was assessed in one RCT.[181] No differences in perinatal outcome, congenital abnormalities, pregnancy complications and other infant outcomes were found between the acupressure, sham acupressure or no treatment. [Evidence level 1b]

Antihistamines (promethazine, prochlorperazine, metoclopramide)

In a meta-analysis of 12 RCTs that included a comparison of antiemetics (antihistamines ± pyridoxine) with placebo or no treatment, there was a significant reduction in nausea in the treated group (Peto OR 0.17, 95% CI 0.13 to 0.21).[173] [Evidence level 1a] Although the results suggest an increase in drowsiness associated with antihistamines (Peto OR 2.19, 95% CI 1.09 to 4.37),[173] a review of the safety of antihistamines in relation to teratogenicity found no significant increased risk (24 studies, n > 200,000; OR 0.76, 95% CI 0.60 to 0.94).[182] [Evidence level 2a] Metoclopramide, however, has insufficient data on safety to be recommended as a first-line agent, though no evidence of association with malformations has been reported.[183]

Phenothiazines

One systematic review of three RCTs (n = 389 women) found that phenothiazines reduced nausea or vomiting when compared with placebo (RR 0.31, 95% CI 0.24 to 0.42).[182] [Evidence level 1a] However, this analysis included different phenothiazines as a group and one of the RCTs recruited women after the first trimester. The bulk of evidence demonstrates no association between teratogenicity and phenothiazines (nine studies, n = 2948; RR 1.03, 95% CI 0.88 to 1.22).[171,182] [Evidence level 2a & 3]

Pyridoxine (vitamin B 6)

RCTs in the two reviews that studied pyridoxine considered doses of 25–75 mg up to three times daily.[173,174] [Evidence level 1a] Although the review suggests a reduction in nausea, it was not effective in reducing vomiting (Peto OR 0.91, 95% CI 0.60 to 1.38). Although concerns about possible toxicity at high doses have not yet been resolved and it is not recommended for use, one cohort study found no association between pyridoxine and major malformations (n = 1369, RR 1.05, 95% CI 0.60 to 1.84).[182] [Evidence level 2a] The Committee on Toxicity of Foods has recommended a safe upper limit of 10 milligrams a day for pyridoxine in the UK.

Cyanocobalamin (vitamin B12)

Two RCTs assessed the effect of cyanocobalamin (one trial gave multivitamins containing cyanocobalamin) compared with placebo and found a significant reduction in nausea and vomiting (pooled RR 0.49, 95% CI 0.28 to 0.86).[182] [Evidence level 1a] No studies assessing the safety of cyanocobalamin were located but this vitamin is thought to play a role in inhibiting malformations associated with neural tube defects.

Summary

Ginger, P6 acupressure and medication with antihistamines reduce the frequency of nausea in early pregnancy. Pyridoxine (vitamin B6) also appears to be effective, although concerns about the toxicity of vitamin B6 remain. Cyanocobalamin (vitamin B12) is also effective in reducing nausea and vomiting, although no data on its safety were located.

Most cases of nausea and vomiting resolve within 16 to 20 weeks with no harm to the pregnancy, prescribed treatment in the first trimester is usually not indicated unless the symptoms are severe and debilitating.[77]

RECOMMENDATIONS

Women should be informed that most cases of nausea and vomiting in pregnancy will resolve spontaneously within 16 to 20 weeks of gestation and that nausea and vomiting are not usually associated with a poor pregnancy outcome. If a woman requests or would like to consider treatment, the following interventions appear to be effective in reducing symptoms [A]:

- nonpharmacological:
  - ginger
  - P6 acupressure
- pharmacological:
  - antihistamines

Information about all forms of self-help and nonpharmacological treatments should be made available for pregnant women who have nausea and vomiting. [Good practice point]

Future research

More information on maternal and fetal safety for all interventions for nausea and vomiting in pregnancy (except antihistamines) is needed.

Further research into other nonpharmacological treatments for nausea and vomiting in pregnancy is recommended.

6.2 Heartburn

Heartburn is described as a burning sensation or discomfort felt behind the sternum or throat or both. It may be accompanied by acid regurgitation reaching the throat or the mouth, causing a bitter or sour taste in the mouth. The pathogenesis of heartburn during pregnancy is unclear but may be the consequence of the altered hormonal status interfering with gastric motility, resulting in gastro-oesophageal reflux. It is not associated with adverse outcomes of pregnancy and therefore its treatment is intended to provide relief of symptoms rather than to prevent harm to the fetus or mother. Heartburn should be distinguished from epigastric pain associated with pre-eclampsia. This may be done by checking the woman's blood pressure and urine for proteinuria.

Heartburn is a frequent complaint during pregnancy. One large study involving 607 pregnant women reported an increased frequency of heartburn with gestation, with 22% of women reporting heartburn in the first trimester, 39% in second and 72% in third trimester.[184] [Evidence level 3] Another study reported a weekly prevalence of 60% from the 31st week of gestation until delivery.[185] [Evidence level 3] An English study that separated white Europeans from Asian women

reported a slightly higher prevalence of 76–87% for white Europeans and 78–81% for Asians.[186] [Evidence level 3]

Treatment options for heartburn include lifestyle modification, use of antacids or alkali mixtures, H_2 receptor antagonists and proton pump inhibitors, which aim to alleviate symptoms by reducing the acid reflux.

Information on lifestyle modification includes awareness of posture, maintaining upright positions, especially after meals, sleeping in a propped up position and dietary modifications such as small frequent meals, reduction of high-fat foods and gastric irritants such as caffeine. Antacids, which neutralise and bind bile acids, may also be considered for the relief of heartburn. An RCT of antacid treatment compared with placebo found that 80% of women reported relief of heartburn pain within one hour compared with 13% from the placebo group.[187] [Evidence level 1b]

Alginate preparations, such as Gaviscon® (Reckitt & Coleman), reduce reflux by inhibiting the regurgitation of gastric contents. One RCT compared alginate with magnesium trisilicate and both were found to relieve symptoms of heartburn and no differences in the effects of each treatment were reported.[188] [Evidence level 1b] The manufacturers of Gaviscon® state that it may be taken during pregnancy.[189]

Another RCT compared acid and alkali mixtures with placebo and reported that there was no difference in relief of heartburn symptoms when women were given either the acid or alkali mixtures but better relief was achieved using these rather than using a placebo.[190] [Evidence level 1b]

H_2 receptor antagonists or blockers, which reduce acid secretion and volume, have also been reported to treat heartburn effectively and safely in pregnant women. Two trials that investigated the effect of ranitidine, an H^2 receptor blocker, given once and twice daily, compared with a placebo found that there was a significant improvement in heartburn symptoms, especially when ranitidine was taken twice daily, morning and afternoon.[191,192] [Evidence level 1b] H_2 blockers in the first trimester have also been assessed for safety in a cohort of 178 women and no association with fetal malformations was found.[193] [Evidence level 2a] Nevertheless, the manufacturers of ranitidine and cimetidine advise the avoidance of these products unless essential.[77]

A meta-analysis (five cohort studies, n = 593 infants) of the safety of proton pump inhibitors such as omeprazole, which suppress gastric acid secretion also reported no association between exposure to proton pump inhibitors and fetal malformations.[194] [Evidence level 2a] However, the manufacturer of omeprazole advises caution with its use in pregnancy due to toxicity shown in animal studies and does not advise its use unless there is no alternative.[77,189]

RECOMMENDATIONS

Women who present with symptoms of heartburn in pregnancy should be offered information regarding lifestyle and diet modification. [Good practice point]

Antacids may be offered to women whose heartburn remains troublesome despite lifestyle and diet modification. [A]

6.3 Constipation

Constipation is the delay in the passage of food residue, associated with painful defecation and abdominal discomfort. Constipation during pregnancy may not only be associated with poor dietary fibre intake but also with rising levels of progesterone causing a reduction in gastric motility and increased gastric transit time.

It is a commonly reported condition during pregnancy that appears to decrease with gestation. One study found that 39% of pregnant women reported symptoms of constipation at 14 weeks of gestation, 30% at 28 weeks and 20% at 36 weeks.[195] [Evidence level 3] The results of this study, however, may be over-estimates, as routine iron supplementation was recommended for all pregnant women in the UK at the time the study was conducted and iron consumption is associated with constipation.

One systematic review of two RCTs (n = 215) randomised women to fibre supplements or nothing.[196] Wheat or bran fibre supplements were significantly more effective in increasing stool frequency (Peto OR 0.18, 95% CI 0.05 to 0.67). When discomfort was not alleviated by fibre supplementation, stimulant laxatives were more effective than bulk-forming laxatives (Peto OR 0.30, 95% CI 0.14 to 0.61). However, significantly more abdominal pain and diarrhoea was observed when stimulants were used and no differences in nausea were reported. [Evidence level 1a]

No evidence was found for the effectiveness or safety of osmotic laxatives (e.g. lactulose) or softeners for use in pregnancy.

RECOMMENDATION

Women who present with constipation in pregnancy should be offered information regarding diet modification, such as bran or wheat fibre supplementation. [A]

6.4 Haemorrhoids

Haemorrhoids are swollen veins around the anus that are characterised by anorectal bleeding, anal pain and anal itching. This is thought to be a result of the prolapse of the anal canal cushions, which play a role in maintaining continence. A low-fibre diet and pregnancy are both precipitating factors for haemorrhoids.

One recent observational study found that 8% of pregnant women experienced haemorrhoidal disease in the last three months of pregnancy.[197] [Evidence level 3]

Treatment for haemorrhoids includes diet modification, creams (such as Anusol-HC®, Kestrel, Anacal®, Sankyo Pharma) oral medication and surgical intervention.

No evidence for the effectiveness or safety of creams used in pregnancy was found. However, the manufacturers of Anusol-HC® and Anacal® state that, 'no epidemiological evidence of adverse effects to the pregnant mother or fetus' has been reported.[189]

One RCT of oral medication or placebo for pregnant women with haemorrhoids found that 84% of women in the treatment group reported an improvement in symptoms compared with 12% in the placebo group, after two weeks. No significant differences in side effects or fetal outcome were reported.[198] [Evidence level 1b]

In another study of oral flavonoid therapy, 50 pregnant women were treated over three phases.[199] The majority of women reported an improvement in symptoms (bleeding, pain, rectal exudation and rectal discomfort) after 7 days, the first phase of treatment. Six women complained of nausea and vomiting, which resolved over the course of treatment. [Evidence level 3]

In extreme circumstances, surgical removal of haemorrhoids has been used. In a study where closed haemorrhoidectomy, under local anaesthesia, was performed on 25 women with thrombosed or gangrenous haemorrhoids in the third trimester, 24 women reported immediate pain relief with no resultant fetal complications related to the surgery.[200] [Evidence level 3] Surgery is rarely considered an appropriate intervention for the pregnant woman since haemorrhoids may resolve after delivery.

RECOMMENDATION

In the absence of evidence for the effectiveness of treatments for haemorrhoids in pregnancy, women should be offered information concerning diet modification. If clinical symptoms remain troublesome, standard haemorrhoid creams should be considered. [Good practice point]

6.5 Varicose veins

Varicose veins are caused by the pooling of blood in the surface veins as a result of inefficient valves that would normally prevent blood draining back down the leg. They can occur as blue

swollen veins on the calves and inside of the legs, and cause itching and general discomfort. Feet and ankles can also become swollen. They are a common complaint in pregnancy.

One systematic review addressed this issue.[119] Three RCTs of three different treatments in 115 women were included. One RCT investigated external pneumatic intermittent compression and another RCT investigated immersion in water and bed rest in pregnant women with leg oedema. The outcomes studied (leg volume, diuresis, blood pressure) did not appear to be important for the women themselves. In addition, only effects immediately after treatment were studied. The third trial administered rutoside capsules or placebo for 8 weeks in the third trimester, which led to a subjective improvement of symptoms at 36 weeks of gestation (Peto OR 0.30 95% CI 0.12 to 0.77). However, no data were provided on the safety or side effects of the administration of rutosides at this stage of pregnancy.

An RCT published after this review was also located.[201] The efficacy of compression stockings (compression class I and compression class II) in preventing emergent varicose veins during pregnancy was compared with no stockings among 42 women at less then 12 weeks of gestation. Both classes of compression stockings failed to prevent the emergence of varicose veins but more treated women reported improved leg symptoms ($p = 0.045$). [Evidence level 1b]

RECOMMENDATION

Women should be informed that varicose veins are a common symptom of pregnancy that will not cause harm and that compression stockings can improve the symptoms but will not prevent varicose veins from emerging. [A]

6.6 Vaginal discharge

The quality and quantity of vaginal discharge often changes in pregnancy. Women usually produce more discharge during pregnancy. If the discharge has a strong or unpleasant odour, is associated with itch or soreness or associated with pain on passing urine, the woman may have bacterial vaginosis (see Section 10.2), vaginal trichomoniasis or candidiasis. However, vaginal discharge may also be caused by a range of other physiological or pathological conditions such as vulval dermatoses or allergic reactions.

Trichomoniasis, infection with the parasitic protozoan Trichomonas vaginalis, is characterised by green-yellow frothy discharge from the vagina and pain upon urination and is one of the most commonly sexually transmitted infections. A systematic review of RCTs assessed the effects of trichomoniasis and its treatment during pregnancy.[202] Two RCTs were located. Both trials used metronidazole as the treatment intervention. However, the dose used in one trial (2 g, 48 hours apart and repeated after 2 weeks), conducted in the USA, was double the dose used in the other trial, which was conducted in South Africa. Both studies demonstrated high rates of cure (two RCTs, n = 703, RR 0.11, 95% CI 0.08 to 0.17) but a higher risk for preterm birth was observed in the treatment group in the US study when compared with the placebo group (RR 1.78, 95% CI 1.19 to 2.66). No significant differences in low birthweight were observed between the two groups in either trial and the South African study also reported no differences in mean birthweight or gestational age when compared with the control group, who received no treatment. Therefore, although trichomoniasis is associated with adverse pregnancy outcomes,[203] the effect of metronidazole for its treatment during pregnancy remains unclear. [Evidence level 1a]

There is no evidence that vaginal candidiasis (also called thrush), which is caused by the yeast *Candida albicans*, harms the unborn child. One systematic review of ten RCTs assessed the effectiveness of topical treatments for vaginal candidiasis in pregnant women.[204] Meta-analysis showed that imidazoles (miconazole cream and clotrimazole pessaries) were more effective than nystatin pessaries or placebo for symptomatic relief and resolution of persistent candidiasis (five RCTs, n = 793, Peto OR 0.21, 95%I 0.16 to 0.29 for nystatin pessaries; one RCT, n = 100, Peto OR 0.14, 95% CI 0.06 to 0.31 for placebo). Two RCTs (n = 91) also demonstrated that treatment with miconazole or econazole for 1 week was just as effective as treatment for 2 weeks (Peto OR 0.41, 95% CI 0.16 to 1.05). However, treatment for 4 days was not as effective as treatment for 1 week (two RCTs, n = 81, Peto OR 11.07, 95% CI 4.21 to 29.15). One RCT (n = 38) found that

terconazole cream was as effective as clotrimazole cream for treatment of vaginal candidiasis (Peto OR 1.41, 95% CI 0.28 to 7.10). [Evidence level 1a]

Although one-dose oral treatments for the treatment of vaginal candidiasis are now available, their safety or efficacy in pregnancy has not yet been evaluated.

RECOMMENDATIONS

Women should be informed that an increase in vaginal discharge is a common physiological change that occurs during pregnancy. If this is associated with itch, soreness, offensive smell or pain on passing urine there may be an infective cause and investigation should be considered. [Good practice point]

A 1-week course of a topical imidazole is an effective treatment and should be considered for vaginal candidiasis infections in pregnant women. [A]

The effectiveness and safety of oral treatments for vaginal candidiasis in pregnancy is uncertain and these should not be offered. [Good practice point]

6.7 Backache

The definition of back pain or back discomfort during pregnancy is subjective, due to the nature of this discomfort. The estimated prevalence of backache during pregnancy ranges between 35% and 61%.[205–210] Among these women, 47–60% reported backache first developing during the 5th to 7th months of pregnancy. It was also reported that the symptoms of backache were worse in the evenings. [Evidence level 3]

Back pain during pregnancy has been attributed to an altered posture due to the increasing weight in the womb and increased laxity of supporting muscles, as a result of the hormone relaxin. Back pain during pregnancy is potentially debilitating, since it can interfere with a woman's daily activities and sleep patterns, particularly during the third trimester.

A systematic review assessed three RCTs to identify the most appropriate interventions for the prevention and treatment of back pain in pregnancy.[211] The three RCTs investigated three types of interventions: water gymnastics compared with no intervention, Ozzlo pillows compared with standard pillows, and acupuncture compared with physiotherapy. [Evidence level 1a] Women who participated in water gymnastics took less sick leave when compared with women who had no specific intervention (OR 0.38, 95% CI 0.16, 0.88). In the second trial, Ozzlo pillows, which are hollowed out nest-shaped pillows, were more effective in relieving back pain and improving sleep for women at more than 36 weeks of gestation compared with a standard pillow (OR 0.32, 95% CI 0.18 to 0.58 for backache relief; OR 0.35, 95% CI 0.20 to 0.62 for sleep). In the third RCT, ten acupuncture sessions were rated more helpful when compared with ten group physiotherapy sessions in pregnant women who developed back pain before 32 weeks of pregnancy (OR 6.58, 95% CI 1.00 to 43.16).

Two additional studies not included in the systematic review were identified. One RCT compared the effect of massage therapy with relaxation classes and found that back pain relief scores diminished significantly with the women who had received massage therapy when compared with the women in the relaxation group ($n = 26$ women, $p < 0.01$)[212] [Evidence level 1b]

The other study, which was excluded from the systematic review because it was quasi-randomised, was conducted in Sweden and compared three management options for backache. These were: group back-care classes, individual back-care classes and routine antenatal care (control).[213] Women who received either individual or group back-care classes reported an improvement in pelvic or back pain compared with the control group ($n = 407$, $p < 0.05$). Women who received individual classes also reported a significant improvement in pain relief while those in the control group and those receiving group sessions did not report any pain relief. The group receiving individual training also reported significantly less sick leave ($p < 0.05$) than those in the control group and those who had group training. [Evidence level 1b]

Another Swedish study compared the effects of a physiotherapy programme (five visits for teaching on anatomy, posture, vocational ergonomics, gymnastics and relaxation) and an exercise programme compared with no specific intervention on 135 pregnant women with backache.[214] This cohort study found a significantly reduced number of sick leave days taken during pregnancy by an average of 24 days per woman ($p < 0.001$). [Evidence level 2a]

Other interventions identified for the treatment of backache and reported to have a beneficial effect were autotraction, a chiropractic, mechanical treatment for back pain,[215] spinal manipulative therapy,[216] rotational mobilisation exercise[217] and manual joint mobilisation applied to symptomatic vertebral segments.[218] [Evidence level 3] However, all these studies had problems with study design or the data were derived from a small sample size.

RECOMMENDATION

Women should be informed that exercising in water, massage therapy and group or individual back care classes might help to ease backache during pregnancy. [A]

Future research

Although many treatments exist for backache in pregnancy, there is a lack of research evaluating their safety and effectiveness.

6.8 Symphysis pubis dysfunction

Symphysis pubis dysfunction has been described as a collection of signs and symptoms of discomfort and pain in the pelvic area, including pelvic pain radiating to the upper thighs and perineum. Complaints vary from mild discomfort to severe and debilitating pain that can impede mobility.

The reported incidence of symphysis pubis during pregnancy varies in the literature from 0.03% to 3%. In Leeds, a hospital survey of women (n = 248) in whom a diagnosis of symphysis pubis dysfunction had been made, estimated that 1/36 deliveries were associated with symphysis pubis dysfunction either during pregnancy or soon after delivery.[219] Among the respondents (57% response rate), 9% reported that symptoms first occurred in the first trimester, 44% reported symptoms in the second trimester, 45% in the third trimester and 2% during labour or the postnatal period. [Evidence level 3]

There is little evidence in the literature on which to base clinical practice. No higher levels of evidence than case reports were located on effective therapies for symphysis pubis dysfunction, although the use of elbow crutches, pelvic support and prescribed pain relief have been suggested.[220] [Evidence level 4] It is important to remember that many medications for pain relief for bones and joints may not be appropriate for use in pregnancy.

Future research

More research on effective treatments for symphysis pubis dysfunction is needed.

6.9 Carpal tunnel syndrome

Carpal tunnel syndrome results from compression of the median nerve within the carpal tunnel in the hand. It is characterised by tingling, burning pain, numbness and a swelling sensation in the hand that may impair sensory and motor function of the hand.

Carpal tunnel syndrome is not an uncommon complaint among pregnant women and estimates of incidence during pregnancy range from 21% to 62%.[221–223] [Evidence level 3]

Interventions to treat carpal tunnel syndrome include wrist splints[224,225] and wrist splints plus injections of corticosteroid and analgesia.[226] However, case series reports were the highest level of evidence identified that evaluated these therapies and the studies were not of good quality.

Future research

There is a lack of research evaluating effective interventions for carpal tunnel syndrome.

7 Clinical examination of pregnant women

7.1 Measurement of weight and body mass index

A retrospective study of 1092 pregnant women found that, after taking into account maternal gestation, age and smoking habit, weekly weight gain and maternal weight at booking were the only factors that had an association with infant birthweight.[227] Low maternal booking weight (< 51 kg) was the most effective for antenatal detection of small-for-gestational-age infants (positive predictive value 20%). Low average weekly maternal weight gain (< 0.20 kg) had a positive predictive value of 13% for detecting small-for-gestational-age infants (lower than the PPV of 16% for maternal smoking). Weight loss or failure to gain weight over a two-week interval in the third trimester was observed in 46% of all women studied.

The normal range of weight gain during pregnancy varies for each pregnant individual. Based on observational data, total weight gain ranges for healthy pregnant women giving birth to babies between three and four kilograms are between 7 and 18 kg.[228] A prospective observational study of 7589 women in their first pregnancy examined the differences in pattern of weight gain according to trimester for women who delivered at term versus preterm.[229] Women who delivered preterm had patterns of weight gain similar to women delivering at term. Underweight status (BMI <19.8 kg/m2) before pregnancy increased the likelihood of delivering preterm (adjusted OR 1.98, 95% CI 1.33 to 2.98). Inadequate weight gain in the third trimester (defined as <0.34, 0.35, 0.30 and 0.30 kg/week for underweight, normal weight, overweight and obese women, respectively) increased the risk by a similar magnitude (adjusted OR 1.91, 95% CI 1.40 to 2.61).

Body mass index (BMI) is calculated by taking a person's weight in kilograms (1 kg = 2.2 lbs) and dividing it by the square of their height (weight [kg]/height[m^2], 1 in = 2.5 cm). A longitudinal study of 156 healthy pregnant women investigated whether BMI was related to energy intake during pregnancy and whether BMI, energy intake and other factors were related to net weight gain.[230] Women at the highest level of BMI were significantly less often in the high-energy intake category than women at the medium or low level of BMI. Net weight gain during pregnancy was independently influenced by BMI status and energy intake. Women at the highest level of BMI gained significantly less weight from first to third trimester compared with women at the medium or low levels of BMI. The mean birth weight in the three BMI groups did not differ and was not influenced by age, marital status, education, parity or smoking.

Routine weighing to monitor the nutrition of all pregnant women was begun in antenatal clinics in London in 1941.[227] There is a correlation between maternal weight gain and infant birthweight but this is not effective for screening for small size (low birthweight) babies. It is still important to measure maternal weight and height at least once; for example, at first contact, in order to document weight and height distributions in various subgroups of the clinic population. However, measuring maternal weight (or height) routinely during pregnancy should be abandoned as it may produce unnecessary anxiety with no added benefit. The exception is pregnant women in whom nutrition is of concern.

Recommendations

Maternal weight and height should be measured at the first antenatal appointment, and the woman's BMI calculated (weight [kg]/height[m^2]). [B]

Repeated weighing during pregnancy should be confined to circumstances where clinical management is likely to be influenced. [C]

7.2 Breast examination

Breast examination at the first antenatal appointment was traditionally used to determine whether any problems with breastfeeding could be anticipated. In particular, women were examined for the presence of flat or inverted nipples as potential obstacles to breastfeeding so that breast shields or nipple exercises could be prescribed to remedy the situation. However, an RCT examining the effectiveness of breast shields versus no breast shields or nipple exercises (Hoffman's exercises) versus no exercises found that the presence of flat or inverted nipples did not mean that women could not successfully breastfeed.[231] In fact, breast shells reduced the chances of successful breastfeeding and no differences in breastfeeding were found between the two exercise groups. [Evidence level 1b]

RECOMMENDATION

Routine breast examination during antenatal care is not recommended for the promotion of postnatal breastfeeding. [A]

7.3 Pelvic examination

Pelvic examination during pregnancy is used to detect a number of clinical conditions such as anatomical abnormalities and sexually transmitted infections, to evaluate the size of a woman's pelvis (pelvimetry) and to assess the uterine cervix so as to be able to detect signs of cervical incompetence (associated with recurrent mid-trimester miscarriages) or to predict preterm labour (see Section 11.3).

Pelvimetry has been used to predict the need for caesarean section in pregnant women. A systematic review of four RCTs (n = 895) assessed the effects of pelvimetry (x-ray) on method of delivery.[232] Women on whom pelvimetry was performed were more likely to be delivered by caesarean section (Peto OR 2.17, 95% CI 1.63 to 2.88). No differences in the perinatal mortality were found, but the numbers were not large enough to assess this adequately. There were also no differences in asphyxia, admission to neonatal unit, scar dehiscence or blood transfusion reported between the two groups. Although the risk of caesarean section was increased, no increased benefit of pelvimetry to the pregnant woman, fetus or neonate was found.

In an RCT that assessed the relationship between antenatal pelvic examinations and premature rupture of the membranes (PROM), 175 women were assigned to no examinations and 174 women were assigned to routine digital pelvic examinations commencing at 37 weeks and continuing until delivery.[233] In the group of women who had no pelvic examination, ten women developed PROM (6%) compared with 32 women (18%) from the group of women who were examined weekly. This three-fold increase in the occurrence of PROM among women who had pelvic examinations was significant (p = 0.001). [Evidence level 1b]

With regard to ovarian cysts, the majority are benign and ovarian cancer is rare in pregnancy: 1/15,000 to 1/32,000 pregnancies.[234] [Evidence level 3] A study that retrospectively reviewed 11,622 antenatal records found 16 cysts, 14 of which were later detected also at ultrasound examination.[235] In total, 57 ovarian cysts were detected, but 40 were detected only by ultrasound scan. [Evidence level 3]

RECOMMENDATION

Routine antenatal pelvic examination does not accurately assess gestational age, nor does it accurately predict preterm birth or cephalopelvic disproportion. It is not recommended. [B]

7.4 Female genital mutilation

WHO defines female genital mutilation as, 'all procedures that involve partial or total removal of the female external genitalia or other injury to the female genital organs whether for cultural, religious or other non-therapeutic reasons'.[236] It is further classified as follows.

Type I	Excision of the prepuce with or without excision of part or all of the clitoris
Type II	Excision of the prepuce and clitoris, together with partial or total excision of the labia minora
Type III	Excision of part or all of the external genitalia and stitching/narrowing of the vaginal opening (infibulation)
Type IV	Unclassified: pricking, piercing or incision of the clitoris or labia; stretching of the clitoris or labia; cauterisation by burning of the clitoris and surrounding tissues; scraping (angury cuts) of the vaginal orifice or cutting (gishiri cuts) of the vagina; introduction of corrosive substances into the vagina to cause bleeding or herbs into the vagina with the aim of tightening or narrowing the vagina; any other procedure that falls under the definition of female genital mutilation given above.

Most of the girls and women who have undergone female genital mutilation live in 28 African countries, although some live in Asia and the Middle East. Prevalence rates at or above 90% are found in Djibouti, Guinea and Somalia, Eritrea, Mali, Sierra Leone and Sudan.[237] They are also increasingly found in Europe, Australia, Canada and the USA, primarily among immigrants from the above countries.[236]

The total number of girls and women who have undergone female genital mutilation, which is also often referred to as 'female circumcision', is estimated to be between 100 and 140 million. Each year, an estimated additional 2 million girls are at risk of undergoing genital mutilation.[236] An estimated 10,000 to 20,000 girls in the UK are thought to have undergone genital mutilation[238] and information on its prevalence among pregnant women in the UK was not located.

Ninety-four percent of referral to specialist African well-woman clinics in the UK is through midwives.[238] Twenty percent of women attending an African well-woman clinic had previously informed their GP that they had undergone genital mutilation because of underlying medical problems. However, it was also reported that some women did not want their GP to know that they had undergone this procedure.[238] In a study of women attending an African well-woman clinic, among pregnant women who required defibulation and were offered it antenatally, 8% (3 out of 39) agreed to the procedure. The rest preferred to be defibulated during the second stage of labour because they would 'rather go through a painful procedure once'.[238]

The reduced vaginal opening affects not only delivery but appears to be the main factor responsible for other obstetric problems caused by genital mutilation, making antenatal assessment, intrapartum vaginal examination or catheterisation difficult or impossible. Inadequate assessments at these times as a result of genital mutilation may compromise mother and fetus physically.[239]

Female genital mutilation type III causes a direct mechanical barrier to delivery; types I, II and IV can produce severe, although perhaps unintentional vulval and vaginal scarring that can act as an obstruction to delivery.[239] In 20 studies (one from the UK and one from the USA), where 75 cases are described, with primary data on second-stage labour, obstruction is described relating to soft-tissue dystocia and many cases of such obstruction are described as being easily overcome by episiotomies.[239]

In a series of African women with genital mutilation in Middlesex, of the 14 primigravid patients, seven had a pinhole introitus or an introitus that would require defibulation for adequate intrapartum care. In all 23 parous women, the introitus was perceived to be adequate for vaginal examination in labour; 13/14 primigravid women had normal vaginal deliveries, although all 13 had episiotomies or perinatal lacerations; 1/14 primigravid women had a caesarean section for obstetric reasons unrelated to the fact that she was infibulated; 14/23 parous women had a normal vaginal delivery, 3/23 had instrumental deliveries and 6/23 were delivered by caesarean section.[240]

Episiotomies and perineal tears are the most common complications reported, with a statistically significant increased episiotomy seen in nulliparous women with female genital mutilation compared with women with no genital mutilation (89% versus 54%).[239] There is also evidence for increased fetal distress and higher Apgar scores among women with female genital mutilation compared with women with no genital mutilation.[239] Evidence that genital mutilation leads to a higher incidence of postpartum haemorrhage, maternal death, fetal death, postpartum genital wound infection and fistulae formulation has also been reported.[239]

In 1985, the UK Parliament passed the Prohibition of Female Circumcision Act, which made female genital mutilation an illegal act punishable by a fine or imprisonment. This includes the

repair of the vulva of a woman who has delivered a baby vaginally; i.e., this Act makes it illegal to repair the labia in a way that makes intercourse difficult or impossible.[241]

The management of birth in women with female genital mutilation will be covered more comprehensively in the Intrapartum Care Guideline.

RECOMMENDATION

Pregnant women who have had female genital mutilation should be identified early in antenatal care through sensitive enquiry. Antenatal examination will then allow planning of intrapartum care. [C]

7.5 Domestic violence

Domestic violence has been defined as 'Physical, sexual or emotional violence from an adult perpetrator directed towards an adult victim in the context of a close relationship'.[242] Surveys suggest a lifetime prevalence of domestic violence against women of between 25% and 30%, with an annual prevalence of 2% to 12%.[243–246] [Evidence level 3] Variability in these estimates has been attributed in part to differences in the definitions used.

Pregnancy is a time when abuse may start or escalate.[242,247] In pregnancy, the prevalence of domestic violence has been shown to be as high as 17% in England.[248] [Evidence level 3]. In the last Confidential Enquiries in to Maternal Deaths for the triennia 1997–1999, eight deaths were due to domestic violence.[143] [Evidence level 3]

Women who experience domestic violence are at increased risk of injury and death, as well as physical, emotional and social problems. During pregnancy, domestic violence can result in direct harm to the pregnancy, such as preterm birth,[249–251] antepartum haemorrhage,[252] and perinatal death,[252] [Evidence level 3] and also indirect harm through a woman's inability to access antenatal care. As such, domestic violence is a major public health problem and priority. Several professional and governmental bodies recommend 'routine enquiry' about domestic violence for all women; for example, the British Medical Association,[242] the Royal College of Midwives,[253] the Royal College of Obstetricians and Gynaecologists[247] and the Royal College of Psychiatrists[254].

Two systematic reviews have been published evaluating screening for domestic violence: the availability of screening tools, the acceptability of screening to women and healthcare professionals and the effectiveness of interventions in improving health outcomes for women.[255,256] [Evidence level 2] Both reviews identified valid screening tools for domestic violence. Screening with a single question was as effective as screening with multiple questions. Screening is likely to increase the number of women identified as experiencing domestic violence. Both reviews reported that screening was acceptable to the majority of women but that acceptance among health professionals was lower. A UK survey of the levels of detection, knowledge and attitudes of healthcare workers to domestic violence found that knowledge about domestic violence as a healthcare issue was poor and that this sometimes resulted in inappropriate referrals to agencies.[257]

Both reviews highlighted that there is insufficient evidence for the effectiveness of intervention in healthcare settings for women identified by screening programmes. Interventions evaluated in these studies included women staying at a shelter, counselling for women, and interventions for the male partner or couple such as counselling. Three of the studies included pregnant women. Both reviews identified the studies as of poorer quality and note that 'surrogate' outcomes rather than substantive health outcomes have been used.

There is a need for additional research to test the effectiveness of interventions on improving health outcomes before recommending routine screening. Healthcare professionals need to be alert to the possibility of domestic violence in women with symptoms or signs of domestic violence.

Further information on domestic violence is offered in the Department of Health publication, *Domestic violence: a resource manual for health care professionals*.[258]

RECOMMENDATION

Healthcare professionals need to be alert to the symptoms or signs of domestic violence and women should be given the opportunity to disclose domestic violence in an environment in which they feel secure. [D]

Future research

Although there are effective screening tools and screening for domestic violence has been shown to be acceptable to women, there is insufficient evidence on the effectiveness of interventions in improving health outcomes for women who have been identified. Therefore, evaluation of interventions for domestic violence is urgently needed.

7.6 Psychiatric screening

Depression in the childbearing years is a recognised problem, as are its associated effects on a child's behavioural and cognitive development. From 1997 to 1999, there were approximately 640,000 live births per year in England and Wales. In that same period, the Confidential Enquiries into Maternal Deaths in the UK[143] received reports of 11 deaths during pregnancy related to psychiatric causes. [Evidence level 3]

An association between antenatal and postnatal depression has been identified. In one systematic review,[259] a strong association between women experiencing antepartum depression and subsequently having postnatal depression was reported. [Evidence level 3] With regard to the effect of depression on obstetric complications, some investigators conclude that there is no relationship,[260] while others report an association between anxiety and depression with preterm labour (OR 2.1, 95% CI 1.1 to 4.1).[261] [Evidence level 3]

Babies of mothers who experience antenatal depression are also reported to have higher norepinephrine levels and demonstrate poorer performance on neonatal assessment tests (orientation, reflex, excitability) when compared with babies of mothers who do not experience antenatal depression.[262] [Evidence level 3]

While the Edinburgh Postnatal Depression Scale (EPDS) has been validated against a 30–60 minute semi-structured psychiatric interview as a tool for screening for antenatal depression.[263] No studies confirming the effective use of the EPDS as a screening tool in practice were located. [Evidence level 3] Using the EPDS to determine the incidence of antenatal depression, however, identified 24% of pregnant women in one survey as having clinically significant depression.[264] An association between depressive symptoms and socio-demographic status, e.g. no educational qualifications, unmarried, unemployed, was also reported. [Evidence level 3] In a cohort study that assessed mood during pregnancy and childbirth with the EPDS (n = 14,541 women), 13.5% of women scored for probable depression at 32 weeks of pregnancy while 9.1% scored for depression at 8 weeks postpartum.[265] [Evidence level 3]

An association between antenatal and postnatal depression has been reported in cohort and case–control studies[259] and numerous studies assessing antenatal prevention of postnatal depression have been conducted. Using antenatal screening as a predictor for postnatal depression, a systematic review of 16 studies found that the two largest studies predicted 16% and 52% of the women would develop postnatal depression but only 35% and 8% of women, respectively, actually developed depression after birth.[266] [Evidence level 3] In an RCT assessing the impact of an antenatal education programme on postnatal depression, no difference in reduction of depression scores was found between the intervention and control groups.[267] [Evidence level 1b]

In another RCT, the benefits of providing a 'preparing for parenthood' course versus routine antenatal care for the prevention of postnatal depression were investigated.[268] Among 209 women screened to be at risk of developing postnatal depression, no reduction in the rates of postnatal depression were observed when the intervention group was compared with the control group (OR 1.22, 95% CI 0.63 to 2.39). [Evidence level 1b] Thus, assessment of antenatal screening for the detection of postnatal depression has poor sensitivity and educational antenatal interventions do not appear to reduce postnatal depression.

However, while antenatal assessment for the detection of postnatal depression appears to have poor sensitivity in the general population, this is not the case among women with previous episodes of puerperal illness. Among these women, there is a 1/2 or 1/3 chance of recurrence and these are also the women who are at higher risk for suicide.[143] Therefore, sensitive questioning of pregnant women about previous or current mental illness is warranted for the identification of this subgroup of women. [Evidence level 3]

RECOMMENDATIONS

Women should be asked early in pregnancy if they have had any previous psychiatric illnesses. Women who have a past history of serious psychiatric disorder should be referred for a psychiatric assessment during the antenatal period. [B]

Pregnant women should not be offered routine screening, such as with the Edinburgh Postnatal Depression Scale, in the antenatal period to predict the development of postnatal depression. [A]

Pregnant women should not be offered antenatal education interventions to reduce perinatal or postnatal depression, as these interventions have not been shown to be effective. [A]

8 Screening for haematological problems

8.1 Anaemia

The most common cause of anaemia in pregnancy worldwide is iron deficiency. Maternal iron requirements increase in pregnancy because of the requirements of the fetus and placenta and the increase in maternal red cell mass. Iron absorption increases to meet this increased demand. In normal pregnancy, maternal plasma volume increases by up to 50% and the red cell mass gradually increases by about 20%. Hence, the haemoglobin (Hb) concentration drops. This normal physiological response may resemble iron deficiency anaemia.[269]

The haemoglobin level, which defines anaemia, is controversial and lacks consistency across studies, although most studies report 11 g/dl to 12 g/dl to be the mean minimum haemoglobin concentration in pregnancy. Because haemoglobin levels vary depending upon the time of gestation, it is recommended that levels are checked against a gestation-sensitive threshold. In the UK, the normal range of haemoglobin in pregnant women up to 12 weeks should be at or above 11 g/dl and 10.5 g/dl at 28 to 30 weeks of gestation.[270]

Low haemoglobin values such as those between 8.5 g/dl and 10.5 g/dl may be associated with reduced risks of low birthweight and preterm labour.[271] [Evidence level 3] Increased risks of poor fetal outcome are associated with particularly low and very high levels of haemoglobin.[271,272] [Evidence level 3]

In order to correctly diagnose iron deficiency anaemia, the impact of gestational age on the change in plasma volume must be considered. Because of the diverse pathogenesis of anaemia (e.g., iron deficiency anaemia, thalassaemia, sickle cell anaemia) the use of haemoglobin as the sole means of diagnosing anaemia is not a sensitive test although this is often used as the first indicator in clinical practice. When there is a suspicion of iron deficiency, more sensitive and specific tests should be considered. Serum ferritin is the most sensitive single screening test to detect adequate iron stores. Using a cutoff of 30 micrograms/litre a sensitivity of 90% has been reported.[273]

Routine iron supplements for women with normal haemoglobin levels

A systematic review of 20 randomised controlled trials compared iron supplementation with either placebo or no iron in pregnant women with normal haemoglobin levels (> 10 g/dl) at less than 28 weeks of gestation.[76] [Evidence level 1a] Routine iron supplementation raised or maintained the serum ferritin level above 10 micrograms/litre (Peto OR 0.12, 95% CI 0.08 to 0.17) and resulted in a substantial reduction in women with a haemoglobin level below 10 g/dl or 10.5 g/dl in late pregnancy (Peto OR 0.15, 95% CI 0.11 to 0.20). There was no evidence of any beneficial or harmful effects on maternal or fetal outcomes. One trial of routine versus selective iron supplementation included in this review showed a reduced likelihood of caesarean section and postpartum blood transfusion, but there were more perinatal deaths in the routinely supplemented group.[76] [Evidence level 1b]

Another systematic review looked at the effects of routine iron and folate supplements on pregnant women with normal levels of haemoglobin.[74] [Evidence level 1a] Eight trials involving 5449 women were included. Routine supplementation with iron and folate raised or maintained the serum iron and ferritin levels and serum and red-cell folate levels. It also resulted in a substantial reduction of women with a haemoglobin level below 10 g/dl or 10.5 g/dl in late pregnancy (Peto OR 0.19, 95% CI 0.13 to 0.27). However, routine supplementation with iron and folate had no detectable effects, either beneficial or harmful, on rates of caesarean section, preterm delivery, low birthweight, admission to neonatal unit or stillbirth and neonatal deaths.

Effect of iron supplementation for iron deficiency in pregnancy

A third review assessed the effectiveness of different treatments (oral, intramuscular and intravenous) for iron deficiency anaemia in pregnancy (defined as haemoglobin less than 11 g/dl) on maternal and neonatal morbidity and mortality. Five trials randomising 1234 women were included. The author concluded that the evidence was inconclusive on the effects of treating iron deficiency anaemia in pregnancy because of the lack of good quality trials. There is an absence of evidence to indicate the timing of, and who should be receiving, iron supplementation during pregnancy.[274] [Evidence level 1a]

RECOMMENDATIONS

Pregnant women should be offered screening for anaemia. Screening should take place early in pregnancy (at the first appointment) and at 28 weeks, when other blood screening tests are being performed. This allows enough time for treatment if anaemia is detected. [B]

Haemoglobin levels outside the normal UK range for pregnancy (that is, 11 g/dl at first contact and 10.5 g/dl at 28 weeks) should be investigated and iron supplementation considered if indicated. [A]

8.2 Screening for haemoglobinopathies (sickle cell disorders and thalassaemia)

Clinical question

What is the diagnostic value and effectiveness of the following screening methods in identifying sickle cell disease/trait?

a) History taking
b) Ethnic background
c) FBC
d) Haemoglobin electrophoresis
e) Blood film
f) Sickledex

This population includes women and their partners, antenatally and preconceptually.

Previous NICE guidance (for the updated recommendations see below)

Future research:

The effectiveness and costs of an ethnic question for antenatal screening for sickle cell and thalassaemia is needed.

The effectiveness and costs of laboratory methods for antenatal screening for sickle cell and thalassaemia is needed.

Introduction and background

Haemoglobin is a substance in red blood cells which binds to oxygen, allowing oxygen to be transported in the circulation around the body and then released into body tissues that require it. Normal adult haemoglobin has one haem part and four globin chains: two of these globin chains are alpha and the other two may be beta (in which case the haemoglobin type is called Hb-A; 96% of adult haemoglobin), delta (Hb-A_2; 3.5%) or gamma (Hb-F; less than 1%). In the developing baby, all haemoglobin is Hb-F type but this is slowly replaced by adult haemoglobin in the first six months after birth.

Sickle cell disorder and thalassaemia are the two most common types of haemoglobin disorders in the UK. They are inherited as an autosomal recessive disorder, meaning that they must be inherited through both parents, who may have the disorder themselves or may be carriers.

Sickle cell disorder

In the commonest type of sickle cell disorder in the UK, the structure of the beta globin chain is abnormal and known as sickle haemoglobin (Hb-S). A person inheriting one sickle cell gene has 'sickle cell trait', and is a carrier without the disorder. Someone who has inherited copies of the sickle cell gene from both parents has sickle cell disorder.

In low oxygen environments, for example during exercise, at high altitude or during stress, the sickle haemoglobin causes red blood cells to change shape and block small blood vessels (sickle crisis). Tissues are starved of oxygen, causing stroke, low immunity to infection, lung problems and chronic disorders of the hip or kidneys, and a sickle crisis is usually associated with severe pain. Abnormal red blood cells are also removed from the circulation resulting in anaemia. Deaths occur as a result of sickle cell disorder each year (0.5% of affected). There is no cure and treatment includes antibiotics, oxygen and painkillers which need to be taken for life. New treatments, such as bone marrow transplant and gene therapy, may become lower risk and available in the future.

In England, there are estimated to be 240,000 healthy carriers of sickle cell trait (*NHS Sickle Cell and Thalassaemia Screening Programme(2005))* and an additional 12,500 people living with sickle cell disorder. Each year, around 3,000 babies are born who are carriers and 160 babies who have sickle cell disorder. The prevalence of sickle cell is highest amongst the black African, black Caribbean and black British populations in the UK.

Thalassaemia

In thalassaemia, the production of alpha and non-alpha globin chains is not balanced and one type of globin chain is lacking, whilst the other is produced in excess. There are two common types of thalassaemia: alpha-thalassaemia in which too few alpha chains are produced, and beta-thalassaemia in which too few beta-chains are produced.

Alpha-thalassaemia trait, inheritance of some abnormal genes results in the production of a reduced amount of alpha-globin and so the affected person has anaemia and a characteristic blood film. If an unborn child inherits too few healthy genes for alpha-globin production, then they have a lethal or very severe disorder known as alpha-thalassaemia major.

Beta-thalassaemia may be inherited as a carrier trait (beta-thalassaemia minor) or a severe disorder (beta-thalassaemia major). In beta-thalassaemia minor, Hb-A_2 comprises more than 3.5% of adult haemoglobin. A carrier does not have the disorder but may pass on the abnormal gene. Beta-thalassaemia major is a severe anaemia which can lead to death of children between one and two years of age. The bone marrow and spleen enlarge as they try to replace damaged red blood cells but there is damage to other organs in the long-term, including skeletal deformity, diabetes, heart failure and liver cirrhosis. Most patients are treated by regular blood transfusion and then iron chelation (to bind the extra iron and remove it from the body) several times a week. An affected person may live to 30-40 years of age with such treatment. Bone marrow transplant and gene therapy may become available in the future.

In England, there are estimated to be 150,000 healthy carriers of beta-thalassaemia and an additional 700 people who are affected by beta-thalassaemia major. Each year, around 2,800 babies are born who are carriers and 17 babies who have beta-thalassaemia major (although a greater number of pregnancies are affected). Beta-thalassaemia is most common in Cypriot, Pakistani , Bangladeshi, Indian and Chinese communities in the UK.

NHS Sickle Cell and Thalassaemia Screening Programme

The NHS Sickle Cell & Thalassaemia Screening Programme is a linked programme of newborn screening for sickle cell disorder and antenatal screening for both sickle cell and thalassaemia disorders in England.

Newborn screening for sickle cell disorder is now an integral part of the newborn bloodspot screening programme. The aim of newborn screening is to identify babies with sickle cell disorder at an early age so that they can receive treatment to prevent or reduce the long-term effects of sickle cell disorder.

Antenatal screening for sickle cell and thalassaemia has been implemented in phases by the National Screening Committee with the screening service offered, varying depending on whether an area is considered to have a high prevalence (sickle cell affecting more than 1.5 per 10,000 pregnancies) or low prevalence (affecting less than or equal to 1.5 per 10,000 pregnancies) of these disorders. In high prevalence areas, universal antenatal testing should be offered whilst in low prevalence areas, it is intended that screening will be offered selectively to women identified as higher risk by a standardised question about 'family origin'. This national screening programme is being rolled out across England and Wales at present. In high prevalence areas all areas have implemented universal screening except one trust (which was previously designated as a 'grey' area). It is expected that implementation will be carried out in this area in the autumn of 2007. In low prevalence areas approximately 50% of trusts have implemented the screening programme, 20% are expected to have implemented by 1 September 2007 and a further 20% are expected to implement in the autumn of 2007 (figures provided by the Haemoglobinopathies National Screening Programme, August 2007).

Laboratory tests for sickle cell disease and thalassaemia

There are several tests which may be used in laboratory screening for thalassaemia or sickle cell disease and an explanation of those most commonly used in the UK are given below:

Full blood count

Red blood cell indices – a series of tests on red blood cells (performed as part of the full blood count which is offered to all pregnant women)

Haemoglobin – the level of haemoglobin in the blood; this is low in anaemia due to iron deficiency or haemoglobinopathy

Mean corpuscular volume (MCV) – average volume of a red blood cell (measured as one of the red blood cell indices on the full blood count); this is low in thalassaemia

Mean corpuscular haemoglobin (MCV) – average haemoglobin level per red blood cell; this is low in thalassaemia

Additional tests

Ferritin – this is a test performed on blood which is low if the anaemia is due to iron deficiency rather than haemoglobinopathy

Electrophoresis – a non-automated test which separates the haemoglobin types present in a sample of blood

High performance liquid chromatography (HPLC) – an automated test which separates the haemoglobin types present in a sample of blood

Sickle cell solubility test – a test which can be used to confirm the presence of sickle haemoglobin in the blood

The screening process involves testing a woman for carrier status early in pregnancy and then testing her partner if she is proven to be a carrier. If both parents are confirmed as carriers, DNA analysis may be undertaken to confirm this before testing the unborn child using amniocentesis or chorionic villus sampling. The aim of antenatal testing for haemoglobin disorders is to inform parents and provide them with the option of pregnancy termination at an early stage of pregnancy if their child has a serious haemoglobin disorder.

Screening for haemoglobinopathies – health economics evidence summary

A systematic search of the literature identified 53 studies potentially related to the clinical questions. The abstracts of all papers were reviewed, and 16 articles were retrieved and critically appraised. 4 papers met the inclusion criteria; 1 study was conducted in the US, 1 in Canada and 3 in the UK.

A Canadian study [710] evaluated the cost-effectiveness of a thalassaemia disease prevention programme through screening and prenatal diagnosis of thalassaemia. The programme screened 80

per cent of at-risk couples and prevented two-thirds of cases in the period of the study. The comparison between the costs of prevention versus the cost of treatment showed that the total direct cost per case prevented in the programme (Carrier screening/Fetoscopy: $6,754 Carrier screening/DNA analysis:$6,638) is less than the cost for a single year of treatment for an individual with the disease ($7,057). Costs are in 1981 Canadian Dollars.

A US study [711] was designed to evaluate the diagnostic ability of two different haemoglobinopathy screening protocols to identify at-risk pregnancies. The main comparison was between universal and selective use of haemoglobin electrophoresis, where the selective screening involved the use of haemoglobin electrophoresis following sickle cell solubility testing and investigation of red blood cell (RBC) indices. Using a retrospective chart review of all patients registering for prenatal care at the New York Hospital/Cornell Medical Centre prenatal clinic the study showed that the selective protocol would not diagnose four patients as carriers of haemoglobinopathy traits and would save $11,384, or $18 per patient (1986 US Dollars), compared with the universal protocol. In this study, universal haemoglobin electrophoresis did not identify any additional pregnancies at risk for clinically significant haemoglobinopathy, although it did identify carriers who would not have been spotted by a selective protocol. The authors concluded that the relative costs of different screening strategies and the frequency of carriers in the population must be taken into account when instituting a protocol for haemoglobinopathy screening.

One UK study [712] compared the cost and potential benefits of universal testing for variant haemoglobins and ß-thalassaemia carrier status (trait) using high performance liquid chromatography (HPLC) and the costs and potential benefits of universal testing for ß-thalassaemia carrier status (trait) using the mean cell haemoglobin (MCH) as a screening test and less automated techniques than HPLC for definitive diagnosis. The universal testing strategy did not identify any additional cases of ß-thalassaemia trait compared with the universal screening and selective testing strategy. Six patients were found to have a haemoglobin A2 variant using universal testing; this can interfere in the diagnosis of ß-thalassaemia carrier status (trait). The universal testing policy cost between £57 and £198 more than the universal screening and selective testing policy. Costs are for the year 1998. The authors argue that a universal testing strategy into British laboratories could be cost neutral, though they believe that in practice this is unlikely.

Another UK study [713] assessed the cost-effectiveness of antenatal haemoglobinopathy screening and follow up in a community programme in terms of the costs of providing full genetic choice to women and couples, and the cost per significant haemoglobinopathy averted. The total savings to the programme as a result of cases averted, which included savings from the averted lifetime treatment costs for affected births, was estimated at £61,000. Also reported were the costs of identifying a woman with abnormal haemoglobinopathy (£209), the cost of identifying an at-risk fetus prior to pre-natal diagnosis (£2455) and the cost of providing genetic information and counselling (£109). Costs are for the year 1999. The analysis showed that antenatal screening with follow up counselling can be self-financing at most levels of prevalence of thalassaemia.

Health economics evidence statement

All the published economic evidence in this clinical area was focused on the cost-effectiveness of antenatal screening for haemoglobinopathies by comparing the relative costs of prevention of births affected by disease and the potential cost of treatment for an affected birth. The conclusion drawn from these studies was that screening and prevention of affected births was likely to produce cost savings in the health care system and would therefore be cost-effective. This result would be more pronounced in areas with a large ethnic minority population and in these areas universal antenatal screening would be cost effective given the higher disease prevalence.

Thalassaemia screening

Clinical question

What is the diagnostic value and effectiveness of the following screening methods in identifying clinically significant thalassaemia and thalassaemia carrier status (trait)?

a. History
b. Ethnic background
c. Full blood count

d. Electrophoresis
e. Ferritin
f. Mean cell volume

Thalassaemias include: ß-thalassaemia intermedia, HbS/ß-thalassaemia

Thalassaemia carrier status (trait) includes: δß-thalassaemia carrier status, ß-thalassaemia carrier status, α-thalassaemia carrier status.

Population includes women and their partners, antenatally and preconceptually

Accuracy of screening for thalassaemia using red blood cell indices

Description of included studies

6 studies were identified for inclusion in this review.

A UK diagnostic case-control study (1995) has been conducted to compare the suitability of mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) for thalassaemia screening, and to determine the correct cut-off points for these indices [714]. [EL III] The study was conducted in a UK hospital where all women booking with a first pregnancy were screened for haemoglobinopathy and full blood counts (FBCs) performed to determine the MCV and MCH. The 2.5 percentiles derived from a sample of healthy non-pregnant women were used as cut off points for MCV (85fl) and MCH (27pg). A diagnosis of β thalassaemia carrier status (trait) was made if the HbA_2 was greater than 3.5%.

Earlier work carried out in the UK (1988) investigated cut off points for MCV and MCH in screening for thalassaemia, again comparing red blood cell indices obtained at booking with Hb electrophoresis and HbA_2 estimation [715].[EL III] . The cut-off points for the red blood cell indices in this study were set at MCV < 83fl and MCH < 27.1pg.

The accuracy of MCV in screening for thalassaemia carrier status (trait) has been tested in Thailand (2005), where thalassaemia is the most common hereditary disease [716]. [EL III]. A sample of 439 pregnant women had blood samples taken and their MCV, HbA2 level and polymerase chain reaction (PCR) measured to test for β thalassaemia carrier status (trait) and the α thalassaemia-1 gene respectively. A cut-off MCV < 80fl was used.

A study carried out in Hong Kong (1985) investigated the accuracy of MCV followed by HbA_2 estimation with that of MCV plus ferritin and Hb level followed by HbA_2 estimation [717]. [EL III]. Pregnant women of < 24 weeks gestation (n = 299) had blood tests performed to estimate their Hb level, MCV, Hb A_2 and plasma ferritin levels. These values were compared against locally ascertained standards for women with normal haemoglobin. Women with an MCV < 80 fl level and a normal HbA2 who were found to be iron deficient were given oral iron therapy and blood tests repeated 4 weeks later.

An antenatal screening programme carried out in Hong Kong has also been described [718]. [EL III]. Over an 11 year period 25834 women were screened for thalassaemia by MCV at booking. A cut off of MCV <= 75fl was used. A similar antenatal screening programme in Singapore (1994) reported findings using a cut off of MCV < 80fl [719]. [EL III]. Following confirmation of a low MCV confirmatory tests for haemoglobinopathies were carried out (blood film, electrophoresis and estimation of levels of HbA_2/HbE and HbF).

Findings

Findings from the UK case-control study [714] showed that over a 2 year period 857 women were identified with either an MCV < 85fl or an MCH < 27pg but did not have a haemoglobinopathy. 784 of these women had microcytic red cells. Of these 857 women, 606 had both an MCV < 85fl and an MCH < 27pg. 56 of these women (6.5%) were β thalassaemia carriers. Of the remaining 251 women, none were carriers of β thalassaemia. Selection of the MCH rather than the MCV for screening purposes would have resulted in a 25% reduction in the number of women requiring Hb A_2 estimation, and at a cut off of MCH < 27pg would have identified all cases of β thalassaemia

carrier status (trait). Further tests regarding storage of samples showed that the MCH is also more stable at room temperature compared with the MCV.

The earlier UK case-series [715] identified 696 women with an MCV at booking of less than 83 fl. These women went on to have further screening. In 96 (13.8%) women the Hb electrophoresis showed an abnormal haemoglobin. In the other 600 women a HbA_2 estimation indicated a further 56 women with β thalassaemia carrier status (trait) (8% of total group screened). All MCH values for women with β thalassaemia carrier status (trait) fell below the cut-off point of 27.1pg, with the highest MCH being 25.9pg. If a cut-off of 26pg had been chosen all women carrying β thalassaemia would have been identified with a 29% decrease in workload.

Findings from the research conducted in Thailand [716] showed that a cut-off of MCV < 80fl as a screen for α and β thalassaemia carrier status (trait) has a sensitivity of 92.9% (39/42) [95% CI 83.7 to 96.4%] and a specificity of 83.9% (333/397) [95% CI 80.8 to 87.6%]. The positive predictive value was 37.9% (39/103) [95% CI 33.8 to 42.7%] and the negative predictive value 99.1% (333/336) [95% CI 98.2 to 99.9%]. It should be noted that these figures are population-specific as prevalence effects the positive and negative predictive values of the test, and consequently their cost-effectiveness.

Findings from the control groups in the Hong Kong case control study gave the following cut-off points for red blood cell indices. An HbA_2 > 4.5% was taken to be diagnostic of β thalassaemia carrier status (trait). 8ng/ml was taken as the lower limit for a normal ferritin level. MCV cut-off point was 80 fl. 18 of the 299 women in the study sample (6%) had HbA_2 levels > 4.5% and were diagnosed to be carrying β thalassaemia. All of these 18 women had an MCV < 75fl (in 15 the MCV was < 70fl). 49 women had an MCV < 80fl, of these women 18 had low ferritin levels (< 8ng/ml). 2 of these women had HbA2 levels over 4.5% and were diagnosed to be carrying β thalassaemia with iron deficiency. 16 women had low ferritin levels and normal HbA_2 estimation and were assumed to be iron deficient. 37 women were found to have Hb levels < 10g/dl. They included 9 β thalassaemia carriers, 19 women with iron deficiency and 9 presumed α thalassaemia carriers. The detection rate of β thalassaemia carriers was investigated for different cut-off levels. At a cut-off of MCV < 80fl all β thalassaemia carriers were detected and the false positive rate was 63%. At a cut-off level of MCV 75fl the detection rate remained 100% and the false positive rate decreased to 47%. At a cut-off of 70fl the specificity of the test increased to 97% with a sensitivity of 83% and false negative rate of 16%. The study was repeated with a larger sample (n=1166), with similar findings. 61 β thalassaemia carriers were identified (5.2%), all with an MCV < 75fl.

Findings from the large descriptive study of an antenatal screening programme in Hong Kong showed that, using a cut-off of MCV < 75fl enabled 1859 thalassaemia carriers to be identified, plus 57 women carrying other haemoglobin variants (86% of those identified by screening test). The number of false positives was 313/2229 (14%). The authors report that 'after reviewing the obstetrics and paediatrics statistics' no case of thalassaemia major was missed. This does not equate, however, to a sensitivity of 100% since it is not known how many women with carrier status were missed.

Similarly, the screening programme described in Singapore [719] identified 494/3696 (13.4%) women with an MCV < 80fl. Of these women, 56 (11.3%) and 23 (4.7%) were confirmed to be carrying thalassaemia and HbE respectively, giving a false positive rate of 84%. Again, since only women who fell below the initial screening cut-off point went on to have further haemoglobinopathy testing, it is not possible to determine how sensitive or specific this screening test is.

Effectiveness of UK national antenatal screening programme

Description of included studies

The UK National Confidential Enquiry into Counselling for Genetic Disorder (CEGEN) has undertaken an audit of risk detection and risk information for thalassaemia during pregnancy in order to assess at a population level the screening objective of providing informed choice [720] [EL 3]. The antenatal records of 136 (88%) of the 156 women with a pregnancy affected by a beta thalassaemia major (1990-1994) were retrospectively reviewed and the woman's care assessed against a minimum standard. The selected standard of care was (a) risk identification and offer of

prenatal diagnosis before 23 weeks of a first pregnancy and (b) offer of prenatal diagnosis in the first trimester in subsequent pregnancies.

Findings

Findings from the CEGEN audit showed that only 50% of at-risk couples were identified and informed of their risk in time for an offer of pre-natal diagnosis in the first pregnancy. Risk was identified too late in 11% of pregnancies and not at all in 38% pregnancies. As failure to identify risk was recurrent, 28% of couples discovered their risk through the diagnosis of an affected child. Review of maternity care records identified common assumptions made by health care professionals that Muslims cannot accept termination of pregnancy and that British Pakistanis 'do not want' prenatal diagnosis. However, among British Pakistanis, the CEGEN review showed that the uptake of prenatal diagnosis was over 70% when it was offered in the first trimester of pregnancy, but less than 40% when offered in the second trimester. The CEGEN concluded that current screening with routine antenatal care does not meet couples' needs for early information and access to early pregnancy diagnosis.

Views and experiences of women towards thalassaemia screening in pregnancy

Description of included studies

A descriptive qualitative study has been conducted in the UK (2006) to explore Pakistani women's views towards antenatal diagnosis for thalassaemia and termination of pregnancy for β thalassaemia major [721] [EL 3]. Interviews were carried out with 43 women by a female researcher. These took place in the woman's home and were conducted in the woman's chosen language. 19 women were identified as thalassaemia carriers, 10 as possible carriers and 14 as non-carriers.

A second recent UK qualitative study (2005) has also explored women's perceptions of thalassaemia screening, with particular reference to information and consent [722]. [EL 3] 110 Pakistani women who were thalassaemia carriers completed a questionnaire. A sub-sample of 14 women was later interviewed. In addition, 36 women who were identified as carriers or potential carriers also completed the questionnaire and were interviewed. The questionnaire asked women whether they were aware they had been tested for thalassaemia carrier status, whether they were asked for their consent and what information they would have liked to receive prior to the screening. Questionnaires were available in English and Urdu, and women were offered a choice of self-completion or with the aid of the researcher. All interviews were conducted by the female researcher in the women's own homes and in her chosen language.

Findings

Findings from the UK qualitative study of Pakistani women's attitudes to prenatal diagnosis revealed that most women would opt for diagnosis because they would want 'to know', not because they would consider termination of pregnancy. Some women, however, preferred not to know about the baby's status, preferring to find out after the baby was born. One woman expressed concern that knowledge that the baby was affected might lead to a negative attitude towards the baby, even though termination of pregnancy was not being considered. Women's attitudes towards termination of pregnancy for an affected baby did not seem to relate to the woman's carrier status and were influenced by, but not solely dependant upon, their religious viewpoint (all women were Muslim). Women's responses suggested that the more severe the perception of thalassaemia major, the more likely the woman was to be in favour of antenatal diagnosis and termination of pregnancy. Some women also expressed the view that termination of pregnancy was only acceptable early in pregnancy, although women's definitions of early ranged from 5-6 weeks to 'before people know you are pregnant'.

Findings from the second UK qualitative study showed that 113/146 women (77.4%) had not been told about thalassaemia carrier testing, and 97 of these (85.8%) said they would have wanted to have been told before the screening was carried out. Although some women mentioned the increased anxiety associated with receiving information prior to screening, most saw this as inevitable part of being pregnant. Women who went on to discover they were thalassaemia carriers felt that prior information would have helped them prepare for this news. Women expressed a

desire to know about the condition itself, when the results would be available, the meaning of positive and negative results and possible action following a positive result. This was not universal however, and carrier status affected women's responses with non-carriers being less likely to say they wanted detailed pre-screening information. Some suggested the provision of a leaflet might address the issue of individual variation, and provide women who later found out they were carriers with something to refer back to for more information. All women who were carriers identified a great need for information on being told of a positive screening result. Barriers to acquiring information included not knowing enough about the condition to be able to ask pertinent questions, belief that health care professionals would automatically provide all the necessary information,and not being able to speak or understand English. It was also highlighted that relatives acting as interpreters do not always provide the woman with all the information she wants. Whilst most women (88.4%) reported that they were not asked their consent for screening, they did not perceive this as a problem, accepting screening as a normal part of routine antenatal care. There was a belief and a trust that health care professionals will do what is best and there was no need to question. Only 3 women were unhappy at being tested without consent. These were articulate, professional women, 2 of whom stated that they would have refused screening had they been asked. Overall, the wish for information far outweighed issues of consent.

Evidence summary

There is some evidence of fair quality that screening for thalassaemias and termination of an affected pregnancy are acceptable to some Pakistani Muslim women.

Preconceptions that religion is the only determinant of views towards reproductive choice are not supported by the evidence.

MCV does not appear useful for screening for β-thalassaemia, but may be more useful where there is a high prevalence of α-thalassaemia.

There is a good amount of evidence of fair quality that screening for β- thalassaemia by MCH has high sensitivity (100%) but low specificity (31%) with a cut-off of 27pg.

CEGEN Audit suggests women are not receiving counselling and testing in time to allow reproductive choice. (1990-1994 evidence so perhaps improved).

Screening for haemoglobinopathies may lead to a reduction in lifetime treatment costs through a reduction in affected births. None of the included studies estimated the benefits accruing to an individual born with haemoglobinopathy with the treatment costs.

HPLC is automated and therefore appears to be cost-neutral according to one economic evaluation.

Universal HPLC may be as cost-effective as a sequential screen based on MCH followed by electrophoresis.

Screening using RBC indices may be cost-effective for beta thalassaemia even in areas of low prevalence.

Sickle cell disease/trait

Clinical question

What is the diagnostic value and effectiveness of the following screening methods in identifying clinically important genotypes of sickle cell disease and sickle cell carrier status (trait) including:

a. History
b. Ethnic background
c. Full blood count
d. Electrophoresis
e. Ferritin
f. Mean cell volume

Sickle cell disease includes: Hb SS and Hb SC

Carrier states include: Hb AS, Hb AC, Hb AD, Hb AE

Population includes women and their partners, antenatally and preconceptually.

Previous NICE guidance (for the updated recommendations see below)

The previous Antenatal Care guideline did not make any clinical recommendations regarding screening for sickle cell disease/trait. Two research recommendations were made (see above).

Universal electrophoresis versus selective electrophoresis following investigation of red blood cell indices and sickle solubility testing

Description of included studies

A case-control study was identified which compared the diagnostic accuracy of universal haemoglobin (Hb) electrophoresis with selective use of haemoglobin electrophoresis following sickle cell solubility testing and investigation of red blood cell (RBC) indices [711] [EL III]. This US study involved retrospective review of antenatal records of 631 women. All women had RBC indices and Hb electrophoresis performed at their initial antenatal visit.

Findings

Findings from the case-control study [711] showed that there were 36 women from the sample of 631 with abnormal Hb electrophoresis. 6 of these women would have had normal sickle solubility test results. In 2 of these cases, abnormal RBC indices would have prompted further testing with Hb electrophoresis. Thus 4 women in total would have remained unidentified using the selective screening model. This gives a sensitivity of 88.9% (32/36) and a specificity of 79.4% (473/595) for the selective screening model. The positive predictive value is low however, 20.8% compared with a high negative predictive value of 99.2%.

Views and experiences of antenatal screening for sickle cell disease/trait

Description of included studies

One descriptive study was identified which aimed to examine the acceptability of pre-natal diagnosis as a means of controlling the number of babies born with sickle cell disease [723] [EL 3]. This interview survey was conducted in Nigeria, targeting well-educated, city-dwelling adults (n = 433).

Findings

The survey respondents were aged 15-50, approximately half of whom were women. 90% of the sample attended school up to secondary and post-secondary level, 67% were in professional occupations (e.g. medicine, law and teaching). Two-thirds of the sample knew their haemoglobin phenotype. Most respondents (88%) perceived sickle cell disease as a serious disease, although 19% thought it was curable. Only 4% of those interviewed had received sickle cell counselling, although 15% reported themselves to have sickle cell trait. 78% of respondents felt prenatal sickle cell diagnosis should be available and 45% reported that they would decide to terminate a baby affected with sickle cell disease. Cross-tabulations showed that neither religion nor educational level significantly affected a person's decision whether or not to terminate an affected pregnancy.

Evidence Summary

There is evidence from one study that screening for sickle cell disease and termination of an affected pregnancy acceptable.

Electrophoresis appears to be necessary for higher sensitivity and specificity compared with selective screening using sickle solubility testing and RBC indices.

Sickle cell carriers are less likely to receive programme in a timely manner – this highlights the need for timely provision if screening is to successfully offer reproductive choice.

Joint screening for sickle cell disease and thalassaemia

Description of included studies

One RCT (n = 4559) was reviewed that compared 2 family origins screening questions for stability and for proportion of carriers missed [724] [EL 1+]. The study was conducted in 4 hospital trusts in the UK with varying prevalence of haemoglobinopathies. The question was embedded within the antenatal booking interview. Question A was a classification question (similar to a census question) plus a 'tick all that apply' subsidiary section to record mixed heritage. Question B was in 2 parts. Part One contained an initial binary question to identify women with ancestors outside the British Isles. Part Two comprised 5 free text boxes for addition of information regarding ancestry. A laboratory test was then offered to screen all women taking part in the study for sickle cell and thalassaemia. The reliability of the screening question was tested by repeating the question at a subsequent antenatal visit. The time taken for the midwife to ask the screening question was also noted.

A UK retrospective descriptive study (1999) compared unselected laboratory-based antenatal screening for sickle cell trait with antenatal unselected laboratory-based screening for thalassaemia trait [725]. [EL 3] All women booking at a UK hospital were screened for haemoglobinopathy (over 20 000 pregnancies) and uptake of services by women found to be less positive for thalassaemia trait (n = 265, 1.3%) compared with uptake by women who were found to be carriers of sickle cell disease (n = 751, 3.7%). A similar comparison was made for a smaller sample of tertiary referrals (n = 95 women with 101 pregnancies).

A whole system participatory action research project (2005) has been used to evaluate a system where women are screened for sickle cell and thalassaemia early in their pregnancy in UK general practice [726] [EL 3]. The study aimed primarily to compare the gestation at screening in general practice compared with the more usual system of screening at first booking visit, and to investigate the feasibility of introducing such a scheme. 6 general practices in North London took part in the research, reflecting different sizes of practices, relating to different hospitals and with different experiences of antenatal haemoglobinopathy screening. 241 women were recruited opportunistically into the study. Two comparison groups of women were also recruited – 276 women attending their booking visit at 2 neighbouring hospital clinics, and 131 women attending nearby community midwife clinics. A range of workshops, public meetings and interviews were conducted throughout the research process in order to gain the views of as many stakeholders as possible.

Findings

From the UK RCT [724] involving the questionnaire the sample of 4559 women who consented to take part in the study represents a high response rate of 87%. However, only 27% of women were invited by midwives to take part in the study, suggesting a level of undisclosed screening being undertaken by midwives prior to asking the ethnicity question. For Question A 3.2% cases were missing or uninterpretable, compared with 4.7% for Question B. Test/re-test error rate for reliability for Question A was 4.3% compared with 9.5% for Question B (CI -8.5% to -1.8%; p = 0.003). For ethnicity Question A 7/122 (5.7%) carriers of clinically relevant haemoglobinopathies were missed at booking. 10/103 (9.7%) women carrying a significant haemoglobinopathy were missed using Question B. This difference is statistically different (p = 0.026 using a chi-square test (chi-square value not reported)). The mean time taken to ask the ethnicity question was very similar for each question (about 4.4 minutes for Question A and 4.5 minutes for Question B).

Comparison of utilisation of services by women found to be carriers of sickle cell disease and women found to be carriers of thalassaemia showed that there were some differences between the 2 groups [725]. Unselected women found to be carriers for sickle cell disease booked 2.7 weeks [95% CI 0.14 to 5.1] later in pregnancy than women who were carrying thalassaemia. Carriers of sickle cell disease were found to be less likely to choose to receive counselling (83% vs. 93%, RR 0.89 [95% CI 0.85 to 0.94]); their partners were less likely to be tested (77% vs. 95%, RR 0.81 [95% CI 0.77 to 0.83]); and they were less likely to choose prenatal diagnosis (22% vs. 90%, RR 0.37 [95% CI 0.24 to 0.57]) compared with women carrying thalassaemia. Uptake of neonatal diagnosis for sickle cell disease varied markedly between the first and second trimester, 80% couples requested antenatal diagnosis in the first trimester compared with 50% after the first trimester. However, only

27 women (42%) who were carriers of sickle cell disease were counselled in the first trimester. Of the tertiary referrals over 99% women attended counselling and had their partners tested. There was no difference in acceptance of prenatal diagnosis between those at risk of sickle cell disease and those at risk of thalassaemia (55% vs. 67%).

Findings from the UK action research project [726] showed that general practices that already had a screening system in place were able to screen a high proportion of women presenting in early pregnancy for haemoglobinopathies (63% - 86%). However, 3 practices without an existing system only managed to screen between 3% and 26% of women. Women who were screened in general practices were screened at an earlier gestation than those screened at their first hospital booking visit (4.1 weeks [95% CI 3.4 to 4.7], $p<0.001$) or at midwifery clinics (2.9 weeks [95% CI 2.1 to 3.7], $p<0.001$). The introduction and maintenance of a new screening system into general practice was seen as requiring more resources than initially appreciated e.g. time taking for pre-and post-test counselling was much longer than had been anticipated. The overall consensus from project participants was that pre-conceptual screening would be ideal so that women of known carrier status could be fast-tracked to existing secondary services. At the end of the study period all practices involved reverted to their pre-study system of screening at hospital or by community midwives.

Evidence Summary

A fixed response question for screening for family origins is supported by findings from an RCT as being a useful screening test.

A screening programme (including counselling and follow-up) based in primary care allows earlier detection of haemoglobinopathy carrier status.

GDG interpretation of evidence

There is limited evidence that antenatal screening and the offer of termination of pregnancy for sickle cell disease appears to be acceptable to women and their partners

Screening of all pregnant women using electrophoresis has a higher sensitivity and specificity to detect sickle cell carriers compared with selection of pregnant women for electrophoresis using sickle solubility testing and red blood cell indices. HPLC is a suitable alternative to electrophoresis as a laboratory test for sickle cell disorder or carrier status.

Antenatal screening and termination of pregnancy for thalassaemia is acceptable to some Pakistani Muslim women, particularly if termination can be offered during the first trimester of pregnancy. The religion of a woman or her partner is not the only factor to determine whether termination of pregnancy will be acceptable and antenatal screening to allow reproductive choice should be offered to all pregnant women regardless of religious belief.

Antenatal screening with MCH is effective as a screening test for beta thalassaemia even in low prevalence areas.

As universal HPLC is cost-effective, it should be the preferred method for thalassaemia screening in high prevalence areas.

If pregnant women are offered antenatal screening for thalassaemia after the first trimester of pregnancy, they are less likely to receive counselling and testing in time to facilitate reproductive choice.

Screening for family origins using a fixed response tick box question is effective in identifying pregnant mothers at risk of haemoglobinopathy

Screening, including counselling and follow-up, can be successfully undertaken in primary care and may allow detection of carrier status at an earlier stage of pregnancy.

Compared with thalassaemia carriers, sickle cell carriers are less likely to receive the antenatal screening programme in a timely manner and, as the timing of the offer of screening influences the choice of antenatal diagnosis, this highlights the need for provision of screening at an early stage of pregnancy to successfully offer reproductive choice.

Recommendations

Pre-conceptual counselling and carrier testing should be available to all women who are identified as being at higher risk of haemoglobinopathies using the Family Origin Questionnaire (NHS Antenatal and Newborn Screening Programmes) See Appendix F.

Screening for haemoglobinopathies should be carried out as soon as possible in pregnancy, in the context of either primary or secondary care.

Prior to screening, women should be provided with information about sickle cell disorders and thalassaemias, including carrier status, and the implications of each.

Screening for sickle cell disorders and thalassaemias should be offered to all pregnant women (ideally by 10 weeks), and be preceded by counselling. The type of screening depends upon the prevalence.

In high prevalence areas (more than 1.5 cases per 10 000 pregnancies) screening using high performance liquid chromatography should be offered to all women to identify carriers of both sickle cell disease and thalassaemia.

In low prevalence areas (less than or equal to 1.5 cases per 10 000 pregnancies) all women should be offered screening for haemoglobinopathies using the Family Origins Questionnaire (National Health Service (NHS) Antenatal and Newborn Screening Programmes). See Appendix F.

- If the Family Origins Questionnaire (NHS Antenatal and Newborn Screening Programmes) indicates high risk of sickle cell disorders, screening using high performance liquid chromatography should be offered.
- If the Family Origins Questionnaire (NHS Antenatal and Newborn Screening Programmes) indicates high risk of thalassaemia and mean corpuscular haemoglobin less than 27pg screening using high performance liquid chromatography should be offered).

All partners of identified carriers of haemoglobinopathies should be offered counselling and screening.

8.3 Blood grouping and red cell alloantibodies

Identifying blood group, RhD status and red cell antibodies in pregnant women is important to prevent haemolytic disease of the newborn (HDN) and to identify possible transfusion problems. 15% of women are RhD negative. It is important to ascertain maternal RhD status so that RhD-negative women can be offered appropriate antenatal and postnatal immunoprophylaxis with the aim of preventing RhD alloimmunisation in subsequent pregnancies.

The reasons for identifying other red cell antibodies in pregnant women are the prevention of haemolytic disease of the newborn, which may cause jaundice, severe anaemia, heart failure and death, and for the identification of possible transfusion problems. These can occur in RhD-positive and -negative women. A significant number of women will have red cell antibodies.[285] The main antibodies that can cause severe alloimmune anaemia in the fetus are anti-D, anti-c and anti-Kell. Of lesser importance but still with the potential to cause HDN are anti-e, -Ce, -Fya, -Jka and-Cw. Anti-Lea, -Leb, -Lua, -P, -N, -Xga and high-titre low-avidity antibodies such as anti-Kna have not been associated with HDN.[286] There is no value in identifying group O pregnant women with high titres of anti-A or anti-B. Antenatal testing for these antibodies has been shown to have no value in predicting the incidence of HDN caused by ABO incompatibility.[287,288]

Antibody screening should be undertaken using an indirect antiglobulin test and a red cell panel conforming to current UK guidelines.[285]

Two Swedish surveys of red cell antibody screening in similar populations used different testing schedules and both concluded that their particular schedule detected all women at risk of HDN, yet one tested once only in early pregnancy[289] and the other tested RhD-positive women twice in pregnancy and RhD-negative women three times in pregnancy.[290]

Routine antenatal serological testing has been practised throughout the UK for about 30 years. There are currently recommendations that all women should be tested as early in pregnancy as

possible, usually at 8 to 12 weeks of gestation.[291] This initial testing should include ABO and RhD typing as well as a screening test to detect any irregular red cell antibodies. Testing should be undertaken again at 28 weeks of gestation for all women with no antibodies on initial testing to ensure that no additional antibodies have developed.[291] No RCTs of different testing schedules were found.

When an antibody is detected, the clinician responsible for the woman's antenatal care must be informed of its likely significance, with respect to both the development of HDN and transfusion problems. Management of pregnancies in which red cell antibodies are detected varies depending upon the clinical significance and titre of the antibody detected.

Guidance on the routine administration of antenatal anti-D prophylaxis for RhD-negative women has been recently issued, which recommends that anti-D is offered to all pregnant women who are RhD negative.[292] However, in the case where a woman is RhD negative, consideration should also be given to offering partner testing because, if the biological father of the fetus is negative as well, anti-D prophylaxis, which is a blood product, will not need to be administered. Other situations where antenatal anti-D prophylaxis may not be necessary include cases where a woman has opted to be sterilised after the birth of the baby or when a woman is otherwise certain that she will not have another child after the current pregnancy.

RECOMMENDATIONS

Women should be offered testing for blood group and RhD status in early pregnancy. [B]

It is recommended that routine antenatal anti-D prophylaxis is offered to all non-sensitised pregnant women who are RhD negative. (See 'Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women' [NICE technology appraisal 41], currently being updated.)

Women should be screened for atypical red cell alloantibodies in early pregnancy and again at 28 weeks, regardless of their RhD status. [B]

Pregnant women with clinically significant atypical red cell alloantibodies should be offered referral to a specialist centre for further investigation and advice on subsequent antenatal management. [D]

If a pregnant woman is RhD-negative, consideration should be given to offering partner testing to determine whether the administration of anti-D prophylaxis is necessary. [Good practice point]

9 Screening for fetal anomalies

9.1 Screening for structural anomalies

Clinical question

What is the diagnostic value and effectiveness of the following screening methods in identifying serious structural abnormalities?

- Ultrasound undertaken in 1st and 2nd trimesters
- Nuchal translucency measurement
- Serum screening – AFP

Previous NICE guidance (for the updated recommendations see below)

Pregnant women should be offered an ultrasound scan to screen for structural anomalies, ideally between 18 to 20 weeks of gestation, by an appropriately trained sonographer and with equipment of an appropriate standard as outlined by the National Screening Committee. [A]

Introduction and background

Since routine ultrasonography has been introduced into ante-natal care women have had the opportunity to visualise the fetus at an early stage of pregnancy. The ultrasound scan has been used by health professionals to assess gestational age more accurately, diagnose multiple births and to detect fetal abnormalities. Improvements in technology have enabled health professionals to identify fetal structures, both normal and abnormal, and also to identify minor abnormalities of uncertain significance, known as 'soft markers'.

Detection of fetal abnormalities on antenatal ultrasound offers women and their partners information that may help them better prepare for the birth of their child, the option of delivery in a setting that will permit rapid access to specialist surgical or medical care, and the possibility of considering pregnancy termination or palliative care in the newborn period. Routine antenatal ultrasound has therefore presented women and their partners with difficult decisions and an abnormal result on ultrasound imaging has the potential to cause great anxiety throughout the remaining weeks of pregnancy. These are important considerations with regard to the timing of routine ultrasound screening and the potential for false positive results or detection of 'soft markers'.

This review/guideline tries to highlight the areas in which ultrasound screening is thought to have a role in the prenatal diagnosis of fetal abnormalities.

Aim of screening for fetal structural abnormalities

The overall aim of fetal anomaly screening is to improve pregnancy outcomes, such as safe birth and delivery, and prevent infant death and disability.

Specifically, antenatal screening to identify fetal abnormalities should allow women and their partners:

- Reproductive choice (a choice about continuing with the pregnancy or choosing termination of pregnancy (ToP))
- Intrauterine therapy
- Managed delivery in specialist centre
- Time to prepare (for termination of pregnancy/postnatal treatment or palliative care/infant disability).

Overall aim is to improve outcomes – safe birth and delivery, later death and disability.

The criteria laid out by Wilson and Jungner/HTA to justify introducing screening fopr a disorder are that:

- Disorders to be screened for should be clinically well-defined – in this situation, which disorders are being screened for?
- The incidence of the conditions (individual malformations) should be known
- Disorders to be screened should be associated with significant morbidity or mortality
- Effective treatmen should bet available e.g. intra-uterine treatment, delivery managed in a specialist centre, and termination of pregnancy
- There should be a period before onset of the disorder (the antenatal period) during which intervention is possible to improve outcome or allow informed choice
- There should be an ethical, safe, simple and robust screening test e.g. ultrasound appears safe, ethical, acceptable
- Screening should be cost effective.

However,it is important to note that many of the studie of antenatal screening for fetalanomalise evaluate ultrasound as a suitable test rather than examine te benefits for women and babies of screening for a range of fetal anomalies during pregnancy.

Diagnostic value of routine ultrasound in second trimester

Diagnostic value of routine ultrasound in the second trimester including both multi-stage and single stage ultrasound screening was reviewed in this section.

Description of included studies

One systematic review[297] including 11 studies, and additional 12 studies[727-741] were identified from the search. The 12 studies were critically appraised against the same criteria applied to the systematic review. 6 studies were excluded either because of incomplete data or irrelevant study populations (i.e. high risk populations). Details of the inclusion/exclusion process are provided on the accompanying CD-ROM. A new systematic review of all identified primary 17 studies, 11 studies in the systematic review and 6 newly identified studies, were conducted by NCC-WCH. [EL II]

Data from one randomised controlled trial, 9 prospective cohort studies, and 7 retrospective cohort studies were extracted. 4 studies were conducted in the UK, while 4 were in the US, 4 in Scandinavia, 2 in Belgium, 2 in Greece and 1 in Korea. Details of the included studies are shown in Table 1. Meta-analysis of 11 studies on positive and negative likelihood ratios are presented in Figures 1-A, 1-B, 1-C and 1-D.

Findings

Overall sensitivity (detection rate), specificity and likelihood ratios:

The results of each study were presented in Table 1, Figures 1-A, 1-B, 1-C and 1-D. Sensitivity and specificity of detecting fetal structural abnormalities before 24 weeks of gestation reported from the included studies were 24.1% (range 13.5% to 85.7%) and 99.92% (range 99.40% to 100.00%), while overall sensitivity and specificity were 35.4%

(range 15.0% to 92.9%) and 99.86% (range 99.40% to 100.00%), respectively. Meta-analysis of likelihood ratios showed positive and negative likelihood ratios before 24 weeks of 541.54 [95%CI 430.80 to 680.76] and 0.56 [95%CI 0.54 to 0.58], respectively. Meta-analysis of likelihood ratios showed overall positive and negative likelihood ratios were 242.89 [95%CI 218.35 to 270.18] and 0.65 [95%CI 0.63 to 0.66], respectively.

Detection by RCOG category[742]:

Sensitivity (detection rate) for each condition according to the RCOG category was also sought, and presented in Table 2. Overall sensitivity for lethal anomalies was 83.6%, while that for possible survival and long-term morbidity was 50.6%, that for anomalies amendable to intra-uterine therapy 100.0%, and that for anomalies associated with possible short-term/ immediate morbidity 16.1%. The sensitivity varies depending upon each condition.

Evidence summary

Second trimester ultrasound seems to show high specificity but poor sensitivity for identifying fetal structural anomalies. Similarly this test showed good summary value for positive likelihood ratio but poor negative likelihood ratio. However, these values ranged widely by centre and condition. The 100% detection rate for conditions amenable to intrauterine treatment is anomalous and arises from the fact that these conditions had to be identified before treatment could be considered.

Diagnostic value of routine ultrasound in first trimester

Diagnostic value of routine ultrasound in first trimester to detect fetal structural anomaly was reviewed in this section.

Description of included studies

One review of literature included in a HTA[297] and additional 4 studies[300,743-746] were identified. However, only one[300,743] from the additional studies was included in this review due to methodological weakness and incomplete data. [EL III]

Findings

The review showed that there were relatively few data on screening an unselected or low risk population, as most studies report results of screening in high risk populations.[297] Results on nuchal translucency measurement are presented later in the soft markers section. The review included five studies of first trimester anomaly screening, though could not draw any conclusion because of the methodological weakness of these studies.

The additional study was published in 1999, though the study did not specify the time when it was conducted.[300,743] The description of details of the study is presented in Table 1. This was a prospective cross-sectional study at a university hospital in the UK, and included 6634 unselected women carrying 6443 fetuses. All women underwent either trans-abdominal or trans-vaginal sonography at 11 to 14 weeks. Nuchal translucency and an anatomical survey were performed. There were 6 clinicians undertaking these examinations. The incidence of an anomalous fetuses was 1.4%, and sensitivity (detection rate) was 59.0% (37/63, [95%CI 46.5 to 72.4%]). The specificity was 99.9%. Positive and negative likelihood ratios were 624.5 and 0.41. When first and second trimester scans were combined, the sensitivity was 81.0% (51/63, [95%CI 67.7 to 89.2%]).

Evidence summary

There are only a few good quality studies conducted whch examine the diagnostic value of routine ultrasound in first trimester. Although high specificity and positive likelihood ratio

were reported, sensitivity and negative likelihood ratio reported from single centre in the UK were at a moderate level.

Effectiveness of routine ultrasound in pregnancy

Clinical effectiveness of routine use of ultrasound compared with no routine use was reviewed in this section.

Routine versus selective ultrasound in before 24 weeks

Description of included studies

One systematic review examined effectiveness of routine ultrasound in early pregnancy (before 24 weeks), compared with selective ultrasound, was identified and included.[57] [EL 1+] The systematic review included 8 randomised controlled trials and 1 quasi-randomised controlled trial, involving 34251women. The quality of these trials was generally good.

Findings

Routine ultrasound screening for fetal abnormalities showed increase in termination of pregnancy for fetal abnormality (4trials, OR 3.19 [95%CI 1.54 to 6.60]), and reduction in number of undiagnosed twins (at 20weeks, 1trial, OR 0.12 [95%CI 0.03 to 0.56]; at 26weeks, 6trials, OR 0.08 [95%CI 0.04 to 0.16]) and number of induction for 'post-term' pregnancy (6trials, OR 0.61 [95%CI 0.52 to 0.72]) compared with selective ultrasound. There is borderline evidence of the effect of routine ultrasound in reducing the number of children admitted to special care (5trials, OR 0.86 [95%CI 0.74 to 1.00]) and with poor spelling at school (1trial, OR 0.73 [95%CI 0.53 to 1.00]), compared with selective ultrasound. There was no evidence of difference in other outcomes.

Evidence summary

There is high level evidence that routine, rather than selective, ultrasound in early pregnancy before 24 weeks enables better gestational age assessment, earlier detection of multiple pregnancies and improved detection of fetal abnormalities with resulting higher rate of termination of affected pregnancies. There is no good quality evidence on long-term outcomes for women and their children.

Routine versus no/concealed/selective ultrasound after 24 weeks

Description of included studies

One systematic review examined effectiveness of routine ultrasound in late pregnancy (after 24 weeks), compared with no/concealed/selective ultrasound, was identified and included.[574] [EL 1+] The systematic review included 5 randomised controlled trials and 1 quasi randomised controlled trial, involving 22202 women. Among them, three trials offered routine ultrasound in the second and third trimester versus selective ultrasound. In one New Zealand trial, all women had a second trimester scan and only the study group had a further third trimester scan. In one UK trial all women were offered second and third trimester scan but the results of the third trimester scan was revealed only for those in the study group. In another UK trial, all women had routine second and third trimester scan, though placental grading at third trimester scans was revealed only for those in the study group. The quality of these trials was generally good.

Findings

Routine ultrasound screening for fetal abnormalities after 24 weeks of gestation showed a reduction in post-term birth after 42 weeks (2trials, OR 0.69 [95%CI 0.58 to 0.81]) but the timing and manner of gestational age assessment differed between the two trials. There was no difference in the overall perinatal mortality (6 trials, OR 1.03 [95%CI 0.75 to 1.42]), stillbirths (4 trials, OR 1.15 [95%CI 0.74 to 1.79]) and neonatal mortality (4 trials, OR 1.04 [0.58 to 1.86]) between the two groups. After exclusion of babies with congenital abnormalities, a statistically significant reduction was observed only for stillbirths (2 trials, OR 0.13, [95%CI 0.04 to 0.50]), but one of the trials had incorporated placental grading into the routine third trimester scan. There was no evidence of difference in other clinically important outcomes including obstetric and neonatal interventions.

Evidence summary

Results shows a reduction in the number of post-term births and stillbirths (for normal babies) with routine third trimester ultrasound, but the evidence is not of high quality. There is no evidence of difference for other clinically important outcomes including obstetric and neonatal interventions and neonatal outcomes between routine and no routine ultrasound after 24 weeks.

Routine versus no/concealed/selective Doppler ultrasound in pregnancy

Description of included studies

One systematic review examined effectiveness of routine Doppler ultrasound in pregnancy, compared with no/concealed/selective use of Doppler ultrasound, was identified and included.[575] [EL 1+] The systematic review included 4 randomised controlled trials involving 11504 women. In one included UK trial, two different protocols were used for high and low risk populations, with the high risk group having serial Doppler examinations and the low risk group Doppler examination on two occasions (19-22 weeks and 32 weeks). The data for each population were not reported separately and it was not possible to analyse separately. Three included trials only studied umbilical artery Doppler and reported different parameters.

Findings

Meta-analysis of the four trials showed no evidence of difference in antenatal admissions, obstetric interventions, and neonatal interventions between routine and no routine use of Doppler ultrasound during pregnancy. Although one UK trial reported significantly increased perinatal mortality in the routine Doppler group compared with the no routine group, there is no evidence of difference in overall perinatal mortality.

Evidence summary

There was no evidence of difference in antenatal admissions, obstetric interventions, neonatal interventions and overall perinatal mortality between routine and no routine use of Doppler ultrasound during pregnancy.

Serial ultrasound plus Doppler versus selective ultrasound in pregnancy

Description of included studies

Two systematic reviews[297,574] reported this comparison. Both reviews included the same trial that compared effectiveness between serial ultrasound plus Doppler and selective ultrasound in pregnancy. [EL 1+] This trial compared combined intensive repeated ultrasound assessment of the fetus plus Doppler study of the umbilical and uterine arteries versus selective ultrasound. The trial included 2834 women.

Findings

The included trial reported significantly more infants with intrauterine growth retardation in the routine serial and Doppler ultrasound than in the selective ultrasound group (Birthweight $<10^{th}$ centile, OR 1.41 [95%CI 1.11 to 1.78]; birthweight $<3^{rd}$ centile, OR 1.67 [95%CI 1.11 to 2.53]), otherwise no evidence of difference in antenatal and obstetric interventions, neonatal interventions and neonatal mortality/morbidity.

Evidence summary

There is little evidence on the effectiveness of routine use of combined serial and Doppler ultrasound, compared with selective ultrasound and there is no evidence of difference in antenatal and obstetric interventions, neonatal interventions and neonatal mortality/morbidity.

First versus second trimester routine ultrasound in pregnancy

Description of included studies

There is one randomised controlled trial identified.[747;748] [EL 1+] The trial compared the antenatal detection rate of malformations in chromosomally normal fetuses between the policy of offering one routine ultrasound examination at 12weeks, including nuchal translucency measurement, and one routine ultrasound examination at 18weeks. The trial was conducted in eight hospitals in Sweden, involving 39572 unselected women. A repeat scan was offered in the 12-week scan group if the fetal anatomy could not be adequately seen at 12-14 weeks or if nuchal translucency thickness was 3.5mm or greater in a fetus with normal or unknown chromosome status.

Findings

Sensitivity of detecting fetuses with a major malformation was 38% (66/176) in the 12-week scan group, while that in the 18-week scan group was 47% (72/152). (P=0.06) In the 12-week scan group, 69% of fetuses with a lethal anomaly were detected at a scan at 12-14 weeks.

Sensitivity of detecting fetuses with a major heart malformation was 11% (7/61) in the 12-week scan group, while that in the 18-week scan group was 15% (9/60). (P=0.60). The proportion of women whose routine ultrasound was the starting point for further investigation resulting in a prenatal diagnosis was 6.6% in the 12-week group (4/61) and 15% in the 18-week group (9/60) (p=0.15)

Evidence summary

There is little evidence in the effectiveness of routine first trimester scan for detecting major fetal malformation compared with routine second trimester scan. The available evidence showed no evidence of difference in any clinical outcomes.

Fetal echocardiography

Diagnostic value and clinical effectiveness of fetal echocardiography to detect fetal cardiac anomaly was reviewed in this section.

Diagnostic value of fetal echocardiography

Description of included studies

Studies examining diagnostic value of fetal echocardiography on low-risk or unselected populations were searched. There is one systematic review including five studies and two

additional studies were identified. [749-751] Description of these studies is presented in Table 3.

Findings

Sensitivity of detecting major cardiac anomaly from included studies ranged from 16.7% to 94.0%, and that for minor cardiac anomaly ranged from 3.6% to 82.1%. Overall sensitivity of detecting cardiac anomaly ranged from 4.5% to 86.1%. Specificity was reported as 99.9% throughout.

Evidence summary

Reported sensitivity of fetal echocardiography is widely ranged by centre and condition, though reported specificity was generally high.

Effectiveness of routine use of fetal echocardiography

Description of included studies

Neither randomised controlled trial nor quasi-randomised trials were identified to address this question. There are two observational studies identified.[752;753] Neither of them controlled for the background severity of conditions.

Findings

One cohort study in France[752] compared outcome of babies between antenatally and postnatally diagnosed Transposition of Great Arteries. The study reported significantly lower preoperative mortality (postnatal diagnosis: 15/250(6.0%) versus antenatal diagnosis 0/68 (0.0%); $p<0.05$) and postoperative mortality (postnatal diagnosis: 20/235 (8.5%) versus 0/68 (0.0%); $p<0.01$) for antenatal diagnosed TGA, though there was no evidence of difference in postoperative morbidity (postnatal diagnosis 25/235 (10.6%); antenatal diagnosis 6/68 (8.8%); $p>0.05$). [EL 2+]

Another population-based study in France[753] compared detection rate of TGA and mortality for babies with TGA between three study periods. Between 1983 and 1988, antenatally diagnosed TGA was 12.5% and mortality for babies with TGA was 23.5%, whereas, between 1989 and 1994, detection rate was 48.1% and mortality was 12.0%, and between 1995 and 2000, detection rate was 72.5% and mortality was 5%.

The similar trend was reported in babies with hypoplastic left heart syndrome (HLHS). [EL 3]

Evidence summary

There was low level evidence that showed babies with antenatally diagnosed TGA had reduced mortality compared with those diagnosed after birth.

Soft markers

Diagnostic value and clinical effectiveness of ultrasound soft marker including nuchal translucency measurement to detect fetal cardiac anomaly was reviewed in this section. Nuchal translucency measurement to detect Down's syndrome was reviewed in another section.

Nuchal translucency measurement

Description of included studies

Studies examining the diagnostic value of nuchal translucency measurement of low-risk or unselected populations on detecting cardiac anomaly were searched. There is one

systematic review including eight studies and four additional studies were identified [754,755,756,757,758]. Since studies used different cut-off points; meta-analysis of these twelve studies to obtain summary likelihood ratios was conducted. (Table 4 and Figures 2-A and 2-B) Neither randomised controlled trials nor quasi-randomised controlled trials were identified to address the effectiveness of routine use of this measurement on clinical outcomes of women and their babies.

Findings

Meta-analysis of the included 11 studies showed positive likelihood ratio of 5.01 [95%CI 4.42 to 5.68] and negative likelihood ratio of 0.70 [95%CI 0.65 to 0.75].

Evidence summary

Reported sensitivity and likelihood ratios of nuchal translucency measurement to detect cardiac anomaly ranged widely by centre and condition, and generally the technique seems to have poor diagnostic value.

Use of maternal serum alpha-fetoprotein to detect structural anomalies

Diagnostic value and clinical effectiveness of biochemical marker including maternal serum alpha-fetoprotein to detect neural tube defects was reviewed in this section.

Alpha-fetoprotein to detect neural tube defects

Description of included studies

Two studies were identified.[759;760] One study investigated value of alpha-fetoprotein in screening for neural tube defects in the US. Another was a case-controlled study comparing the ability of routine ultrasound and maternal serum alpha-fetoprotein levels to detect neural tube defects in the US.

Findings

The first study[759] which investigated maternal serum alpha-fetoprotein as a screening test was conducted between 1991 and 1994 in the US, and involved 27140 women. Prevalence of neural tube defects was reported as 1.03 per 1000. Sensitivity, specificity, positive and negative likelihood ratios were reported as 85.7%, 97.6%, 35.16, and 0.15, respectively.

In the case-control study[760], an integrated database of 219000 consecutive pregnancies between 1995 and 2002 was used. Among 189 identified neural tube defects, 102 received maternal serum alpha-fetoprotein screening, and 25% of 102 cases were test negative. Of the 186 neural tube defects identified prenatally, 62% were initially detected by routine second trimester ultrasound, 37% were detected by targeted ultrasound prompted by high maternal serum alpha-fetoprotein level, and the remaining 1% was diagnosed by pathology examination after miscarriage.

Evidence summary

There are only 2 studies dealing with the diagnostic value and effectiveness of maternal serum alpha-fetoprotein level as a screening test. Results from a single study indicate maternal serum alpha-fetoprotein level to have good diagnostic value in predicting and ruling out structural anomalies, but evidence from another study shows it to have less value as a screening test than routine ultrasound. There is no evidence assessing the diagnostic value and effectiveness of combining maternal serum alpha-fetoprotein and routine ultrasound.

Women's views on screening for structural abnormalities

Three studies on women' views regarding ultrasound screening during pregnancy, their responses to detection of soft markers, and antenatal counselling by specialist staff have been included under this section.

Description of included studies

The first study was a review[297] [EL 2++] which focussed on women's views and experiences of antenatal US. As the topic was very wide, it was decided to limit the review to studies where antenatal US used for any purpose and direct data were obtained from pregnant women. Studies and reviews about prenatal screening and diagnosis were excluded. After a broad initial search to identify material related to women's views in all screening and diagnostic tests, studies related to antenatal US use were selected after going through their abstracts. A series of 6 questions was prepared – i) women's knowledge about US and what a scan can do ii) women's value about scans iii) her views about how US is conducted iv) impact of the result v) psychological impact of US, and vi) wider impact of US on society. Studies were tabulated according to the question asked and data entered accordingly.

In the second study[761] qualitative interviews were conducted to determine maternal experiences and responses to detection of a minor structural variant, the choroid plexus cyst (CPC), in their fetuses on prenatal US. 34 pregnant women with isolated CPC detected during mid-trimester scan who had already been counselled by their physicians regarding the findings at a university-based hospital in USA, were enrolled for the study. Interviews lasting approximately 15 minutes were conducted by a trained research assistant or nurse clinician at 24 weeks gestation, and no information was given about CPCs by the research team. The interview included both open-ended and more specific questions, and all were audio taped and transcribed verbatim. Common themes were identified, and several categories of responses identified for each theme. Initial validation was undertaken by an independent qualitative study consultant not involved in the research. T-test was used for comparing means and chi-square for categorical variables. Results are reported as mean ± standard deviation. [EL 3]

The aim of the last study [762] was to evaluate parental anxiety after diagnosis of a congenital malformation and to assess if counselling by a consultant pediatric surgeon and a neonatal nurse practitioner could decrease parent's psychological distress. Participants were all parents attending a Fetal Medicine Unit in the UK with an antenatal diagnosis of surgical anomaly (principally abdominal wall defects, gastrointestinal and thoracic anomalies). Subjects unable to read English and booked to deliver somewhere else were excluded. Anonymous questionnaires were used to get information and Spielberger State-Trait Anxiety Inventory (STAI) for measuring anxiety levels. It consists of 2 parts – STAI-S score measuring anxiety at the time of completing inventory, and STAI-T score measuring the inherent trait anxiety levels. Subjects were asked to complete STAI after US at the fetal centre. Then each couple had a detailed consultation with the paediatric consultant and the clinical nurse specialist. Before leaving, the subjects were given a second STAI and asked to complete and return within 1 week. A control group comprising of pregnant women with a normal US scan and uncomplicated pregnancy was recruited, and asked to complete STAI as the other group. Non-parametric tests were used for comparison, and data is quoted as medians and interquartile ranges (IQR). [EL 3]

Findings

In the first study[297], a total of 82 reports representing 64 studies were selected (including 5 studies which were added later). There was wide variation among the selected studies in terms of questions addressed, methods used, and when and where they were conducted.

The studies were not graded in terms of research quality or removed because of poor quality, although many had problems of design and reporting. This was done because in spite of poor quality, these studies gave useful information. The main findings of the review were:

Antenatal US is very attractive to pregnant women and their partners as it provides early visual confirmation of pregnancy, direct contact with their baby, and reassurance about fetal well-being. At the same time these features may augment the potential for feelings of anxiety, shock and disappointment when the scan shows a problem.

Recent trends in the use of US have led to more findings of uncertain clinical importance, and this is likely to have important psychological and social consequences for women.

Though earlier it was reported that some women feared that US might harm their babies, there is paucity of evidence about it from the later studies.

Reports of a reduction in anxiety after US examination are likely to reflect increased anxiety before the scan rather than a real benefit.

No reliable evidence is available for any positive health behaviour (e.g reduced smoking) as a consequence of antenatal US.

None of the trials comparing US use with no US use has looked at its social and psychological impact on parents and babies.

In general participants in the second study [761] were college educated (mean years of education 16.6 $\pm$ 2.5), married (85.7%), employed (100%), and had private insurance (97%). Mean maternal age was 32.2 $\pm$ 5.2 years. About 60% were primiparous and 80% had a planned pregnancy. Women's responses have been organized into categories as below:

Diagnostic situation – Mean gestational age at CPC detection was 18.86 $\pm$ 1.29 weeks. Majority of the participants (71%) were informed about CPC by an attending or local obstetrician at the conclusion of the US examination. 35% women were shown the CPC on US.

Accuracy of knowledge – Most of the women (79%) had never heard of CPC before the diagnosis. When asked about the significance of the CPC, 82% felt that it was likely benign, 71% expressed it is a marker for trisomy, and 53% mentioned that it could be both. Among those who expressed it as a marker for trisomy, 79% understood that other factors (maternal age, serum markers) also influenced the probability of trisomy. Women with positive serum screening results were less likely to describe CPC as benign compared to women with normal serum screen (OR 0.04, 95% CI 0.004-0.36, $p<0.001$). No statistically significant difference was observed between the older women (>34 years) and younger ones.

Information seeking – 77% women reported seeking additional information about CPCs beyond that given by their provider at the original scan, with most common source being the Internet. When asked about the usefulness of this additional information, 62% found it more useful than the primary information given at the time of US screening.

Subsequent testing – The majority of women (65%) already had a serum screening test before detection of CPCs. After detection of an isolated CPC and in spite of accurate counselling about low-risk, 3 women (9%) sought diagnostic tests purely for reassurance.

Affective responses – When asked in an open-ended way to describe their emotions, 88% women described intensely negative immediate reaction, with most (68%) reporting their initial reaction as temporary. But only half of the women with a reassuring serum screen

and none with abnormal a serum screen described their reaction as temporary. 68% women revealed that they continued experiencing negative emotions even after receiving the diagnostic tests results, but neither increased maternal age nor visualization of CPC on US were associated with persistence of initial negative response. The later emotional responses included anxiety (23.5%), shock/grief (26.5%), decreased attachment (14.7%), decreased pleasure in pregnancy (14.7%), and thoughts of abortion/miscarriage (11.8%), confusion (8.8%), guilt (2.9%) and fear (5.9%).

56 prospective mothers (subjects 26, control 30) completed the questionnaire in the third study [762]. The most common congenital malformation present was gastroschisis followed by diaphragmatic hernia and cystic adenomatoid malformation. Maternal age was significantly lower in subjects (median 26.5) than control group (median 32) [p = 0.006].

No significant difference was found between STAI-T scores of subjects and controls. No correlation was found between the score and maternal age or social class, and between maternal and paternal scores.

STAI-S scores of subjects were significantly higher than those of controls before paediatric consultation (p = 0.0004), but not after (p = 0.31). There was a significant reduction in the anxiety levels of both subjects' (mothers and fathers) after consultation (on comparing their scores before and after paediatric consultation) [p = 0.01 for mothers, p = 0.006 for fathers]. After grouping the subjects into fetal diagnostic groups, a significant decrease in anxiety levels was found for those with anterior abdominal defects but not with cystic adenomatoid malformation. No correlation was found between the scores and maternal age.

The study showed that there was a high anxiety state in both prospective mothers and fathers diagnosed with congenital malformations on US which is over and above that associated with pregnancy. Counselling by a specialist staff reduced levels of parental anxiety significantly.

Evidence summary

Results from a well conducted structured review show that visual confirmation of fetal well-being is the primary reason why women seek US during pregnancy. There is lack of evidence regarding its other benefits and harms.

Evidence from a qualitative study indicates that detection of an isolated CPC on antenatal US leads to negative emotions and anxiety in the majority of women, who then seek additional information from other sources. In spite of reassurance in the form of a negative serum screening test for Downs Syndrome, a few women also opt for an invasive test for confirmation.

Detection of surgically treatable congenital anomalies on antenatal US led to increased anxiety levels in the parents but counselling by specialist staff helped to alleviate it significantly.

Health economics evidence

See Appendix B for full details. All reference to the 5 chamber view in the appendix should be taken to mean the 4 chamber view plus outflow tracts.

For the health economics evidence for the combined Down's syndrome and structural anomalies screening, please see section 9.2 (Screening for Down's Syndrome)

GDG interpretation of the evidence (screening on structural abnormalities)

Routine ultrasound screening

Ultrasound appears acceptable to women. Prenatal ultrasound scanning for fetal anomalies is now undertaken at around 20 weeks (rather than 18 weeks). However the screening window should be between 18 weeks and 20 weeks and 6 days. Screening later than 20 weeks and 6 days may delay the diagnosis of an abnormality to a point where termination of an affected pregnancy becomes problematic and may involve additional procedures such as feticide.

Prevalence of fetal abnormalities and their detection rates can be evaluated either individually or after categorizing them into four groups based on the RCOG criterion – lethal anomalies, anomalies with possible survival and long-term morbidity, anomalies amenable to intra-uterine therapy, and anomalies with possible short-term or immediate morbidity (Table 2). Ultrasound cannot reassure women that their baby is normal as many abnormalities are missed. Ultrasound may not offer improved outcomes despite antenatal diagnosis, but may offer reproductive choices and the opportunity to plan intrauterine therapy or managed delivery.

Evidence from a single study shows that first trimester scan with nuchal translucency measurement is equally effective as the second trimester scan in detecting fetal malformation overall. However this may not be true for individual conditions, e.g. spina bifida is more likely to be detected by the second trimester scan, while anencephaly and anterior abdominal wall defects may be detected in the earlier scans.

There is insufficient evidence that routine ultrasound between 10 and 24 weeks improves long-term outcomes after birth.

There is no evidence to support the use of selective compared to routine ultrasound scan for fetal anomaly, gestational age determination and the diagnosis of multiple pregnancies.

Diagnostic accuracy of fetal echocardiography

Sensitivity of fetal echocardiography for detecting major malformations varies widely (from 17 to 94%) depending on gestation, skill of operator and equipment. However there is some evidence that better training leads to improved performance of fetal cardiac screening and some limited evidence that antenatal diagnosis of transposition of the great arteries leads to better outcome for the babies.

Diagnostic accuracy nuchal test: soft markers

Studies evaluating nuchal translucency as a marker of cardiac anomaly found it to have poor sensitivity. Different cut-off points across centres and for different cardiac defects affected sensitivity and false positive rates, which are important considerations for women undergoing this test.

Diagnostic accuracy AFP

AFP has lower diagnostic value than routine ultrasound in screening for neural tube defects. There is no evidence for effect on outcomes. However, the introduction of screening using AFP has led to a reduction in the number of affected babies born at term with neural tube defects.

Women's views on screening for structural abnormalities

Ultrasound screening provides reassurance if no anomaly is detected but heightens anxiety if a possible problem is identified

Recommendations

Ultrasound screening for fetal abnormalities should be routinely offered between 18 and 20 weeks.

Women should be given information regarding the purpose and implications of the anomaly scan in order to enable them make an informed choice as to whether or not to have the scan. The purpose of the scan is:

To identify fetal abnormalities and allow:

- reproductive choice (Termination of pregnancy: TOP)
- intrauterine therapy
- managed delivery in specialist centre
- parents to prepare (for TOP/palliative care/Rx/disability).

Women should be informed of the limitations of routine ultrasound screening including the fact that detection rates vary by the type of fetal abnormality.

Following the anomaly scan women should be given information of the findings to enable them to make an informed choice as to whether they wish to continue with the pregnancy or have a termination of pregnancy.

Participation in regional congenital anomaly registers is strongly recommended to facilitate the audit of detection rates.

Fetal echocardiography involving four chamber and outflow tract view is recommended as part of the routine ultrasound scan at 18-20 weeks for fetal abnormalities.

Routine screening for cardiac anomaly by nuchal translucency is not recommended.

When routine ultrasound screening is performed at 18-20 weeks for neural tube defects, alpha-feto protein testing is not required.

Research recommendation

Research should be undertaken to elucidate the relationship between increased nuchal translucency and cardiac defects.

Table 1 Description of included studies and detection rates of structural abnormalities by antenatal ultrasound (first and second trimester)

Study	Type	Population	Ultrasound screening	Number of fetuses	Prevalence of anomalous fetuses /anomalies	Detection <15weeks	Detection <24weeks	Detection >24weeks	Overall Detection	Termination of pregnancy	Termination of normal pregnancy
Chitty 1991 [297]	Retrospective	1988-1989 UK (Luton) Unselected District general hospital	By Radiographers Number of scans not mentioned Scanned at 18-20 weeks Soft markers: yes	8785 (Multiple pregnancies not mentioned)	Anomalous fetuses: 1.50% (130 fetuses) Anomalies: not reported		93 Sensitivity: 71.5% Specificity: 99.98% LR+ 3095.83 LR- 0.44		93 False-positive: 2 Sensitivity: 71.5% Specificity: 99.98%	52 0.6%	0
Shirley 1991 [297]	Retrospective	1989-1990 UK (Hillingdon) Unselected District general hospital	By Radiographers Number of scans not mentioned Scanned at 19 weeks Soft markers: no	6412 (73 multiple pregnancies)	Anomalous fetuses: 1.40% (89 fetuses) Anomalies: not reported		61 Sensitivity: 57.3% Specificity: 99.97%		51 False-positive: 1 Sensitivity: 57.3% Specificity: 99.97%	29 0.45%	0
Levi 1991 [297]	Prospective	1984-1989 Belgium (Brussels) Unselected 5 hospitals	By obstetricians, technicians and sonographers Scanned at 1st trimester, 16-20 weeks and 3rd trimester Soft markers: no	15654 (? 240 multiple pregnancies)	Anomalous fetuses: 2.30% (381 fetuses) Anomalies: 2.66% (417 anomalies)		(54) Sensitivity: (21.0%) Specificity: (100.00%) (Calculated taking only those defects exposed to scan at 12-24 weeks (n-259))	(135) Sensitivity: (37.2%) Specificity: ? (Calculated taking only those defects exposed to scan at 12-24 weeks (n-259))	154 False-positive: 8 Sensitivity: 40.4% Specificity: 99.94%	?	0

Study	Type	Population	Ultrasound screening	Number of fetuses	Prevalence of anomalous fetuses /anomalies	Detection <15weeks	Detection <24weeks	Detection >24weeks	Overall Detection	Termination of pregnancy	Termination of normal pregnancy
Luck 1992 [297]	Prospective	1988-1991 UK (Ascot) Unselected District general hospital	By radiographers Scanned at 12-14 weeks and 19 weeks Soft markers: yes	8844	Anomalous fetuses: Not reported Anomalies: 1.90% (164 anomalies)		(140) Sensitivity: (85.3%) Specificity: 99.90% (The numbers based on number of anomalies)		(140) False-positive: 3 Sensitivity: 85.3% Specificity: 99.90% (The numbers based on number of anomalies)	19 0.21%	0
Crane 1994 [297]	RCT	1987-1991 USA (RADIUS) Low risk Primary plus 28 laboratories	By technicians, physicians, sonologists and radiologists Scanned at 15-22 weeks and 31-35 weeks Soft markers: no	7575 (Multiple pregnancies not mentioned)	Anomalous fetuses: 2.30% (187 fetuses) Anomalies: (232 anomalies)		31 Sensitivity: 16.6% Specificity: 99.90%	34 Sensitivity: 18.2% Specificity: ?	65 False-positive: 7 Sensitivity: 34.8% Specificity: 99.90%	9 0.12%	0
Levi 1995 [297]	Prospective	1990-1992 Belgium (Brussels) Unselected 5 hospitals	By obstetricians, technicians, sonographers Scanned at 1st trimester, 16-20 weeks, and 3rd trimester Soft markers: no	9601 (? 209 multiple pregnancies)	Anomalous fetuses: 2.45% (235 fetuses) Anomalies: 2.81% (270 anomalies)		(69) Sensitivity: (25.6%) Specificity: Not reported (The numbers based on number of anomalies)	(109) Sensitivity: (40.4%) Specificity: Not reported (The numbers based on number of anomalies)	120 (178) False-positive: 9 Sensitivity: 51.0% (65.9%) Specificity: 99.90% (The numbers based on number of anomalies)	?	?

Study	Type	Population	Ultrasound screening	Number of fetuses	Prevalence of anomalous fetuses /anomalies	Detection <15weeks	Detection <24weeks	Detection >24weeks	Overall Detection	Termination of pregnancy	Termination of normal pregnancy
Skupski 1996 [297]	Retrospective	1990-1994 USA (Texas) Low risk Tertiary, single centre	By experienced sonographers Scanned at 18-20 weeks Soft markers: no	860 (6 twins)	Anomalous fetuses: 1.16% (20 fetuses) Anomalies: Not reported		3 Sensitivity: 15.0% Specificity: 99.90%		False-positive: 1 Sensitivity: 15.0% Specificity: 99.80%	2 0.23%	0
Magriples 1998 [297]	Retrospective	? 18months USA (Connecticut) Low risk Tertiary, single centre	By sonographers Scanned at 16-09 weeks and 3rd trimester Soft markers: yes	911 (10 twins)	Anomalous fetuses: 3.07% (28 fetuses) Anomalies: (40 anomalies)		20 Sensitivity: 71.4% Specificity: 99.40%		20 False-positive: 5 Sensitivity: 71.4% Specificity: 99.40%	6 0.67%	0
Lee 1998 [297]	Retrospective	1990-1994 Korea Low risk Tertiary, single centre	By trained obstetric fellow Scanned at 18-20 weeks and 32-34 weeks Soft markers: no	3004 (Twins excluded)	Anomalous fetuses: 0.76% (23 fetuses) Anomalies: (37 anomalies)		3(5) Sensitivity: 13.5% (13.5%) Specificity: 100.00% (The numbers based on number of anomalies)	5(6) Sensitivity: 21.7% (16.2%) Specificity: 100.00% (The numbers based on number of anomalies)	8 (11) False-positive: 0 Sensitivity: 34.8% (29.7%) Specificity: 100.00% (The numbers based on number of anomalies)	3 0.09%	?
Van Dorsten 1998 [297]	Prospective	1993-1996 USA (S.Carolina) Unselected Mixed two sites	By registered diagnostic medical sonographers Scanned at 15-22 weeks Soft markers: no	1611 (Twins excluded)	Anomalous fetuses: 1.30% (21 fetuses) Anomalies: (29 anomalies)		10 Sensitivity: 47.6% Specificity: 99.90%		10 False-positive: 1 Sensitivity: 47.6% Specificity: 99.90%	4 0.25%	0

Study	Type	Population	Ultrasound screening	Number of fetuses	Prevalence of anomalous fetuses /anomalies	Detection <15weeks	Detection <24weeks	Detection >24weeks	Overall Detection	Termination of pregnancy	Termination of normal pregnancy
Boyd 1998 [297]	Retrospective	1991-1996 UK (Oxford) Unselected Tertiary single centre	Sonographers not mentioned Scanned at 18-22 weeks Soft markers: no	33376 (? Twins)	Anomalous fetuses: 2.17% (725 fetuses) Anomalies: not reported		298 Sensitivity: 41.1% Specificity: 99.90%		298 False-positive: 15 Sensitivity: 41.1% Specificity: 99.90%	169 0.51%	2 (1 soft marker)
Whitelow 1999 [300,743]	Prospective	Not known UK (London) Unselected Single university hospital	Sonographers: 6 different clinicians Scanned at 11-14weeks either trasnabdominally or transvaginally Soft markers: yes	6443 (77 twins; 4 triplets)	Anomalous fetuses: 1.4% (92 fetuses) Anomalies: not reported	37 Sensitivity: 58.7% Specificity: 99.90%	51 Sensitivity 81.0%			36 0.56%	?
Eurenius 1999 [727]	Prospective	1990-1992 Sweden (Uppsala) Unselected Tertiary, single centre	By trained midwife Scanned at 15-22 weeks Soft markers: no	8324 (111 twins, 3 triplets)	Anomalous fetuses: 0.74% (145 fetuses) Anomalies: not reported		32 Sensitivity 22.1% Specificity 99.80%		32 False-positive: 20 Sensitivity 22.1% Specificity 99.80%	16 0.19%	?
Stefos 1999 [728]	Prospective	1990-1996 Greece (Ioannina) Unselected Tertiary, single centre	By experienced obstetricians Scanned at 18-22 weeks Soft markers: no	7236 (86 twins)	Anomalous fetuses: 2.24% (162 fetuses) Anomalies: not reported		130 Sensitivity: 80.25% Specificity: 99.88%		130 False-positive 8 Sensitivity: 80.25% Specificity: 99.88%	40 0.55%	?

Study	Type	Population	Ultrasound screening	Number of fetuses	Prevalence of anomalous fetuses /anomalies	Detection <15weeks	Detection <24weeks	Detection >24weeks	Overall Detection	Termination of pregnancy	Termination of normal pregnancy
Taipale 2004 [729]	Prospective	1994-1996 Finland (Helsinki) Low risk Tertiary, single centre	By obstetrician and trained midwives Scanned at 13-14 weeks transvaginally and 18-22 weeks transabdominally	4855 (Multiples excluded)	Anomalous fetuses: 0.7% (33 fetuses) Anomalies: not reported		16 Sensitivity 48.5% Specificity 99.96%		16 False-positive: 2 Sensitivity 48.5% Specificity 99.96%	?	?
Nakling 2005 [730]	Prospective	1989-1999 Norway (Oppland), Unselected District general hospitals	By trained midwives and obstetricians Scanned at 13-24 weeks Soft markers: no	18181 (? Multiples)	Anomalous fetuses: 1.47% (267 fetuses) Anomalies: not reported		104 Sensitivity: 39.0% Specificity: 99.94%		104 False-positive 11 Sensitivity: 39.0% Specificity: 99.94%	57 0.31%	0
Souka 2006 [731]	Prospective	2002 Greece (Athens) Unselected Tertiary, single hospital	By obstetricians Scanned at 11-14 weeks on Nuchal translucency measurement and at 22-24 weeks Soft markers: yes	1148 (? Multiples)	Anomalous fetuses: 1.21% (14 fetuses) Anomalies: Not reported		6 Sensitivity: 85.7%		13 False-positive: 3 Sensitivity: 92.9% Specificity: 99.74%	9 0.78%	?
Nikkila 2006 [732]	Retrospective	1984-1999 Denmark (Malmohus) Unselected 5 hospitals	Sonographers not mentioned Scanned at 18 weeks, some had scan at 33 weeks, as well Soft markers: yes	141240	Anomalous fetuses: 2.56% (3614 fetuses) Anomalies: not reported		503 Sensitivity: 38.9% Specificity: Not obtained		1028 False-positive 265 Sensitivity: 28.4% Specificity: 99.81%	386 0.27%	3

Study	Type	Population	Ultrasound screening	Number of fetuses	Prevalence of anomalous fetuses /anomalies	Detection <15weeks	Detection <24weeks	Detection >24weeks	Overall Detection	Termination of pregnancy	Termination of normal pregnancy
Total				277638	6074 (2.19%)	Sensitivity: 58.7% Specificity: 99.90%	Sensitivity 24.1% Specificity 99.92%		Sensitivity 35.4% Specificity 99.86%	0.36%	

Review: diagnostic value of ultrasound screening during pregnancy for structural abnormalities of fetus
Comparison: 01 Likelihood ratios of antenatal ultrasound before 24 weeks
Outcome: 01 Positive likelihood ratios

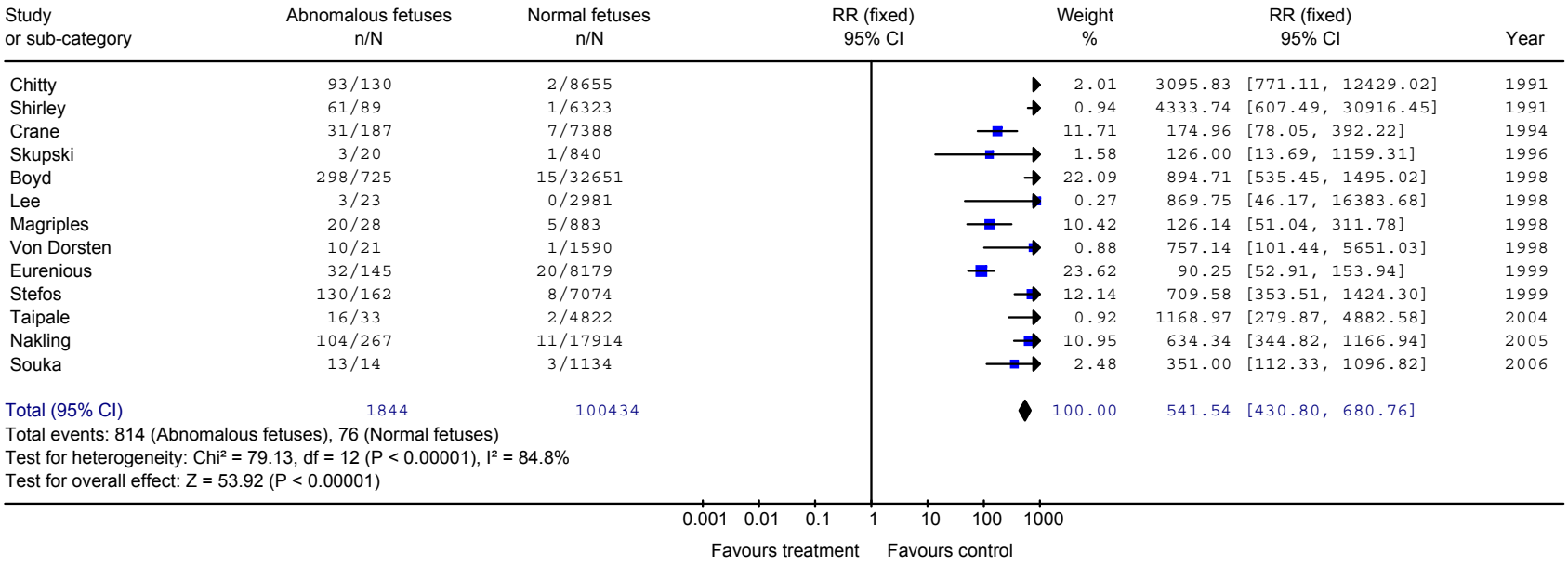


Figure 1-A Meta-analysis of positive likelihood ratios by routine ultrasound to detect fetal anomaly before 24 weeks

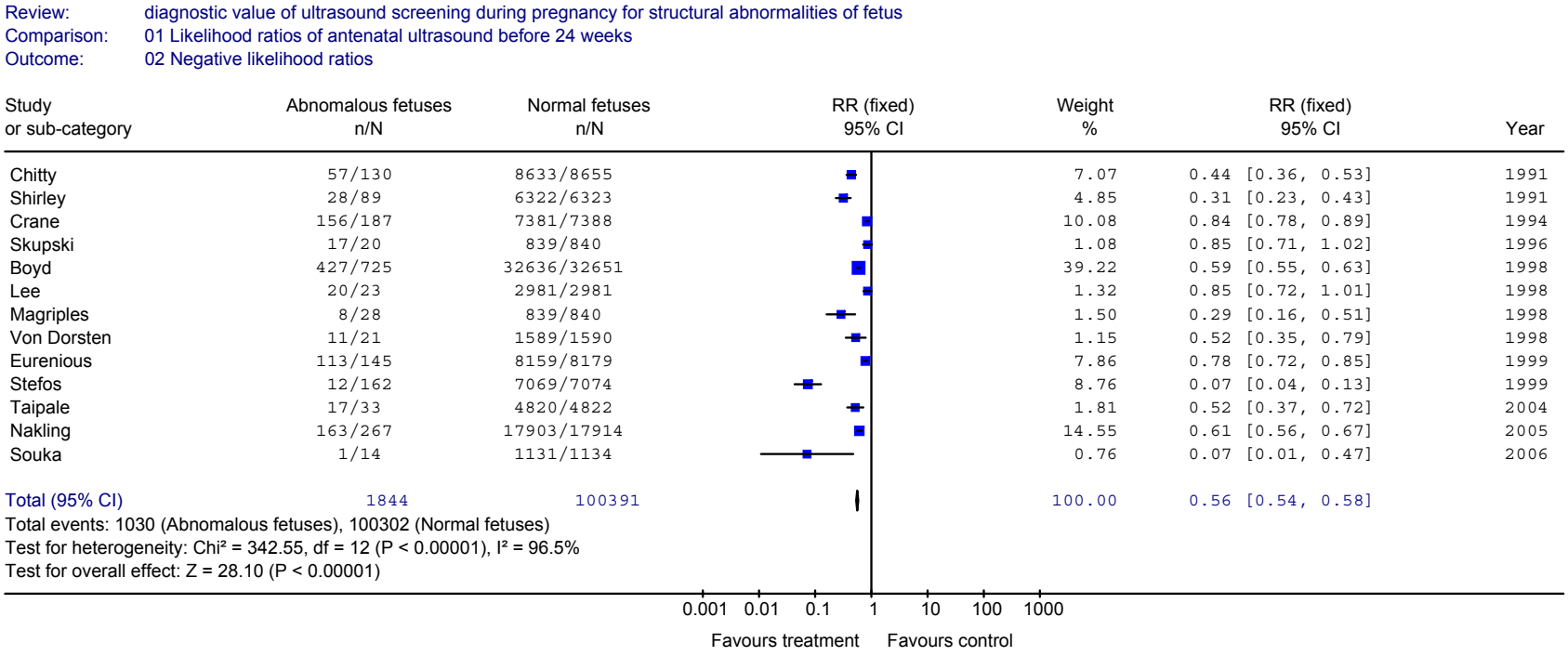


Figure 1-B Meta-analysis of negative likelihood ratios by routine ultrasound to detect fetal anomaly before 24 weeks

Review: diagnostic value of ultrasound screening during pregnancy for structural abnormalities of fetus
Comparison: 02 Likelihood ratios of antenatal ultrasound (overall)
Outcome: 01 Positive likelihood ratios

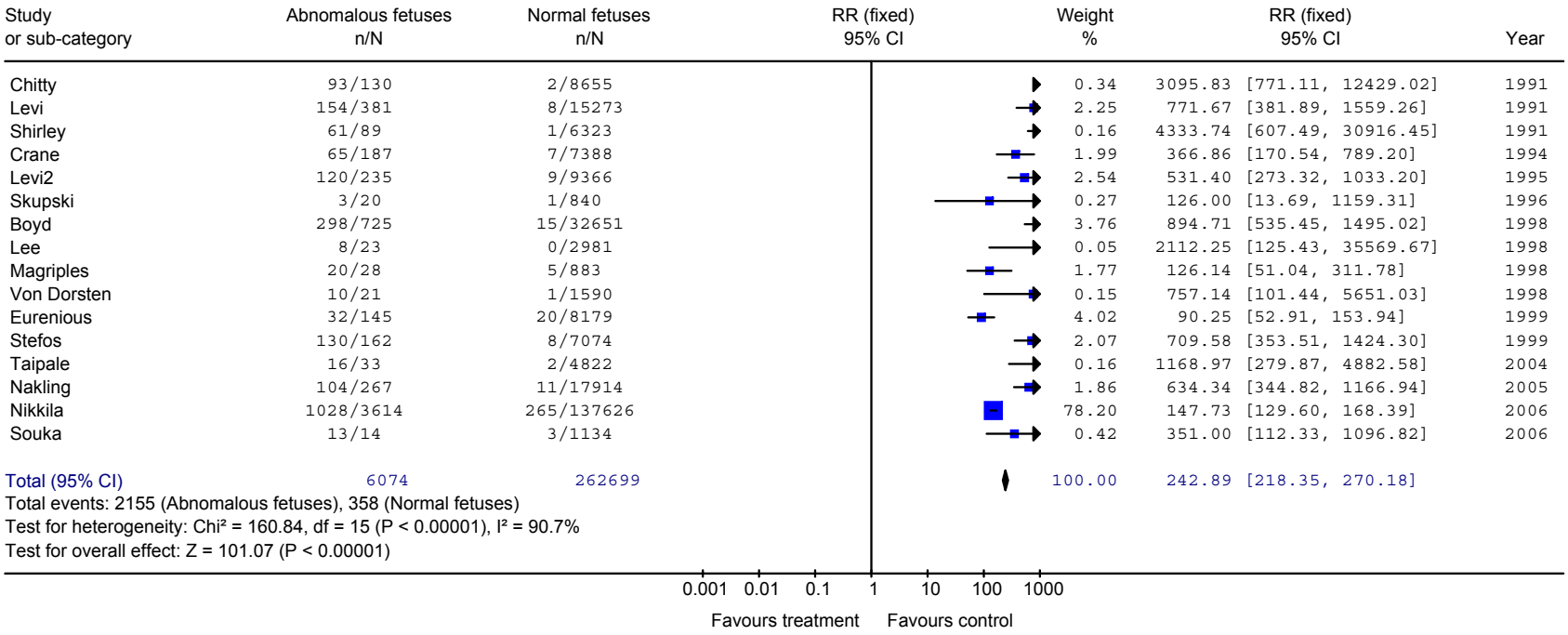


Figure 1-C Meta-analysis of overall positive likelihood ratios by routine ultrasound to detect fetal anomaly

Review: diagnostic value of ultrasound screening during pregnancy for structural abnormalities of fetus
Comparison: 02 Likelihood ratios of antenatal ultrasound (overall)
Outcome: 02 Negative likelihood ratios

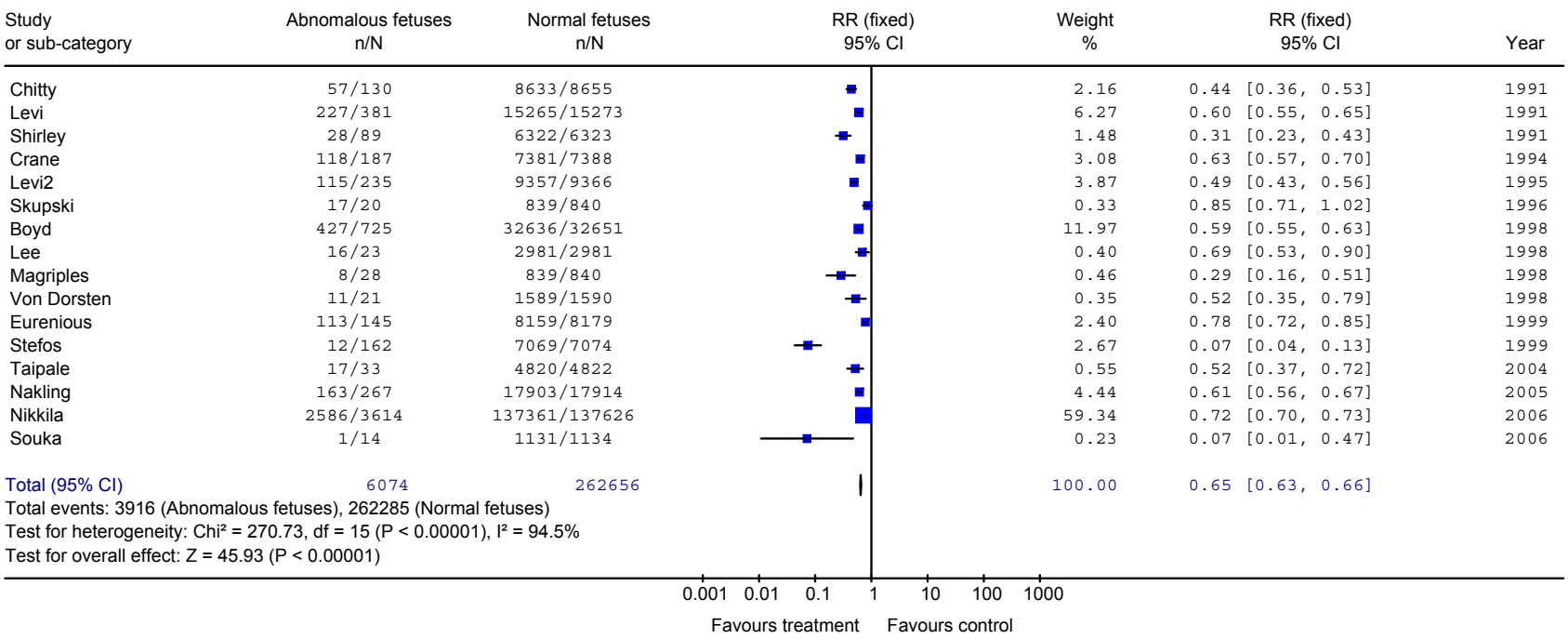


Figure 1-D Meta-analysis of overall negative likelihood ratios by routine ultrasound to detect fetal anomaly

Table 2 Prevalence and detection of congenital anomalies at second trimester antenatal ultrasound according to RCOG subgroup

	Prevalence per 1000	Chi [297]	Shi [297]	Le1 [297]	Luc [297]	Cra [297]	Le2 [297]	Sku [297]	Mar [297]	Lee [297]	Van [297]	Boy [297]	Eur [727]	Ste [728]	Tai [729]	Nak [730]	Sou [731]	Nik [732]	Total (Detection rate in %)
Number of fetus		8785	6412	15654	8844	7575	9601	860	911	3004	1611	33376	8345	7236	4855	18181	1148	141240	277638
Lethal anomalies (total)	0.74	13/16	13/13	7/11	13/17	3/3	9/13		2/3	0/3			4/5	8/10	2/7	32/40	3/3	69/69	178/213 (83.6)
Anencephaly	0.52	6/6	10/10	6/6	7/7	3/3	4/4		1/2				3/3	4/5	0/1	11/11		69/69	124/127 (97.6)
Trisomy 18	0.30	1/1	3/3							0/2					0/1	7/10	2/2		13/19 (68.4)
Trisomy 13	0.11	1/2																	1/2 (50.0)
Hypoplastic Left Heart	0.21	1/3		1/1	4/8		3/3			0/1			0/1	2/3	2/3	4/9	1/1		18/33 (54.5)
Bilateral renal agenesis	0.37	4/4			2/2				1/1					2/2	0/2	9/9			18/20 (90.0)
Lethal musculo-skeletal disorders	0.08			0/4			2/6						1/1			1/1			4/12 (33.3)
Possible survival and long-term morbidity	1.57	48/68	20/36	16/88	20/36	12/30	11/38	0/6	6/8	4/13	13/16	11/70	9/56	70/82	5/11	47/92	4/4	141/210	437/864 (50.6)
Spina bifida	0.47	5/5	3/3	2/5	2/2	4/5	4/11				2/2		3/4	8/9	2/2	6/6		71/115	112/169 (66.3)
Hydrocephalus	0.49	3/3	1/2	4/15			5/6			1/1	4/5		2/5	10/10	1/3	9/9	2/2		42/61 (68.9)
Encephalocoele	0.15	2/2	1/1	2/2	1/1				1/1				1/2			2/2			10/11 (90.9)
Holoprosencephaly	0.14	2/3		0/1	1/1				1/1	0/1						4/4			8/11 (72.7)
Down's syndrome	0.24	1/14	3/10							0/3		11/70			1/1	2/25			18/123 (14.6)
Complex cardiac	0.35	5/6	4/8	2/44	3/14	5/19	1/5	0/1	0/1		4/5		0/26	5/10		4/16			33/155

malformations																		(21.3)
AVSD	0.09			0/6			1/5	0/1		0/1			0/14	2/3			1/1		4/31 (12.9)
Non-lethal dwarfism	0.11															2/2			2/2 (100.0)
Anterior abdominal wall defects	0.33	4/4	2/2	4/4	4/4	1/1				1/1	1/1		2/2	4/4	1/3	4/5		49/55	77/86 (89.5)
- Gastroschisis	0.19	3/3	1/1	2/2	2/2	1/1				1/1	1/1			2/2	0/1	3/3			16/17 (94.1)
- Exomphalos	0.16	1/1	1/1	2/2	2/2				1/1					2/2	1/2	1/2			11/13 (84.6)
CDH	0.15	2/2	2/3	1/3	2/5	1/1	0/2			0/2	1/2		0/3	4/4		0/5	1/1	21/40	35/73 (47.9)
Tracheo-oesophageal atresia	0.03	0/2		1/7	0/1	0/3				0/1	1/1		0/7		0/1	0/4			2/27 (7.4)
Small bowel obstruction/ atresia	0.13	0/1	0/1	0/1	1/1	1/1	0/9			0/1			0/3	11/12	0/1	0/1			13/32 (40.6)
CAML	0.25	4/4	1/1		1/1														6/6 (100.0)
Renal dysplasia (bilateral)	0.77	2/3	0/1						1/1		?			16/20		13/13			32/38 (84.2)
Multiple abnormality/ syndrome	0.67	18/19	3/4		5/6			0/4	2/3	2/2			1/4	10/10		1/2			42/54 (77.8)
Anomalies amendable to intra-uterine therapy																3/3			3/3 (100.0)
Obstructive uropathy																2/2			2/2 (100.0)
Pleural effusion or hydrothorax																1/1			2/2 (100.0)
Anomalies associated with possible short-term/ immediate	0.38	12/28	4/16	4/51	8/9	5/53	3/49	1/11	2/3	0/12	0/3	27/78	0/29	15/26		1/54	0/1	21/240	103/663 (15.5)

morbidity																			
Non complex cardiac abnormalities																			
- ASD/VSD	0.09	1/1	1/1	0/26	0/1	0/19	0/25	0/6	0/1	0/4	0/3		0/19	7/15		0/23			9/144 (6.3)
- Isolated valve abnormalities	0.10	0/1		0/1	2/2		2/7		1/1				0/10						5/22 (22.7)
Facial clefts	0.20	2/9	3/9			3/10		0/2		0/6		12/25		4/7		1/24	0/1	21/240	46/333 (13.8)
Talipes	0.27	6/12	0/6	4/24	2/2	2/24	1/17	0/2		0/2		15/53				0/7			30/149 (20.1)
Renal dysplasia (unilateral)	0.49	3/5			4/4			1/1	1/1		?			4/4					13/15 (86.7)

Table 3 Diagnostic value of fetal echocardiography: description of included studies and reported sensitivity and specificity

Study Study design	Setting	Ultrasound methods	Study population	Sensitivity	Specificity
Rustico 1995[749] Prospective study	Italy Tertiary referral centre	20-22 weeks Four-chamber view plus outflow tracts 5/3.5 MHz Results confirmed by neonatal and paediatric examination, autopsy postnatally (neonatal echo and ECG, 24month follow up)	Low risk women N=7024 Prevalence of congenital heart disease: 9.3 per 1000	Major defects: 84.6% [95%CI 54.6 to 98.1] Minor defects 23.1% [95%CI 12.5 to 36.8] Non-structural defects/ arrhythmias Not reported All defects 35.4% [95%CI 23.9 to 48.2]	Major defects: 99.9% [95%CI 99.9 to 100] Minor defects 99.9% [95%CI 99.9 to 100] Non-structural defects/ arrhythmias Not reported All defects 99.9% [95%CI 99.8 to 99.9]
Anandakumar 2002[749] Retrospective study	Singapore Tertiary referral centre	21-22 weeks Four-chamber view plus outflow tracts, and Doppler colour-flow mapping if suspected 5/3.5MHz Results confirmed by neonatal examination (6months follow up)	Unselected women N=39808 Prevalence of congenital heart disease: 7.6 per 1000	Major defects: 94.0% [95%CI 84.4 to 98.5] Minor defects 82.1% [95%CI 76.5 to 86.9] Non-structural defects/ arrhythmias 95.2% [95%CI 76.2 to 99.9] All defects 85.4% [95%CI 80.9 to 89.2]	Major defects: 100.0% [95%CI 99.9 to 100] Minor defects 99.9% [95%CI 99.9 to 99.9] Non-structural defects/ arrhythmias 99.9% [95%CI 99.9 to 99.9] All defects 99.9% [95%CI 99.9 to 99.9]
Hafner 1998[749] Prospective study	Austria District general hospital	22 and 34 weeks Four-chamber view plus outflow tracts, and Doppler colour-flow mapping if suspected Results confirmed by neonatal examination (neonatal echo)	Low risk women N=6541 Prevalence of congenital heart disease: 13.6 per 1000	Major defects: 87.5% [95%CI 65.1 to 97.9] Minor defects 32.4% [95%CI 21.5 to 44.8] Non-structural defects/ arrhythmias 83.3% [95%CI 17.7 to 19.9] All defects 46.1% [95%CI 35.4 to 57.0]	Major defects: 99.9% [95%CI 99.9 to 100] Minor defects 99.9% [95%CI 99.9 to 100] Non-structural defects/ arrhythmias 99.9% [95%CI 99.9 to 100] All defects 99.6% [95%CI 99.5 to 99.8]
Achiron 1992[749] Prospective study	Israel Tertiary referral centre	18-24 weeks Four-chamber view plus outflow tracts, and Doppler colour-flow mapping if suspected 5/3.5MHz Results confirmed by neonatal examination and autopsy (Neonatal echo)	Low risk women N=5347 Prevalence of congenital heart disease: 4.3 per 1000	Major defects: 83.3% [95%CI 55.6 to 97.1] Minor defects 50.0% [95%CI 11.8 to 88.2] Non-structural defects/ arrhythmias 87.5% [95%CI 28.4 to 99.9] All defects 78.3% [95%CI 56.3 to 92.5]	Major defects: 99.9% [95%CI 99.9 to 100] Minor defects 99.9% [95%CI 99.9 to 100] Non-structural defects/ arrhythmias 99.9% [95%CI 99.9 to 100] All defects 99.9% [95%CI 99.9 to 100]

Stumpflen 1996[749] Prospective study	Austria Tertiary referral centre	18-28 weeks Four-chamber view plus outflow tracts and Doppler colour-flow mapping 3.5MHz Results confirmed by neonatal examination and autopsy (diagnostic investigations)	Low risk women N=2181 Prevalence of congenital heart disease: 7.8 per 1000	Major defects: Not reported Minor defects Not reported Non-structural defects/ arrhythmias Not reported All defects 86.1% [95%CI 61.9 to 97.6]	Major defects: Not reported Minor defects Not reported Non-structural defects/ arrhythmias Not reported All defects 99.9% [95%CI 99.8 to 100]
Buskens 1996[750] Prospective study	Netherlands Tertiary referral centre	16-24 weeks Four-chamber view plus outflow tracts 3.5Mhz Results confirmed by neonatal examination and autopsy (Neonatal echo)	Low risk women N=5319 Prevalence of congenital heart disease: 8.3 per 1000	Major defects: 16.7% [95%CI 2.1 to 48.4] Minor defects Not reported Non-structural defects/ arrhythmias Not reported All defects 4.5% [95%CI 0.6 to 15.0]	Major defects: Not reported Minor defects Not reported Non-structural defects/ arrhythmias Not reported All defects 99.9% [95%CI 99.8 to 100]
Tegnander 2006[751] Prospective study	Norway Tertiary referral centre	16-22 weeks Four-chamber view plus outflow tracts for first 5 years, then four-chamber view plus outflow tract plus venous return for next 5 years 5/3.5Mhz Results confirmed by neonatal examination and autopsy (Neonatal echo)	Unselected women N=29460 Prevalence of congenital heart disease: 14.6 per 1000	Major defects: 56.7% [95%CI 46.9 to 66.5] Minor defects 3.6% [95%CI 3.4 to 3.8] Non-structural defects/ arrhythmias Not reported All defects 15.6% [95%CI 12.1 to 19.0]	Major defects: Not reported Minor defects Not reported Non-structural defects/ arrhythmias Not reported All defects Not reported

Table 4 Diagnostic value of Nuchal translucency measurement on fetal cardiac anomaly

Study Study design	Ultrasound measurement	Population	Cut-off	Sensitivity	Specificity	Likelihood ratios
Bilardo 1998[754] Prospective study	10-14weeks	N=1590 Excluded chromosomal abnormalities=50	3.0mm or greater	2/4 50.0%	1541/1586 97.2%	+ LR = 17.6 [6.35 to 48.94] - LR = 0.51 [0.19 to 1.37]
Hafner 1998[754] Prospective study	10-13weeks	N=4214 Excluded chromosomal abnormalities=19	2.5mm or greater	4/14 28.6%	4141/4200 98.6%	+ LR = 20.34 [8.55 to 48.36] - LR = 0.72 [0.52 to 1.01]
Josefsson 1998[754] Prospective study	CRL 31-84mm	N=1460 Excluded chromosomal abnormalities=0	2.5mm or greater	5/13 38.5%	1318/1447 91.1%	+ LR = 4.31 [2.13 to 8.75] - LR = 0.68 [0.44 to 1.04]
			3.5mm or greater	0/13 0.0%	1441/1447 99.6%	
Hyett 1999[754;763] Retrospective study	10-14weeks	N=29154 Excluded chromosomal abnormalities=323	Greater than 95th centile	28/50 56.0%	27310/29104 93.8%	+ LR = 9.08 [7.08 to 11.66] - LR = 0.47 [0.34 to 0.64]
			Greater than 3.5mm	20/50 40.0%	28809/29104 99.0%	
Schwarzler 1999[754;764] Prospective study	10-14weeks	N=4474 Excluded chromosomal abnormalities=23	2.5mm or greater	1/9 11.1%	4344/4465 97.3%	+ LR = 4.10 [0.64 to 26.24] - LR = 0.91 [0.73 to 1.15]
Michailidis 2001[754;765] Retrospective study	12-13weeks	N=6606 Excluded chromosomal abnormalities=44	Greater than 95th centile	4/11 36.4%	6364/6595 96.5%	+ LR = 10.38 [4.70 to 22.92] - LR = 0.66 [0.42 to 1.03]
			Greater than 99th centile	3/11 27.3%	6525/6595 98.9%	
Marides 2001[754;766] Prospective study	10-14weeks	N=7339 Excluded chromosomal abnormalities, not defined	2.5mm or greater	4/26 15.4%	7059/7313 96.5%	+ LR = 4.43 [1.78 to 11.0] - LR = 0.88 [0.74 to 1.03]
			3.5mm or greater	3/26 11.5%	7256/7313 99.2%	
Orvos 2002[754] Retrospective study	10-13weeks	N=3655 Excluded chromosomal abnormalities=15	3.0mm or greater	18/35 51.4%	3537/3620 97.7%	+ LR = 22.43 [15.25 to 32.99] - LR = 0.50 [0.35 to 0.70]
Atzei 2005[756] Prospective study	11-13weeks	N=6921 Chromosomal abnormalities excluded (no	95th centile or greater	105/132 79.5%	3454/6789 50.9%	

		number obtained)	3.5mm or greater	64/132 48.5%	5776/6789 85.1%	+ LR = 3.25 [2.70 to 3.91] - LR = 0.61 [0.51 to 0.71]
			4.5mm or greater	41/132 31.1%	6407/6789 94.4%	
			5.5mm or greater	28/132 21.2%	6596/6789 97.2%	
Bahado-Singh 2005[755] Retrospective study	10-13weeks	N=8167 Excluded chromosomal abnormalities=101	2.0mm or greater	8/21 38.1%	6744/8146 82.8%	
			2.5mm or greater	3/21 14.3%	7771/8146 95.4%	+ LR = 3.10 [1.08 to 8.89] - LR = 0.90 [0.75 to 1.07]
			3.5mm or greater	1/21 4.8%	8104/8146 99.5%	
Westin 2006[757] Retrospective study	12-14 weeks	N=16383 Excluded chromosomal abnormalities=80	Greater than 95th centile	8/55 14.5%	15902/16328 97.4%	+ LR = 5.58 [2.92 to 10.65] - LR = 0.88 [0.79 to 0.98]
			3.0mm or greater	5/55 9.0%	16197/16328 99.2%	
			3.5mm or greater	3/55 5.4%	16279/16328 99.7%	
Simpson 2007[758] Retrospective study	10 3/7 to 13 6/7 weeks	N=34,266 Excluded chromosomal abnormalities=104	2.0 MoM or greater (98.3rd centile)	8/52 15.4%	33653/34214 98.4%	+ LR = 9.38 [4.93 to 17.84] - LR = 0.86 [0.77 to 0.97]
			2.5 MoM or greater (99.4th centile)	7/52 13.5%	34012/34214 99.4%	
			3.0 MoM or greater (99.7th centile)	5/52 9.6%	34118/34214 99.7%	
Total						+ LR = 5.01 [4.42 to 5.68] - LR = 0.70 [0.65 to 0.75]

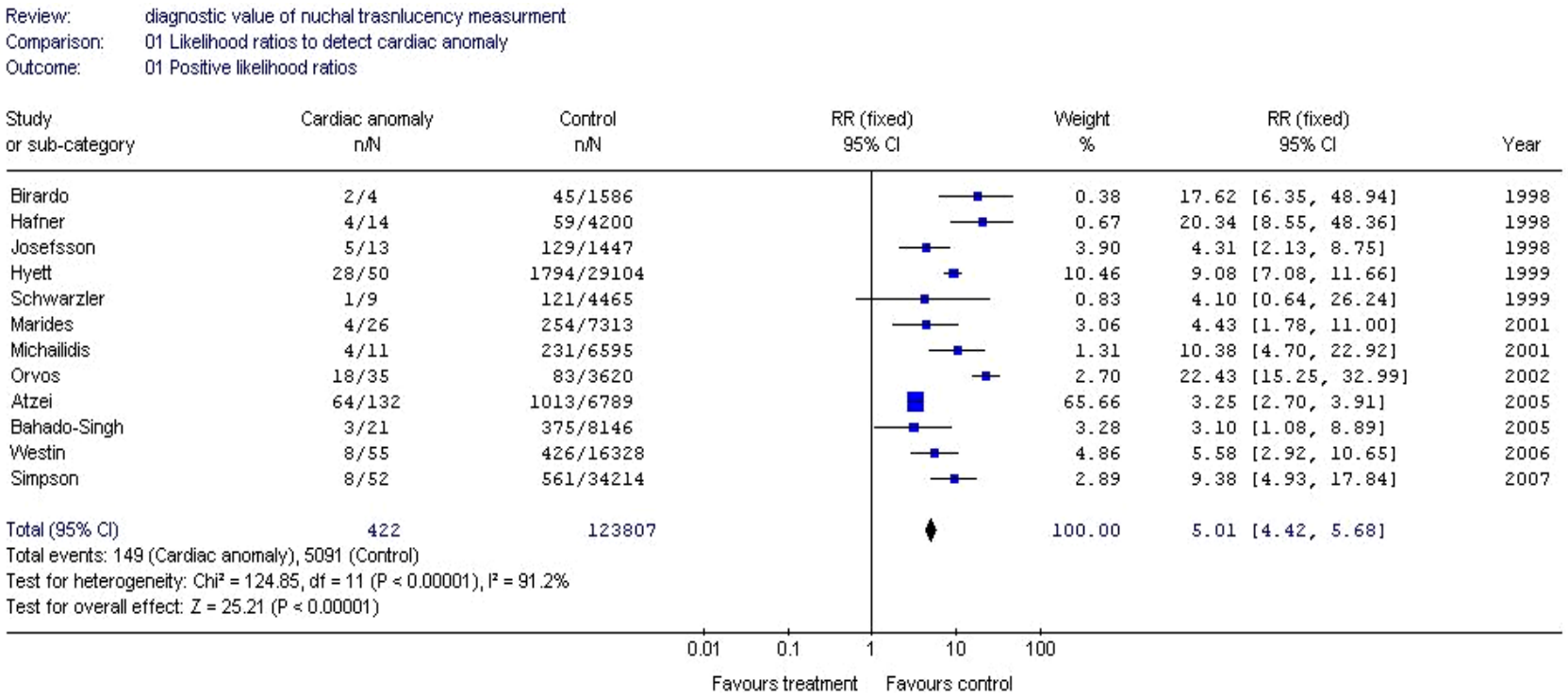


Figure 2-A Meta-analysis of positive likelihood ratios by nuchal translucency measurement to detect fetal cardiac anomaly

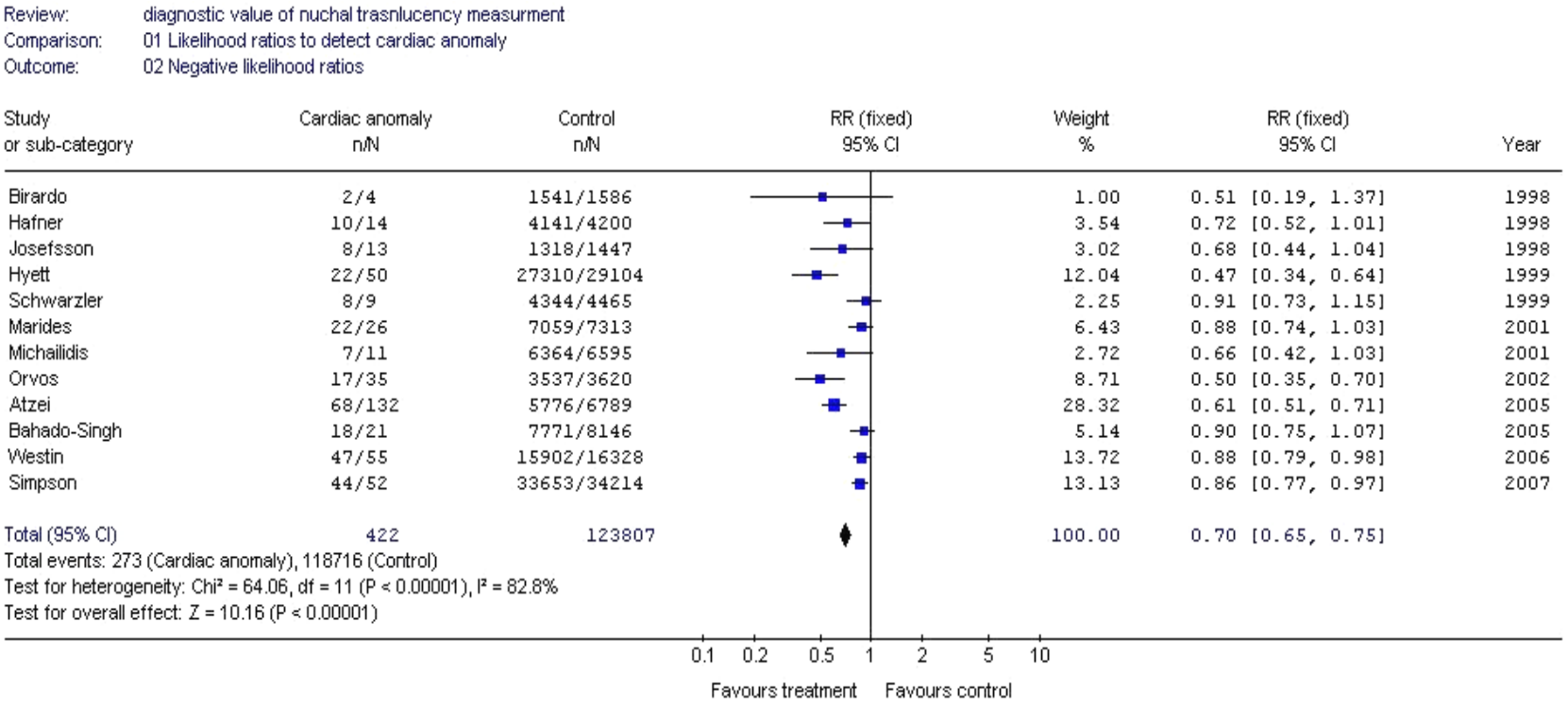


Figure 2-B Meta-analysis of negative likelihood ratios by nuchal translucency measurement to detect fetal cardiac anomaly

9.2 Screening for Down's syndrome

Clinical question

What is the diagnostic value and effectiveness of the following screening methods in identifying babies with Down's Syndrome?

- Blood tests
- Nuchal translucency
- Maternal age
- Ultrasound – soft markers (choroid plexus cyst, thickened nuchal fold, echogenic intracardiac focus, echogenic bowel, renal pyelectasis, humeral and femoral shortening)
- Ultrasound – nasal bone
- Different timings include:

  i. First trimester
  ii. Second trimester
  iii. Integrated

Previous NICE guidance (for the updated recommendations see below)

Pregnant women should be offered screening for Down's syndrome with a test that provides the current standard of a detection rate above 60% and false positive rate of less than 5%.

By April 2007, pregnant women should be offered screening for Down's syndrome with a test which provides a detection rate above 75% and false positive rate of less than 3%. These performance measures should be age standardised and based on a cutoff of 1/250 at term.

Pregnant women should be given information about the detection rates and false positive rates of any Down's syndrome screening test being offered and about further diagnostic tests that may be offered. The woman's right to accept or decline the test should be made clear.

Introduction and Background

Also known as Trisomy 21

Incidence in UK in 1998 was 6.2/10000 live births.

Main clinical feature is intellectual impairment and about 80% are affected with profound to severe intellectual disability.

Increased incidence of cardiac malformations with 46% babies affected.

In later life there is increased incidence of leukaemia, thyroid disorders, epilepsy and Alzheimer's disease.

Diagnostic accuracy tests

Some studies have presented data on the screening performance as observed directly, while others have estimated diagnostic accuracy based on the study results. Where possible, results have been presented using a fixed false-positive rate (FPR) of 5% (wherever calculated) in order to allow comparison between the findings, but the unadjusted results are also given.

The included studies have been stratified according to

a) The timing of the screening test, that is, conducted in the first trimester only, in the second trimester only, or both, and
b) The type of abnormality detected – babies with Down's syndrome only or both Down's syndrome and other chromosomal anomalies.

First trimester studies

Description of included studies

A total of 15 studies have been included under first trimester screening. Initially 9 studies were identified for inclusion - all prospective cohort, including 6 multi-centre, studies. Objectives in all studies have been clearly defined. Three studies comprised an unselected population, one both selected and unselected, and five selected population only. Except for a single study [767], the screening test and the quality measures used to monitor the study were adequately explained. All the studies used a validated reference test (karyotyping or postnatal assessment of babies or pregnancy records). The screening tests were performed before the reference tests in most studies, but it is difficult to ascertain blinding of the reference test operator. As the three studies on nasal bone gave conflicting results, six more studies were reviewed. All these studies were prospective cohorts but the quality of the studies was not good (all are Evidence Level III studies either due to selected population, incomplete follow-up or inadequate quality control).

Findings

The first trimester studies have been divided into the anomalies they looked at:

a) Down's syndrome and other chromosomal anomalies – Three studies evaluated the serum combined test [768],[769],[770] and three fetal nasal bone on ultrasound [771],[772],[773]. These studies have been tabulated in Table I A1 and Table I A2 respectively. The additional 6 studies on evaluation of fetal nasal bone[771],[774], [773], [775], [776], [777] are given in Table I A3.

Results from a good quality cohort with large sample size [768] showed serum combined test to have a DR of 92.6% at FPR of 5.2% for the detection of DS, and slightly lower DR for T18/13 and other chromosomal anomalies. Similar results were observed in another study [770], while the third study [769] showed lower DR but higher FPR for the combined test.

Conflicting results were seen for the diagnostic accuracy of fetal nasal bone (Table I A2). While one study [772] showed fetal nasal bone to increase the DR of DS from 90 to 93% (fixed FPR 5%) compared to using combined test only, the other study [771] showed it to have very poor diagnostic value. The third study [773] had variable diagnostic accuracy results for the selected and unselected population.

Results from the additional 6 studies evaluated for fetal nasal bone have also been inconclusive and wide variation was observed in them (Table I A3). In two studies [771], [773] it improved the DR compared to using serum combined test alone, but in one study [775] there was a reduction in the DR. The sensitivity and DR of fetal nasal bone alone in rest of the studies varied from 32% to 70%.

From these nine included studies on nasal bone characteristics, various factors have been identified which seem to influence the finding of absent nasal bone on first trimester ultrasound. These factors are experience/training of the ultrasound operator, gestational age at which ultrasound is conducted - ideally CRL to be more than 45 mm as ossification of nasal bone starts after this age, type of population screened – low-risk or high-risk, and marker used for diagnosis – complete absence or hypoplasia of the nasal bone.

b) Down's syndrome only – Diagnostic accuracy results of the three included studies for serum combined test were similar (Table I B). While one multi-centre study [778] found DR of 79.6% at FPR of 2.9%, the other two showed DR of 90.3% and 82% at a fixed FPR of 5%.

Table I A1 First trimester screening for Down's syndrome and other chromosomal anomalies

Study ID	**34245**	**34291**	**34276**
	768	769	770
Type of study	Prospective Cohort	Prospective Cohort	Prospective Cohort
(Year of publication)	(2005)	(2003)	(2004)
Period	1998-2003	Not specified	3 years
Setting	6 hospitals, 1 fetal medicine unit UK	12 prenatal diagnostic centres USA	ANC clinic of 1 hospital UK
Study population	Unselected (booked for maternity care)	Selected (12 diagnostic centres) (Small sample)	Selected (75% screening uptake, 27% ≥ 35 years)
Exclusions	Adequately described	Adequately described	Adequately described
Test conducted	Combined (NT + β-HCG + PAPP-A)	Combined	Combined
Monitoring of test quality	Adequate	Adequate	Adequate
Validated Reference standard	Yes (prenatal karyotype, pregnancy records)	Yes (karyotype-pre/postnatal, pregnancy records)	Yes (prenatal karyotype, pregnancy records)
Sample size (% of study population)	75,821 (96.7)	8216 (93.2)	5000 (98.3)
Maternal age	Median – 31 Range – 13 to 49	Mean – 34.5 SD – 4.6	Median – 31.5 Range – 14 to 45

Number of cases	DS 325 (0.43)	DS 61 (0.74)	DS 15 (0.3)
(Prevalence in %)	T18/13 122 (0.16)	T18 11 (0.13)	All 26 (0.52)
	Others 97 (0.13)		
Results			
	Estimated Detection Rate for FPR 5.2%	Observed Detection Rate & FPR (with 95%CI)	Observed Detection Rate
	DS 92.6	*DS* 85.2 (73.8-93.0) with FPR 9.4% (8.8-10.1)	*DS* 93 at FPR 5.9%
	T 18/13 88.5		
	Others 85.6	*T 18* 90.9 (58.7-99.8) with FPR 2% (1.7-2.3)	*All* 96 at FPR 6.3%
Risk cut-off	≥ 1 in 300 for all	1:270 for DS, 1:150 for T 18	≥ 1:250 for all
Evidence level	Ib	II	II

Study 34245: Apart from estimating diagnostic accuracy of combined test, it also evaluated potential impact of individual risk oriented two-stage screening using three new ultrasound markers. The population was subdivided into high risk (risk > 1 in 100), intermediate risk (1 in 101 to 1 in 1000), and low risk (< 1 in 1000). The intermediate risk group was further assessed by first trimester ultasound using: absence of nasal bone, abnormal doppler waveform in ductus venosus or presence of tricuspid regurgigation. Using a risk cut-off of 1 in 100, detection rate (DR) and fasle positive rate (FPR) were found to vary with the method used – absence of nasal bone (DR 92% with FPR 2.1%), abnormal ductus venosus waveform (DR 94.2% with FPR 2.7%), and tricuspid regurgitation (DR 91.7% with FPR 2.7%).

Study 34291: For Downs syndrome, the estimated DR for fixed FPR of 5% at the same risk was 78.7% (95% CI 66.3 – 88.1), and for fixed FPR of 1% was 63.9% (95% CI 50.6 – 75.8).

Study 34276: The study was carried out following poor nuchal translucency measurements obtained from an earlier study (Study ID 11194 given under first trimester screening for Downs's syndrome only). Efforts were made to allow more time for nuchal translucency measurement and compulsory quality control of all ultrasound operators was introduced.

Table I A2 First trimester screening for Down's syndrome and other chromosomal anomalies using nasal bone evaluation

Study ID	**34233**	**34199**	**34264**
	771	772	773
Type of study	Prospective Cohort	Prospective Cohort	Prospective Cohort
(Year of publication)	(2005)	(2006)	(2006)
Period	8 months	2001-2004	2001-2003
Setting	15 specialist centres USA	1 fetal medicine unit UK	1 fetal medicine unit UK
Study population	Selected (Small sample)	Selected (Single centre)	Both Unselected & Selected (Routine ANC & referrals)
Exclusions	Adequately described	Adequately described	Adequately described
Test conducted	Fetal nasal bone (NB)	Combined ± NB	Fetal nasal bone (NB)
Monitoring of test quality	Adequate	Adequate	Adequate
Validated Reference standard	Yes (prenatal karyotype, pregnancy records)	Yes (karyotype, pregnancy records)	Yes (prenatal karyotype, pregnancy records)
Sample size	6228	20,418	7626 *Selected* - 6.7%
(% of study population)	(98.5)	(96.9)	(100) *Unselected* – 93.3%
Maternal age	Mean – 30.1, SD – 5.7 Range – 16 to 47	Median – 35 Range – 18 to 50	Median – 31.6 Range – 14.5 to 50.2
Successful NB image	4801	20,175	6872 *Selected* 91.8%
(% of sample size)	(75.9)	(98.8)	(90.1) *Unselected* 90%

Number of cases	DS	11 (0.18)	DS	140 (0.68)	DS	35 (0.5)
(Prevalence in %)	T18	2 (0.03)	T18	40 (0.13)	*Selected*	23 (4.5)
	All	13 (0.21)	Others	73 (0.36)	*Unselected*	12 (0.2)
					All	64 (0.8)

Results

Observed Detection Rate & FPR (with 95% CI)		Estimated Detection Rate (Risk 1:51 to 1:1000)	Observed performance (with 95%CI)		
		FOR DS CASES ONLY		FOR DS CASES ONLY	
DS	0 (no case detected)	*Combined*		*Selected*	*Unselected*
		90 with 5% FPR	Sensit.	47.6 (25.7-70.2)	16.7 (2.1-48.4)
All	7.7 (0.2-36)	*Combined + NB*	Specif.	95.3 (92.9-97.1)	97.3 (96.9-97.7)
	with FPR 0.3 (0.2-0.5)	93.6 with 5% FPR	PPV	33.3 (17.3-52.8)	1.1 (0.1-4.1)
			NPV	97.4 (95.3-98.7)	99.8 (99.7-99.9)

Evidence level II II II

Study 34233: This study was a part of a larger prospective muti-centric trial evaluating the diagnostic accuracy of both First & Second trimester screening. NB assessment was started in the last 8 months of the trial.

Study 34276: Absence of NB was evaluated in all the study subjects undergoing Combined test, and also in a sequential manner for women having risk between 1 in 51 to 1 in 1000 based on combined test. The results were the same under both conditions.

Study 34264: The study population consisted of both selected and unselected population. Different values for these have been given in the table.

Table I A3 First trimester screening for Down's syndrome using nasal bone evaluation – additional studies

Study ID	**34293**	**34265**	**34254**
	779	774	780
Type of study	Prospective Cohort	Prospective Cohort	Prospective Cohort
(Year of publication)	(2006)	(2006)	(2005)
Period	2002-2004	2003-2004	Not specified
Setting	1 reference centre France	1 fetal medicine unit Spain	1 fetal medicine unit Italy
Study population	Both Unselected & Selected (Single reference centre)	Selected (Single centre, Only 45% participated)	Selected (Details not specified)
Exclusions	Adequately described	Not described	Not described
Test conducted	NT ± NB	Fetal nasal bone (NB)	Combined ± NB
Monitoring of test quality	Adequate	Adequate	Adequate
Validated Reference standard	Yes (prenatal karyotype, pregnancy records)	Yes (karyotype, pregnancy records)	Yes (prenatal karyotype, pregnancy records)
Sample size	2044 *Selected* - 33%	1800	2411
(% of study population)	(91.5) *Unselected* – 67%	(45)	(Not specified)
Maternal age	Median - 32 Range – 16 to 47	Mean – 30.09, SD 5.37 Range – 15 to 46	Mean – 30.5, SD - 4.115
Successful NB image	1260	1682	2411
(% of sample size)	(61.6)	(93.4)	(100)

Number of cases (Prevalence in %)	DS 30 (1.47) T18 14 (0.68) Others 35 (1.71)	DS 7 (0.39) Others 3 (0.17)	DS 15 (0.62)
Results			
	i) Observed performance for DS Risk 1:250 (NT), ≤ 0.60 MoM (NB)	Observed performance of NB for DS	i) Observed performance of NB for DS
	NT / *NT + NB* ST 88 (86-90) / 100 FPR 23 (21-26) / 5 (3-6)	ST 33.3 (4.3-77.7) FPR 1.13 SP 98.9 (98.5-99.4) PPV 9.5 (1.2-30.4) NPV 99.7 (99.4-99.9)	ST 53.3 (26.6-78.7) SP 99.5 (99.3-99.8) PPV 47.1 (23.3-70.8) +LR 142 (63-318) -LR 0.47 (0.27-0.80)
	ii) Performance of only NB ST 32 FPR 10 +LR 4.4 (2.0-9.4)		ii) Estimated performance (Risk 1:250) *Comb.* / *Comb.+ NB* DR 87 / 90 FPR 4.3 / 2.5
Evidence level	III	III	III

Study 34233: The population was low-risk and mainly unselected (67%) but not representative. Feasibility of NB measurement was low (62%), but its inclusion improved the screening performance for DS detection.

Study 34265: The population was low-risk but not representative (only 45% opted for the test).

Study 34264: Details about study population (low-risk or high risk) and exclusions were not specified. The estimated performance of adding NB into Combined test was evaluated from modelling using data from author's previous studies.

Table I A3 First trimester screening for Down's syndrome using nasal bone evaluation – additional studies (continued)

Study ID	**34226**	**18931**	**34285**
	775	776	777
Type of study	Prospective Cohort	Prospective Cohort	Prospective Cohort
(Year of publication)	(2006)	(2003)	(2003)
Period	2002-2004	2001-2002	2001-2002
Setting	1 prenatal centre Germany	1 prenatal diagnosis unit Italy	1 prenatal diagnosis unit Italy
Study population	Selected (Single centre, 46% > 35 yrs)	Selected (Single centre)	Selected (referred women)
Exclusions	Adequately described	Adequately described	Adequately described
Test conducted	Combined ± NB	Fetal nasal bone (NB)	Fetal nasal bone (NB)
Monitoring of test quality	Adequate	Adequate	Not described
Validated Reference standard	Yes (prenatal karyotype, pregnancy records)	Incomplete info. for 35% of study population	Yes (prenatal karyotype, pregnancy records)
Sample size	2973	3503	1906
(% of study population)	(92.4)	(64.6)	(Not specified)
Maternal age	Median - 34 Range – 14 to 46	Median – 32 Range – 15 to 48	Median – 32.2 Range – 18 to 47
Successful NB image	3194/3218	5525/5532	1752
(% of sample size)	(99.3% of study population)	(99.8% of study population)	(91.9% of sample size)

Number of cases	DS 18 (0.60)		DS 27 (0.77)	DS 10 (0.57)
(Prevalence in %)	Others 22 (0.74)		Others 13 (0.37)	Others 9 (0.51)
Results				
	Estimated performance for DS Risk cutoff 1:300		Observed performance of NB for DS	Observed performance of NB for DS
	Comb.	*Comb.+ NB*	DR 70	DR 60
	DR 94.4	77.8	FPR ??	FPR 1.4
	FPR 5.5	2.8		
Evidence level	III		III	III

Study 34226: The study population was high-risk. This study compared the two algorithm of Fetal Medicine Foundation – the Old algorithm using combined test vs. New algorithm which allows inclusion of nasal bone and some refinements in distribution of 1st trimester parameters.

Study 34265: The population was low-risk/unselected but follow-up was not available for 35% (1922/5532) of pregnancies. Moreover reported data was inadequate for calculating FPR and other screening parameters.

Study 34264: The population was high risk referred to the Centre for CVS, amniocentesis or NT measurement. The results are given for absent nasal bone. If hypoplastic nasal bone (<10th centile) is added, the DR becomes 80% with FPR 3.7%.

TABLE I B First trimester screening for Down's syndrome only

Study ID	**36250**	**34178**	**11194**
	778	781	767
Type of study	Prospective cohort	Prospective Cohort	Prospective Cohort
(Year of publication)	(2006)	(2005)	(2002)
Period	2001-2002	1999-2001	2 years
Setting	10 perinatal units France	1 hospitals, 1 fetal medicine unit UK	15 maternity units UK
Study population	Unselected (in a health authority)	Selected (48.5 % ≥ 35 years)	Unselected (for routine ANC care)
Exclusions	Adequately described	Adequately described	Not applicable (100% follow-up)
Test conducted	Combined	Combined	Combined
Monitoring of test	Adequate	Adequate	Inadequate (NT in 73% study population)
Quality			(34/45 DS cases had combined test)
Validated Reference standard	Yes (prenatal karyotype, pregnancy records)	Yes (prenatal karyotype, pregnancy records)	Yes (prenatal karyotype, pregnancy records)
Sample size	14,380	30,564	17,229
(% of study population)	(96.3)	(95.8)	(100)
Maternal age	Median – 30.7 25^{th}-75^{th} centile – 28 to 33.9	Median – 34 Range – 15 to 49	Median – 29.9 Range – 15 to 49
Number of DS cases	51	196	45

(Prevalence in %)	(0.34)	(0.64)	(0.57)
Diagnostic accuracy (95% CI)	Observed results	Estimated results	Observed results
Detection Rate (%)	79.6	90.3	82 (65-93) with 34 cases
FPR (%)	2.7	5 (fixed)	5
Risk cut-off	1:250	≥1 in 300	1:250
Evidence level	Ib	II	II

Study 36250: This study also evaluated the diagnostic value of 'first trimester combined test followed by routine second trimester ultrasound screening at 20-22 weeks for all the subjects' and the results showed DR of 89.7% with FPR of 4.2%. The 20-22 weeks scan was considered positive if at least 1 major structural malformation was present or if nuchal fold was more than 6 mm. Further a cost analysis was also performed.

Study 11194: Combined test could not be performed in all women and NT was done in 73% study population. 34 of 45 DS cases had completed screening. Considering entire series of affected pregnancies, DR is reduced to 62%.

Second trimester screening

Compared with the first trimester only and first and second trimester together, few studies were found related to serum screening tests done exclusively in the second trimester. Good quality serum marker studies comparing both the first and second trimester tests have been grouped under the next section on combined first and second trimester screening (Section III). A number of studies were identified which evaluated the use of ultrasound for identifying 'soft markers' – nuchal fold thickening, choroid plexus cyst, echogenic intracardiac foci, renal pyelectasis and shortening of femur, but the general quality was low (below Level II).

Five studies were selected for inclusion under the second trimester – three meta-analyses, one prospective cohort study and one retrospective cohort study. As these studies were quite different from each other, their data could not be tabulated and have been described in a narrative manner.

The second trimester studies have been further divided into the anomalies they looked at:

a) Down's Syndrome (DS) & other chromosomal anomalies

Description of included studies

A single retrospective cohort [782] study with evaluation of maternal serum screening (MSS) using quadruple test for Down's syndrome, trisomy-18, and neural tube defects (NTD) was carried out in an Australian state using record linkage and manual follow-up. As initially the quadruple test used free alpha-HCG instead of Inhibin-A, data from that period was not used for analysis. The period covered was 1998 to 2000. Increased risk result was defined as > 1:250 for Down's syndrome, and > 1:200 for trisomy 18. Levels of AFP > 2.5 MoM were considered as high risk for NTD. Three databases were used for record linkage – state's MSS database, register of births held at the Perinatal Data collection unit, and Birth Defects Register. No mention has been made about monitoring of test quality. An automated probabilistic record linkage technique was used to link these databases. Detection rate (DR), False positive rate (FPR), and PPV were calculated for each condition [EL II]

Findings

In this retrospective cohort study, pregnancy outcome information was ascertained for 99.2% of all pregnancies screened during the period. The study population was 19,143 and 154 pregnancies were lost to follow-up. Mean maternal age was 30.3 years (range 14-51) and 20.1% were above 35 years. Sample size for analysis was 16,607 (86.7%) for DS and T18, and 17,288 (90.3%) for NTD. The sample size for DS and T18 was smaller due to exclusion of pregnancies where alpha-HCG was used before Inhibin-A was introduced. The prevalence of DS, T18 and NTD was 0.16%, 0.05%, and 0.08% respectively.

The Observed performance of the quadruple testing was as follows:

	DR	FPR	PPV
For DS			
Quadruple test (Risk ≥ 1:250)	85 (72-99)	6.8	2
Quadruple test (FPR fixed at 5%)	78	5.0	2.5
For T18			
Quadruple test (Risk ≥ 1:200)	44 (12-77)	0.5	4.7
For NTD (AFP ≥ 2.5 MoM)			
All NTD	73	1.1	5.6
Spina bifida	50	1.1	2.1
Anencephaly	100	1.1	3.1

b) Down's syndrome only – four studies (three meta-analyses and one prospective cohort study). Meta-analysis studies were related to use of ultrasonographic soft markers, effectiveness of triple marker, and evaluation of intracardiac echogenic foci. The fourth study is a good quality prospective study evaluating the screening performance of fetal pyelectasis detected on ultrasound.

Description of included studies

A meta-analysis[315] was conducted to evaluate accuracy of second trimester ultrasound in detecting Down's syndrome. It included all the studies of 'soft markers' – choroid plexus cyst, thickened nuchal fold, echogenic intracardiac focus, echogenic bowel, renal pyelectasis, humeral and femoral shortening. Exclusion criteria were well defined but quality assessment of studies was not specified. Studies were independently reviewed, selected, and abstracted by 2 reviewers. Retrospective studies were included provided that the original ultrasound interpretation was used. Sensitivity, specificity and 95% CI was calculated for each ultrasound finding individually. A summary measure (ST, SP, +LR, -LR, PPV) with 95% CI and fetal loss per case diagnosed was calculated for each marker when identified as an isolated abnormality [EL II].

Another meta-analysis[320] evaluated effectiveness of Triple marker screen for DS. Only cohort studies were considered. Inclusion & exclusion criteria were well defined. Quality assessment criteria included selection of study subjects, description of methods, estimates of sensitivity, screen-positive rate & false-positive rate, cut-offs used, blinding of outcome assessors, follow-up, and accuracy estimated independently of test threshold. Studies were independently reviewed, selected, and abstracted by 2 reviewers. Results of sensitivity and false-positive rate from different sub-groups of study sample were compared by using summary ROC analysis. [EL III]

A third meta-analysis [783] was conducted to evaluate the diagnostic performance of intracardiac echogenic foci. Both prospective and retrospective studies (including case-control) were considered. Eligibility criteria for studies was availability of adequate information about both chromosomally normal and abnormal fetuses (so that 2 by 2 table could be made), fetal karyotype unknown at the time of ultrasound, and chromosomal status of fetuses confirmed by either karyotyping or postnatal clinical examination. Studies were independently reviewed, selected, and abstracted by two reviewers. Diagnostic performance was assessed in 2 different

settings – 'combined' which included women regardless of whether they had other US finding, and 'isolated' where women did not have any other US finding. Weighted sensitivity and specificity values was calculated and summary ROC analysis performed using both the fixed and random effects model separately for both the settings [EL II]

A prospective cohort study [784] carried out (1998-2002) in a single medical centre in Italy with the aim to determine if isolated pyelectasis is a risk factor for DS. The study population was low-risk and the centre served the needs of a group of 30 obstetricians. Inclusion criteria were well defined and a thorough US examination was carried out for all the soft markers between 16-23 weeks of gestation. Monitoring of the quality of US was not specified. Complete follow-up was obtained of the study population by karyotyping, postnatal records, or information from mother. ST, SP, PPV, NPV, +LR, and –LR (with 95% CI) were calculated separately for an 'isolated' finding, and in association with other anomalies. The sample size was 12,672 (77.8%) after excluding high risk and referred women. None of the women had a first trimester aneuploidy screen. [EL II]

Findings

The first meta-analysis[315] included 56 studies involving 1930 babies with Down's syndrome and 130,365 unaffected fetuses. 49 studies were carried out in high-risk women. Overall prevalence of Down's syndrome was 1.5%, and outcome was assessed by karyotyping in 53 studies. There was marked heterogeneity in the results for all ultrasound findings. Two factors were found to be responsible for heterogeneity – 1) Study design (retrospective or prospective) and 2) whether the marker was seen in isolation or together with other fetal structural anomalies. The sensitivity for Down's syndrome detection with an isolated ultrasound finding was low (1% for choroid plexus cyst to a maximum 16% for shortened femur). The specificity for each marker when seen individually was greater than 95%. Except for nuchal fold thickness (+ LR of 17), + LR for others was lower.

Summary measures (with 95% CI) for US markers when seen individually

Marker	**ST**	**SP**	**+LR**	**-LR**	**Fetal loss Per case**
Thickened Nuchal fold	0.04 (0.02-0.01)	0.99 (0.99-0.99)	17 (8-38)	0.97 (0.94-1.00)	0.6
Choroid plexus Cyst	0.01 (0-0.03)	0.99 (0.97-1.00)	1.00 (0.12-9.4)	1.00 (0.97-1.00)	4.3
Femur length	0.16 (0.05-0.40)	0.96 (0.94-0.98)	2.7 (1.2-6.0)	0.87 (0.75-1.00)	1.2
Humerus length	0.09 (0-0.60)	0.97 (0.91-0.99)	7.5 (4.7-12)	0.87 (0.67-1.1)	1.9
Echogenic bowel	0.04 (0.01-0.24)	0.99 (0.97-1.00)	6.1 (3.0-12.6)	1.00 (0.98-1.00)	1.0
Echogenic Intracardiac focus	0.11 (0.06-0.18)	0.96 (0.94-0.97)	2.8 (1.5-5.5)	0.95 (0.89-1.00)	2.0
Renal pyelectasis	0.02 (0.01-0.06)	0.99 (0.98-1.00)	1.9 (0.7-5.1)	1.00 (1.00-1.00)	2.6

The second meta-analysis involving the triple marker[320] included 20 cohort studies involving a total of 194,326 pregnant women. There was strong evidence of study-to-study variation implying heterogeneity ($p < 0.001$). The cut-offs used in these studies ranged from 1:190 to 1:380. No study reported on the independence of assessment. Only four studies obtained fetal karyotypes (validated reference test) for all the women studied. In other studies CVS or amniocentesis was offered to screen-positive women and proportion of women accepting prenatal diagnostic testing ranged from 67 to 92. Follow-up information on pregnancy outcome was incomplete in eight studies. The mean maternal age varied between 24.5 and 33.5 years. The triple marker had a high ST for women more than 35 years, but did not perform well in the younger age group.

The Summary ST and FPR based on various cut-offs and maternal age are given below:

Cut-offs 1:190-200	ST (Range)	FPR (Range)
Maternal age ≥ 35 years	89 (78-100)	25 (20-29)
All ages	67 (48-91)	4 (3-7)
Cut-offs 1:250-295		
Maternal age ≥ 35 years	80 (75-100)	21 (20-21)
Maternal age < 35 years	57 (53-58)	4 (3-6)
All ages	71 (48-80)	6 (4-7)
Cut-offs 1:350-380		
All ages	73 (70-80)	8 (7-13)

The third meta-analysis concerning an echogenic focus in the heart [783] had included 11 studies (5 retrospective including 2 case-controls). Eight studies gave data on combined setting, while 7 on isolated setting independently. Data included 51,831 fetuses with 333 Down's syndrome cases ('combined'- 27,360 with 321 Down's syndrome cases, 'isolated' – 39,360 with 130 Down's syndrome cases). Mean age of mothers ranged between 29 to 35 years, and 7 studies had high risk women as their study population. Regarding ST, there was no statistically significant heterogeneity as the CI's were widely overlapping. For SP, there was significant between-study heterogeneity ($p < 0.001$).

The weighted Sensitivity (ST) and Specificity (SP) estimates with the 95% CI's using the 2 models – random effects model (REM) and fixed effects model (FEM) are given below:

	REM		FEM	
	ST	**SP**	**ST**	**SP**
'Combined' setting	0.26 (0.19-0.35)	0.963 (0.937-0.979)	0.30 (0.25-0.36)	0.927 (0.924-0.931)
'Isolated' setting	0.22 (0.14-0.33)	0.959 (0.910-0.982)	0.22 (0.15-0.30)	0.964 (0.961-0.966)
All	0.26 (0.19-0.34)	0.958 (0.922-0.978)	0.30 (0.25-0.36)	0.940 (0.937-0.942)

Further it was estimated that the probability of DS (assuming + LR of 6.2) after an intracardiac echogenic foci has been detected would be 0.44% in a population with prevalence of 1:1400, 0.62% with prevalence of 1:1000, and 1.03% with prevalence of 1:600. Also the probability of a case of DS being detected was equal to the probability of an unnecessary miscarriage caused by amniocentesis, when the background prevalence of DS was 1:770.

In the prospective cohort study on pyelectasis [784] the mean maternal age was 27.2 ± 5.5 years and prevalence of Down's syndrome 0.09% (11 cases). In the study population, prevalence of pyelectasis was 2.9%, with 83.3% of these as an isolated finding. Only one case of Down's syndrome was identified with pyelectasis. The presence of isolated pyelectasis had ST 9.1% (1.62-37.4), SP 97.6% (97.32-97.85), PPV 0.33% , NPV 99.9%, +LR 3.8 (0.58-24.61), and –LR 0.9 (0.77-112).

Among fetuses with pyelectasis and other associated markers, the ST, SP, PPV, NPV and +LR were 9.1%, 99.5%, 1.6%, 99.9%, and 19.2 (95% CI 2.91-126.44).

Combined first and second trimester studies

Description of included studies

Four good quality studies were included – three prospective cohort studies [785], [786], [787] and one nested case-control study [788]. All the studies were multi-centred with clearly defined objectives. One of the two studies with a selected population had first trimester screen-positive and screen-negative women together in its sample population [787]. In all studies the screening test and monitoring of its quality measures have been adequately explained. Reference test in all is a validated one (karyotyping/postnatal assessment/pregnancy records). (Table III)

Findings

All the selected studies looked at Down's syndrome only. The best quality study [785] showed the Integrated test to have the best DR of 96% at a fixed FPR of 5%, followed by the Serum Integrated test (DR 88%), Combined test (DR 87%) and the Quadruple test (DR 81%). Similar results were observed in the nested case-control study.[316] Another study [786] found the Serum Integrated test to have better diagnostic accuracy compared to the second trimester serum triple and quadruple tests. In the last study [787], sequential screening using the triple test after first trimester combined test had a DR of 85.7% at FPR of 8.9%.

Table III First and second trimester screening for Down's syndrome only

Study ID	**34234**	**12873**
	785	316
Type of study	Prospective Cohort	Nested Case-control (within a cohort)
(Year of publication)	(2005)	(2003)
Period	1999-2002	1996-2001
Setting	15 medical centres	25 maternity centres
	USA	UK & Austria
Study population	Unselected	Unselected
Exclusions	Adequately described	Adequately described
Test conducted	All serum tests with NT (Combined, Quad, Integrated & Serum Integrated)	All serum & urine biochemical markers with NT
Monitoring of test quality	Adequate	Adequate, Double blinding
Validated Reference standard	Yes (prenatal karyotype, pregnancy records)	Yes (karyotype-pre/postnatal, pregnancy records)
Sample size (% of study population)	33,547 (88.2) with complete data from both trimesters	43,712 (92) 98 cases, 490 controls for screening performance; 600 controls added for statistical power.
Maternal age	Mean – 30.1 SD – 5.8	Not specified Median- 29 years
Number of cases	92	101
(Prevalence in %)	(0.27)	(0.23)

Results

Estimated Detection Rate at fixed FPR 5% (95% CI)	
Combined (11 weeks) –	87 (82-92)
Quadruple (15-17 weeks) –	81 (70-86)
Serum integrated –	88 (81-92)
Fully Integrated -	96 (92-97)

Estimated Detection Rate at fixed FPR 5%

1st trimester (10-13 wk)		2nd trimester(15-20)	
PAPP-A + NT -	76	*Double -*	71
Combined -	84	*Triple -*	77
Combined+Inhibin-A	87	*Quad. -*	83

Integrated screening (both 1st and 2nd trimester)

NT (10 wks) + Quad. -	90
Serum Integrated -	90
Integrated -	93

Evidence level Ib II

Study 34234: The observed performance characteristics were:

First trimester combined screening with risk cut-off 1:300 – DR 82% with FPR 5.6%

Second trimester quadruple screening with risk cut-off 1:100 - DR 85% with FPR 8.5%

Sequential screening in both the trimesters - DR 94% with FPR 11%

Note: The DR is subject to bias as the study excluded fetuses with hygroma which might have aborted spontaneously when most of the DS cases were ascertained.

Study 12873: Screening performance was also evaluated for NT and all serum & urine markers individually.

For NT – Failure to obtain satisfactory NT image was lowest (14%) at 11 weeks, and highest (19%) at 10 and 13 weeks.

Success rate increased with sonographer experience – 86% with $\geq$ 400 images VS 81% with $<$ 200 images experience.

For urine markers – Invasive Trophoblastic Antigen (ITA) was the best marker and only discriminatory in 2nd trimester. On combining with Quad. Test, FPR was decreased from 6.2 to 4.2%, and with Integrated test from 0.9 to 0.6% (both tests at fixed DR of 85%).

The study also evaluated the safety and cost-effectiveness of various markers. Safety will be discussed separately under effectiveness.

Table III First and second trimester screening for Down's syndrome only *(contd.)*

Study ID	**34225**	**34262**
	786	787
Type of study	Prospective Cohort	Prospective Cohort
(Year of publication)	(2005)	(2004)
Period	2001-2003	Not specified
Setting	229/260 prenatal care practitioners USA	12 prenatal diagnostic centres USA
Study population	Selected (61% enrolled for study)	Selected (low uptake of 2nd trimester screening) (Small sample)
Exclusions	Adequately described	Adequately described
Test conducted	Integrated serum screening	Sequential screening using Triple marker after 1st trimester Combined test
Monitoring of test quality	Adequate	Adequate
Validated Reference standard	Yes (prenatal karyotype, pregnancy records)	Yes (karyotype-prenatal, pregnancy records)
Sample size	8773	4325 *1st trimester screen-positive* 180
(% of study population)	(78.6)	(52.7) *1st trimester screen-negative* 4145
Maternal age	Mean – 27.8 SD – 5.5	Mean – 34.5 SD – 4.6

Number of cases	16	13
(Prevalence in %)	(0.18)	(0.30)

Results

	Observed screening performance with 95% CI			Observed screening performance with 95% CI among 1st trimester screen-negative women	
	Triple	*Quad.*	*Serum Integrated*		
Risk	1:270	1:150	1:100	Risk	1:270
DR	67 (43-84)	56 (33-76)	79 (55-92)	DR	85.7 (42.1-99.6)
FPR	6.4 (5.9-6.9)	3.3 (2.9-3.7)	3.2 (2.8-3.6)	FPR	8.9 (8.0-9.8)

Evidence level	II	II

Study 34262: The study population was the same as that of Study 34291 (described in First Trimester screening for Down's Syndrome and other chromosomal anomalies). After undergoing Combined test in the first trimester, risks were disclosed to the women. Triple test was offered to all screen-negative women and those screen-positive women who decided not to undergo diagnostic tests after the first trimester positive test.

Modelling studies

Description of included studies

Two studies were identified which used modelling as a way of comparing different screening tests for Down's syndrome detection.

To demonstrate the potential value of three-stage sequential screening for Down's syndrome, DR and FPR were estimated by multivariate Gaussian modelling using Monte-Carlo simulation [789]. UK data was used for modelling. Known as 'Contingent screening', the protocol involves measuring free β-HCG and PAPP-A in all pregnant women at 10 weeks in the first stage. Those with low risk were screened negative at this stage, the remainder underwent NT measurement in the second stage and the risk reassessed (for combined test). After the second stage, those with low risk were screened negative and those with very high risk were offered diagnostic tests. In the third stage, women with intermediate risk received second trimester quad test. Risk was reassessed according to the integrated test and high risk women were offered diagnosis. [EL III]

Using Monte Carlo simulation for modelling, this study [790] compared the Integrated test in three policies for screening – i) Integrated screening for all women ii) Sequential screening (based on first trimester tests, high risk pregnancies to be diagnosed and remaining to undergo integrated test) iii) Contingent screening.

Detection and false-positive rates were estimated based on the data from a large cohort (nested case-control study) done in UK. [EL III]

Findings

The first modelling study suggested that with full adherence to a three stage policy, an overall detection rate of nearly 90% and a false-positive rate of below 2% can be achieved. About two-thirds of the women can be screened on the basis of first trimester biochemistry alone and about 80% by the combined test. The DR for first trimester screening is about 60%.

This protocol allows most of the Down's syndrome pregnancies to be detected in the first trimester. Moreover it provides an efficient way of screening for Down's syndrome where nuchal translucency measurements cannot be performed in all women due to scarcity of resources. But it requires the selection of four different cut-offs during the three stages, each of which will affect the overall performance. Selecting a set of appropriate cut-offs is therefore complex and difficult to practise. Moreover the psychological impact of possibly receiving four different results for pregnant women needs to be evaluated.

The second modelling study concluded that integrated screening had the best screening performance. As the first trimester test FPR was decreased, the performance of other two policies approached that of the integrated screen. Setting the first trimester risk cut-off to $\geq$ 1 in 300 with a fixed DR of 90%, sequential and contingent screening gave overall FPR's of 2.3% and 2.4% respectively, and 66% of affected pregnancies were detected by the first trimester tests. The integrated test on all women gave a FPR of 2.2%.

If pregnancies with a first trimester risk of $\leq$ 1 in 2000 are classified screen negative and receive no further testing, then 99.5% of women with sequential screening or 30% with contingent screening would proceed to integrated screening.

Effectiveness studies

Five studies were identified – four related to adverse outcomes/fetal losses and one related to threshold measurement of nuchal translucency. One was a multi-centre RCT, one nested case control study, one modelling study and the fourth study was a meta-analysis to evaluate diagnostic value of second trimester ultrasound for Down's syndrome. The nuchal translucency study analyzed the database from an earlier multi-centre prospective study.

Description of included studies

A multi-centric RCT [791] in maternity care units affiliated to 8 Swedish hospitals was carried out with an aim of comparing the effectiveness of two screening policies for detecting Down's syndrome – routine ultrasound scan at 12-14 weeks by nuchal translucency (12-week policy) *versus* routine ultrasound at 15-20 weeks of gestation (18-week policy). An unselected population with well

defined eligibility criteria was involved. After taking informed consent, the population was randomized block-wise at the level of maternity units using internet-based software. Appropriately trained operators carried out the ultrasound examination. Karyotyping was offered to all women with increased risk of DS (> 1:250 based on nuchal translucency the in first group and on maternal age in the second), detection of a structural anomaly on scan, history suggestive of increased risk, or preference/desire of women due to worry. Follow-up of results (karyotyping, pregnancy outcome) was adequate. Evaluation of primary outcome (number of babies born alive at $\geq$ 22 weeks with Down's syndrome) and secondary outcomes (total number of babies born with Down's syndrome, number of babies born with other chromosomal abnormalities, number of pregnancy terminations for Down's syndrome, and rate of invasive tests for fetal karyotyping) was done using intention-to-treat analysis. Sample size was calculated to detect a difference of 0.1% in live born Down's syndrome cases between the two groups at 5% significance level with 90% power. Chi-square test (for proportions) and Student's two-sample test (for continuous data) were used for comparison. [EL 1+]

This nested case-control study[316] has been covered under combined first and second trimester screening. Apart from evaluating screening performance of various tests, it also examined their safety in terms of number of unaffected fetal losses per 100,000 women screened, and number of DS pregnancies detected for each procedure-related unaffected fetal loss. Both calculations were done at different detection rates. [EL 2+]

A decision analysis model [792] was used to compare 5 screening strategies – (1) first trimester combined screen (2) second trimester quad screen (3) second trimester triple screen (4) integrated screen (5) sequential screen. A hypothetical cohort of 1,000,000 women below 35 years was analyzed assuming entire cohort would present for antenatal care before 10 weeks and accept prenatal screening for Down's syndrome. After positive triple or quad test, genetic sonogram would be performed and then prenatal diagnosis would be available. Four separate outcomes were examined – I) overall cost effectiveness ii) Down's syndrome cases detected iii) Down's syndrome live births averted iv) euploid losses from invasive procedures. [EL 3]

Clinical parameters used for modelling were synthesized from review of published data (mainly UK data). Prevalence of Down's syndrome at 10 weeks gestation was estimated as 1 in 595 pregnancies, and baseline live birth rate 1 of 1030. 70% women were estimated to opt for invasive diagnostic techniques after positive screening test, and 90% to opt for termination of affected pregnancies. Baseline fetal loss after amniocentesis and CVS were estimated to be 0.9% and 1.6% but this was also varied over a range. Spontaneous fetal loss of euploid pregnancies was estimated at 1% between 10 and 14 weeks, and additional 1% between 15 weeks and delivery. The screening performance of various tests was derived from published data. [EL 3]

Details of the fourth study[315] have already been covered under Second trimester testing for diagnostic value.

The last study [793] analyzed the database from the FASTER trial (multi-centre prospective trial in USA) to determine whether there is a NT measurement above which immediate invasive testing should be offered, without waiting for serum testing and computerized aneuploidy risk assessment. Pregnant women were eligible for inclusion if they were above 16 years of age, had singleton pregnancy and a CRL of 36 to 79 mm (gestation 10 weeks 3 days to 13 weeks 6 days) at the time of first trimester sonography for NT. Cases with cystic hygroma were excluded. NT was measured in the first trimester using a standardized protocol by specially trained ultrasonographers at the same time as when serum levels of PAPP-A and beta-HCG were obtained. At 15-18 weeks, a quad serum screening test was also obtained, but the present study used only the risks as assessed from the first trimester tests. A formal quality control programme was used throughout the study. [EL 2+]

Findings

In the multi-centre RCT a total of 39,572 women were randomized in the two groups (19,796 in 12 weeks, 19,776 in 18 weeks). Demographically the two groups did not differ in mean age, mean parity and other characteristics. In the 12-week group, nuchal translucency measurement could not be carried out in 9% population due to increased CRL or fetal demise; and was successfully measured in 96% of the remaining population. The prevalence of Down's syndrome during the study period was 0.25% (98/39,572).

Results in numbers (%) are as follows:

Outcome	*12-week group*	*18-week group*	*p-value*
Prevalence rate	55/19,796 (0.28)	43/19,776 (0.22)	0.18
Rate of liveborn DS babies (at ≥ 22 weeks)	10/19,796 (0.05)	16/19,776 (0.08)	0.25
Antenatal detection rate (< 22 weeks in living fetus)	42/55 (76)	25/41* (61)	0.12
Antenatal detection rate (if karyotyping performed only for defined policy)	39/55 (71)	21/41* (51)	0.06
Detection rate (other chromosomal anomalies)	20/35 (57)	25/35 (71)	0.32
Terminations done for DS	39/19,796 (0.20)	24/19,776 (0.12)	0.08
Fetal loss rate in DS fetuses (terminations and miscarriages)	45/19,796 (0.23)	27/19,776 (0.14)	0.04
Rate of invasive tests (for karyotyping)	1593/19,796 (8)	2118/19,776 (0.14)	< 0.001
Spontaneous fetal loss rate after invasive tests in normal fetuses	14/1507 (0.9)	15/2041 (0.7)	0.58
No. of invasive tests per one case of DS detected (< 22 weeks) (if karyotyping performed only for defined policy)	16	89	

* of the 43 cases of DS, diagnosis was made in one case by amniocentesis at < 22 weeks but pregnancy continued, and in other diagnosis made at 35 weeks – leaving 41 cases for calculating DR.

In the second study, safety of various tests was evaluated at fixed DR of 85%. Integrated test had about one-fifth of fetal loss compared to the combined and quadruple test, and half of the serum integrated test. Number of Down's syndrome cases detected for each fetal loss was almost three times higher with the Integrated test compared to combined & quadruple test.

Test	*FPR(%)*	*Unaffected fetal losses per 100,000 women*	*DS cases detected for each procedure related fetal loss*
Combined	6.1	44	3.9
Double	13.1	94	1.8
Triple	9.3	67	2.6
Quadruple	6.2	45	3.8
Serum Integrated	2.7	19	9.1
Integrated	1.2	9	19.2

The modelling study found sequential screening to be the most cost-effective. Compared to other screens, it was shown to detect antenatally most cases of Down's syndrome and avert most live births of affected fetuses. But it also had the highest number of euploid losses due to diagnostic procedure. From the point of safety, integrated screen performed the best with lowest euploid losses. Addition of genetic sonogram to triple and quad screen increased the cost but brought the euploid losses to very low levels.

Strategy	*Cost of Programme (million US$)*	*DS cases detected (n)*	*DS live births averted (n)*	*Euploid losses due to procedure (n)*
No screening	662	0	0	0
Triple screen				
No sonogram	497	529	366	311
With sonogram	566	365	253	25
Quad screen				
No sonogram	472	618	427	311
With sonogram	554	426	295	25
Combined screen	486	941	490	559
Integrated screen	521	750	520	62
Sequential screen	455	1213	678	859

The meta-analysis concluded that the number of fetal losses per case diagnosed when identified as an isolated 'soft marker' abnormality on ultrasound was highest with choroid plexus cysts (4.3) and lowest with thickened nuchal fold (0.6).

For others the values were – femur length (1.2), humerus length (1.9), echogenic bowel (1.0), echogenic cardiac foci (2.0), and renal pyelectasis (2.6)

In the nuchal translucency study, the sample population included 36,120 pregnancies with complete first trimester results. The mean and median NT measurements increased from 10 through 13 weeks and there was considerable variation in proportion of cases with NT ≥ 2.0 mm at each gestational week, but there was minimal gestational age variation in NT once a threshold of 3.0 mm was passed. All the results given below are in percentages.

	≥ 2 mm	***≥ 3 mm***	***≥ 4 mm***	***≥ 5 mm***
10 weeks	2.0	0.4	0.16	0
11 weeks	1.5	0.5	0.1	0.04
12 weeks	2.5	0.3	0.1	0.09
13 weeks	5.1	0.4	0.05	0
Total	3.0	0.4	0.09	0.05

On comparison of outcome of pregnancies based on the various nuchal translucencies cut-offs, the following results were observed:

Outcome	***≥ 2 mm***	***≥ 3 mm***	***≥ 4 mm***
Number (%)	1081 (3.0)	128 (0.4)	32(0.09)
Aneuploidy	51	22	10
T 21	39	17	6
T 18	5	4	4
Others	7	1	0
ST for DS / T 21(in %)	42	19	7
FPR for DS / T 21(in %)	3	0.3	0.06
Final risk of DS less than 1:200 with the combined test (% of total number)	533 (49.0)	10 (8.0)	0 (0)

There were 32 women with NT ≥ 4 mm, and the addition of first trimester serum markers to NT measurements did not reduce the final risk in any patients. By contrast, for patients with NT ≥ 3 mm, subsequent addition of serum markers reduced the final risk to less than 1:200 in only 8% (10 women) of cases. For women with NT ≥ 2 mm, large number of women (49%) had their risk reduced to less than 1:200 by addition of first trimester test results.

The authors concluded that the use of 4.0 and 3.0 mm cut-off of NT measurement for estimating pregnancies art risk of DS, would lead to just 0.09% and 0.4% population being subjected to invasive testing based on the two cut-offs. By waiting for serum assays and computerized risk assessment, no benefit (0%) was observed in the women with NT ≥ 4 mm and only a minimal benefit (8.0%) in women with NT ≥ 3 mm, that is, who had their final risk reduced to less than 1 in 200. This will increase the screen positive rate for the whole population by a very small proportion, but will be beneficial in providing immediate results to the health care providers and reducing anxiety of the pregnant women.

Evidence summary

Reported evidence shows that the combined test in the first trimester has good diagnostic accuracy for Down's syndrome and other chromosomal anomalies.

Among the currently available second trimester serum tests, the quadruple test seems to have the best screening performance.

There is high quality evidence to indicate that combining results of first and second trimester screening tests improves the diagnostic performance for Down's syndrome and other chromosomal anomalies and is better than when either of them is used alone.

The Integrated test seems to have a higher detection rate and a lower false positive rate compared to other currently used combined screening tests.

There is little evidence on the diagnostic value of other policies of combining first and second trimester results.

There is conflicting evidence regarding the performance of nasal bone ultrasound assessment as a screening tool for Down's syndrome.

'Soft markers' on ultrasound have low sensitivity and positive LR when seen individually, except for nuchal fold thickening. When found in association with other anomalies, they seem to improve the diagnostic value but the evidence is not strong enough.

Retrospective analysis of database from a high quality prospective study shows that a NT measurement of 3 mm or more in the first trimester (any gestational age) identified majority of pregnant women with DS, and increased the screen positive rate/risk of invasive testing by only a small fraction compared to first trimester risk evaluated by the combined test.

Women's views / psychosocial aspects

Seven studies have been included under this section – two systematic reviews, three cross-sectional surveys, and two prospective observational studies. Though the HTA's have been well conducted, but as the principal question involved women's views/preferences/experiences/feelings which is quite subjective and difficult to interpret, other descriptive studies (even with poor quality) were included so that important information is not missed out. Grading the two reviews according to the NICE quality criterion is difficult – they are high quality systematic reviews but with a definite risk of confounding, bias or chance as individually studies have not been assessed for quality.

Description of included studies

A systematic review [794] carried out to understand the psychosocial aspects of genetic screening of pregnant women and newborns. The review aimed to address five broad questions concerned with i) knowledge ii) anxiety iii) other emotional aspects iv) factors associated with participation in the programmes and v) long-term sequelae of the results. Any genetic screening programme aimed at pregnant women or newborn babies was included. Both comparative and descriptive studies which reported data collected directly from pregnant women or parents were included. There were no geographical or methodological limits except that studies asking hypothetical questions, case reviews and those where US was done to detect structural anomalies only (and not include chromosomal anomalies) were excluded. Five electronic databases and two journals were hand searched. The retrieved articles were equally divided among the five authors for quality assessment and data extraction, and these processes were completed using well defined criterion and validated forms. A new quality score was devised for quality assessment which was not found to be useful later on. Literature on 'other emotional aspects' and 'long term sequelae' was too fragmented (except in neonatal screening programmes) for useful conclusions to be drawn. [EL 2++]

A prospective cohort study [795] was carried out in four antenatal clinics in Australia to assess informed choice in pregnant women to participate in second trimester serum screening using a validated measure, and to compare anxiety levels in women who are well informed versus poorly informed. Participants included pregnant women between 8 and 14 weeks attending at their first prenatal visit and with sufficient English to complete a written questionnaire. Written and oral information was provided to all participants as per the existing hospital policy. Informed choice was measured by Multidimensional Measure of Informed Choice (MMIC), a validated measure of informed choice which assesses knowledge and attitude dimensions and also confirms whether woman's participation in screening test matches her attitude. The Hospital Anxiety and Depression Scale (HADS) were used to measure anxiety and this scale specifically distinguishes between anxiety and depression. Both the scales were administered at the booking visit and HADS was repeated at 20 weeks (after participation in the test) and at 30 weeks using postal questionnaires. [EL 2+]

In the third study, a smaller sample drawn from the RCT described above (Study ID 34267) was used to study the effect of screening on women's anxiety during pregnancy and after birth, with a specific focus on worries about the health of the baby [796]. The 12-week group was the intervention group and 18-week group acted as the control. Principal outcome of women's worries about the

'possibility of something being wrong with the baby' was measured by the Swedish version of Cambridge Worry Scale questionnaire including 16 items of common concerns during pregnancy. The State-Trait Anxiety Inventory (validated tool for evaluating general anxiety) and Edinburgh Postnatal Depression Scale (validated for evaluating anxiety in antenatal/postnatal period) were also used. Information was collected at 3 different timings – first questionnaire was filled at the antenatal clinic, second was sent at 24 weeks gestation (mid-pregnancy), and the last was posted 2 months after delivery. Same instruments were used for all the three questionnaires. [EL 3]

A cross-sectional survey [797] was carried out in 3 Canadian cities to investigate the relationship between maternal serum screening (MSS) use and maternal attachment to pregnancy following the receipt of favourable results (i.e lowered risk ratio). Building on the preliminary evidence that MSS results are not reassuring to women, it was predicated that favourable MSS results would not be sufficient to allow women to move beyond tentative pregnancy stage. Hence it was hypothesized that

1) there would be no difference in prenatal attachment between women receiving favourable amniocentesis results (amniocentesis group) and who opt against testing (no testing group)

2) there would be lower level of attachment among women who receive favourable MSS results and did not undergo amniocentesis (MSS group) compared to the other two testing groups, and this difference would be evident in the second and third trimesters.

Participants included high risk pregnant women (maternal age > 35 years) who opted for MSS or amniocentesis or did not opt for any testing. Informational posters were placed at various places (physician offices, laboratories, maternity stores), and interested women who met the eligibility criteria were enrolled. The instrument used to collect information was a self-administered questionnaire by mail, and prenatal attachment was measured by 21-item Prenatal Attachment Inventory (construct validity and reliability of this scale were established). The three groups were compared using ANOVA and ANCOVA for statistical analysis. [EL 3]

To address the question of whether there are social and ethnic inequalities in the offer and uptake of prenatal screening and diagnosis in UK, a systematic review [798] was carried out employing a broad search strategy. In order to address the review question, studies were assessed in terms of

a) utilization - number of women screened as a proportion of those eligible
b) offer - number of women offered screening as a proportion of those eligible, and
c) uptake – number of women screened as a proportion of those offered screening.

Studies were reviewed and summarized by one reviewer. Two key aspects of the studies were assessed independently by two reviewers and summarized as indicators of quality – non participation rate and whether the distinction between utilization, offer and uptake was recognized in the study. Due to heterogeneity, meta-analysis could not be performed. [EL 2+]

A prospective descriptive study [799] was carried out in two UK district hospitals to find out reasons for lower uptake of screening tests in women from minority ethnic groups and socio-economically (SE) disadvantaged sections of society. Screening uptake was evaluated from hospital records. Attitudes towards undergoing the test were assessed by women's responses to a structured question with 4 items. Knowledge about the test was assessed using an 8 item questionnaire deemed important in professional guidelines for informed consent in screening. Choices were classified as 'informed' depending on the consistency between test uptake, women's attitude towards the test, and their knowledge about it. [EL 3]

Another cross-sectional survey [800] was carried out in 6 UK maternity units (3 in Scotland, 3 in England) to ascertain by means of a structured questionnaire women's preference for type of screening test. Pregnant women attending antenatal clinics were asked to put in order of preference four different approaches for screening (all with FPR of 5%) – (1) first trimester testing – 90% detection with results available in 1 hour (2) first trimester testing – 90% detection with results within 2-3 days (combined test) (3) first trimester plus second trimester detection, 93% detection and results within 2-3 days of second test (integrated test) (4) second trimester testing, 75% detection and results available within 2-3 days. [EL 3]

Findings

In the first systematic review 106 out of 288 identified studies met the eligibility criterion – 78 concerned with antenatal screening and 28 with neonatal screening. Results pertaining to antenatal

screening programmes have only been specified below. Findings from antenatal carrier testing for Cystic Fibrosis and other diseases prevalent in minority ethnic groups have also not been mentioned.

Most of the antenatal studies were descriptive and only 33% (26/78) were RCT's or comparative. Questionnaire was the most common instrument used to collect data (in 79% studies), either alone or together with other methods. Participants in only 16 studies (20%) included both people who were tested and those who were not. 54 studies were concerned with screening for Down's syndrome (DS) and other chromosomal anomalies. Sample size of studies varied from 10 to 6442 participants. Data was collected after the test results in 40 studies, and in just 3 studies it was collected at three different times - before test, after test, and after test results. A large number of studies assessed knowledge (64.6%), anxiety (46.8%), or attitudes/beliefs (46.2%). 34 antenatal studies (43.6%) had an apparent input from a psychologist or a social scientist. The various findings have been divided into 3 sections:

1) Knowledge and understanding of screening for DS – 30 studies were selected: 7 used pre-test measures only, 6 employed both before and after test measures (ideal for comparing), and 17 employed after test measures only. Eight areas of information as specified in RCOG 1993 professional guidelines were used as a 'validated/gold standard questionnaire' for evaluating knowledge in the selected studies. 30 studies related to knowledge were reviewed, but owing to disparate research aims, poorly operationalised measures for evaluation, and variation in timing of assessment, it was concluded that none of the study evaluated all the 8 areas and hence knowledge was inadequately assessed by all of them. Broad conclusions drawn from these studies:

   a) Compared with the RCOG list, only limited aspects of knowledge have been the subject of intervention studies.
   b) Levels of knowledge adequate for decision making are not being achieved.
   c) Leaflets giving information about tests improve knowledge, but substantial gaps in understanding of the written information still remain, especially concerning risk calculations.
   d) Substantial social and cultural inequalities exist in knowledge about testing.
   e) Other findings that emerged
   f) Pre-screening information can increase knowledge scores, but does not necessarily mean that concept of risk is understood.
   g) Women seem to value personally delivered information rather than group-based.
   h) Videos may be slightly more effective in communicating certain types of information than leaflets.

2) Influence on anxiety in prenatal screening for DS – Of the 24 studies measuring anxiety, 13 used a validated scale (mainly State-Trait Anxiety Inventory). Most studies were carried out in UK. As knowledge influences anxiety and attitudes, the findings from studies represents the feelings and views of many people who are in fact not well informed about the topic under discussion. Due to number of methodological concerns (as with knowledge), robust conclusions could not be drawn. The main findings are as follows:

   a) Increasing women's knowledge by providing more information prior to testing does not raise post-test anxiety.
   b) There is unconvincing data to suggest that knowledge has a moderating role on anxiety in the period after screening but before receipt of test results.
   c) Receipt of screen-positive result raises women's anxiety score, but return to normal levels if no abnormality is detected upon diagnostic testing.

   Due to application of inappropriate theoretical frameworks in these studies, 2 basic misconceptions about knowledge and anxiety came out:

   i. Information that increases knowledge is the same as that which reduces anxiety
   ii. Increased anxiety is inappropriate, abnormal and undesirable as most studies assume that increased anxiety is an abnormal response and/or iatrogenic consequence of prenatal testing.

3) Understanding decision making about screening – Of the 52 studies included, 34 were concerned with DS screening and 11 of them compared differences in those screened with those not screened. Most studies employed questionnaire or interview survey methods. The principal findings are

a) Most women evaluate screening programs positively but some are concerned of their usefulness and impact on pregnancy.
b) The reasons as to why women had screening test were – information to help avoid nasty surprises (range 11 to 82%), need to know for certain whether or not the child had abnormality (8 to 73%), reassurance that everything was OK (17 to 88%), following the recommendation of a health professional or spouse (6 to 24%), and (16 to 26%) could think of no reason.
c) The reasons as to why women chose not to have a test were – not wanting to act on or worry about the test results (17 to 71%), not wanting to have an abortion (32 to 100%), the test results were unreliable and did not provide a definite answer (10 to 55%), not perceiving themselves at high risk and/or the abnormality to be serious (21 to 64%), and their own or others poor screening experience (1 to 32%).
d) Most women are not making informed choices about screening although they want to do so. There is evidence to suggest a gap between women's desire to make informed choices with their awareness of what constitutes an informed decision, and the skills with which to achieve it.
e) Informed decision making results in better post decision outcomes.

Of the initial 134 recruited women completing the first assessment in the second study, 63.9% returned the second questionnaire and 57.8% the third. The mean age of the sample was 29.1 $\pm$ 4.7 years and 89.6% were married. Using MMIC, 48.1% women were classified as having 'good knowledge' and 87.2% having a 'positive attitude' to screening. Overall only 37.3% of decisions to participate in screening were informed; those who participated in screening were more than twice as likely to have made an informed choice than those who did not participate (47% versus 20%, $p=0.01$). Informed decisions were not significantly associated with participant's age, gravidity, country of birth, or whether pregnancy was unwelcome or unexpected. No significant association was found between the knowledge levels and attitude to the test ($p=0.27$). Some important misconceptions were revealed about further testing; 31% did not know that miscarriage was a possible consequence of diagnostic testing subsequent to an increased risk screening result, and only 62% correctly identified that termination of pregnancy would be offered if Down syndrome was diagnosed. Regarding anxiety, no significant difference was found between the informed and not informed group in psychological outcomes at any of the three assessments, even after adjusting for repeated measures on individual participants. It was concluded that many women participating in prenatal genetic screening are inadequately informed regarding aspects of testing, including the management of pregnancy in event of increased risk.

A total of 2026 women were enrolled for the third study. Analysis was carried out in 82.7% (854/1030) women in 12-week group, and 84.1% (837/996) in the 18-week group respectively who responded to all 3 questionnaires. The demographic characteristics of the two groups were similar. Emotional well-being at baseline in early pregnancy was also similar. In the early pregnancy 39.1% women in 12-week group and 36.0% in 18-week group were worried about something being wrong with the baby, but the difference was not statistically significant.

The prevalence decreased to 29.2% versus 27.8% during mid-pregnancy, and finally to 5.2% versus 6.6% at 2 months after delivery in the 2 groups. No statistically significant difference was found between the 2 groups during these periods also.

Within both trial groups, there was statistically significant decrease in the levels of major worry about baby's health from early to mid-pregnancy ($p<0.001$), and from mid-pregnancy to 2 months after delivery ($p<0.001$).

In the fourth study, a cross-sectional survey, 101 women formed the study group and included 31 in the amniocentesis group, 32 in MSS group, and 38 in no test group. The mean gestational age at the time of participation was 28.3 $\pm$ 7.0 weeks. The mean maternal age in amniocentesis group was higher than the other 2 groups ($p = 0.005$), while no statistically significant difference was found between the 3 groups with respect to gestational age, number of previous pregnancies or previous miscarriages. Significant difference was found between the amniocentesis and no test group regarding attitude towards abortion.

One-way ANOVA indicated that attachment levels for MSS group (mean 51.7, SD 9.4) were significantly lower than those reported by amniocentesis group (mean 58.5, SD 10.7) and no test group (mean 57.0, SD 8.3) [$t(68) = 0.68$, $p = 0.02$]. Moreover amniocentesis group did not differ

in bonding levels compared to the no testing group [t (67) = 0.66, p = 0.51], thereby proving the hypothesis.

This difference persisted even after removing the influence of maternal age and attitude towards abortion. There was no significant interaction between testing status of the 3 groups and timing of conducting survey (second or third trimester) when they were used as independent variables with PAI as the dependant variable.

The results suggest that MSS may disrupt the developmental trajectory of the maternal-fetal bond even after favourable results are known. This may be due to the probabilistic nature of MSS results which creates confusion rather than reassurance.

For the second systematic review 600 studies were identified and 19 met inclusion criterion – 10 related to screening/diagnosis for Down's syndrome (DS) and neural tube defects (NTD), 3 for haemoglobin disorders, and 6 studies for HIV. Several studies were limited by small sample size and poor reporting of data & statistical analysis. Findings from 10 studies of DS and NTD have only been stated.

Nine studies reported on utilization and/or uptake of prenatal screening or diagnosis. One of these suggested that compared to White women, utilization of testing was lower in Asian women, two others indicated that both utilization and uptake was lower, and fourth study found both acceptance and uptake of amniocentesis lower in women from Asia. In the remaining 5 studies, no statistically significant association was found between socio-demographic factors and test utilization.

Four studies reported on the offer of screening or diagnosis for DS. Two of these suggested that Asian women were less likely to be offered amniocentesis, while in the third study fewer Bangladeshi than White women were offered screening, although this result was not statistically significant. The fourth study did not analyze the results according to the social class or ethnic group.

It was concluded that there is evidence that women from some ethnic groups, particularly South Asian women, may be less likely to receive prenatal diagnosis for DS. Significant proportion of these women will take up prenatal testing if offered, but that these women may be less likely to be offered testing. This point to the need to identify the factors associated with the offer and uptake of prenatal screening, barriers to offer screening at institutional and professional levels, and reasons for failure to take up screening when offered.

In the sixth study 2059 women were included and 1791 (89%) returned questionnaires but only 84% of these were completed on time.

a) Screening uptake – overall uptake was 49% (95% CI 47-52). Uptake was higher in white and SE advantaged women.
b) Knowledge – Overall the mean knowledge score was above the mid-point of the scale. Knowledge was higher for white, SE advantaged and older women.
c) Attitudes towards test: The mean overall score was above the scale mid-point, that is, overall women had positive attitude towards the test. No difference in attitudes was found related to ethnicity, SE status or parity; but older women had more positive attitude than younger ones.
d) Uptake-attitude consistency – In women with positive attitudes, white and SE advantaged women were more likely to act in line with their attitudes (76% white women had test compared to 45% South Asian women, $p < 0.001$) and (78% SE advantaged women had test compared with 63% SE disadvantaged women, $p < 0.001$).

In women with negative attitude, no difference was found between ethnic or social groups.

e) Informed choice – rates of informed choice were higher for white women (56% vs 20% South Asian, $p < 0.001$) and SE advantaged women (59% vs 14% for SE disadavantaged, $p < 0.001$).

After controlling for confounding variables (ethnicity, age, SE status, and hospital attended), it was found that both South Asian women and SE disadvantaged women with positive attitudes were less likely to act consistently with their attitudes compared to white and SE advantaged women (OR 0.22, 95%CI 0.10-0.45 for South Asian vs white) and (OR 0.62, 95%CI 0.41-0.93 for social groups).

The study was not able to determine the cause of lower consistency between positive attitudes and behaviour of these women.

In the last study 1127 women returned the questionnaire. A total of 75% women selected first trimester screening (option 1 or option 2) as their first choice, with 68.2 % preferring results within 1 hour (option 1) and 6.8% preferring combined test. 24% opted for integrated test and just 1% opted for second trimester testing as their first choice.

Evidence summary

There is high quality evidence to indicate that pregnant women do not have sufficient knowledge to make informed decisions that need to be made regarding Down's syndrome screening and find the concept of risk calculation particularly difficult to understand. Moreover providing them more information does not lead to an increase in their anxiety level.

Good evidence from a cohort study shows that women taking part in prenatal screening programme are inadequately informed regarding aspects of testing and the further pathway of management when an increased risk is identified.

Results from a cross-sectional study indicate that women undergoing serum screening test for Down's syndrome develop less attachment for the baby due to the uncertainty surrounding interpretation of the test result.

Evidence from a review of literature shows that pregnant women from Asia have a lower rate of uptake, acceptance and utilization of screening tests.

For the screening tests in general, white women and women from socio-economically advantaged sections of society have a higher uptake, better knowledge, more consistency of actions related to positive attitude, and a higher rate of informed decision making when compared to women from South Asia and socio-economically disadvantaged sections of society.

Health economics evidence

A systematic search of the literature was conducted to identify economic evaluations of screening for Down's Syndrome. The search identified 132 abstracts, of which 40 full papers were retrieved for further consideration. Six studies are included in the review.

One study[801] was conducted to examine the performance of integrated Down Syndrome screening (first- and second –trimester measurements integrated into a single screening test) when ratios of the levels of the same serum markers measured in both these trimesters (cross-trimester ratios) are added as new screening markers. The addition of CT ratios to an integrated test significantly improves the efficacy and safety of prenatal screening for Down syndrome. So, the addition of CT is cost effective and could be usefully introduced into screening programmes.

Another UK study[802] was conducted to compare the effects, safety, and cost effectiveness of antenatal screening strategies. The main outcomes of the study were the number of liveborn babies with Down's syndrome, miscarriages due to chorionic villus sampling or amniocentesis, healthcare costs of screening programme, and additional costs and additional miscarriages per additional affected live birth prevented by adopting a more effective strategy. Compared with now screening, the additional cost per additional liveborn baby with Down's syndrome prevented was £22000 for measurement of nuchal translucency. The cost of the integrated test was £51,000 compared with the measurement of nuchal translucency. All other strategies were more costly and less effective, or cost more per additional affected baby prevented. Depending on the cost of the screening test, the first trimester combined test and the quadruple test would also be cost effective options. The main conclusions of the study were that the choice of screening strategy should be between the integrated test, first trimester combined test, quadruple test, or nuchal translucency measurement depending on how much service providers are willing to pay, the total budget available and values on safety. Screening based on maternal age, the second trimester double test, and the first trimester serum test was less effective, less safe and more costly than these four options.

One HTA study[316] was conducted to identify the most effective, safe and cost-effective method of antenatal screening for Down's syndrome using nuchal translucency (NT), maternal serum and urine markers in the first and second trimesters of pregnancy and maternal age in various combinations. The cost-effectiveness analysis showed that the screening using the integrated test is less costly than might be expected because the extra screening costs tend to be offset by savings in the cost of diagnosis arising from the low false-positive rate. It was estimated that to achieve an

85% detection rate the cost to the UK NHS would be £15,300 per Down's syndrome pregnancy detected. The corresponding cost of using the second trimester quadruple test would be £16,800 and using the first trimester combined test it would be £19,000.

For the health economics modelling for structural abnormalities please see appendix B

Antenatal screening (Down's syndrome + structural abnormalities)

One HTA[297] study was conducted and one of the aims of this study was to refine and update a decision model of cost effectiveness of options for routine scanning for fetal anomalies. The initial 8 options considered were reduced to 3 dominating options: one second trimester scan alone, one third trimester scan alone and a combination of the one second trimester scan followed by one third trimester scan. More representative cost data are required before precise estimates of the additional costs and benefits of alternative options can be determined. Also, it is clear from the analysis one second trimester analysis scan emerged as a clear reference case, being one of the cheapest options yet still detecting a significant number of anomalies. When termination is acceptable and available, a third trimester scan alone or the combination of one second with one third scan, although comparable in economic terms, may be impractical because of the delay in identifying anomalies.

Another study[803] was conducted to compare the cost effectiveness of different programmes of routine antenatal ultrasound screening to detect four key fetal anomalies: serious cardiac anomalies, spina bifida, Down's syndrome and lethal anomalies. The study showed that there was a substantial overlap between the cost ranges of each screening programme demonstrating considerable uncertainty about the relative economic efficiency of alternative programme consisted of one second trimester ultrasound scan. The cost per target anomaly detected (cost effectiveness) for this programme was in the range £5,000-£109,000, but in any 1000 women it will also fail to detect between 3.6 and 4.7 target anomalies. The model highlighted the weakness of the available evidence and demonstrated the need for more information both about the current practice and costs.

Finally, a study[804] was conducted in the UK to determine the most clinically and cost effective policy of scanning and screening for fetal abnormalities in early pregnancy. The number of the abnormalities detected and missed, the number of iatrogenic losses resulting from invasive tests, the total cost of strategies and the cost per abnormality detected were compared between strategies. First trimester screening for chromosomal abnormalities costs more than the second trimester screening but results in fewer iatrogenic losses. Strategies which include a second trimester ultrasound scan result in more abnormalities being detected and have lower costs per anomaly detected.

GDG interpretation of evidence

Accuracy and Effectiveness studies

Whilst integrated testing will result in fewest losses of normal fetuses, there are concerns regarding the practicality of screening by this method There is also evidence that women prefer a one stage test to the integrated test

Evidence shows that the combined test in the first trimester has good diagnostic value for detection of Down's syndrome and other chromosomal anomalies.

Among the currently used second trimester tests, the quadruple test seems to have the best screening performance but the measurement of inhibin (the fourth analyte is not generally available in the UK.

Although isolated 'soft markers' on second trimester ultrasound (18-23 weeks) with the exception of thickened nuchal foldhave limited effectiveness in screening for Down's syndrome, two or more soft markers should prompt referral for fetal medicine opinion.

Other than the presence of increased nuchal fold thickening, isolated soft markers noted on the second trimester scan should not be used to adjust the risk for Down's syndrome which has been derived from an established, nationally approved screening programme.

Women's views

Levels of knowledge among women are not currently adequate for informed decision-making about whether or not to undergo screening

The biggest gap in knowledge is in understanding risk

Increasing pre-screen knowledge does not raise anxiety levels

Fewer Asian women than Caucasian women are offered screening and fewer of those who are offered it choose to go ahead with it. Some health care professionals appear to have misconceptions regarding the likely attitudes of Asian women to screening and termination of pregnancy

Knowledge of those opting out of screening seems better than of those who are screened (16-26% don't know why they are being screened)

Serum screening can have a detrimental affect on women's attachment to pregnancy even with a low risk result, due to uncertainty created by presentation (probabilistic nature) of result

Recommendations

All pregnant women should be offered screening for Down's syndrome. Women should understand that it is their choice to embark on screening for Down's syndrome.

Screening for Down's syndrome should be performed by the end of first trimester (13 weeks and 6 days gestation), but provision should be made to allow later screening (up to 20 weeks gestation) for women booking later in the pregnancy

The screening test for Down's syndrome offered should be the 'combined test' (nuchal translucency, beta-human chorionic gonadotrophin, pregnancy-associated plasma protein-A) between 11 weeks and 13 weeks and 6 days. Between 15 and 20 weeks the most clinically and cost effective serum screening test should be offered (triple or quadruple test).

The integrated test should not be routinely used as a screening test for Down's syndrome.

Information about the screening options for Down's syndrome which can be understood by all women, including those whose first language is not English, should be given to women as early as possible and ideally before the booking visit, allowing the opportunity for further discussion before embarking on screening.

It should include:

a) the screening pathway for both screen positive and screen negative
b) the decisions needing to be made at each point along the pathway and their consequences
c) the fact that screening does not provide a definitive diagnosis
d) information about chorionic villus sampling and amniocentesis
e) balanced and accurate information about Down's syndrome

If a woman receives a screen positive result, she should have rapid access to appropriate counselling by trained staff.

The second trimester ultrasound scan (at 18-20 weeks) should not be routinely used for Down's syndrome screening using soft markers

The presence of an isolated soft marker with an exception of increased nuchal fold noted on the routine anomaly scan (at 18-20weeks gestation), should not be used to adjust the a priori risk for Down's syndrome.

The presence of an increased nuchal fold or two or more soft markers should prompt the offer of fetal medicine referral.

Research recommendations

There should be multicentred studies to evaluate the practicality and acceptability of the integrated test for Down's syndrome

Further studies should be undertaken to establish the feasibility of the measurement of inhibin, including quality control, in routine laboratory use.

10 Screening for infections

10.1 Asymptomatic bacteriuria

Asymptomatic bacteriuria (ASB) is defined as persistent bacterial colonisation of the urinary tract without urinary tract symptoms. Its incidence has been quoted as being 2–10% in studies conducted in the USA, with the higher incidence among women of lower socio-economic status.[328] Studies in the UK have shown that it occurs in 2–5% of pregnant women.[329–331] [Evidence level 3]

Evidence from randomised controlled trials that were conducted to show the benefit of treatment among women with ASB indicate an increased risk between ASB and maternal and fetal outcomes, such as preterm birth and pyelonephritis, among untreated women compared with women without bacteriuria.[329,331–337] [Evidence level 1b] The reported increased risk of pyelonephritis among pregnant women with ASB ranges from a risk difference of 1.8% to 28%.[329,331–333,335,338] [Evidence levels 2a & 1b]

These trials also indicate an increased risk of preterm birth in women who have untreated ASB compared with women who do not have ASB. The risk difference ranges from 2.1% to 12.8%.[329,332,333,338] [Evidence level 1b] The large range in risk difference may be due to variation in effect size over time because earlier studies reported larger effects than more recent studies. Also, with regards to randomisation, many of the older studies did not specify the method of randomisation or were open to bias because of quasi-random allocation to treatment versus control groups.

Urine culture (midstream) has been used as the reference standard for diagnosis of ASB. In studies of ASB, a growth of 105 organisms of a single uropathogen per millilitre in a single midstream sample of urine is considered significant,[339,340] although some tests have used figures such as 104 and 108.[330] When urine culture is used in screening for ASB, the drawbacks include the time lag: results are not usually available for at least 24 hours,[341] and the cost: £1.40 in a 1993 UK study[342] compared with the maximum cost of a reagent strip test of £0.14. Its advantages are in being able to identify causative organisms and determine antibiotic sensitivities.

A number of rapid tests have been evaluated against urine culture in test evaluation studies. These include:

- reagent strip tests which test for one or more of the following:
  - nitrite
  - protein
  - blood
  - leucocyte esterase
- microscopic urinalysis
- Gram stain with or without centrifugation
- urinary interleukin
- rapid enzymatic screening test (detection of catalase activity)
- bioluminescence assay.

Reagent strip testing

This has the advantage of being rapid and inexpensive and requiring little technical expertise. Reagent strips have panels that have nitrites and leucocyte esterase,[343–346] and in which the presence of either nitrites or leucocyte esterase is considered positive.[345,347] Other strips have protein, blood, nitrite and leucocyte esterase.[348] In test evaluation studies with all four panels, a positive test result is defined as a strip showing any of the following:

- more than a trace of protein
- more than a trace of blood
- any positive result for nitrite

- any positive result for leucocyte esterase.[348]

The sensitivity of reagent strip testing, using two or four panels in combination (all tests positive) ranges from 8.18% to 50.0%.[342,343,345,347,348] [Evidence level 2a] With either test positive, in the case of the nitrite and leucocyte esterase test, two studies from the USA conducted in 2001 and 1993, respectively, showed sensitivities of 45% and 50%,[343,347] [Evidence level 2a] whereas a 1988 study, also from the USA, showed a sensitivity of 92%.[346] [Evidence level 2a] These findings are confirmed in another study, where the reported sensitivity of testing for protein alone for ASB was 57% with a specificity of 93.2%.[342] [Evidence level 2a] This implies that, at best, reagent strip testing will detect 50% of women with ASB.

Microscopic urinalysis

This test consists of microscopic analysis of urinary sediment and pyuria is deemed significant with ten cells per high-power field.[345,347] [Evidence level 2a] A study that examined a population of women attending an antenatal clinic found a sensitivity of 25%, which means that 75% of women with ASB will be missed using this test.[347] Two other studies report higher sensitivities but the population in one of the studies was a mixture of women attending an antenatal clinic and women in preterm labour and the second study used a wide range of pyuria of between one and eight per high-power field.[345,349]

Gram stain

Two American studies were identified in which Gram staining was compared with urine culture. In one study, a specificity of 7.7% was reported when urine was centrifuged and considered positive if the same morphotype of bacteria was seen in more than 6 of 12 high-power fields.[345] [Evidence level 2a] In the other study, urine was not centrifuged and a positive smear was defined as more than two organisms per high-power field. This yielded a specificity of 89.2%.[347] [Evidence level 2a] With the low specificity in the more rigorous estimation, more than 90% of women who do not have ASB will be incorrectly identified as cases.[345] [Evidence level 2a]

Other tests

Other tests identified include the urinary interleukin-8 test[343] and the rapid enzymatic test,[344] both of which have a sensitivity of 70% and will potentially miss 30% of women with ASB. [Evidence level 2a] A bioluminescence test has been described, with a sensitivity of 93% and a specificity of 78 %.[350] [Evidence level 2a]

Treatment

A systematic review of 14 RCTs compared antibiotic treatment with no treatment or placebo. Antibiotic treatment reduced persistent bacteriuria during pregnancy (Peto OR 0.07, 95% CI 0.05 to 0.10), reduced risk of preterm delivery or low-birthweight babies (OR 0.60, 95% CI 0.45 to 0.80), and reduced the risk of development of pyelonephritis (OR 0.24, 95% CI 0.19 to 0.32, NNT 7).[351] [Evidence level 1a]

A systematic review that compared single-dose antibiotic treatment with a 4 to 7 day course of antibiotic treatment for asymptomatic bacteriuria showed no difference in the prevention of preterm birth (RR 0.81, 95% CI 0.26 to 2.57) or pyelonephritis (RR 3.09, 95% CI 0.54 to 17.55). Longer duration of treatment, however, was associated with increased reports of adverse effects (RR 0.53, 95% CI 0.31 to 9.91).[352] [Evidence level 1a]

Economic considerations (see Appendix B)

Screening antenatally for asymptomatic bacteriuria can have important healthcare resource consequences associated with the reduction of maternal and infant morbidity. Using resources to screen women antenatally could save the future costs of treating pyelonephritis (which can have severe symptoms in pregnant women) and preterm birth and the consequent lifetime costs of disability associated with preterm birth. Screening and treating pregnant women can lead to healthier mothers and infants and does not lead to a choice to end a pregnancy. Therefore, screening and consequent treatment has only positive benefits for pregnant women and their children.

Implementing either of the screening strategies is more cost effective than a policy of no screening. There is controversy around whether to use a dipstick or a culture test for screening. The culture test is relatively more expensive but has a higher sensitivity and specificity. One economic study concluded that the urine culture, which is regarded as the gold standard, is not cost beneficial when compared with the dipstick strategy.[600] However, this study did not consider the cost consequences of preterm birth in their analysis. Since these costs may be quite high (considering the lifetime costs of an infant born with disability), it was decided to try and model the alternative screening programmes and include these costs.

For that reason, a decision analytic model was created to compare the two strategies:

1. screening with urine culture
2. screening with leukocyte esterase-nitrite dipstick.

The economic data used in the model were extracted from five papers that met the criteria for high-quality economic evaluation (see Appendix B). The clinical effectiveness data were extrapolated from the evidence tables of the present guideline document.

The model indicated the difference in costs and benefits of adopting a dipstick method when compared with the culture method (the current gold standard). The unit of effectiveness was defined as cases of pyelonephritis averted and cases of preterm birth averted. The value and non-resource consequences of averting these cases could not be explored as data were not available.

The costs were expressed in three different ways:

1. the cost of screening only
2. the cost of screening and treatment (of ASB and pyelonephritis)
3. the cost of screening, treatment and the cost of preterm birth.

The model showed that the mean cost per case of pyelonephritis averted for the dipstick method was £4,300 when preterm birth was excluded and £115,000 when preterm birth was included. The mean cost per case averted for the culture method was £82,500 with and £36,500 without preterm birth. The results of the models indicate that it would cost an extra £32,400 for an extra case of preterm birth prevented if the dipstick method was followed instead of the culture.

The analysis supports the conclusion that the culture method is favourable, taking into account the wider cost consequences of ASB. The model indicated that if the policy of using a dipstick test led to only one additional case of preterm birth, then this is no longer the more favourable screening option, relative to the urine culture method.

Threshold analysis was also undertaken to explore the circumstances under which the screening options would have similar costs. The analysis indicated that for the two screening strategies to have equal overall costs (including the cost of preterm birth), the sensitivity of the dipstick method would have to be equal to or greater than 0.912, which is very high for this method of screening. Any sensitivity below this makes the culture method more cost effective in comparison to the dipstick method.

This result has not yet been fully explored in primary cost effectiveness studies and should be considered a priority for future research.

RECOMMENDATION

Pregnant women should be offered routine screening for asymptomatic bacteriuria by midstream urine culture early in pregnancy. Identification and treatment of asymptomatic bacteriuria reduces the risk of preterm birth. [A]

Future research

Up-to-date RCTs are needed to confirm the beneficial effect of screening for asymptomatic bacteriuria.

10.2 Asymptomatic bacterial vaginosis

Bacterial vaginosis results from the relative deficiency of normal *Lactobacillus* species in the vagina and relative overgrowth of anaerobic bacteria. These may include *Mobiluncus* species, *Gardnerella vaginalis*, *Prevotella* species and *Mycoplasma hominis*. This results in a reduction of the normal

acidity of the vagina. It is the most common cause of vaginal discharge and malodour,[353] although 50% of women with bacterial vaginosis infection during pregnancy will be asymptomatic.[354] Why these organisms, many of which are present in small numbers in the vagina normally, multiply is not well understood. The condition is not sexually transmitted, although it is associated with sexual activity.

The presence of bacterial vaginosis during pregnancy varies according to ethnicity and how often a population is screened. In a cross-sectional study of 13,747 pregnant women in the USA, 8.8% of white women had bacterial vaginosis compared with 22.7% in black women ($p < 0.05$), 15.9% in Hispanic women ($p < 0.05$) and 6.1% in Asian-Pacific Islander women.[355] [Evidence level 3] In a northwest area of London, screening before 28 weeks of gestation found a prevalence of 12%.[356] [Evidence level3]

Bacterial vaginosis is associated with preterm birth. In a review of case–control and cohort studies, women with bacterial vaginosis infection were found to be 1.85 times more likely (95% CI 1.62 to 2.11) to deliver preterm than women without bacterial vaginosis.[357] [Evidence levels 2 & 3] The higher risk of preterm birth remains in women diagnosed with bacterial vaginosis early in pregnancy even if the bacterial vaginosis spontaneously recovers later in pregnancy.[358] [Evidence level 3]

Bacterial vaginosis may be diagnosed by either Amsel's criteria (thin white-grey homogenous discharge, pH greater than 4.5, release of 'fishy odour' on adding alkali, clue cells present on direct microscopy)[359] or Nugent's criteria (Gram-stained vaginal smear to identify proportions of bacterial morphotypes with a score of less than 4 normal, 4–6 intermediate, and greater than 6 bacterial vaginosis).[360] Culture of *G. vaginalis* is not recommended as a diagnostic tool because it is not specific. Cervical Papanicolaou tests have limited clinical utility for the diagnosis of bacterial vaginosis because of low sensitivity.

One RCT was located which investigated the efficacy of yoghurt in treating bacterial vaginosis compared with vaginal metronidazole and vaginal placebo.[361] Although metronidazole was the most effective treatment against persistence of infection (relative risk reduction 62%, 95% CI 50 to 72%), yoghurt was two-thirds as effective as metronidazole when compared with the placebo group (relative risk reduction 46%, 95% CI 31 to 58%). [Evidence level 1b]

A systematic review of ten RCTs (n = 4249) found oral or vaginal antibiotics to be highly effective in the eradication of bacterial vaginosis in pregnancy when compared with placebo or no treatment (Peto OR 0.21, 95% CI 0.18 to 0.24)[362] [Evidence level 1a] Antibiotics used in the interventions included oral metronidazole (four RCTs), oral metronidazole plus erythromycin (one RCT), amoxicillin (one RCT), vaginal metronidazole cream (one RCT) and intravaginal clindamycin cream (three RCTs). No significant differences in the rates of preterm birth (birth before 37, 34 or 32 weeks) or perinatal death were observed between the two groups. However, a reduction in risk of preterm premature rupture of membranes was associated with antibiotics (three RCTs, n = 562 women, Peto OR 0.32, 95% CI 0.15 to 0.67). There were no differences in maternal side effects due to treatment found between the treated and non-treated or placebo groups. There was also no evidence of the effect of treatment on the subsequent risk of preterm birth among women with a prior preterm birth (five RCTs, n = 622 women, OR 0.83, 95% CI 0.59 to 1.17). Most women in these trials did not have symptoms of bacterial vaginosis because symptomatic women were treated and therefore excluded.

One trial that was not included in the above systematic review was located.[363] This study identified women between 12 to 22 weeks of gestation with bacterial vaginosis (n = 485) using Nugent's criteria. The study was double blind and women in the intervention group (n = 244) took 300 mg oral clindamycin twice daily for 5 days, while women in the control group (n = 241) took placebos. Women receiving clindamycin had significantly fewer spontaneous preterm deliveries, which were defined as birth occurring between 24 and 37 weeks of gestation, than women in the control group (11 (5%) versus 28 (12%), p = 0.001). [Evidence level 1b] When analysed with the ten trials from the systematic review, the effect of treatment for bacterial vaginosis on preterm birth was not statistically significant (Peto OR 0.93, 95% CI 0.76 to 1.13).

In addition, although oral clindamycin is not known to be harmful in pregnancy, its use as a general antibiotic is limited because of serious adverse effects.[77] In particular, antibiotic-associated colitis may arise and this can be fatal.

Evidence from randomised controlled trials indicates that screening and treating healthy pregnant women (i.e. low risk for preterm birth) for asymptomatic bacterial vaginosis does not lower the risk for preterm birth nor for other adverse reproductive outcomes.

RECOMMENDATION

Pregnant women should not be offered routine screening for bacterial vaginosis because the evidence suggests that the identification and treatment of asymptomatic bacterial vaginosis does not lower the risk for preterm birth and other adverse reproductive outcomes. [A]

10.3 Chlamydia trachomatis

Clinical question

What is the diagnostic value and effectiveness of the following screening methods in identifying genital Chlamydia?

age

urine testing

endocervical swabs

serum antibody testing

history

Previous NICE guidance (for the updated recommendations see below)

Pregnant women should not be offered routine screening for asymptomatic chlamydia because there is insufficient evidence on its effectiveness and cost effectiveness. However, this policy is likely to change with the implementation of the national opportunistic chlamydia screening programme. [C]

Future research

Further investigation into the benefits of screening for chlamydia in pregnancy is needed.

Introduction and background

Genital Chlamydia is the most common sexually transmitted infection in England with a high disease burden of 1 in 10 positives among men and women aged 16 - 25 years (NCSP 2005/6). The majority of persons infected with Chlamydia trachomatis are not aware of their infection because they do not have symptoms that would prompt them to seek medical care. Untreated infections in women can lead to serious complications such as pelvic inflammatory disease, infertility, ectopic pregnancy and chronic pelvic pain. During pregnancy Chlamydia infection can lead to neonatal conjunctivitis and pneumonia, and maternal postpartum endometritis. (CDC report www.cdc.gov)

Nineteen studies have been included in this review – 13 for diagnostic value and 6 for effectiveness of treatment. The review has been divided into two sections – the first section deals with diagnostic accuracy of the various tests while the second deals with effectiveness of treatment.

Diagnostic accuracy

13 studies are included under this section and all are prospective cohort studies with mostly Evidence level 2 due to absence of blinding. The study population in some of the included publications includes non-pregnant symptomatic women and symptomatic men in addition to asymptomatic pregnant women, but results of predictive accuracy have been calculated for asymptomatic pregnant women only. This review was limited to include tests carried out on urine and endocervical specimens only. The screening tests covered under this section are:

1) Antigen detection tests - Enzyme linked Immunosorbent Assay (EIA) or Direct Fluorescent Antibody test (DFA)
2) Nucleic acid amplification tests (NAAT) - Polymerase Chain Reaction (PCR) or Ligase Chain Reaction (LCR) test
3) Nucleic acid hybridization test – DNA probe test
4) Gram staining or Pap smear

5) Culture

Antigen detection tests (EIA or DFA)

Description of included studies

A prospective cohort study[805] was carried out in an obstetric and gynaecology clinic in a county hospital in USA. Study population included both pregnant (n = 231) and non-pregnant women under the age of 35 years (n = 827). Excluded were women suspected of having a sexually transmitted infection, those desiring abortion, and those with acute salpingitis. EIA and DFA were compared with culture (with blind passage) as the reference test, and specimens were collected in random sequence from the endocervix for the three tests. All the tests have been described in detail. Each test was performed independently without knowledge on the part of technicians of the results of other tests. Specimens which were not positive in all three of the tests but were positive by at least one of the tests were re-evaluated by all the three systems. Threshold of a positive DFA test was $\geq$ 10 elementary bodies (EB) per slide, while for EIA it was optical density 0.100 greater than mean optical density of three negative controls. Specimens were considered to be 'True positive' if they were positive by initial culture or repeat culture. [EL Ib]

A study in Canada[805] compared EIA and DFA with tissue culture in a cohort of consecutive pregnant women opting for abortion. Excluded were women with lower genital tract infection, who declined to give detailed sexual history, or where laboratory specimens were lost. Separate specimens were collected for the three tests but details of testing have not been described. Blinding of technicians was not specified. Thresholds for positive DFA and EIA results have not been clearly explained. Tissue culture without blind passage was used as the reference test to define 'true positive'. Diagnostic accuracy was also compared separately by defining 'true positive' as positive results for any two of the three tests. [EL II]

Another prospective cohort study [806] was carried out in a regional medical centre in USA comparing EIA (Chlamydiazyme) and DFA (MicroTrak, Syva) with cell culture. The study comprised of 255 indigent pregnant women from a population showing a Chlamydia isolation rate consistently above 20%. Exclusion criteria have not been specified, but the tests have been described in detail. Specimens were sequentially collected from the cervix and technicians performing the tests were unaware of the results of other tests. Positive EIA was defined as absorbance greater than the mean value of negative controls plus 0.1, while for DFA it was the presence of one or more typical inclusion bodies. Isolation of chlamydia in cell culture was taken as the 'reference test' and single positive test defined as 'true positive'. [EL II]

A multi-centre cohort study[807] was carried out in the USA recruiting symptomatic men and women from sexually transmitted disease clinics, and asymptomatic pregnant women attending abortion clinic or prenatal clinic. Exclusion criteria have not been specified. Pregnant women were selected from two centres and cervical specimens collected for DFA and culture. Tests performed have been described adequately and laboratory personnel were blinded from other test results. Smears showing two or more elementary bodies were considered positive for DFA. Culture was performed twice and a 'true positive' was taken as isolation of chlamydia on either culture. [EL Ib]

Findings

Of the 231 pregnant women in the first study, 28 were true positive (prevalence 12.1%). Given below are the results for diagnostic accuracy of the tests when compared with 'True positive' results.

Method	**ST**	**SP**	**PPV**	**NPV**
EIA (n=231)	85.7	95.6	72.7	98.0
DFA (n=144)	84.6	96.6	84.6	96.6
First culture with blind passage	82.1	-	-	98.8
First culture without blind passage	60.7	-	-	94.7

In the second study, cultures were positive for 56 women out of initial sample of 531 (prevalence 10.8%), while results of all the three tests were available for 462 women only. Women with chlamydial infection were more likely to be $\leq$ 20 years (p = 0.0009) and have a prior history of gonorrhoea (p = 0.013). No difference was observed for number of lifetime sex partners or more

than one sexual partner in the 6 months before study. Results with two different definitions of 'true positive' are as follows:

a) Isolation in cell culture defined as 'true positive'

	ST	SP	PPV	NPV
DFA	89	99	78	99
EIA	96	95	69	99.5

b) Any two positive test results defined as 'true positive'

	ST	SP	PPV	NPV
Culture	80	99.8	98	97
DFA	93	100	100	99
EIA	98	98	87	99.8

54 culture-confirmed infections were detected (prevalence 21.2%) in the third study. For a comparison of diagnostic accuracy, the sample size was 247 for DFA and 250 for EIA due to non-interpretable culture results (4) and loss of slides or assays (4 slides for DFA and 1 assay for EIA). Compared to cell culture as the 'reference tests, the results are:

	ST	SP	PPV	NPV
DFA	98.1	95.4	85.0	99.5
EIA	96.3	92.9	78.8	98.9

In the last study sample size was 1396 including 225 pregnant women. The prevalence of Chlamydia infection was 13%. Results are:

	ST	SP	PPV	NPV
DFA	86.2	99.0	92.6	98.0

Nucleic acid amplification tests (PCR, LCR)

Description of included studies

In the first study[808] consecutive pregnant women going for legal termination of pregnancy were enrolled at a tertiary hospital in Australia over a 12-month period. Women refusing to participate and those with incomplete test results were excluded from the final analysis. The specimens collected were first catch urine and self inserted tampon for both PCR and LCR testing, and endocervical swabs for testing by PCR and culture. The methods for collecting specimens and the tests have been described in detail. All assays on clinical samples were performed blinded to the results of one another. A women was considered 'true positive' if the endocervical specimen was positive by culture and/or at least one of first catch urine, tampon, or endocervical swab was positive by PCR and LCR. [EL Ib]

The other study was a prospective cohort study[809] carried out in the USA, and which recruited predominantly unmarried, publicly funded pregnant women with many having risk factors for Chlamydia genital tract infection (young age, history of STD, reported drug use, education level less than 12 years). The tests employed were LCR for the voided urine sample, and LCR and culture of endocervical swabs. Method of specimen collection and the tests have been described in detail, but blinding has not been specified. A 'true positive' result was defined as a positive culture result or negative culture with positive LCR test confirmed by supplementary testing it with DFA or MOMP-LCR. If either of these supplementary tests gave positive result, then the original positive LCR was considered 'true positive' and the negative culture as false negative result. [EL II]

Findings

In the first study, the initial population was 1245 but 70 had incomplete specimens leaving a sample size of 1175 women for determining diagnostic accuracy. The overall prevalence of

Chlamydia infection was 2.8% (33/1175). The breakdown of true positive results according to the site and test used is as follow:

Specimen	PCR	LCR	Culture
First catch urine	34	31	Not done
Tampon	31	29	Not done
Endocervical swab	27	29	15

No statistically significant difference was observed between the diagnostic value of PCR and LCR test from the three specimens – urine ($p = 0.25$), tampon ($p = 0.5$) or endocervical swab ($p = 0.5$).

On comparing the diagnostic value of PCR/LCR with culture for endocervical swabs, detection by PCR/LCR was significantly better ($p = 0.0005$).

With 'true positive' as the reference standard, sensitivities of the three tests for endocervical specimens were 45.5% (15/33) for culture, 81.8% (27/33) for PCR, and 87.9% (29/33) for the LCR test.

The study population in the second study consisted of 478 women and the mean maternal age of the cohort was 22.9 $\pm$ 5.6 years. 16 women were excluded from the final analysis due to non-availability of specimens. Prevalence of infection was 20.1% (93/462). Compared to the reference standard, the diagnostic accuracy of the three tests was:

Test	Sensitivity	Specificity
Culture endocervix	30.1	100
LCR endocervix	90.3	100
LCR urine	83.9	99.5

Comparison of EIA/DFA versus PCR/LCR or/and CULTURE

Description of included studies

A multi-centre prospective cohort study[810] carried out in Sweden at three hospitals recruited consecutively pregnant women seeking abortion during a six month period. No exclusion criteria have been described. This study evaluated the diagnostic efficacy of culture, DFA, EIA and PCR tests performed on specimens from endocervical region. Method for collecting specimens and the procedure of various tests have been adequately described, but blinding of laboratory personnel to the results has not been specified. When the initial culture was negative, the specimen was recultured using multiple passages. For the reference standard, 'true positive' was defined as positive culture in any passage (first time or on reculturing) or at least two positive non-culture tests. The threshold of a positive test for DFA was taken as $\geq$ 10 elementary bodies per slide, but the diagnostic value of DFA was also calculated for $\geq$ 1 elementary body. [EL II]

Four methods of screening were compared in a prospective cohort study[811] in the UK – EIA of endocervical swab and LCRs for first void urine sample, vaginal swab and endocervical swab. Study sample comprised of consecutive women less than 25 years of age attending abortion, family planning, and antenatal clinics. Women with symptoms of pelvic infection and ruptured membranes were excluded. Method of specimen collection and the test performed have been described adequately, but blinding has not been specified. All positive EIA results were confirmed by DFA (another antigen detection test), while LCR positive results were confirmed by another LCR test coding for major outer membrane protein (MOMP-LCR). Discrepancy in test results was resolved by supplementary testing – DFA performed for negative EIA but positive LCR from any site, and MOMP-LCR performed for LCR negative but EIA positive result. For calculating diagnostic accuracy, 'true positive' was defined as one or more specimens from any site confirmed positive by two independent tests, i.e EIA confirmed by DFA or negative EIA but positive LCR confirmed by MOMP-LCR. [EL II]

Another prospective cohort study in the UK[812] recruited women presenting for termination of pregnancy at a family planning clinic. Criteria for study exclusion were not defined but specimen collection and test have been adequately described. LCR and DFA tests were performed separately

on cervical, vaginal and urine specimens obtained from each subject. Blinding of laboratory personnel has not been specified. The 'reference test' was taken as a positive result for any test at any site. [EL II]

Findings

Results of culture, EIA, DFA were available for 419 women in the multi-centre Swedish study, and PCR test results were missing for further 38 women. 175 women (41.8%) were below 24 years of age. Using the reference standard, prevalence came out to be 4.3% (18/419). Below are the results for diagnostic accuracy of the various tests:

	ST	**SP**	**PPV**	**NPV**
Culture	66.7	100	100	98.5
DFA (≥10 EB)	61.1	99.8	91.7	98.3
DFA (≥1 EB)	77.8	99.5	87.5	99.0
EIA	64.7	100	100	98.5
PCR (n=381)	71.4	100	100	98.9

In the first UK study, mean maternal age of 303 women was 20 years (SD 2.7). 67% of the study population was pregnant (204/303) – 104 at the abortion clinic and 100 at antenatal clinic. One patient from the antenatal population was excluded from the final analysis as her positive LCR was not available for confirmation. Overall prevalence of Chlamydia infection was 9.9% (30/302) while it was 10.8% (22/203) among the pregnant women. Results of diagnostic accuracy of the four tests in pregnant women are as follows:

Test	**Sensitivity (95% CI)**	**Specificity (95% CI)**
EIA	82 (62-93)	100 (98-100)
LCR endocervix	82 (62-93)	100 (98-100)
LCR vagina	100 (85-100)	100 (98-100)
LCR urine	91 (72-98)	100 (98-100)

Of the 863 women recruited in the second UK study, 74 were infected by Chlamydia (prevalence 8.5%). Median age of infected women was significantly lower than that of the uninfected group ($p < 0.0001$). Compared to the reference standard, sensitivities of various tests were:

Site	**LCR (95% CI)**	**DFA (95% CI)**
Cervical swab	97 (93-99)	93 (87-99)
Vaginal swab	94 (88-99)	92 (86-99)
Urine	83 (75-92)	78 (68-88)

Sensitivity and specificity of the DFA test was also compared with LCR test as the reference test using results from the same test-site.

Site	**Sensitivity (95% CI)**	**Specificity (95% CI)**
Cervical swab	93.8 (93.2-94.4)	99.9 (99.8-100)
Vaginal swab	92.1 (92.0-93.2)	99.5 (99.2-99.9)
Urine	89.3 (81.2-97.4)	99.7 (99.4-99.9)

Nucleic acid hybridization tests (DNA probe test)

Description of included studies

A prospective cohort study[813] in USA compared the diagnostic value of DNA probe tests with that of culture for both Chlamydia and gonorrhoea. Study population comprised consecutive low-income pregnant women attending a university medical centre, but no exclusions were specified. Endocervical specimens were collected during their first prenatal examination, and the methods and test performed have been adequately described. Technologists performing the tests were

blinded to other test results. Presence of one or more fluorescing inclusion was considered a positive DFA test, and isolation of Chlamydia on culture was taken as the 'reference standard'. [EL II]

Another USA based prospective cohort study[814] compared a DNA probe test with standard tissue culture method for the detection of endocervical Chlamydia infection. The study population comprised both asymptomatic pregnant women attending for routine prenatal care, and women with symptoms of lower genital tract infection or history of STD. Excluded were women receiving antibiotics within 4 weeks of specimen collection. Method of collecting specimen and the tests have been described in detail, but blinding of laboratory personnel to the results has not been specified. In case of discrepant results 'probe competition assays' were performed. Cut-off range for positive DNA probe test was calculated on the basis of difference between the response in relative light units of the specimen and mean of three negative reference values. 'True positive' results were defined as those specimens positive by culture or positive by two non-culture tests, (i.e DNA probe test and probe competition assay) if the culture was negative. [EL II]

Findings

In the first study, there were overall 322 women with a median age of 21 years and average gestational age of 22 weeks at the time of testing. Results for both tests for Chlamydia were available for 246 women only (76.4% of the study population) and 33 were positive by culture (prevalence 13.4%). DNA probe test for Chlamydia had a sensitivity of 93.9%, specificity of 99.1%, PPV of 93.9% and NPV of 99.1%.

The study population in the second USA study was 426 consisting of 257 asymptomatic pregnant women and 169 symptomatic women. Prevalence of infection among pregnant women was 8.6% (22/257). Diagnostic accuracy results for pregnant women are as follows:

	ST (95% CI)	**SP**	**PPV**	**NPV**
DNA probe test	86.4 (75-100)	100	100	98.7
Culture	95.4 (87-100)	100	100	99.6

When culture alone was taken as the reference standard, then the ST, SP, PPV and NPV of DNA probe test was 85.7%, 99.6%, 94.7% and 98.7% respectively.

Gram staining / Pap smear

Description of included studies

A prospective cohort study in USA[815] compared the diagnostic accuracy of a Gram stain of cervical mucus with that of DNA probe test and PCR for the detection of Chlamydia and gonorrhoea. Pregnant women examined at their initial visit to the obstetric clinic or at 36 weeks gestation were enrolled. No specific exclusion criterion has been mentioned. Procedure for specimen collection and methodology of the tests has been adequately described. Examiners for Gram stain were masked to other tests results. Positive Gram stain was defined as having $\geq$ 10 polymorphonuclear leucocytes per high power field and a positive DNA probe test was taken as the reference standard. [EL Ib]

Another prospective study of unselected pregnant women seeking first or second trimester termination of pregnancy was conducted at a tertiary hospital in USA[816] to compare Pap smear with culture. Women who had received Tetracycline or erythromycin within two weeks of procedure were excluded. Specimens were collected 2-10 days prior to abortion and the tests have been described in detail. Pap smear findings were grouped into inflammation, consistent with Chlamydia infection, others and negative. The reference test employed was a positive growth on culture. [EL II]

Findings

The study population included 519 pregnant women in the first study, and DNA probe results were unavailable for one. 63% of the sample population was less than 24 years of age. Prevalence of Chlamydia identified by DNA probe test was 6.8% (35/518). Age less than 20 years ($p<0.0001$) and unmarried status ($p=0.005$) were found to be significant predictors of the disease by logistic regression.

Compared to the DNA probe test as the 'reference standard' values for diagnostic accuracy of Gram staining were – sensitivity 91%, specificity 18%, PPV 7.5% and NPV 96.7%.

In the second study, mean age of the sample population of 300 women was 21.4 years and the majority of them (80.3%) were single. Chlamydia was isolated in 43 women (prevalence 14.3%).

When a Pap smear consistent with Chlamydia infection was used as the threshold, the ST and SP were 2.3% and 98.1% respectively. When the threshold was increased to include smear findings of inflammation, then ST was 60.5% and SP was 56.4%.

Evidence summary

There is high quality evidence to show that both antigen detection and nucleic acid amplification tests have high sensitivity and specificity for detecting Chlamydia infection [EL Ib]

Evidence indicates that the diagnostic accuracy of both antigen detection and nucleic acid amplification tests is better than that of tissue culture method for endocervical specimens [EL II].

There is some evidence that nucleic acid amplification tests (PCR, LCR) carried out on first void urine and endocervical specimens might have better diagnostic ability in detecting chlamydial infection compared to the antigen detection tests [EL II].

DNA probe test has high sensitivity and specificity in detecting Chlamydia infection, but the evidence is of moderate quality and is also limited. [EL II].

Evidence from a single study shows that Gram staining has high sensitivity but poor specificity for detecting Chlamydia infection. [EL Ib]

Effectiveness studies

Six papers have been included in this review which includes 1 RCT and 5 cohort studies (4 prospective and 1 retrospective).

Description of included studies

A randomized placebo-controlled double-blinded trial by[817] was carried out in USA to determine if treatment of pregnant women with Chlamydia infection would lower the incidence of preterm delivery and/or low birth weight. This study was part of a large multi-centre trial known as Vaginal Infection and Prematurity (VIP) Study. Pregnant women at 23-29 weeks gestational age and with Chlamydia isolated from endocervical specimens by culture were enrolled for the trial if they successfully completed a 1 week placebo run-in. Women were randomized to the treatment group (erythromycin base 333 gms TDS for 7 days, n = 205) or the placebo group (n = 209) using computer randomization and method of allocation was concealed. At the mid-study stage (2-4 weeks after starting study), random samples for culture were obtained to ensure quality control and drug efficacy. Baseline characteristics of the two groups were similar. When data from all the study sites was combined using intention-to-treat analysis, the treatment group showed fewer LBW infants (8% vs 11%), fewer preterm deliveries < 37 weeks (13% vs 15%), and fewer instances of PROM (3% vs 4%) compared to the placebo group but the difference was not statistically significant for all the outcomes. No difference was observed for stillbirth and neonatal deaths. Results from mid-study culture showed two centers having low culture positive recovery rates in the placebo group (high clearance group) which could not be explained even after controlling for factors like quality and use of antibiotics outside the trial. The trial outcome was then stratified into two groups: data from study sites with high clearance vs. low clearance of Chlamydia infection in the placebo-treated women. At sites with low clearance, LBW occurred in 8% of treatment group vs. 17% in placebo group (p = 0.04), while preterm delivery occurred in 13% vs. 17% respectively (p = 0.4). In the high clearance group, no statistically significant difference was seen for the two outcomes although there was no reason given why some women cleared infection better. [EL 1++]

A USA based prospective study 1990[818] sought to determine whether treatment of Chlamydia infections during pregnancy could reduce the effect of the infections on adverse pregnancy outcomes. Endocervical cultures for Chlamydia were obtained from 11,544 consecutive new obstetric patients - 9111 were negative and 2433 were culture positive. No treatment was recommended for women with positive culture during the first 16 months of the study. But after reviewing high rate of Chlamydia infection among the cohort, a treatment protocol was instituted (with erythromycin 500/250 mg QID for 7 days or sulfisoxazole 1 gm QID for 7 days) for women with positive culture for the remaining study period of 20 months. Baseline characteristics of the

three groups have not been compared and all the information was collected from the computerized database. Of the 2433 initial culture positive pregnant women, 1323 were successfully treated and 1110 were untreated. The results showed a 21.1% prevalence of Chlamydia that was inversely related to age and parity. Prevalence was 32% in women under the age of 17 and 20% in the 20-to 24-year-old group. The treated group as compared to the untreated group showed a significantly lower frequency of premature rupture of membranes 2.9% vs 5.2%, and low birth weight 11% vs 19.6% respectively ($p < 0.001$ for both). The newborn survival was significantly higher ($p < 0.001$) in the treated group as compared to the untreated group 99.4% vs 97.6%. Similar results were observed when the culture negative group was compared with the untreated group. Multiple logistic regression analysis was then used to control for confounding variables. Incidence of PROM was significantly higher in the untreated group compared to the treated group ($p < 0.01$). Perinatal mortality was also observed to be higher in the untreated group but the difference was not statistically significant ($p = 0.08$). On comparing outcomes between the treated group and negative culture group, infants born to mothers in the treated group were more likely to survive ($p < 0.01$) but no difference was seen for PROM as an outcome. It was concluded that screening of populations at high risk of chlamydia is recommended and treatment may improve pregnancy outcomes. [EL 2+]

A USA based retrospective study[819] compared the clinical outcome in pregnant women whose cervical Chlamydial infection was successfully treated with erythromycin 500 mg QID for 7 days (Group 1, n = 244) with the outcome of pregnant women who remained Chlamydia positive throughout pregnancy/ at the end of pregnancy (Group 2, n = 79), as well as to a group of Chlamydia free matched control patients (Group 3, n = 244). These 3 groups were selected from a cohort of low income, indigent, and urban pregnant women considered at high risk for infection with Chlamydia trachomatis. Demographic characteristics of the three groups were similar. On comparing pregnancy outcomes between the groups, Group 1 was associated with significantly lower frequency of premature rupture of membranes (7.4% vs 20.3%), premature contractions (4.1% vs 24.1%) and small for gestational age babies (13.1% vs 25.3%) when compared to Group 2, but no such differences were observed between Group 1 and Group 3. The frequency of premature delivery was significantly lower in Group 1 than either Group 2 (2.9% vs 13.9%) or Group 3 (2.9% vs 11.9%). No difference was found between the three groups regarding other pregnancy outcomes - frequency of vaginal deliveries, caesarean sections, postpartum endometritis, antepartum hemorrhage or still birth. The authors concluded that there can be a significant reduction in certain adverse outcomes in a pregnant population at high risk for infection with Chlamydia with repeated prenatal chlamydial testing plus successful erythromycin treatment. [EL 2−]

A USA based prospective study 1990[820] sought to determine whether a rapid enzyme immunoassay antigen detection system (Chlamydiazyme) can be used reliably in a screening program to identify and treat chlamydial infections in pregnant women to prevent perinatal transmission of the organism to their infants. Chlamydiazyme was used to screen 199 asymptomatic pregnant women in the third-trimester. 52 were Chlamydiazyme-positive (prevalence 26%) and were treated with erythromycin 500 mg QID for 7 days whereas 128 were Chlamydiazyme-negative. The results showed no significant differences in the incidence of respiratory tract illnesses or conjunctivitis in infants born among the two groups (n = 50 study group, n = 48 control group). There were no significant differences in the incidence of rupture of membranes, preterm birth, caesarean section and postpartum endometritis among the erythromycin treated Chlamydiazyme-positive and Chlamydiazyme-negative group. It was concluded that Chlamydiazyme can be used in a screening program to identify and treat third-trimester women infected with Chlamydia trachomatis. [EL 2−]

A prospective study in USA 1997[821] compared maternal, neonatal and infant outcomes between two groups of pregnant women with chlamydial cervicitis – one group correctly identified by antigen detection tests and treated with erythromycin 800mg QID for 7 days (n = 23), and the second group missed by antigen detection tests (positive by culture) and hence did not receive any treatment (n = 58). The two groups in this study were formed as a result of an earlier study done to evaluate diagnostic value of antigen detection tests and their demographic characteristics were similar. Clinicians were blinded to culture results but not antigen detection tests results. Maternal complications including abortion, PROM, preterm delivery and chorioamnionitis were similar in the two groups. Similarly no difference was observed for neonatal (stillbirth, premature birth, RDS, tachypnea, sepsis) and infant complications (conjunctivitis, pneumonia, otitis, bronchitis, diarrhea).

The authors concluded that further prospective, controlled, culture based studies are needed before recommending routine screening for Chlamydia. [EL 2+]

A USA based prospective cohort study 1985[822] compared the clinical outcome of chlamydia infection treated mothers and infants with that of untreated ones. Routine cervical cultures for chlamydia were obtained during the third trimester of pregnancy to identify infected mothers (n=85) whose infants may also be infected and 38 were treated with erythromycin 500mg BD for 10 days. A total of 16 culture positive infants born to treated mothers were compared with 21 culture positive, from untreated ones. Baseline characteristics of the two groups were not compared and blinding not specified. The results showed that in the culture positive, treated group none of the infants developed infection with chlamydia, while five of 21 infants of untreated mothers ($p < 0.04$) were culture-positive and symptomatic (four with conjunctivitis, one with pneumonia). The follow-up of infants born to chlamydia-positive mothers showed no evidence of more frequent episodes of upper respiratory infection and otitis media during the first six months of life. The authors concluded that diagnosis and treatment of cervical chlamydia infection during the third trimester of pregnancy provides a practical approach to the prevention of infection in the newborn. [EL 2 -]

Evidence summary

There is some evidence to indicate that treatment of chlamydia infection during pregnancy is effective in reducing incidence of PROM, premature delivery and low birth weight babies, but the studies are not of good quality.

There is no significant evidence to show that treating chlamydia infection during pregnancy leads to decreased incidence of adverse neonatal outcomes (conjunctivitis, pneumonia).

GDG interpretation of evidence

There is no good quality evidence which would support routine antenatal screening for genital Chlamydia.

There are concerns regarding the practicality of undertaking adequate counselling, contact tracing, partner testing and follow-up in the antenatal care setting.

In addition, it seems likely that the implementation of the National Chlamydia Screening Programme should itself lead to reduction in the prevalence of Chlamydia infection in women under the age of 25.

Recommendations

Chlamydia screening should not be offered as part of routine antenatal care.

Health care professionals need to inform pregnant women under the age of 25 about the high prevalence of chlamydia infection in their age group, and give details of their local National Chlamydia Screening Programme provision.

Research recommendation

Further research needs to be undertaken to assess the effectiveness, practicality and acceptability of chlamydia screening in an antenatal setting.

10.4 Cytomegalovirus

Cytomegalovirus (CMV) is a member of the herpesvirus family. It remains latent in the host after primary infection and may become active again, particularly during times of compromised immunity.

In England and Wales in 1992 and 1993 (n = 1.36 million live births) there were 47 reported cases of CMV infections in pregnant women with 22 resulting in intrauterine death or stillbirth.[374] [Evidence level 3] Congenital infection is thought to occur in 3/1000 live births[375,376] [Evidence level 3] This is likely to be an underestimate, as women who suffer a stillbirth or intrauterine death are more likely to be investigated for CMV infection.

At present, antenatal screening for this condition is thought to be inappropriate, as it is not currently possible accurately to determine which pregnancies are likely to result in the birth of an infected

infant,[376] [Evidence level 3] there is no way to determine which infected infants will have serious sequelae, there is no currently available vaccines or prophylactic therapy for the prevention of transmission and no way to determine whether intrauterine transmission has occurred.[377,378] [Evidence level 4]

RECOMMENDATION

The available evidence does not support routine cytomegalovirus screening in pregnant women and it should not be offered. [B]

10.5 Hepatitis B virus

Hepatitis B is a virus that infects the liver and many people with hepatitis B viral infection have no symptoms. The hepatitis B virus has an incubation period of 6 weeks to 6 months, it is excreted in various body fluids including blood, saliva, vaginal fluid and breast milk; these fluids may be highly infectious.

The prevalence of hepatitis B surface antigen (HBsAg) in pregnant women in the UK has been found to range from 0.5% to 1%.[379–381] [Evidence level 3] An older study of the prevalence of hepatitis B virus in pregnant women in the West Midlands from 1974–1977 reported a lower rate of 0.1%.[382] [Evidence level 3] The range in prevalence rates is most likely due to wide variation in prevalence among different ethnic groups, as Asian women in particular appear to have a higher prevalence of HBsAg.[379] [Evidence level III] Consequently, Asian babies also have higher rates of mother-to-child transmission of HBsAg.[382] [Evidence level 3]

As many as 85% of babies born to mothers who are positive for the hepatitis e antigen (eAg) will become HBsAg carriers and subsequently become chronic carriers, compared with 31% of babies who are born to mothers who are eAg negative (RR2.8, 95% CI 1.69 to 4.47).[383] [Evidence level 3] It has been estimated that chronic carriers of HBsAg are 22 times more likely to die from hepatocellular carcinoma or cirrhosis than noncarriers (95% CI 11.5 to 43.2).[384] [Evidence level 2b]

Approximately 21% of hepatitis B viral infections reported in England and Wales among children under the age of 15 years is due to mother-to-child transmission.[385] [Evidence level 3] Mother-to-child transmission of the hepatitis B virus is approximately 95% preventable through administration of vaccine and immunoglobulin to the baby at birth.[386–392] [Evidence level 1b]

To prevent mother-to-child transmission, all pregnant women who are carriers of hepatitis B virus need to be identified. Screening of blood samples is the accepted standard for antenatal screening for hepatitis B virus. Screening consists of three stages: screening for HBsAg, confirmatory testing with a new sample upon a positive result and, where infection is confirmed, testing for hepatitis B e-markers in order to determine whether the baby will need immunoglobulin in addition to vaccine.[393] Using risk factors to identify 'high-risk' women for HBsAg screening would miss about half of all pregnant women with HBsAg infection.[394] [Evidence level 3] Screening for HBsAg in saliva samples found a sensitivity of 92% (95% CI 84.5% to 99.5%) and a specificity of 86.8% (95% CI 76.0% to 97.6%) when compared with serum samples.[395] [Evidence level 3] Because of the high proportion of cases of mother-to-child transmission that can be prevented through vaccination and immunisation and because risk factor screening fails to identify carriers, the UK National Screening Committee recommends that all pregnant women be screened for hepatitis B virus (Health Services Circular 1998/127).

RECOMMENDATION

Serological screening for hepatitis B virus should be offered to pregnant women so that effective postnatal intervention can be offered to infected women to decrease the risk of mother-to-child transmission. [A]

10.6 Hepatitis C virus

As one of the major causes of liver cirrhosis, hepatocellular carcinoma and liver failure, hepatitis C virus (HCV) is a major public health concern.[396] Acquisition of the virus can occur through infected blood transfusions (pre-1992 blood screening), injection of drugs, tattooing, body piercing and

mother-to-child transmission. HCV prevalence observed in studies of antenatal populations in England ranges from 0.14 in the West Midlands (95% CI 0.05 to 0.33) to 0.8 in London (95% CI 0.55 to 1.0).[397] Based on estimates from other European countries, the risk of mother-to-child transmission in the UK is estimated to lie between 3% and 5%.[397] Another study estimated that 70 births each year are infected with HCV as a result of mother-to-child transmission in the UK, which represents an overall antenatal prevalence of 0.16% (95% CI 0.09 to 0.25).[398] [Evidence level 3]

Although there is consistent evidence that the risk of mother-to-child transmission of HCV increases with increasing maternal viral load,[399,400] whether a threshold level for transmission exists remains unknown. [Evidence level 3]

A higher proportion of infected babies has been observed among those delivered vaginally compared with those delivered by caesarean section but only one study has demonstrated a statistically significant difference.[401] [Evidence level 3]

The clinical course of HCV in infants who have acquired the disease through mother-to-child transmission is unclear. Among 104 children studied who were infected through mother-to-child transmission, two developed hepatomegaly with no other clinical symptoms related to HCV infection reported.[402] [Evidence level 3] It has also been suggested that a proportion of infected children subsequently become HCV-RNA negative. In one study of 23 infants, five infants tested HCV-RNA positive 48 hours after birth. All five infants became HCV-RNA negative and lost HCV antibodies by 6 months after birth.[403] [Evidence level 3] Although HCV infection in infants may be benign in the short to medium term, given that HCV infection in adults has a long latency period, it is possible that infected children may develop long-term clinical outcomes.

Screening for HCV in the UK involves detection of anti-HCV antibodies in serum by enzyme immunoassays (EIAs) or enzyme-linked immunosorbent assays (ELISA). Upon a positive result, a second ELISA or a confirmatory recombinant immunoblot assay (RIBA) is performed on the same sample. If the second test is positive, the woman is informed and a second sample is taken to confirm the diagnosis. Using polymerase chain reaction (PCR) as the gold standard, the sensitivity and specificity of third-generation assays are reported to be 100% and 66%, respectively.[404] [Evidence level 3] Other estimates of specificities from studies of blood donors using ELISA and RIBA report ranges between 96% and 99%.[405,406] Upon confirmation of a positive screening test, a woman should be offered post-test counselling and referral to a hepatologist for management and treatment of her infection.

RECOMMENDATION

Pregnant women should not be offered routine screening for hepatitis C virus because there is insufficient evidence on its effectiveness and cost effectiveness.[C]

10.7 HIV

Infection with human immunodeficiency virus (HIV) begins with an asymptomatic stage with gradual compromise of immune function eventually leading to acquired immunodeficiency syndrome (AIDS). The time between HIV infection and development of AIDS ranges from a few months to as long as 17 years in untreated patients.[353]

The prevalence of HIV infection in pregnant women in London in 2001 was about 1/286 (0.35%), a 22% increase from the year 2000 (1/349 or 0.29%). Elsewhere in England, the prevalence of HIV infection is reported to be around one in 2256 (0.044%).[407,408] [Evidence level 3]

In the absence of intervention, mother-to-child transmission was reported to occur in 25.5% of deliveries and was reduced to 8% with antiretroviral treatment with zidovudine.[409] [Evidence level 1b] The combination of interventions (i.e. combination antiretroviral therapy, caesarean section and avoidance of breastfeeding) can further reduce the risk of transmission to 1%.[410] In the UK, mother-to-child transmission rates were 19.6% (95% CI 8.0% to 32%) in 1993 and declined to 2.2% (95% CI 0% to 7.8%) in 1998.[411]

By the end of January 2001, a total of 1036 HIV-infected children had been reported in the UK (excluding Scotland). Mother-to-child transmission of HIV accounted for about 70% of the cases.[412] [Evidence level 3] Some 1885 children have been born in the UK (excluding Scotland) to HIV-positive mothers, of which 712 were known to be HIV positive (457 indeterminate, 716 not infected) by the end of January 2001.[412] [Evidence level 3]

In the year 1999, there were 621,872 live births in England and Wales (ONS Birth Statistics, 2000). In the same year, 404 babies were born to HIV infected mothers resulting in 66 HIV-positive babies, 244 not infected and 94 as yet undetermined.[412] [Evidence level 3]

The most common way to diagnose HIV infection is by a test for antibodies against HIV-1 and HIV-2. HIV antibody is detectable in at least 95% of patients within 3 months of infection.[353] Early HIV diagnosis improves outcomes for the mother and can reduce the rate of disease progression.

Currently available HIV tests are more than 99% sensitive and specific for the detection of HIV antibodies.[413] The sensitivities and specificities of various commercial HIV screening assays can be found at the Medicines and Healthcare products Regulatory Agency website at www.mhra.gov.uk. Available tests for HIV diagnosis in pregnant women include the EIA and Western blot protocol, which is at least 99% and 99.99% sensitive and specific,[413] and the 'two-ELISA approach' protocol.[414] [Evidence level 3]

In both protocols, an EIA is initially used and if the results are unreactive, a negative report may be generated.[415] [Evidence level 4]

If the reaction is positive, further testing with different assays (if EIA, then at least one of which is based on a different principle from the first) is warranted. If both confirmatory tests are nonreactive, a negative report may be issued. If the confirmatory tests are reactive, one more test with a new specimen should be obtained in order to ensure no procedural errors have occurred.

Mother-to-child transmission of HIV infection can be greatly reduced through diagnosis of the mother before the baby's birth so that appropriate antenatal interventions can be recommended.[416] [Evidence level 1a] [417] [Evidence level 1b] Interventions to reduce mother-to child transmission of HIV during the antenatal period include antiretroviral therapy, elective caesarean section delivery and advice on avoidance of breastfeeding after delivery (see evidence table).

The risk of infant mortality and maternal death was found to be reduced with zidovudine treatment compared with treatment with placebo (infant mortality: OR 0.57, 95% CI 0.38 to 0.85, maternal death: OR 0.30, 95% CI 0.13 to 0.68). All other outcomes measured (i.e. incidence of stillbirth, preterm delivery, low birthweight, side effects in child, side effects in mother) did not show a significant difference between the treated and untreated groups.[416] [Evidence level 1a] Similarly, nevirapine compared with zidovudine did not show any significant difference in the above mentioned outcomes.[416] [Evidence level 1a] There were also no significant adverse effects reported when caesarean section was compared with vaginal delivery.[418] [Evidence level 1b] Newer antiretrovirals, which are likely to be in use in developed countries, exist. However, these treatments have not yet been evaluated in RCTs.

The use of antiretrovirals to reduce mother-to-child transmission has resulted in resistant mutations. This has raised concerns about the efficacy of antiretroviral treatment decreasing with time.[419,420] [Evidence level 3] In a substudy to the Pediatric AIDS Clinical Trials Group Protocol, 15% of the women (95% CI 8 to 23%) developed nevirapine resistant mutations by 6 weeks' postpartum.[419] [Evidence level 3] In another study, although 17.3% of the women and 8.3% of the HIV infected infants developed zidovudine- or nucleotide reverse-transcriptase inhibitor-resistant mutations, respectively, there was no significant association detected between perinatal transmission and the presence of any resistant mutations.[420] [Evidence level 3]

Since 1999, the NHS has recommended that all pregnant women (i.e., not just in areas of higher prevalence as recommended in 1992) be offered and recommended an HIV test as an integral part of antenatal care, and that the offer be recorded (Health Service Circular 1999/183). The Expert Advisory Group on AIDS (www.advisorybodies.doh.gov.uk/eaga/index.htm) and the UK National Screening Committee (www.nsc.nhs.uk/) websites can be checked periodically for updates on HIV screening information.

RECOMMENDATIONS

Pregnant women should be offered screening for HIV infection early in antenatal care because appropriate antenatal interventions can reduce mother-to-child transmission of HIV infection. [A]

A system of clear referral paths should be established in each unit or department so that pregnant women who are diagnosed with an HIV infection are managed and treated by the appropriate specialist teams. [D]

10.8 Rubella

The aim of screening for rubella in pregnancy is to identify susceptible women so that postpartum vaccination may protect future pregnancies against rubella infection and its consequences. Hence, rubella screening does not attempt to identify current affected pregnancies.

Rubella infection is characterised by a febrile rash but may be asymptomatic in 20% to 50% of cases.[421] There is no treatment to prevent or reduce mother-to-child transmission of rubella for the current pregnancy.[422] [Evidence level 4] Detection of susceptibility during pregnancy, however, enables postpartum vaccination to occur to protect future pregnancies.

Surveillance in England and Wales by the National Congenital Rubella Surveillance Programme (NCRSP) indicates that susceptibility in the antenatal population varies with parity as well as with ethnicity. Susceptibility is slightly higher in nulliparous women (2%) than in parous women (1.2%).[423] [Evidence level 3] Certain ethnic groups also appear to have higher susceptibility, such as women from the Mediterranean region (4%), Asian and black women (5%) and Oriental women (8%), compared with less than 2% in white women, with an overall susceptibility of about 2.5% reported for pregnant women.[424] [Evidence level 3]

In 1995, the incidence of rubella in susceptible nulliparous women was 2/431 (risk/1000 = 4.6) and 0/547 in parous women, resulting in an overall risk of 2/1000 susceptible women.[423] [Evidence level 3]

From 1976 to 1978, among 966 pregnant women in England and Wales with confirmed rubella infection, 523 (54%) had elective abortions, 36 (4%) had a miscarriage, 9 women had stillbirths (4 of which had severe anomalies) and 5 infants died in the neonatal period.[425] [Evidence level 2b]

Since the introduction of the measles, mumps and rubella vaccine, an average of three births affected by congenital rubella a year and four rubella-associated terminations were registered with the NCRSP (births) and Office for National Statistics (terminations) from 1996 to 2000.[422] [Evidence level 4]

For pregnant women who are offered a rubella susceptibility test, the protective level of antibodies was originally set at 15 international units (iu). However, newer, more sensitive screening tests[426] [Evidence level 2a] have resulted in the detection of women with low but protective levels of antibodies being reported as rubella susceptible and therefore a lower cutoff of 10 iu is the level recommended in the National Screening Committee draft document for the UK in 2002.[422] [Evidence level 4] Results of rubella screening should be reported as rubella antibody detected or not detected as opposed to reports of 'immune' or 'susceptible', to avoid misinterpretation.[422] [Evidence level 4] If rubella antibody is **not** detected, rubella vaccination after pregnancy should be advised.[427]

A Public Health Laboratory service (PHLS) guideline offers an algorithm for the management of pregnant women who present with rash illness.[427]

Detection of rubella does not protect against mother-to-child transmission in the current pregnancy. However, protection of subsequent pregnancies against the rubella virus will prevent future mother-to-child transmission of rubella and reduce the risk of stillbirth and miscarriage due to rubella infection.

In a cohort study of pregnant women with confirmed rubella infection at different stages of pregnancy, a follow-up of nearly 70% of the surviving infants (n = 269) found that 43% (n = 117) of infants were congenitally infected.[425] [Evidence level 2b] Congenital infection in the first 12 weeks of pregnancy among mothers with symptoms was over 80% and reduced to 25% at the end of the second trimester. 100% of infants infected during the first 11 weeks of pregnancy had rubella defects.[425] [Evidence level 2b]

In another study, a decline in the rate of infection was seen from weeks 9 to 16 of gestation (rate of infection 57% to 70%) compared with weeks 17 to 20 (22%) and weeks 21 to 24 (17%) and a minimal risk of deafness only was observed in the children who were born to mothers infected during the 17th to 24th weeks of gestation.[428] [Evidence level 2b]

About 10% of congenital rubella cases reported since 1990 are associated with maternal reinfection[422] [Evidence level 4] and maternal reinfection is usually diagnosed through changes in antibody concentration only.[427] In a study of seven asymptomatic rubella reinfections in early

pregnancy, six pregnant women went to term and the infants showed no evidence of intrauterine infection. One pregnancy was terminated and the rubella virus was not identified in the products of conception.[429] [Evidence level 3] Symptomatic maternal reinfection is very rare and risk of fetal damage, which is presumed to be significant, has not been quantified.[427]

Vaccination during pregnancy is contraindicated because of fears that the vaccine could be teratogenic.[422] [Evidence level 4] However, in an evaluation of surveillance data from the USA, UK, Sweden and Germany of 680 live births to susceptible women who were inadvertently vaccinated during or within 3 months of pregnancy (with HPV-77, Cendehill or RA27/3), none of the children was born with congenital rubella syndrome.[430] [Evidence level 3]

Screening for the rubella antibody in pregnancy helps to identify susceptible women so that rubella vaccination can be offered postpartum to protect future pregnancies.

RECOMMENDATION

Rubella susceptibility screening should be offered early in antenatal care to identify women at risk of contracting rubella infection and to enable vaccination in the postnatal period for the protection of future pregnancies. [B]

10.9 Streptococcus group B

Group B streptococcus (GBS), *Streptococcus agalactaie*, is the leading cause of serious neonatal infection in the UK.[431] Although GBS can affect a pregnant woman or her fetus or both, it may exist in the genital and gastrointestinal tract of pregnant women with no symptoms and may also exist without causing harm.

It is estimated that GBS can be recovered from 6.6% to 20% of mothers in the USA.[432,433] [Evidence level 3] In the UK, the prevalence has been estimated at 28%, with no association to maternal age or parity.[434] [Evidence level 3] Maternal intrapartum GBS colonisation is a risk factor for early-onset disease in infants.[435] [Evidence level 3] Early-onset GBS disease (occurring in infants within the first week of life) can result in many conditions, including sepsis, pneumonia and meningitis.[436] The prevalence of early-onset GBS disease in England and Wales is estimated to range from 0.4/1000 to 1.4/1000 live births,[435,437,438] [Evidence level 3] which is equivalent to approximately 340 babies per annum. A 2001 UK surveillance study identified 376 cases of early-onset GBS (prevalence in England 0.5, 95% CI 0.5 to 0.6), among which 39 infants died.[431] [Evidence level 3] In 2000, there were 2519 neonatal deaths from all causes in the UK.

The collection of cultures between 35 and 37 weeks of gestation appears to achieve the best sensitivity and specificity for detection of women who are colonised at the time of delivery.[439] [Evidence level 3] Swabs of both the vagina and rectum provide the highest predictive value for identification of women colonised by GBS.[440] [Evidence level 3] Studies have also indicated that women who obtain their own screening specimen, with appropriate instruction, have comparable sensitivity to specimens collected by a physician. With any positive culture used as the reference standard, self-collected sensitivity ranged from 79% to 97% and physician sensitivity was 82% to 83%.[441,442] [Evidence level 3] When asked about preference, 75% of women either preferred to collect their own specimen or were indifferent as to who collected their swab.[441] [Evidence level 3]

A comparison of screening methods (obtaining cultures from all pregnant women or identifying women for intrapartum treatment through clinical risk factor assessment) in a large interstate study in the USA found that the risk of early-onset disease was more than 50% lower in the universally screened group compared with those screened by assessment of clinical risk factors to identify candidates for intrapartum antibiotics (adjusted relative risk 0.46, 95% CI 0.36 to 0.60).[443] [Evidence level 2b]

However, a systematic review of RCTs of intrapartum antibiotics for the reduction of perinatal GBS infection have not yet demonstrated an effect on neonatal deaths from infection (Peto OR 0.12, 95% CI 0.01 to2.0), although a reduction in infant colonisation rate (Peto OR 0.10, 95% CI 0.07 to 0.14), as well as a reduction in early-onset neonatal infection with GBS, was observed (Peto OR 0.17, 95% CI 0.07 to 0.39).[444] [Evidence level 1a] A review of trials of antibiotics administered in the antenatal period found that two of four studies reported a reduction in maternal colonisation at delivery and that results from five other trials showed a reduction of 80% in early-onset GBS with

intrapartum treatment.[445] [Evidence level 2a] In a trial that compared 5 ml 2% clindamycin cream intravaginally with no treatment in women admitted in labour who had had a positive culture for GBS at 26 to 28 weeks of gestation, no difference was found in the reduction of colonisation.[446] [Evidence level 1b]

With an assumption of 80% effectiveness for the prevention of early-onset GBS disease in infants with intrapartum antibiotics, the number of babies affected each year will decrease from an estimated 340 to 68. This means that for every 1000 women treated with intrapartum antibiotics for GBS, 1.4 cases of early-onset disease may be prevented. However, this estimate assumes that screening will identify all GBS carriers and therefore, in practice, the number of women treated to prevent one case is most likely higher.

No trials comparing antenatal screening with no antenatal screening have been conducted, nor have any trials comparing different screening strategies been identified. Therefore, estimates of efficacy of screening strategies are based only on observational studies. In the USA, an analysis of the incidence of early-onset GBS disease from 1993 to 1998 found a decline from 1.7/1000 live births in 1993 to 0.6/1000 live births in 1998 (65% decrease, $p < 0.001$),[447] [Evidence level 3] which is the incidence observed in the UK in 2001.[431] [Evidence level 3] This 65% decrease in early-onset GBS disease coincided with efforts in the USA to promote the wider use of intrapartum antibiotics for the prevention of GBS disease in infants less than 7 days old. An Australian study that determined the incidence of GBS in the population before implementing a screening programme found a significant decrease from 4.9/1000 to 0.8/1000 live births after the intervention.[448] [Evidence level 3]

Further information on GBS, such as guidance for when GBS is incidentally detected during pregnancy, can be found in the RCOG guideline on the prevention of early onset neonatal Group B streptococcal disease (www.rcog.org.uk/index.asp?PageID=520).

Economic considerations (see Appendix B)

The review of the economic literature on GBS found 26 articles including the guideline published by the Royal College of Obstetrics and Gynaecology on the prevention of early onset neonatal Group B streptococcal disease. Of these studies, 25 were relevant to the topic and were examined in detail. However, almost all the economic studies were conducted in the USA setting (one was from Australia). The extrapolation and generalisability of the results of the US studies was limited also because the prevalence of the disease used was not comparable with a UK setting. Four of the US studies were of sufficient quality to extrapolate data for the economic model.

An economic model was constructed to estimate the number of early-onset GBS cases in infants averted due to screening and treatment. The model also took into consideration how many cases of early-onset GBS were missed following each screening method and how many cases of early-onset GBS were prevented through the screening and subsequent treatment of the pregnant women. The benefit or harm to the pregnant women and infants over and above the financial costs to the NHS were not included in the model because of the lack of data. The only unit of benefit included in the model was 'case of early-onset GBS averted'. This is a limitation of the model.

The model set out to calculate the following outcomes:

- the number of pregnant women treated per case of early-onset GBS averted
- the number of cases of early-onset GBS averted by screening and subsequent treatment
- an estimate of the total financial cost to the health service provider of the different screening methods
- the average cost per case prevented and the incremental cost effectiveness of the two screening methods.

During the course of developing this model, it became clear that data on a number of crucial parameters in the model were not available in the clinical literature. These were:

- the prevalence of early-onset GBS in infants of women who have been screened positively using the universal (bacteriological) screening strategy
- the number of women screened as falsely negative (who have the disease but are screened as negative) in the universal screening strategy
- the prevalence of GBS among the women with the risk factors (the proportion of 'true positive' women who have risk factors for GBS).

The true prevalence of GBS among women with risk factors would indicate the proportion of women treated unnecessarily for GBS (who have risk factors but do not have the disease). This would probably give an idea of the avoidable cases of severe anaphylaxis due to treatment of women in the risk factor group.

Without good estimates of the prevalence of disease, it was not possible to calculate the overall number of cases of early-onset BGS avoided and costs of implementing each screening strategy. Early-onset GBS is a severe disease and the treatment has very high costs for the NHS. Therefore, missing even one case could presumably change the cost effectiveness of the two methods. More clinical evidence is required in order to undertake an economic model of different screening methods for GBS.

RECOMMENDATIONS

Pregnant women should not be offered routine antenatal screening for group B streptococcus (GBS) because evidence of its clinical effectiveness and cost effectiveness remains uncertain. [C]

Future research

Further research into the effectiveness and cost effectiveness of antenatal screening for GBS are needed.

10.10 Syphilis

Syphilis is a sexually acquired infection caused by *Treponema pallidum*. The body's immune response to syphilis is the production non-specific and specific treponemal antibodies. The first notable response to infection is the production of specific anti-treponemal immunoglobulin M (IgM), which is detectable towards the end of the second week of infection. By the time symptoms appear, most people infected with syphilis have detectable levels of immunoglobulin G (IgG) and IgM.[449] [Evidence level 4] However, syphilis may also be asymptomatic and latent for many years.[353]

The incidence of infectious syphilis in England and Wales is low, but four outbreaks of infectious syphilis occurred in England from 1997 to 2000.[450] In the USA, an epidemic of syphilis translated into an epidemic of congenital syphilis with rates increasing from 4.3/100,000 live births in 1982 to 94.7/100,000 in 1992.[451]

The prevalence of syphilis in pregnant women as estimated by reports from genitourinary medicine clinics in England and Wales was 0.068/1000 live births (95% CI 0.057 to 0.080) from 1994 to 1997, ranging from zero in East Anglia to 0.3/1000 live births in the North East Thames region.[452] [Evidence level 3] [453] [Evidence level 4] Thirty-four cases of early congenital syphilis (under age 2 years) were reported by genitourinary medicine clinics in England and Wales between 1988 and 1995,[453] [Evidence level 4] and 35 cases were reported from 1995 to 2000,[454] [Evidence level 3] giving an incidence of 0.92/100,000 live births per year (calculated with livebirth rates from ONS Birth Statistics, 2000).

In pregnant women with early untreated syphilis, 70% to 100% of infants will be infected and one-third will be stillborn.[455] [Evidence level 3] [456,457] [Evidence level 4]

Mother-to-child transmission of syphilis in pregnancy is associated with neonatal death, congenital syphilis (which may cause long-term disability), stillbirth and preterm birth. However, because penicillin became widely available in the 1950s, no data from recent prospective observational studies in developed countries are available. Data from two observational studies in the USA in the 1950s and, more recently, from developing countries, provide a picture of the effects of untreated syphilis compared with women who did not have syphilis or who had been treated for syphilis. Among pregnancies in women with early untreated syphilis, 25% resulted in stillbirth compared with 3% among women without syphilis; 14% died in the neonatal period compared with 2.2% among women without syphilis and 41% resulted in a congenitally infected infant (compared with 0% among women without syphilis).[455] [Evidence level 3] These findings were reported to be significant, but the level of significance was not specified in the study. In the other US study, 25% of babies were born preterm to mothers with syphilis compared with 11.5% among women without syphilis. The sample size was small and this finding was not reported to be significant.[458]

[Evidence level 3] The risk of congenital transmission declines with increasing duration of maternal syphilis prior to pregnancy.

Among 142 pregnant women in South Africa who tested positive for syphilis, 99 were 'adequately' treated with at least two doses of 2.4 mega-units of benzathine penicillin and 43 received 'inadequate' treatment of less than two doses. Among inadequately treated women, perinatal death occurred in 11 (26%) cases compared with 4 (4%) cases among adequately treated women ($p < 0.0001$).[459] [Evidence level 3]

There are two main classifications of serological tests for syphilis: non-treponemal and treponemal. Non-treponemal tests detect non-specific treponemal antibodies and include the Venereal Diseases Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests. Treponemal tests detect specific treponemal antibodies and include EIAs, *T. pallidum* haemagglutination assay (TPHA) and the fluorescent treponemal antibody-absorbed test (FTA-abs).

EIA tests that detect IgG or IgG and IgM are rapidly replacing the VDRL and TPHA combination for syphilis screening in the UK.[449] [Evidence level 4] Screening with a treponemal IgG EIA is useful for detecting syphilis antibodies in patients who are infected with HIV and is comparable to the VDRL and TPHA combination in terms of sensitivity and specificity.[460,461]

EIAs are over 98% sensitive and over 99% specific. Non-treponemal tests, on the other hand, may result in false negatives, particularly in very early or late syphilis, in patients with reinfection or those who are HIV positive. The positive predictive value of non-treponemal tests is poor when used alone in low prevalence populations. In general, treponemal tests are 98% sensitive at all stages of syphilis (except early primary syphilis) and more specific (98% to 99%) than non-treponemal tests. None of these serological tests will detect syphilis in its incubation stage, which may last for an average of 25 days.[453] [Evidence level 3]

A reactive result on screening requires confirmatory testing with a different treponemal test of equal sensitivity to the one initially used and, preferably, one with greater specificity. A discrepant result on confirmatory testing needs further testing, which is provided by Birmingham Public Health Laboratory (PHL), Bristol PHL, Manchester PHL, Newcastle PHL and Sheffield PHL.[449] [Evidence level 4]

Following confirmation of a reactive specimen, testing of a second specimen to verify the results and ensure correct identification of the person should be done. Whether or not the pregnant woman should then be referred for expert assessment and diagnosis in a genitourinary medicine clinic should be considered. To assess the stage of the infection or to monitor the efficacy of treatment, a quantitative non-treponemal or a specific test for treponemal IgM should be performed.[449] [Evidence level 4]

Not all women who test positive will have syphilis, as these serological tests cannot distinguish between different treponematoses (e.g. syphilis, yaws, pinta and bejel). Therefore, positive results should be interpreted with caution.

In the UK, the Clinical Effectiveness Group of the Association for Genitourinary Medicine and the Medical Society for the Study of Venereal Disease recommend screening for syphilis at the first antenatal appointment.[456] [Evidence level 4]

Parenteral penicillin effectively prevents mother-to-child transmission of syphilis, although available evidence is insufficient to determine whether or not the current treatment regimens in use in the UK are optimal.[462] [Evidence level 1a] In a US study of the effectiveness of treatment with penicillin, a 98.2% success rate for preventing congenital syphilis was observed.[463] [Evidence level 2b] Treatment of syphilis in pregnancy with penicillin has not shown any difference in adverse pregnancy outcomes when compared with untreated seronegative women.[464] [Evidence level 2a] Although erythromycin is useful in the treatment of syphilis for non-pregnant women who are allergic to penicillin, treatment of pregnant women with erythromycin has been shown to be ineffective in some cases.[465] [Evidence level 3] The European and UK guidelines on the management of syphilis in pregnant women with penicillin allergy suggest desensitisation to penicillin followed by treatment with penicillin as an alternative.[456,457] All women testing positive for syphilis should be referred to a specialist for treatment.

Economic considerations (see Appendix B)

An economic model was constructed to consider three screening options: no screening, universal screening and selective, ethnicity-based screening. Clearly, the prevalence of syphilis in each strategy was assumed to be different, higher for the ethnicity-based strategy than for the universal strategy. The ethnicity-based approach will be associated with varying levels of prevalence depending upon how the strategy is constructed, based on geographical location (and proportion of women of specific ethnic origins in each group) or on screening for ethnicity during antenatal check-ups.

The costs incorporated in the model were only the costs incurred by the health service. A societal perspective would increase the overall costs of providing screening and would be greater for the universal group but data do not exist on whether these costs would differ by screening method. If more couples were subject to the test using a universal approach, there would be potentially more harm incurred by undertaking unnecessary tests.

The benefits and harm of syphilis screening (to the couples undertaking the screening test) has not been explored in the literature. The test is not associated with a choice to end the pregnancy and the treatment for syphilis is not associated with adverse effects that should be incorporated into the analysis. However, the psychological cost and benefit of undergoing the test have not been estimated in the model, since these data were unavailable.

The model also incorporated the costs of the economic consequences of syphilis cases missed due to the different screening methods. The economic consequences of syphilis were considered to be preterm birth, miscarriage and fetal death and the lifetime treatment costs of the cases of congenital syphilis.

RECOMMENDATIONS

Screening for syphilis should be offered to all pregnant women at an early stage in antenatal care because treatment of syphilis is beneficial to the mother and fetus. [B]

Because syphilis is a rare condition in the UK and a positive result does not necessarily mean that a woman has syphilis, clear paths of referral for the management of women testing positive for syphilis should be established. [Good practice point]

10.11 Toxoplasmosis

Caused by the parasite *Toxoplasma gondii*, primary toxoplasmosis infection is usually asymptomatic in healthy women. Once infected, a lifelong antibody response provides immunity from further infection.

A total of 423 cases of toxoplasmosis related to pregnancy were reported to the PHLS, Communicable Disease Surveillance Centre (PHLS CDSC) in England and Wales from 1981 to 1992, during which time there was an average of 667,000 live births per year (ONS, Population Trends). A systematic review from 1996 identified 15 studies that reported toxoplasmosis incidence among susceptible (i.e., antibody negative) women in Europe.[466] [Evidence level 3] Although no data specific to England or Wales were found, incidence rates for other countries ranged from 2.4/1000 women in Finland to 16/1000 women in France. Approximately 75% to 90% of pregnant women in the UK are estimated to be susceptible to toxoplasmosis.[467,468] The prevalence of congenital toxoplasma infection was recently reported to be approximately 0.3/1000 live births in Denmark.[469] [Evidence level 3]

Toxoplasmosis infection is acquired via four routes in humans:

- ingestion of viable tissue cysts in undercooked or uncooked meat (e.g., salami, which is cured) or tachyzoites in the milk of infected intermediate hosts
- ingestion of oocytes excreted by cats and contaminating soil or water (e.g., unwashed fruit or vegetables contaminated by cat faeces)
- transplanted organs or blood products from other humans infected with toxoplasmosis
- mother-to-child transmission when primary infection occurs during pregnancy.

A study in six European centres identified undercooked meat and cured meat products as the principal factor contributing to toxoplasma infection in pregnant women.[470] [Evidence level 3] Contact with soil contributed to a substantial minority of infections.

When primary infection with *T. gondii* occurs during pregnancy, the risk of mother-to-child transmission increases with gestation at acquisition of maternal infection.[471–473] [Evidence level 3] The reported overall risk of congenital toxoplasmosis ranges from 18% to 44%. The risk is low in early pregnancy at 6% to 26% from 7 to 15 weeks of gestation and rising to 32% to 93% at 29 to 34 weeks of gestation.[471–473] [Evidence level 3]

Clinical manifestations of congenital toxoplasmosis include inflammatory lesions in the brain and retina and choroids that may lead to permanent neurological damage or visual impairment. Reported overall rates of clinical manifestations range from 14% to 27% among infants born to infected mothers.[472,473] [Evidence level 3] In contrast to the risk of transmission, the risk of an infected infant developing clinical signs of disease (hydrocephalus, intracranial calcification, retinochoroiditis) is highest when infection occurs early in pregnancy, declining from an estimated 61% (95% CI 34 to 85%) at 13 weeks to 9% (95% CI 4% to 17%) at 36 weeks.[472] [Evidence level 3]

As primary toxoplasma infection is usually asymptomatic, infected women can only reliably be detected by serological testing. Antenatal screening for toxoplasma infection involves initial testing to determine IgG and IgM positivity. Subsequently, in women in whom antibodies are not detected (i.e., susceptible), monthly or three-monthly re-testing to determine seroconversion is necessary. Positive results should then be confirmed by multiple tests.[474] [Evidence level 3] However, available screening tests to determine seroconversion cannot distinguish between infection acquired during pregnancy or up to 12 months beforehand and women who have acquired the infection before conception are not at risk of fetal infection.[475]

For pregnant women with a diagnosis of primary toxoplasma infection, an informed decision as to whether or not to undergo prenatal diagnosis needs to be made. To calculate the risk of clinical signs in a fetus born to an infected woman, it is possible to multiply the risk of congenital infection by the risk of signs among congenitally infected children. For example, at 26 weeks of gestation the risk of maternal–fetal transmission is 40% and the risk of clinical signs in an infected fetus is 25%. The overall risk is therefore 10% (0.4 x 0.25). If this calculation is repeated for all gestational ages, a positively skewed curve results that reaches a maximum of 10% at 24 to 30 weeks of gestation. In the second and third trimesters, the risk never falls below 5% and is 6% just before delivery.

Knowledge of these risks allows women to balance the risks of harm and benefit when deciding about treatment, amniocentesis or ending the pregnancy. The possible reduction in this risk that might be achieved by prenatal treatment must be balanced against the risk of fetal loss of 1% associated with amniocentesis.[307] Most importantly, they need to know the risk of disability due to neurological damage or visual impairment. Unfortunately, information on these latter outcomes is less reliable and the effect of gestation is not known.

Primary prevention of toxoplasmosis with the provision of information about how to avoid toxoplasma infection before or early in pregnancy should be given. Women should be informed about the risks of not cooking meat thoroughly, possible contact with cat faeces, not washing their hands after touching soil, not washing vegetables thoroughly and eating cured meat products.

Of two systematic reviews on the effects of antiparasitic treatment on women who acquire primary toxoplasmosis infection during pregnancy, the first identified no RCTs.[476] The second identified nine cohort studies that compared treatment (spiramycin alone, pyrimethaminesulphonamides or a combination of the two) with no treatment.[477] [Evidence level 2a] Five of the studies reported a treatment effect and four reported no treatment effect and none of the studies accounted for the rise in the risk of transmission with gestation at maternal infection.

Treatment with spiramycin and pyrimethamine-sulphonamides is reported to be well tolerated and non-teratogenic, although sulpha drugs may carry a risk of kernicterus in infants and also of bone marrow suppression in the mother and infant.[478]

In a comparison of antenatal screening strategies for toxoplasmosis in pregnancy, although universal screening with antenatal treatment reduced the number of cases of congenital toxoplasmosis, an additional 18.5 pregnancies were lost for each case avoided.[479] [Evidence level 3] Other costs include the unnecessary treatment or termination of uninfected or unaffected fetuses and the distress and discomfort of repeated examinations and investigations, both antenatal and

postnatal. A further problem is that, even when antenatal diagnostic tests are negative, absence of congenital toxoplasmosis cannot be confirmed until the child is 12 months old. Finally, children with confirmed congenital toxoplasmosis, most of whom are asymptomatic, are labelled as at risk of sudden blindness, or even mental impairment, throughout childhood and adolescence.

An alternative to antenatal screening for toxoplasmosis is neonatal screening. Neonatal screening aims to identify neonates with congenital toxoplasmosis in order to offer treatment and clinical follow up. The vast majority of congenitally infected infants are asymptomatic in early infancy and would be missed by routine paediatric examinations. Neonatal screening is based on the detection of toxoplasma-specific IgM on Guthrie-card blood spots and has been found to detect 85% of infected infants. There are no published studies that have determined the effect of postnatal treatment compared with no treatment, or treatment of short duration compared with 1 year or more on the risk of clinical signs or impairment in children with congenital toxoplasmosis in the long term.

The UK National Screening Committee recently reported that screening for toxoplasmosis should not be offered routinely.[475] There is a lack of evidence that antenatal screening and treatment reduces mother-to-child transmission or the complications associated with toxoplasma infection.

There are also important and common adverse effects associated with antenatal screening, treatment and follow up for mother and child. Antenatal screening based on monthly or 3-monthly re-testing of susceptible women would be labour intensive and would require substantial investment without any proven benefit. Primary prevention of toxoplasmosis through avoidance of undercooked or cured meat may prove a good alternative to antenatal screening, which cannot currently be recommended.

RECOMMENDATION

Routine antenatal serological screening for toxoplasmosis should not be offered because the harms of screening may outweigh the potential benefits. [B]

Pregnant women should be informed of primary prevention measures to avoid toxoplasmosis infection such as:

- washing hands before handling food
- thoroughly washing all fruit and vegetables, including ready-prepared salads, before eating
- thoroughly cooking raw meats and ready-prepared chilled meals
- wearing gloves and thoroughly washing hands after handling soil and gardening
- avoiding cat faeces in cat litter or in soil. [C]

11 Screening for clinical problems

11.1 Gestational diabetes

Clinical question

What is the diagnostic value and effectiveness of screening tests to identify women at risk of diabetes in pregnancy?

Previous NICE guidance (for the updated recommendations see below)

The evidence does not support routine screening for gestational diabetes and therefore it should not be offered. [B]

Introduction and background

Gestational Diabetes (GD) is defined as carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy and with a return to normal after birth[823]. It includes women who have both DM and impaired glucose tolerance. Definitions and diagnosis in pregnancy are blurred by the fact that blood glucose levels are higher in pregnancy and there is an overlap between women who are clearly diabetic (and at increased risk) and women who are technically diabetic but are actually not at increased risk. Women who develop GD are at increased risk of developing type II diabetes in later life[823] and the escalating rise in the incidence of this in the population at large creates a compelling argument for screening normal women in pregnancy, whose subsequent health may benefit from education about diet and lifestyle. However a decision to implement screening of normal women in pregnancy has to be made on a judgement of the contribution of each of the following:

- the potential reduction in perinatal morbidity and mortality
- the possible reduction in maternal morbidity remembering that increased obstetric intervention may bring about an iatrogenic increase in maternal morbidity
- the increase in health service expenditure
- the potential long term health benefits for the woman.

There has been uncertainty about the value of screening for GD for many years and indeed this uncertainty was reflected in the previous ANC guideline. However the recent

Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial[824] group showed that women treated for GD had a significantly lower rate of serious perinatal complications as compared to women with routine care. These women had a higher rate of induction of labour than the women in the routine-care group.

Not only has there been uncertainty about the value of screening but there is little agreement about a suitable screening method. A UK survey of obstetric units in 1999[825] indicated that of the blood tests, 43% used the random blood glucose, 11% used random plasma glucose, and 10% used 50g GCT. 67% used a risk factor assessment. An earlier survey in 1994[826] involving one District Health Authority in England found a variety of screening practices for GD and in fact only 8 out of 18 hospitals operated a screening policy. Six did random blood glucose; one did fasting blood glucose and one a GCT. They noted that GCT was the most thoroughly evaluated method of screening for GD. A survey of gynaecologists in Italy[827] reported that 53% (151/283) carried out screening with a glucose load. Of these, 36% gave a 50-g GCT to all

women, 17% a 100-g GCT to all women and 40% restricted the test to women with risk factors. In an American survey[828] 98.5% of clinicians used the 50-g GCT.

Risk factors

The use of risk factors such as obesity, ethnicity and the birth of a previous macrosomic baby have been used by health care practitioners for many years and indeed often appear as alerts on antenatal care notes.

Description of included studies and findings

A Health technology assessment (HTA) in 2002[483] [EL 2+] conducted a systematic review on screening for gestational diabetes. The results showed that the risk factors for gestational diabetes included obesity, advanced maternal age advanced maternal age, family history of diabetes, minority ethnic background, increased weight gain in early adulthood and current smoker.

The HTA review included a retrospective analysis in the UK, 1992[829] [2-] aimed to determine the frequency of gestational diabetes according age, BMI, parity and ethnic origin in women without known pre-existing diabetes and to analyse the influence of risk factors separately for each ethnic group. 170/11205 (1.5%) women were diagnosed with gestational diabetes. Women with gestational diabetes were significantly older (32.3 versus 28.3 years; $p<0.001$) had higher BMI (27.7 versus 23.8; $p<0.001$) and more likely to be from an ethnic minority (55.4% versus 15.3%; $p<0.0001$). Rates of gestational diabetes by ethnicity were: white 0.4% (26/6135), Black 1.5% (29/1977); South East Asian 3.5% (20/572); Indian 4.4% (54/1218). After adjusting for age, BMI and parity the RR (with white as the reference category) was as follows: Black 3.1 (95% CI 1.8 - 5.5); South East Asian 7.6 (95% CI 4.1 – 14.1); Indian 11.3 (95% CI 6.8-18.8).

An observational study in Australia, 1995[830] [EL 3] sought to determine the proportion of women with gestational diabetes missed if testing was confined to risk factors. The results showed that women without GD were significantly younger (26.4:28.1, $p < 0.02$) and had a lower BMI (24.2:25.9, $p < 0.05$) than women with GD. 31 women (39.2%) with GD had no historical risk factors and would have been missed if only selective testing undertaken.

A case control study in Australia, 2001[831] [EL 2+] assessed risk factor screening as a practical alternative to universal screening. The results showed for age ≥ 25 years OR 1.9, 95% CI 1.3-2.7, for body mass index ≥ 27kg/m^2 OR 2.3, 95% CI 1.6-3.3, for high-risk racial heritage OR 2.5, 95% CI 2.0-3.2, and for family history of diabetes OR 7.1, 95% CI 5.6-8.9. It was found that using these four criteria for screening, 313 cases (0.6%) would have been missed and could have saved screening up to 1,025 women without GD (17%).

A USA randomised controlled trial, 2000[832] [EL 2+] compared a risk factor-based screening programme with a universally based one. The risk factor group were given a 3-hr 100g OGTT at 32 weeks gestation if any risk factor appeared. The universal screening group was given 50g glucose challenge test and then given a 3h 100g OGTT if the plasma glucose at 1hour was ≥ 7.8mmol/l. The results showed the various PPV of risk factors: first degree relative with type2 diabetes was 6.7%, first degree relative with type 1 diabetes was 15%, previous baby >4.5 kg was 12.2%, glycosuria in current pregnancy was 50%, macrosomia in current pregnancy was 40% and polyhydramnios in current pregnancy was 40%. The detection rate using the universal screening was significantly more than the risk factor screening 2.7% vs 1.45%.

A study in Denmark, 2004[833] [EL 2-] retrospectively investigated the power of the pre-screening to identify GD and screening to predict adverse clinical outcomes. Risk factors for developing gestational diabetes were used for pre screening. Pregnant women with at least one risk factor were offered capillary fasting blood glucose in weeks 20 and 32. If the cFBG measurements were ≥4.1 mmol.l and <6.7 mmol/l, then a 3h 75g OGTT was offered. If cFBG values were ≥6.7 mmol/l, the woman was diagnosed as having gestational diabetes. The most frequent pre screening risk factors were BMI ≥27 kg/m^2 (present in 65% of cases) and age ≥35 years (present in 16% of cases). No single factor seemed the best indicator for GD. The best OR for developing GD was 9.04 (95% CI, 2.6 to 63.7) for glycosuria.

A cross sectional 5 year investigation in the Netherlands, 2006[834] [EL 2-] examined the clinical usefulness of antepartum clinical characteristics, along with measures of glucose tolerance, in Dutch multi-ethnic women with GD for their ability to predict type 2 diabetes within 6 months of delivery (early postpartum diabetes). The following risk factors were assessed for all women: age and gestational age at entry into the study; pre-pregnancy body mass index (BMI); ethnicity; obstetric and clinical history, including the onset of early postpartum diabetes; pregnancy outcome. The results showed that apart from family history of diabetes no other risk factor showed an association with the development of early postpartum diabetes.

A prospective population-based study in Sweden [EL 2+]offered all non diabetic pregnant women a 75g OGTT at 28-32 weeks of gestation[835].Traditional risk factors used were family history of diabetes (first degree relative), obesity (≥90 kg), prior large for gestational age baby (≥ 4500g) or prior GD. The results showed that women who did not take the OGTT were more likely to be multiparous and of non-nordic origin but were less likely to have a family history of diabetes, prior macrosomic baby or prior gestational diabetes. 1.7% of women who were given OGTT were diagnosed with gestational diabetes. The risk factors with the strongest association were prior gestational diabetes (12/61, OR 23.6, 95% CI 11.6-48.0) and prior macrosomic baby (9/61, OR 5.59, 95% CI 2.68-11.7). Other risk factors were family history of diabetes (13/61, OR 2.74, CI 1.47-5.11) non-nordic origin (13/61, OR 2.19, 95% CI 1.18-4.08) weight (≥90kg: 8/61, OR 3.33, 95% CI 1.56-7.13) BMI (≥30: 11/61, OR 2.65, 95% CI 1.36-5.14) and age (≥ 25: 55/61, OR 3.37, 95% CI 1.45-7.85).

A systematic review in 2007[836] [EL 2++] examined the rates and factors associated with recurrence of GD among women with a history of GD. A total of 13 studies were included. The results showed the recurrence rate of glucose intolerance during subsequent pregnancies varied markedly across studies. The most consistent predictor of future recurrence appeared to be nonwhite race/ethnicity, although the racial breakdowns within a study were not always clearly described. The recurrence rates varied between 30 and 84% after the index pregnancy. The recurrence rates were higher in the minority populations (52–69%) as compared to lower rates found in non-Hispanic white populations (30–37%). No other risk factors were consistently associated with recurrence of GD across studies. Other risk factors, such as maternal age, parity, BMI, oral glucose tolerance test levels, and insulin use inconsistently predicted development of recurrent GD across studies.

Evidence summary

Evidence shows that risk factors for developing gestational diabetes are: pre-pregnancy obesity, advanced maternal age, prior gestational diabetes, family history of diabetes, minority ethnic background, prior macrosomic baby ≥ 4.5 kg, increased maternal weight gain in early adulthood and current smoker. The recurrence rates for GD varied between 30 and 84% after the index pregnancy.

The alternative to the use of risk factors is the use of some form of biochemical test either of urine or blood.

Accuracy of biochemical screening tests

Urine test for glucose

2 studies have been identified in this section.

Description of included studies

A USA based retrospective observational study (3217 women), 1995[494] [EL II] assessed the ability of urine testing for glucose to predict GD or pregnancy outcomes. For this review, only the prediction of GD has been taken into consideration. Study participants had complete urinalysis at the first prenatal visit and dipstick at each subsequent visit together with a screening 50 g GCT at 24-28 weeks. Women with at least 2 urinalysis tests during first 2 trimesters were included. 2965 women were categorized into 2 groups, negative or positive for glycosuria. Those with positive GCT screens (cut-off 140 mg/dl) started a 3-day CHO load, and had a 100 g GTT.

A German study, 1990[493] [EL II] compared urine and blood screening tests to detect gestational diabetes. Random urine glucose screening values from each antenatal visit of 500 consecutive pregnant women were compared with a serum glucose test done at 28 weeks' gestation after ingestion of a 50 gm glucose-containing beverage. A positive test of a serum glucose level of 140 mg/dl or more was followed by a 100 gm-3 hr OGTT. Glycosuria was considered present if a trace or greater values were found on at least two prenatal visits. Severe glycosuria was defined as a 2+ (250 mg/dl) level or greater on urine screening on at least two prenatal visits.

Findings

The US study found a higher incidence of GD in women with positive glycosuria in the first two trimesters (12.8% vs. 2.9% for negative screens). The sensitivity of glycosuria in the first trimester as a predictor of GD was 7.1%, specificity was 98.5%, PPV was 12.8% and NPV was 97.1%.

In the German study any degree of glycosuria had a sensitivity of 27.3%, specificity of 83.5%, efficiency of 81%, and positive predictive value of 7.1%. Severe glycosuria had sensitivity of 18.2%, specificity of 96.9%, and positive predictive value of 21.1%. The incidence of glycosuria was not increased in gestational diabetics when compared to pregnant women with normal glucose tolerance. Severe glycosuria occurred in only 18% of these patients.

Random blood glucose test

2 studies have been identified in this section (Table 1)

Description of included studies

A prospective population based study conducted in Sweden, 2004[837] [EL II] aimed to find out if repeated random blood glucose (R-B-glucose), with different cut-off levels, with or without anamnestic factors could be an effective universal screening test method identifying high-risk women for the OGTT as the second step. All nondiabetic pregnant women (n=4918) visiting the maternal health care clinics over a 2 –year period were offered a 75-g OGTT between 28-32 weeks gestation. Random blood glucose was proposed every 4-6 weeks.

A study in Kuwait, 1988[838] [EL II] tested the predictability of random plasma glucose test in women who had their last meal within 2 hrs and those who had their last meal > 2hrs. 276 unselected pregnant women had RPG followed by 75 g OGTT at 28-32 weeks gestation.

Findings

In the Swedish study traditional risk factors and values of repeated R-B-glucose measurements were registered as well as results of the OGTT in terms of fasting B-glucose and 2-h B-glucose. A total of 3616 women had an OGTT. Results showed that an R-B- glucose cut-off level ≥ 8.0 mmol/L as the only indicator for an OGTT was optimal for detecting GD with regard to sensitivity (47.5%) and specificity (97.0%). It had the same sensitivity for detecting GD as using traditional risk factors, but reduced the need to carry out the OGTT from 15.8% to 3.8% of the population.

The Kuwait study used the Lind and Anderson threshold[839], 7.0 mmol/l if eaten < 2 h, 6.4 if eaten > 2 h. This gave a sensitivity of 16%, specificity of 96% and PPV of 47%. Using the 90th percentile of study group sensitivity of 29%, specificity 89% and PPV of 38% were reported.

50 g Glucose challenge test

Description of included studies

A total of 4 studies tested the diagnostic value of 50g GCT (see table 2). All studies had an evidence level of II.

Findings

4 studies [840;499;841;842]) in which a diagnostic test was performed on all participants, showed sensitivities of 79.8%, 59%, 59%, and 78.9% and specificities of 42.7%, 91%, 92%, and 87.2% respectively. The PPV was 24.5%, not reported, 32% and 13.8% respectively.

Comparison studies

3 studies were identified in this section (table 3)

Description of included studies

A prospective study in Germany, 2003[843] [EL II] tested the usefulness of glucose meters in screening pregnant patients for gestational diabetes. 193 pregnant women were administered the 50-g glucose challenge test and their blood glucose levels were simultaneously measured with five portable meters and a HemoCue. The results were compared to a standard Hexokinase method. A cut-off value of 7.8 mmol/L was used. The 6 portables meters used were Accu-Chek, Euro flash, Gluco Touch, HemoCue, One Touch and Precision.

A USA based randomized trial with no control, 1992[844] [EL II] compared 3 carbohydrate sources; 50 g glucose polymer, 50g standard glucose solution and 50g milk chocolate bar. A New Zealand based randomized controlled trial, 1985[845] [EL II] compared the 100g glucose screening test with 100g glucose polymer test.

Findings

All meters showed an excellent correlation ($r > 0.9$, $p < 0.01$). The different specificities were as follows: Accu-Check 84%, Euro flash 100%, Gluco Touch 98%, Hemo Cue 57%, One touch 92%, Precision 90%. The specificities were Accu check 98%, Euro flash 79%, Gluco touch 86%, Hemo Cue 100%, One touch 92%, Precision 91%.

The overall sensitivity in American study was 60%, for standard glucose, 33.3% and 100% for polymer. The specificities for overall, standard glucose and polymer were 84%, 73.6% and 92.8% respectively and PPV was 16%, 9% and 49% respectively.

In the New Zealand based study the sensitivity of glucose polymer test was 89%, specificity was 81% and PPV was 29%.

Fasting plasma glucose test

Description of included studies:

2 studies were identified that tested the diagnostic value of fasting plasma glucose (see table 4).

A Brazilian study 1998[498] [EL II] used baseline data from a cohort study of consecutive pregnant women to evaluate the performance of fasting plasma glucose as a screening test for gestational diabetes as defined by WHO in an unselected group of pregnant Brazilian women. 5,579 women aged ≥20 years with gestational ages of 24-28 weeks at the time of testing and no previous diagnosis of diabetes were included. A standardized 2-h 75-g oral glucose tolerance test was performed in 5,010 women.

A cross-sectional, population-based study in Sweden, 2006[846] [EL II] evaluated the diagnostic properties of fasting capillary glucose as a screening test in an unselected low risk Swedish population (n=3616). They compared fasting capillary glucose (measured at 28-32 weeks' of gestation) with traditional risk factors (registered) and repeated (4-6 times during pregnancy) random capillary glucose measurements as screening models for GD. A 75g OGTT was used to diagnose GD.

Findings

The Brazil study showed that for the detection of gestational diabetes, a fasting plasma glucose of 89 mg/dl jointly maximizes sensitivity (88%) and specificity (78%), identifying 22% of the women as test-positive. Lowering the cut point to 81 mg/dl increases sensitivity (94%), decreases specificity (51%) and identifies 49% women as test positive. For detection of impaired glucose tolerance, a value of 85 mg/dl jointly maximises sensitivity and specificity (68%), identifying 35% women as test positive. A cut off point of 85 mg/dl for the detection of gestational diabetes gives sensitivity (94%) and specificity (66%).

The Swedish study found that 1.52% (55/3616) of women were diagnosed before 34 weeks of gestation. For fasting capillary glucose cutoff values between 4.0 and 5.0 mmol/l, the sensitivity ranged between 87% to 47% and specificity between 51% and 96%. The +LR and –LR was the

best at ≥5.0 mmol/l. The combination of traditional risk factors with fasting capillary glucose only slightly increased the sensitivity as compared to the use of fasting capillary glucose alone.

Jelly beans

2 studies were identified in this section (see table 5).

Description of included studies

A US study, 1999[847] [EL II] tested the hypothesis that a standardized dose of jelly beans could be used as an alternative sugar source to the 50-g glucose beverage to screen for gestational diabetes. This prospective study recruited 160 pregnant women at 24 to 28 weeks' gestation to compare 2 sugar sources for serum glucose response, side effects, preference, and ability to detect gestational diabetes. Patients were randomly given 50-g glucose beverage or 28 jelly beans (50 g simple carbohydrate) and serum glucose values were determined 1 hour later. A 100-g 3-hour oral glucose tolerance test was performed finally.

Another American study, 1995[848] [EL II] tested the diagnostic value and patient tolerance of jelly beans as an alternative to a 50 gm glucose solution. Pregnant women between 26 to 30 weeks of gestation were recruited to participate in the study. Each participant was given cola beverage containing 50 gm of glucose and blood glucose was tested 1 hour later. Within 2 weeks of this test, each patient ate 18 jelly beans and had glucose level tested within 1 hour. Within 2 weeks of the jelly bean test, all participants were given a 3h 100g GTT.

Findings

In the US study 136 participants completed the study and a comparison of efficacies of jelly beans and 50-g glucose beverage as sugar sources in detection of gestational diabetes was made. There was not much difference between serum glucose values after ingestion of jelly beans (116.9 ± 23.6 mg/dL) and of 50-g glucose beverage (116.5 ± 27.0 mg/dL). There was significantly lower incidence of side effects after consumption of the jelly beans 20% as compared to 50-g glucose beverage 38%. 76% of the participants preferred jelly beans as compared to 50-g glucose beverage 24%.

In the second study the sensitivity, specificity and PPV of the cola beverage using 140 mg/dl as threshold were 46%, 81% and 18%. The sensitivity, specificity, and PPV of jelly beans using threshold of 120 mg/dl were 54%, 81%, and 20% respectively. Participants tolerated jelly beans better than the cola beverage.

In order to compare the various blood tests for screening gestational diabetes, likelihood ratios were calculated (Fig 1).

Test	No. of studies/ Population	Heterogeneity for LR+ (I^2)	LR+ [95% CI]	Heterogeneity for LR- (I^2)	LR- [95% CI]
RBG	2 studies 5168 women	0%	15.49 [11.44-20.99]	0%	0.55 [0.44-0.69]
FPG	3 studies 9146 women	94.8%	4.77 [3.16-7.21]	97.4%	0.27 [0.10-0.78]
50g GCT	4 studies 2437 women	98%	4.34 [1.53-12.26]	0%	0.42 [0.33-0.55]

Figure 1 Likelihood ratios for 3 blood tests

Table 1 Random Blood glucose

Author, Year, Country, Evidence level, Study design	Study population, weeks of gestation	Screening test/tests, cut-off value for giving D_x, Diagnostic test, Prevalence/ Incidence	Threshold, sensitivity, specificity, PPV, NPV	Comments and conclusion
Ostlund, 2004, Sweden, EL II, Prospective population based study	3616 28-32 weeks	Random blood glucose, Risk factors, All were offered diagnostic test, 75g OGTT, 61/3616 or 1.7%	≥ 8 mmol/l Sens: 47.5% Spec: 97%	Traditional risk factors have poor sensitivity for GD.
Nasrat, 1988, Kuwait, EL II, Prospective study	250 28-32 weeks	RPG, Lind and Anderson threshold used 7.0 mmol/l < 2h 6.4 mmol/l > 2h, 75 g OGTT, 3/250 or 1.2%	7.0 mmol/l < 2h 6.4 mmol/l > 2h Sens: 16% Spec: 96% PPV: 47% 90th percentile cut-off Sens: 29% Spec: 89% PPV: 38%	Random plasma glucose has limited predictive value

Table 2 Glucose Challenge test

Author, Year, Country, Evidence level, Study design	Study population, weeks of gestation	Screening test/tests, cut-off value for giving Dx, Diagnostic test, Prevalence	Threshold, sensitivity, specificity, PPV, NPV	Comments and conclusion
Seshiah, 2004, India, II, Prospective consecutive population based study	1251 891 positive screens, Second or third trimester	1h 50g GCT, 2 hr 75g OGTT, given to all, 168/891 or 18.9%	No threshold used, Sens: 79.8%, Spec: 42.7%, PPV: 24.5%, NPV: 90.1%	Using 2h plasma glucose ≥ 140 mg/dl as once step procedure is simple and economical for countries more prone to GD
Perucchini, 1999, Switzerland, II, Prospective population based observational study	772 eligible 558 consented 520 completed study, 24-28 wks	FPG, 50 g GCT, 3 hr 100g OGTT, given to all, 52/520 or 10.2%	FPG 4.8mmol/l, 50 g GCT 7.8 mmol/l Sens: FPG 81%, 50g GCT 59% Spec: FPG 76%, 50g GCT 91%	Sample representative of general population. Measuring FPG is easier than 50g GCT and allows 70% women to avoid the GCT.
Cetin and Cetin, 1997, Turkey, II, Prospective study	291/344 eligible, 274/291 completed study, 24-28 wks	1h 50g GCT, 100g OGTT, given to all, 17/274 or 6.2%	Sens: < 2hr cut off 140 mg/dl 75%, cut off 148 mg/dl 63% 2-3hr cut off 140 mg/dl 60%, cut off 142 mg/dl 60% > 3hr cut off 140 mg/dl 50%, cut off 150 mg/dl 50% Spec: < 2hr cut off 140 mg/dl 86%, cut off 148 mg/dl 91% 2-3hr cut off 140 mg/dl 89% cut off 142 mg/dl 92% > 3hr cut off 140 mg/dl 89%, cut off 150 mg/dl 92% PPV: < 2hr cut off 140 mg/dl 27%, cut off 148 mg/dl 33% 2-3hr cut off 140 mg/dl 30% cut off 142 mg/dl 30% > 3hr cut off 140 mg/dl 25%, cut off 150 mg/dl 33%	Sample too small. Standard cut off 140 mg/dl Sens 65% Spec 88% PPV 27% Suggested cut off Sens 59% spec 92% PPV 32%.
O'Sullivan, 1973, USA, III, Cohort study	752/ 986 (76%) eligible, weeks of gestation not mentioned	1h 50g GCT, 3h OGTT given to all, 15/752 or 2%	1hr 50g GCT ≥ 130mg/100ml cut off Sens: 78.9% Spec: 87.2% PPV: 13.8% NPV: 99.4%	Timing of testing in relation to stage of pregnancy not reported No quantity of glucose stated for GTT Sample collected between 1956 and 1957

Table 3 Comparison studies

Author, Year, Country, Evidence level, Study design	Study population, weeks of gestation	Screening test/tests, cut-off value for giving Dx, Diagnostic test, Prevalence	Threshold, sensitivity, specificity, PPV, NPV	Comments and conclusion
Buhling, 2003, Germany, II, Prospective study	193 weeks of gestation not mentioned	Comparison of 50g GCT with five portable meters, 7.8 mmol/l, Hexokinase method, prevalence not calculated	Sens: Accu check 84% Euro flash 100% Gluco touch 98% Hemo Cue 57% One touch 92% Precision 90% Spec: Accu check 98% Euro flash 79% Gluco touch 86% Hemo Cue 100% One touch 92% Precision 91%	The accuracy of Accu check, Gluco touch, One touch and precision was acceptable for use in GD screening.
Murphy,1992, USA, II, Randomized trial, no control	124 women randomly assigned to 1 of 3 CHO sources, 24-28 wks	Comparison of 3 CHO sources 50 g glucose polymer, 50g standard glucose solution and 50g milk chocolate bar, No cut-off used, 3h 100g OGTT, 5/108 or 4.6%	Glucose ≥ 7.5 mmol/l Sens: overall 60% standard glucose 33.3% polymer 100% Spec: overall 84% standard glucose 73.6% polymer 92.8% PPV: overall 16% standard glucose 9% polymer 49%	The polymer is an inexpensive and well tolerated but the use of candy bar needs further research.
Court,1985, New Zealand, II, RCT	100 women randomized to glucose screening test (48) and glucose polymer test (52) glucose polymer test given to additional 178 women so total 230 women received polymer test. 28 wks	100g glucose screening test and 100g glucose polymer screening test, No cut-off value used, 3h 100g OGTT, 12/230 or 5.2%	8 mmol/l or 144 mg/dl, For glucose polymer Sens: 89% Spec: 81% PPV: 29%	The glucose polymer is preferable to glucose for CHO loading in pregnancy because of lower rates of nausea, better reproducibility of test results.

Table 4 Fasting plasma glucose

Author, Year, Country, Evidence level, Study design	Study population, weeks of gestation	Screening test/tests, cut-off value for giving D_x, Diagnostic test, Prevalence	Threshold, sensitivity, false positive rate, specificity, PPV, NPV	Comments and conclusion
Reichelt, 1998, Brazil, II, Cohort study	5,579, 5,010 remaining in the study 24-28 wks	FPG D_x test given to all, 2 hr 75 g OGTT, 379/5,010 or 7.6%	1. 81 mg/dl or 4.5 mmol/l Sens: 94% Spec: 51% PPV: 0.6 NPV: 100 2. 85 mg/dl or 4.7 mmol/l Sens: 94% Spec: 66% PPV: 0.9 NPV: 100 3. 89 mg/dl or 4.9 mmol/l Sens: 88% Spec: 78% PPV: 1.3 NPV: 100	FPG is a useful screening test for GD, a threshold of 89mg/dl maximizes sensitivity and specificity.
Fadl, 2006, Sweden, II, cross-sectional population based study	3616 28-32 wks for fasting capillary glucose	FPG D_x given to all, 2 hr 75g OGTT, 55/3616 or 1.52%	FPG Cutoff values between 4.0 and 5.0 mmol/l, Sensitivity 87% to 47% Specificity 51% and 96%. +LR and –LR best at ≥5.0 mmol/l.	

Table 5 Jelly Beans studies

Author, Year, Country, Evidence level, Study design	Study population, weeks of gestation	Screening test/tests, cut-off value for giving D_x, Diagnostic test, Prevalence	Threshold, sensitivity, specificity, PPV, NPV	Comments and conclusion
Lamar, 1999, USA, II, Prospective study	160, 136 completed the study 24-28 wks	Jelly beans vs. standard glucose (randomization done), Blood glucose ≥ 140 mg/dl, 3h 100g fasting GTT, 5/136 or 3.7%	140 mg/dl, standard glucose: Sens: 80% Spec: 82% PPV: 15% NPV: 99% Jelly beans: Sens: 40% Spec: 85% PPV: 9% NPV: 97%	There is no significant difference in screening performance for jelly beans and the standard glucose. Patients report fewer side effects after a jelly bean challenge than after a 50-g glucose beverage test. So jelly beans may be used an alternative to the 50g glucose beverage test.
Boyd, 1995, USA, II, Prospective study	157 26-30 wks	Cola beverage vs. Jelly beans, Diagnostic test given to all participants, 3h 100g GTT, 13/157 or 8.3%	140 mg/dl for cola beverage Sens: 46% Spec: 81% PPV: 18% 120 mg/dl for jelly beans Sens: 54% Spec: 81% PPV: 20%	Patient tolerance was greater for jelly beans as compared with the 50 gm cola beverage. Jelly beans may serve as an alternative to a cola beverage containing 50 gm of glucose.

Effectiveness of screening test

Description of included studies

A USA based randomised controlled trial, [832] [EL 2+] compared a risk factor-based screening programme with a universally based one. The risk factor group had a 3h 100g OGTT at 32 weeks if any risk factor for GD was present. The universal group had a 50g GCT and if their plasma glucose at 1h was ≥ 7.8mmol/l, a formal 3h 100g OGTT was then performed.

A study in Denmark, 2004[833] [EL 2-] retrospectively investigated in 1 year the clinical outcome of pregnant women in relation to separate components of the pre-screening procedure, presence of GD and the capillary blood glucose 120 min after glucose load ($CBG_{120\ min}$) concentration after a 75 g glucose load. The aim was to investigate the power of the pre-screening to identify GD and for the screening to predict adverse clinical outcomes.

A cross sectional 5 year investigation in the Netherlands, 2006[834] [EL 2-] examined the clinical usefulness of antepartum clinical characteristics, along with measures of glucose tolerance, in Dutch multiethnic women with GD for their ability to predict type 2 diabetes within 6 months of delivery (early postpartum diabetes). The following data were collected for all women: age and gestational age at entry into the study; prepregnancy body mass index (BMI); ethnicity; obstetric and clinical history, including the onset of early postpartum diabetes; pregnancy outcome; level of fasting C-peptide; and glycaemic parameters of 50-g 1-h glucose challenge test and 100-g 3-h oral glucose tolerance test (diagnostic OGTT). 11/168 or 6.6% women developed early postpartum diabetes.

A prospective cohort study, 1998[849] [EL 2+] in UAE compared the outcome of pregnancy in women with GCT screening levels > 7.7 mmol/l and ≥ 8.3 mmol/l. Pregnancy outcomes were compared for the following groups:

A, GCT > 7.7 and < 8.3 mmol/l (194 women)
B. GCT ≥ 8.3 mmol/l (194 women)
C. GCT < 7.7 mmol/l (194 women matched for age, parity and weight with group B)

The screening test used was blood glucose 1h after a 50g glucose load (GCT) given in fasting state between 28 and 32 weeks. If the blood glucose was ≥ 7.7mmol/l then 3 h GTT was given.

A prospective cohort study of 6854 participants, 2005[850] [EL 2+] in the USA evaluated the association between obesity, glucose challenge test and pregnancy outcome. A 50g GCT was performed at 24-28 weeks gestation and a screening value of ≥ 130 mg/dl was followed by a 100g OGTT. For the purpose of analysis women were categorized by prepregnancy BMI and by different GCT thresholds. Maternal outcome was defined by the rate of pre-eclampsia, gestational age at delivery, cesarean section (CS) rate and the need for labor induction. Neonatal outcome was defined by fetal size (macrosomia/LGA), arterial cord pH, respiratory complications and neonatal intensive care unit (NICU) admission.

A prospective study, 1987[851] [EL 2+] in a midwestern, USA population compared the value of routine versus selective diabetes screening in a group of predominantly middle-class, healthy, Caucasian pregnant women. 2000 women were divided into two groups (they were otherwise similar):

1. Those to undergo routine screening between 24 and 28 weeks gestation
2. Those to be tested selectively in the presence of standard risk factors.

The screening test involved a 50g GCT followed by a 3h OGTT if necessary.

A prospective randomized study, 1995[852] [EL 2+] in China was conducted to determine the relationship between the 50g GCT and pregnancy outcomes. 622 pregnant women underwent a 50g GCT and a 75g OGTT was performed if screening tests value was ≥ 7.8 mmol/l.

Findings

The American study showed that universal screening detected a GD prevalence of 2.7%, 1.45% more than in the risk factor screened group. Universal screening for GD was found to be superior to risk factor based screening as it detected more cases, facilitated early diagnosis and is associated with improved pregnancy outcomes.

The results of the Danish study showed that screening using a cFBG of 4.1 mmol/l was unable to predict GD and adverse outcome. The best predictor of complicated delivery was a high BMI. The best predictor of fetal adverse outcome was cBG120 min ≥ 9.0 mmol/l after a 75 g glucose load. Identical pregnancy complications were present in GD and non-GD.

The Netherlands study showed that only a family history of diabetes showed an association with early postpartum diabetes. ROC curve analysis identified all three glucose challenge-test parameters, including fasting glucose concentration, as poor diagnostic tests, with a PPV of 22%, whereas PPV associated with the area under the diagnostic OGTT curve increased progressively over the duration of the test from 20.6% to 100%. Using a 3-h OGTT glucose area threshold of 35.7 mmol·h/L resulted in 100% sensitivity and 100% specificity, identifying the 11 women who developed early postpartum diabetes.

In the UAE study 197/3400 or 5.8% women were considered to have abnormal GTT plus 199/3400 or 5.8% had impaired glucose tolerance. There was no significant difference in pregnancy induced hypertension between groups. Pre-term delivery was significantly more in group B. Birth weight > 4.5 kg was 4% in group C, 6% in group A and 9% in group B. The APGAR > 6 at 1 min found no significant differences between groups.

In the USA based study a positive GCT result (GCT ≥130 mg/dl) was identified in 2541/6854 or 37% women. 464/6854 or 6.8% of women were diagnosed with GD. In both groups of screening results (> 130 mg/dl and < 130 mg/dl), the obese women were significantly older, gained more weight during pregnancy and had a lower rate of nulliparity in comparison to the non obese women. The obese women had higher rates of macrosomia, LGA and induction of labor. No difference was found in mean birth weight, the total rate of cesarean section, preterm delivery, 5 minute Apgar score < or = 7, mean arterial cord pH, NICU admission and a need for respiratory support in comparison to non obese women in both groups of screening results.

A gradual increase in the rate of macrosomia, LGA and cesarean section was identified in both obese and non-obese women in relation to increasing GCT severity categories.

The midwestern American study showed that the incidence of GD in the selectively screened group was twice (19/453, 4.2%) that in routinely screened group (21/1000, 2.1%). Glucose intolerance without a risk factor was found in only one case (1/1000, 0.1%) in the routinely screened group.

In the Chinese study 103/622 or 16.6% women underwent the diagnostic test, among whom, 32 were identified as having gestational impaired glucose tolerance (GIGT) and 12 as GD. The sensitivity of 50gGCT was 42.7% (44/103). The incidences of oedema-proteinuria-hypertension syndrome (EPH-syndrome), premature rupture of membranes, fetal macrosomia, operative deliveries and perinatal morbidity were higher in women with GIGT/GD than in women without GIGT/GD.

Women's views on screening for gestational diabetes

Description of included studies

A prospective survey, 2002[853] [EL 2-] in Australia surveyed women on their experiences of being screened for GD in a hospital that screens all women in pregnancy. They tested the hypothesis that women with a positive result on the screen test will experience a reduction in quality of life, their health and that of their baby when compared with women with a normal screening result. The study took place at a level III teaching hospital with a high-risk pregnancy service and neonatal intensive care unit. A Spielberger State-Trait Anxiety Inventory, Edinburgh Postnatal Depression Scale and Short Form 36 Item Health Survey were used to study the main outcome measures: anxiety, depression, health status, concerns about the health of the baby and perceived health. Prior to being screened, a total of 158 women participated in the study whereas 51 women participated after being screened.

A prospective cohort study, 1997[854] [EL 2+] in Canada investigated whether false positive results of 50g glucose challenge test for GD were associated with adverse psychological effects. Women between 12 and 14 weeks' gestation with no previous history of diabetes or GD were included. 897 women had complete data both at enrollment and 32 weeks including 88 who had false positive GCT results. A total of 809 women completed questionnaires at baseline, 32 weeks, and 36 weeks' gestation.

Findings

The Australian study found no differences in the levels of anxiety, depression or the women's concerns about the health of their babies. When positively screened women for GD were compared with negatively screened women, the positively screened group had significantly lower health perceptions, were significantly less likely to rate their health as 'much better than one year ago' and were significantly more likely to rate their health as 'fair' rather than 'very good' or 'excellent'.

The Canadian study showed that at 32 weeks, 20% women with false positive GCT results significantly perceived their health as excellent as compared to 38% women with negative results or not tested. These results were sustained at 36 weeks. The study showed no significant association between false positive test result and anxiety levels, depression or woman's concern for health of baby. These results were neither significant between baseline and 32 weeks nor at 36 weeks.

Clinical characteristics and screening

Description of included studies

A Canada based prospective study, 1997[855] (EL 2+) tested the hypothesis that using clinical characteristics for assessing women's risks of gestational diabetes could enhance the efficiency of screening. 3131 women were randomly divided into two groups- a derivation group and a validation group. The screening strategies were derived from the derivation group data which were then tested in the validation group by comparing the effectiveness and efficiency with those with usual care. The strategies used were; no screening for low-risk women, usual care for

intermediate-risk women, and universal screening with lower thresholds -- plasma glucose values of 130 mg per deciliter (7.2 mmol per liter) or 128 mg per deciliter (7.1 mmol per liter) -- for high-risk women.

Findings

In the Canadian study there was a 34.6% reduction (95% CI, 32.3 to 37.0) in the number of screening tests performed after using the new strategies. The detection rate of gestational diabetes with new strategies was 81.2 to 82.6 % compared with the 78.3% detected through usual care. There was a significant reduction in the percentage of false positive screening tests from 17.9 % with usual care to 16.0 % or 15.4 % ($P<0.001$) with the new strategies, depending on the threshold values for high-risk women.

Evidence summary

Due to the heterogeneity among studies for different screening tests there is no obvious best test available to screen for gestational diabetes.

There is low grade evidence from the effectiveness studies that impaired glucose tolerance in pregnancy or frank GD is associated with macrosomia, possible increase in the incidence of pre-eclampsia and pre-term delivery. On the other hand obesity was the factor most likely to be associated with complicated delivery and family history seemd to relate to post delivery diabetic risk.

The ACHOIS study seems to suggest that treating women who have mild GD in pregnancy is likely to be effective in reducing the risks of complications.

There is some evidence suggesting that receiving a positive screen result reduces women's health perceptions and makes them more likely to rate their health as 'fair' rather than 'very good' or 'excellent'.

Health economics evidence summary

Screening and treatment of GD

A systematic search of the literature identified 337 studies potentially related to the clinical question. After reviewing the abstracts 33 articles were retrieved for further appraisal and eight have been included in this section of the review. Two papers were identified in the literature that examined the cost-effectiveness of screening for and treating GD, seven papers were identified that examined the cost-effectiveness of screening only for GD and XX papers examined the cost-effectiveness of treating GD. None of these papers was suitable for answering the question addressed in the guideline. Results of the systematic review are reported in Appendix B.

The recently published Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) demonstrated potential benefit of treatment for mild gestational diabetes. Evidence of clinical effectiveness is not always sufficient for a treatment to be considered cost-effective - often times those patients that would benefit from treatment must be identified from a group of patients who do not require treatment. This is the case with GD; the cost-effectiveness of screening and treatment for GD are highly inter-dependent. As a result a single cost-effectiveness model covering screening and treatment for GD was developed to aid the Guideline Development Groups tasked by NICE to make recommendations on this area of care for pregnant women.

A full description of the model structure, data inputs and results, with sensitivity analysis, are reported in Appendix B. Under the base-case assumptions, the strategy of offering women from high-risk ethnic backgrounds a GTT (Strategy 21 in the model) has an ICER, when compared to screening or treatment, of £3,678. A strategy of offering a GTT to all women who are defined as high risk by the ADA criteria (Strategy 6) has an ICER of £21,739 when compared with Strategy 21.

The GDG expressed concerns over the number of women that would have to undergo a GTT if Strategy 6 were adopted. A large proportion of women tested would be tested based on age criteria alone. Using age as a risk factor for screening has a high sensitivity - that is, it will

identify the majority of women with GD For reasons outlined in Appendix B, the cost-effectiveness of using a combination of the single risk factors identified is not possible. In the absence of this approach, an analysis of the cost-effectiveness of each single risk factor, followed by a GTT test has been estimated, with each being compared to a strategy of no screening or treatment. The results are presented in Table X.

Table X ICER for single risk factor strategies followed by a diagnostic test when compared with a strategy of no screening or treatment.

Strategy	QALY	cost	Incremental QALY	Incremental cost	ICER
Ethnicity		£66,736			
BMI		£80,445			
Family history		£82,754			

GDG interpretation of the evidence

Currently an unselected pregnant population will have the risk of GD assessed using risk factors such as:

- BMI > 30
- Previous macrosomic baby ≥4.5kg
- Previous gestational diabetes (see Diabetes in pregnancy guideline unpublished [636])
- Family history of diabetes (first degree relative with type 1 or type 2 diabetes)
- Women from a high risk ethnic group, which would include[856]:
  - South Asian (Indian, Pakistani, Bangladeshi)
  - Black Caribbean
  - Chinese

According to a 1999 survey[825], 67% of UK maternity service providers currently screen using a combination of these factors.

The evidence for screening using risk factors is unclear. However, whilst screening using risk factors is less sensitive than performing a glucose challenge or glucose tolerance test, it is more practical and less disruptive for women. The biochemical tests considered (glucose challenge test, fasting plasma glucose, random blood glucose and urine testing) perform only moderately well in terms of diagnostic value.

Recommendations

Screening for gestational diabetes using risk factors is recommended in a normal healthy population. Risk factors which should be used are:

- body mass index > 30 kg/m^2
- previous macrosomic baby ≥4.5 kg
- previous gestational diabetes (see the Diabetes in pregnancy guideline, currently in development [636])
- family history of diabetes (first degree relative with type 1 or type 2 diabetes)
- women from a high-risk ethnic group, which would include:
  - South Asian (Indian, Pakistani, Bangladeshi)
  - Black Caribbean
  - Chinese.

Screening via fasting plasma glucose, random blood glucose, glucose challenge test and urinalysis for glucose should not be undertaken.

Diagnosis of gestational diabetes should be made using a 75g 2hr oral glucose tolerance test at 24-28 weeks of gestation using the World Health Organization (WHO) criteria (see the Diabetes in pregnancy guideline, currently in development [636])

In order to make an informed decision about gestational diabetes (GD) screening and testing, women should be informed that:

- in most women GD will respond to changes in diet and exercise
- a small number of women may need insulin therapy or tablets if diet and exercise is not effective in controlling GD
- if GD is not controlled there is a small risk of birth complications such as shoulder dystocia
- a diagnosis of GD may lead to increased monitoring during both pregnancy and labour.

11.2 Pre-eclampsia

Clinical question

What is the diagnostic value of different screening methods in identifying women at risk of developing pre-eclampsia?

Previous NICE guidance (for the updated recommendations see below)

At first contact, a woman's level of risk for pre-eclampsia should be evaluated so that a plan for her subsequent schedule of antenatal appointments can be formulated. The likelihood of developing pre-eclampsia during a pregnancy is increased in women who:

- are nulliparous
- are age 40 years or older
- have a family history of pre-eclampsia (e.g., pre-eclampsia in a mother or sister)
- have a prior history of pre-eclampsia
- have a BMI at or above 35 at first contact
- have a multiple pregnancy or pre-existing vascular disease (for example, hypertension or diabetes). [C]

Whenever blood pressure is measured in pregnancy, a urine sample should be tested at the same time for proteinuria. [C]

Standardised equipment, techniques and conditions for blood-pressure measurement should be used by all personnel whenever blood pressure is measured in the antenatal period, so that valid comparisons can be made. [C]

Pregnant women should be informed of the symptoms of advanced pre-eclampsia because these may be associated with poorer pregnancy outcomes for the mother or baby. Symptoms include headache, problems with vision, such as blurring or flashing before the eyes, bad pain just below the ribs, vomiting, and sudden swelling of face, hands or feet. [D]

Future research

Research is needed to determine the optimal frequency and timing of blood pressure measurement and on the role of screening for proteinuria.

Introduction and background

Pre-eclampsia is a condition usually associated with hypertension and proteinuria, occurring in the second half of pregnancy. Hypertension is defined as a single diastolic blood pressure of 110 mmHg or any consecutive readings of 90 mmHg on more than one occasion at least 4 hours apart. Proteinuria is defined as 300mg excretion of protein in a 24-hour collected urine, 2 clean catch urine specimens at least 4 hours apart with; 2+ proteinuria by dipstick.[535]

Pre-eclampsia and eclampsia remain among the major causes of maternal mortality in the UK (CEMACH 2004) though the reduction in the number of deaths since the 1950s may have been at least in part due to the monitoring of blood pressure during pregnancy. Current knowledge on the patho-physiology of pre-eclampsia has identified that it is a complex disorder with widespread endothelial damage which can involve every organ of the body. Therefore presenting signs and symptoms may be more varied than a rising blood pressure and proteinuria. However the antenatal care of all pregnant women is an opportunity to screen for

rising blood pressure especially in groups who are at increased risk and to educate them about the symptoms which might signal fulminating disease.

Accuracy of screening tests

The overall quality of studies included in this review was variable with deficiencies in many areas of methodology. In particular studies suffered from lack of blinding and relatively small sample sizes. There was heterogeneity regarding the reference standard used in each study.

Only a few tests reached specificity above 90%. These were AFP, β-hCG and uterine artery Doppler (bilateral notching). The sensitivities of these tests were variable and generally low.

It was often not possible to be certain about the definition of pre-eclampsia used in studies. There was lack of information on exact technique of blood pressure measurement and Korotkoff threshold for abnormality or whether the proteinuria was in the absence of urinary tract infection and pre-existing renal disease or whether there was normalization of blood pressure within 6 weeks of giving birth.

Alpha feto protein

2 studies have been identified in this section. (Table 1)

Description of included studies

An American prospective cohort study,[857] 1999 [EL II] evaluated the value of AFP as predictor of pregnancy outcomes. Maternal serum markers were analyzed over a 5-year period (March 1991-May 1996) from 60,040 women who underwent serum marker screening at 14-22 weeks' gestation. All women had maternal serum AFP measurements. A value of at least 2.5 MoM was used for calculation.

A population based cohort study in Finland,[858]1998 [EL II] sought to determine whether maternal midtrimester AFP can predict pre-eclampsia. 1037 nulliparous women were included, of whom 637 were analyzed. Measurement of AFP was made from maternal serum collected at 15-19 weeks' gestation. Sensitivity, specificity and predictive values were calculated for elevated AFP (at least 2.0 MoM).

Findings

The American study gave a very low sensitivity of 4.3% but a high specificity of 97.4% for AFP measurement. The overall incidence of pre eclampsia was 3.2%.

The Finland based study calculated a poor sensitivity of 3% and a specificity of 98%. The incidence of pre eclampsia reported was 5.3%

Both these studies used slightly different reference standards.

Fetal DNA

A total of 2 studies have been included. (Table 2)

Description of included studies

A case control study in Ireland,[859]2004 [EL II] investigated if the presence of fetal DNA in the maternal circulation in early pregnancy might be a marker for the prediction of pre-eclampsia. A total of 264 women (88 cases and 176 controls) were analysed in the study. Blood was obtained from women attending for a first antenatal clinic. Cases were asymptomatic women who subsequently developed pre-eclampsia matched to control women for parity and gestational age. Fetal DNA was quantified by real-time polymerase chain reaction (PCR) using TaqMan primers and probes directed against SRY gene sequences.

A Hong Kong based case control study,[860] 2001 [EL II] aimed to test whether the abnormal increase in circulating DNA concentrations can be detected in susceptible subjects before onset of the clinical disease. A total of 51 women (18 cases and 33 controls) were analysed in this study. The gestational age at testing was 11-22 wks.

Findings

The Ireland study found that the presence of fetal DNA in the maternal circulation is associated with an 8-fold increased risk of developing pre-eclampsia. In this study, SRY copies/mL <10,000 gave a sensitivity of 94.32% and specificity of 32.39%. SRY copies/Ml <50,000 gave a sensitivity of 81.82% and specificity 64.77%. SRY copies/mL >50,000 gave a sensitivity of 38.64% and a specificity of 90.34%.

In the Hong Kong base study a SRY value of ≥ 33.5 Genome equivalents/mL was found to be significant and this gave a sensitivity of 67% and specificity of 82%.

β- hCG

A total of 3 studies were included. (Table 3)

Description of included studies

A USA based prospective cohort study,[857]1999 [EL II] evaluated the value of β-human chorionic gonadotropin as predictor of pregnancy outcomes. Maternal serum markers were analyzed over a 5-year period (March 1991-May 1996) from 60,040 women who underwent serum marker screening at 14-22 weeks' gestation. 45,565 women had maternal serum β-hCG measurements. A value of at least 2.5 MoM was used for calculation.

A USA based case control study,[861] 2000 [EL II] sought to determine whether second trimester (15-21 wks) serum levels of human chorionic gonadotropin is predictive of the later onset of pre-eclampsia in pregnancy. A total of 359 women (60 cases and 299 controls) were included. Levels of each analyte were compared in women with pre-eclampsia and controls using matched rank analysis.

A prospective cohort study,[862] 1997 [EL II] in USA investigated the association of elevated second-trimester (15-22 wks) β-hCG with the subsequent development of hypertension in pregnancy and to evaluate its utility as a screening test for later development of preeclampsia. A total of 6138 women were analyzed in the study. A value of 2.0 MoM was used as the cut off for the index test.

Findings

The first study found a 3% incidence of pre eclampsia. The sensitivity at 2.5 MoM cut off was found to be 5.5% and specificity was 96%.

The second study used 2.0 MoM cut off and found a 3.2% incidence of preeclampsia. With 95% specificity, a modeled sensitivity of 15% was found.

The third study found a 3.2% incidence of preeclampsia. The sensitivity was 17.5% whereas the specificity was 89.8%.

Urinary Calcium

A total of 2 studies were included. (Table 4)

Description of included studies

A USA based prospective longitudinal study,[863]1991 [EL II] was designed to determine whether an alteration in calcium excretion precedes the signs and symptoms of pre-eclampsia and therefore would be useful early maker for this disease. A total of 99 women were analyzed in this study. The index test was administered between 10-24 wks gestation and a value of ≤ 195 mg/24hrs was considered significant.

A UK based prospective non-interventional study,[864]1994 [EL II] assessed the potential of urinary calcium/ creatinine as screening tests for pregnancy-induced hypertension in a white population. A total of 500 women were included in the study who provided a urine sample at 19 weeks' gestation.

Findings

The American study found 8.1% incidence of pre-eclampsia. The index cut off found a sensitivity of 86%, specificity of 84%, PPV of 46% and NPV of 98%.

The UK study found a sensitivity of 31% and a specificity of 72%. The overall incidence of pre-eclampsia was 2.6%.

Calcium creatinine ratio

A total of 4 studies were included. (Table 5)

Description of included studies

A Hong Kong based cohort study,[865]1994 [EL II] attempted to clarify some of the changes that occur in enzyme and electrolyte excretion in pregnancy, before onset of clinical signs, and to relate these changes to the antenatal development of preeclampsia or gestational hypertension. A total of 199 women were included and the gestational age at test was between 18-26 wks. A cut off value of 0.3 was used.

One Argentina based prospective cohort study,[866]1994 [EL II] investigated the usefulness of calcium/creatinine ratio and other laboratory tests as predictors in the development of hypertensive disorders of pregnancy. 387 women were included in the study and test was administered at 20 weeks gestation. A value of 0.07 was considered significant.

A prospective cross sectional study,[867]2003 [EL II] in Iran determined the relationship between pre-eclampsia and calcium/ creatinine ratio .A total of 102 women were included and the test was administered at 20-24 wks gestation. A value of $\leq$ 0.229 was found to be significant.

A UK based prospective non-interventional study,[864]1994 [EL II] assessed the potential of urinary calcium/ creatinine as screening tests for pregnancy-induced hypertension in a white population. A total of 500 women were included in the study who provided a urine sample at 19 weeks' gestation.

Findings

The Hong Kong study found a sensitivity of 49% and specificity of 90%. The overall incidence was 4%.

The Argentina study found an overall incidence of 3.4%. The study gave a sensitivity of 33%, specificity of 78%, positive predictive value of 5%, and negative predictive value of 97%.

The Iran study found an incidence of 7.8%. The test showed a sensitivity of 75%, specificity of 77.7%, PPV of 20.7%, and NPV of 97%.

UK study reported an incidence of 2.6%. The test sensitivity was 31% and specificity was 55%.

Bilateral Uterine Artery Notching

A total of 4 studies were included. (Table 6)

Description of included studies

A multicentre cohort study,[868] 2001 [EL II] conducted in UK examined the value of transvaginal uterine artery Doppler velocimetry at 23 weeks of gestation in the prediction of pre-eclampsia in singleton pregnancies. A total of 7851 women were analyzed at 22-24 wks gestation. The presence of an early diastolic notch in the waveform was noted, and the mean pulsatility index of the two arteries was calculated. Screening characteristics in the prediction of pre-eclampsia was calculated.

A cohort study conducted in UK,[869]1997 [EL II] aimed to establish the predictive value of transvaginal uterine artery Doppler studies in early pregnancy for the prediction of preeclampsia. A total of 626 women were included and the test administered between 12-16 weeks of gestation.

A case control study in UK,[870]2003 [EL II] aimed to evaluate the clinical usefulness of the Doppler velocimetry test used to screen pre-eclampsia in the period 2000-2001. A total of 895 women were included and the test was conducted at 20 weeks gestation and then at 24 weeks.

A prospective study conducted in Germany,[871] 2005 [EL II] examined the use of uterine artery Doppler at 19-22 weeks and 23-26 weeks' gestation in a low-risk population as a screening test for the prediction of pre-eclampsia. A total of 346 women were included.

Findings

The first study found a sensitivity of 25.4%, specificity of 90.9%, PPV of 2.5% and NPV of 99.3%. The overall incidence reported was 1.4%.

The second study reported incidence of 4.8%. The sensitivity of the test was 92.9%, specificity was 85.1%, PPV was 23.6% and NPV was 99.5%.

An incidence of 2.9% was reported in the third study. The test sensitivity was 72%, specificity 94%, PPV 26% and NPV 99%.

The Germany based study compared the results at 19-22 wks vs. 23-26 wks gestation. A sensitivity of 40% vs. 67%, specificity of 82% vs. 84%, PPV of 10% vs. 17% an NPV of 97% vs. 98% was reported for the two periods of gestation respectively.

Integrated Doppler test with serum markers

A total of 2 studies identified. (Table 7)

Description of included studies

A prospective study in Turkey,[872]2005 [EL II] aimed to analyse the predictive power of maternal serum inhibin A, activin A, hCG, uE_3, AFP levels and uterine artery Doppler, either alone or in combination, in the second trimester of pregnancy in screening for pre-eclampsia. 178 women were included in whom serum samples were collected between 16-18 weeks of gestation and Doppler investigation was performed between 24-26 weeks of gestation.

A cohort study in France,[873]2005 [EL II] assessed the performance of early screening for pre-eclampsia and IUGR by combining maternal serum screening with uterine Doppler ultrasound. 2615 women were analyzed in whom both a double test between 14-18 weeks gestation (by maternal serum AFP and total serum hCG assay), and a uterine Doppler ultrasound between 18-26 weeks were performed.

Findings

The Turkish study found a 7.9% incidence of pre-eclampsia. The presence of a notch on Doppler investigation reported a sensitivity of 85.7% and specificity of 97.6%. The addition of high serum activin to the presence of a notch decreased the sensitivity to 78.6% and increased the specificity to 100%. The addition of high serum inhibin to the presence of a notch decreased the sensitivity to 71.4% and increased the specificity to 100%. The integrated test of presence of a notch or high serum activin increased the sensitivity to 100% and decreased the specificity to 86%.

In the French study, the bilateral notch test reported a sensitivity of 21.6% whereas a specificity of 95.9%. An integrated test-history of pre-eclampsia or bilateral notch or hCG > 2.5 MoM increased the sensitivity to 41.1% and reduced the specificity to 91.6%.

Time interval between pregnancies

Description of included studies

A Norwegian study, 2002[531] [EL 2+] used a large registry in Norway to evaluate the effects on the risk of pre-eclampsia of both the interbirth interval and a change of partner. 551,478 women who had 2 or more singleton deliveries and 209,423 women who had 3 or more singleton deliveries were studied.

A retrospective cross sectional study from Uruguay, 2000[874] [EL 3] studied the impact of interpregnancy interval on maternal morbidity and mortality. A total of 456,889 parous women delivering singleton infants were studied.

A Danish cohort study, 2001[875] [EL 2+] evaluated whether the interpregnancy interval may confound or modify the paternal effect on pre-eclampsia. The outcome of the second birth in a cohort of Danish women with pre-eclampsia in the previous birth (8,401 women) and in all women with pre-eclampsia in second (but not first) birth together with a sample of women with two births (26,596 women) was studied.

Findings

The results from Norwegian study showed that the risk in a second or third pregnancy was directly related to the time elapsed since the previous delivery. The association between risk of pre-eclampsia and interval was more significant than the association between risk and change of partner. When the interval was 10 years or more the risk of pre-eclampsia was about the same as that in nulliparous women. After adjustment for the presence or absence of a change of partner, maternal age, and year of delivery, the probability of pre-eclampsia was increased by 1.12 for each year increase in the interval (odds ratio 1.12, 1.11 to 1.13).

The Uruguay study showed that women with more than 59 months between pregnancies had significantly increased risks of pre-eclampsia (relative risk 1.83, 1.72 to 1.94) compared with women with intervals of 18-23 months. The authors concluded that interpregnancy intervals < 6 months and > 59 months are associated with an increased risk of adverse maternal outcomes.

The Danish study found that a long interval between pregnancies was associated with a significantly higher risk of pre-eclampsia in a second pregnancy when pre-eclampsia had not been present in the first pregnancy and paternity had not changed.

Blood pressure at booking

Description of included studies

A USA based study, 1987[876] [EL 2-] reviewed the outpatient charts of all patients with preeclampsia who received prenatal care at their clinics during the past 3 years. 30 patients met their criteria for preeclampsia and were matched for age, race, and parity with normotensive control subjects.

A USA based large clinical trial, 1995[877] [EL 1+] sought to determine whether any maternal demographic or clinical characteristics are predictive of preeclampsia. A total of 2947 healthy women with a single fetus were prospectively followed up from randomization at 13 to 27 weeks' gestation to the end of pregnancy.

A population based nested case-control Norwegian study, 2000[878] [EL 2+] studied the associations between established risk factors for pre eclampsia and different clinical manifestations of the disease. A total of 323 Cases of pre-eclampsia and 650 healthy controls were selected.

A USA based retrospective cohort study, 2000[530] [EL 2-] was undertaken to develop a clinical prediction rule for severe preeclampsia that was based on clinical risk factors and biochemical factors. Cases with severe preeclampsia were compared with control subjects with respect to clinical data and multiple-marker screening test results. Patients were assigned a predictive score according to the presence or absence of predictive factors.

Findings

The first study found that both systolic and diastolic blood pressures were significantly higher ($p < 0.05$) in the first trimester for women with preeclampsia than for normal control subjects beginning in the first trimester. This difference persisted throughout pregnancy and was also present at the 6-week postpartum visit ($p < 0.025$).

The second study showed that higher systolic and diastolic blood pressures at the first visit were associated with an increased incidence of pre-eclampsia (3.8% in women with diastolic blood pressure of < 55 mm Hg, 7.4% in those with diastolic blood pressure 70-84 mm Hg).

However, their recruitment was limited to women with a first blood pressure reading of ≤ 135/85 mm Hg.

The third Norwegian study found that a systolic blood pressure ≥ 130 mm Hg compared with < 110 mm Hg at the first visit before 18 weeks was significantly associated with the development of pre-eclampsia later in pregnancy (adjusted OR 3.6 [2.0 to 6.6]). The association with a diastolic pressure ≥ 80 mm Hg compared with < 60 mm Hg was similar but not significant (adjusted OR 1.8 [0.7 to 4.6]).

The fourth study results showed that the only variables that remained significantly associated with severe preeclampsia were nulliparity (relative risk, 3.8; 95% confidence interval, 1.7-8.3), history of preeclampsia (relative risk, 5.0; 95% confidence interval, 1.7-17.2), elevated screening mean arterial pressure (relative risk, 3.5; 95% confidence interval, 1.7-7.2), and low unconjugated estriol concentration (relative risk, 1.7; 95% confidence interval, 0.9-3.4). This predictive model for severe preeclampsia, which included only these 4 variables, had a sensitivity of 76% and a specificity of 46%.

Proteinuria

Description of included studies

A USA based retrospective study, 1992[879] [EL 2-] evaluated varying degrees of chronic proteinuria as a predictor of pregnancy outcome. Their purpose was to determine the significance of otherwise 'asymptomatic' proteinuria identified during pregnancy. Perinatal outcomes of 65 pregnancies in 53 women with the following criteria: proteinuria exceeding 500 mg per day, no previously known renal disease, no reversible renal dysfunction, and no evidence for preeclampsia at discovery were studied.

Findings

The results showed that 58% of the women with proteinuria combined with renal insufficiency developed pre eclampsia. 100% of women with preteinuria combined with chronic hypertension developed preeclampsia whereas 77% of women with with all three together developed preeclampsia.

Evidence summary

Given quality, level and precision of the evidence, no single test has emerged as a front runner in the quest to predict and prevent pre-eclampsia. Tests that offer high specificity, e.g. AFP, β-hCG, and uterine artery Doppler (bilateral notching), have the potential to minimize unwarranted inconvenience, expense and morbidity associated with false positive results. There is evidence to show that when the interval between two pregnancies was 10 years or more the risk of pre-eclampsia was about the same as that in nulliparous women.

GDG interpretation of evidence

None of the current screening tests offer a high enough diagnostic value, all being EL II, to be used in routine care. In addition, the purpose of screening for pre-eclampsia is only to idneitfy those women who require additional care since there is no effective intervention. However, the following risk factors for the development of pre-eclampsia should be noted:

- Age 40 or over
- Nulliparity
- Pregnancy interval of more than 10 years
- Family history of pre-eclampsia
- Previous history of pre-eclampsia
- BMI of 35 or over
- Pre-existing vascular disease such as hypertension
- Pre-existing renal disease
- Multiple pregnancy

The routine measurement of blood pressure and of proteinuria should be undertaken on the schedule outlined in the algorithm.

Recommendations

Pregnant women should be made aware of the need to seek immediate advice from a health care professional if they experience symptoms of pre-eclampsia. Symptoms include: severe headache; problems with vision, such as blurring or flashing before the eyes; severe pain just below the ribs; vomiting and sudden swelling of face, hands or feet.

The presence of significant hypertension and/or proteinuria should alert the healthcare professional of the need for increased surveillance

At the first antenatal appointment the following risk factors should be determined:

- age 40 or over
- nulliparity
- pregnancy interval of more than 10 years
- family history of pre-eclampsia
- previous history of pre-eclampsia
- body mass index of 35 kg/m^2 or over
- pre-existing vascular disease such as hypertension
- pre-existing renal disease
- multiple pregnancy.

More frequent blood pressure measurements should be considered for women who have any of the above factors.

Blood pressure measurement and urinalysis for protein should be carried out at each antenatal visit to screen for pre-eclampsia.

Blood pressure should be measured by standard mercury sphygmomanometer or semi automatic device as outlined below:

- Remove tight clothing, ensure arm is relaxed and supported at heart level
- Use cuff of appropriate size
- Inflate cuff to 20-30 mmHg above palpated systolic blood pressure } Only devices using auscultation (mercury/hybrid)
- Lower column slowly, by 2 mm per second or per beat
- Read blood pressure to the nearest 2 mmHg
- Measure diastolic as disappearance of sounds (phase V)

Hypertension in which there is a single diastolic blood pressure of 110 mmHg or two consecutive readings of 90mmHg at least 4 hours apart and/or significant proteinuria (1+) should prompt increased surveillance.

Although there is a great deal published on alternative screening methods for pre eclampsia, none has satisfactory sensitivity and specificity, and therefore are not recommended.

Research recommendations

Further research using large prospective studies may produce useful findings particularly into alpha feto protein, beta human chorionic gonadotrophin, fetal DNA in maternal blood and uterine artery dopplers or potentially a combination of these.

Table 1 Alpha fetoprotein

Author, Year, Country, Evidence level, Study design	No. of women analysed, Inclusion/ Exclusion criteria, age, gestational age at test	Reference standard used, Incidence of PE (%)	Index test cut off	Results	Conclusions/ Comments
Yaron,1999, USA, EL II, Prospective cohort study	60040, EX: structural or chromosomal anomalies Age n.r. 14-22 wks	SBP ≥140 mmHg or DBP ≥90 mmHg; presence of proteinuria, 3.2%	Competitive RIA (Sanofi Diagnostics) 2.5 MoM	Sens: 4.3% Spec: 97.4%	Multiple marker screening can be used for the detection of not only fetal anomalies and aneuploidy but also for detection of high-risk pregnancy
Pouta ,1998, Finland, EL II, Population-based cohort study	637, IN: nulliparas EX: multiple pregnancies, foetal defects 27.7 ± 4.5 yrs 15-19 wks	BP ≥140/90 mmHg 6hrs apart or rise 30/15 mmHg; Prot. ≥300 mg/24 hrs, 5.3%	time resolved FIA (Wallac) 2.0 MoM	Sens: 3% Spec: 98%	AFP not helpful in predicting preeclampsia

Table 2 Foetal DNA

Author, Year, Country, Evidence level, Study design	No. of women analysed, Inclusion/ Exclusion criteria, age, gestational age at test	Reference standard used, Incidence of PE (%)	Index test cut off	Results	Conclusions/ Comments
Cotter, 2004, Ireland, EL II, Case control study (nested and matched)	264 (88 cases and 176 controls) IN: Normotensive non-proteinuric women, male fetuses EX: aneuploid fetuses 26.1 ± 5.9 yrs, 15.7 ± 3.6 wks	BP ≥ 140/90 mmHg; Prot. ≥ 0.3 g/ 24 hrs or 1+/2+ dipstick, Incidence n.r.	fDNA Real-time PCR TaqMan SRY < 10,000 copies/mL < 50,000 > 50,000	SRY copies/mL < 10,000 Sens: 94.32% Spec: 32.39% +LR: 1.39 < 50,000 Sens: 81.82% Spec: 64.77% +LR: 2.32 > 50,000 Sens: 38.64% Spec: 90.34% +LR: 4.00	Increased fetal DNA is present in the maternal circulation in early pregnancy in women who subsequently develop pre-eclampsia and there appears to be a graded response between the quantity of fetal DNA and the risk of developing pre-eclampsia.
Leung, 2001, Hong Kong, EL II, Case control study (nested and matched)	51 (18 cases and 33 controls), IN: singleton pregnancies, male fetuses Age n.r. 11-22 wks	DBP ≥ 90 mmHg 2x ≥4 hrs apart or DBP ≥ 110 mmHg; Prot. ≥ 0.3 g/ 24 hrs or 2+ dipstick 2x ≥4 hrs apart, Incidence n.r.	fDNA Real-time PCR TaqMan SRY ≥ 33.5 Geq/mL	SRY ≥ 33.5 Geq/mL Sens: 67% Spec: 82% (cant calculate LRs)	Maternal plasma fetal DNA might be used as a marker for predicting pre-eclampsia.

Table 3 ß-hCG

Author, Year, Country, Evidence level, Study design	No. of women analysed, Inclusion/ Exclusion criteria, age, gestational age at test	Reference standard used, Incidence of PE (%)	Index test cut off	Results	Conclusions/ Comments
Yaron,1999, USA, EL II, Prospective cohort study	45565, EX: structural or chromosomal anomalies Age n.r. 14-22 wks	SBP ≥140 mmHg or DBP ≥90 mmHg; presence of proteinuria, 3.0%	ß-hCG IRMA 2.5 MoM	Sens: 5.5% Spec: 96%	Multiple marker screening can be used for the detection of not only fetal anomalies and aneuploidy but also for detection of high-risk pregnancy
Lambert-Messerlian , 2000, USA, EL II, Case control study	359 (60 cases, 299 controls) IN: singleton pregnancies EX: chronic hypertension, diabetes; 26.9 ± 7.3 yrs 15-21 wks	BP> 140/90 mmHg; Prot. >300mg/24 hrs or ≥2+ dipstick, 16.7%	Total hCG (Serono MAIO Clone) 2.3 MoM	With 95% specificity a modeled sensitivity of 15% (cant calculate LRs)	2nd trimester serum levels of hCG is a modest predictor of later onset preeclampsia.
Ashour, 1997, USA, EL II, Prospective cohort study	6138, IN: singleton pregnancies EX: foetal/ chromosomal abnormalities, diabetes, chronic hypertension 28.1 ± 5.3 yrs 15-22 wks	SBP ≥140 mmHg or DBP ≥90 mmHg 2x 6 hrs apart; Prot. >300 mg/24 hrs or ≥1+ dipstick 2x 6 hrs apart, 3.2%	ß-hCG (IMx Abbott) 2.0 MoM	Sens: 17.5% Spec: 89.8% PPV: 5.3%	The utility of an elevated second-trimester β-hCG level as a screening test for preeclampsia is limited.

Table 4 Urinary calcium excretion

Author, Year, Country, Evidence level, Study design	No. of women analysed, Inclusion/ Exclusion criteria, age, gestational age at test	Reference standard used, Incidence of PE (%)	Index test cut off	Results	Conclusions/ Comments
Sanchez-Ramos, 1991, USA, EL II, Prospective longitudinal study	99, IN: Normotensive nulliparas EX: diabetes mellitus, renal disease, chronic hypertension, other chronic medical illnesses 18.7 ± 0.5 yrs, 10-24 wks	BP ≥ 140/90 mmHg twice ≥ 6 hrs apart or rise SBP ≥ 30 mmHg or DBP ≥ 15 mmHg Prot. ≥ 0.3 g/ 24 hrs or ≥ 1+ dipstick, 8.1%	Colorimetric/ colorimetric autoanalyzer ≤ 195 mg/24 hrs	Sens: 86% Spec: 84% PPV: 46% NPV: 98%	The study suggests a pathophysiologic role for altered urinary calcium excretion in women with preeclampsia that may contribute to early identification of patients at risk for the disease.
Baker, 1994, UK, EL II, A prospective, non-interventional study	500, IN: Normotensive nulliparas EX: renal disease, chronic hypertension Median 27 yrs (range 24-31), 18-19 wks	DBP ≥ 90 mmHg twice ≥ 4 hrs apart Prot. ≥ 0.3 g/ 24 hrs, 2.6%	Perspective analyzer (colorimetric)/ Monarch centrifugal analyzer (kinetic) n.r.	Sens: 31% Spec: 72% (correctly predicted 71%)	

Table 5 Calcium creatinine ratio

Author, Year, Country, Evidence level, Study design	No. of women analysed, Inclusion/ Exclusion criteria, age, gestational age at test	Reference standard used, Incidence of PE (%)	Index test cut off	Results	Conclusions/ Comments
Rogers, 1994, Hong Kong, EL II, Cohort study	199, IN: normotensive primigravidas, singleton pregnancies EX: congenital malformations 27.1 ± 3.8 yrs, 18-26 wks	BP ≥ 140/90 mmHg ≥ twice Prot. ≥ 0.3 g/L, 4.0%	Cresolphtalein method (American Monitor)/ Beckman Astra-8 analyzer 0.3	Sens: 49% Spec: 90%	
Conde, 1994, Argentina, EL II, Prospective cohort study	387 women, IN: normotensive nulliparas, singleton pregnancies EX: diabetes mellitus, renal disease, proteinuria, chronic hypertension, other chronic medical illnesses 23.8 ± 5.7 yrs, 20 wks	SBP ≥ 140 or DBP ≥ 90 mmHg twice ≥ 6 hrs apart Prot. ≥ 0.3 g/L, 3.4%	Colorimetric (direct)/ picrato alcalino method 0.07	Sens: 33% Spec: 78% PPV: 5% NPV: 97%	Poor predictive values suggest that changes in the biochemical and hematologic tests occur only when preeclampsia has been established.
Kazerooni, 2003, Iran, EL II, Prospectivecross sectional study	102, IN: nulliparas (18-35 years) EX: renal disease, diabetes mellitus, proteinuria, chronic hypertension, other chronic medical illnesses 22.8 ± 4.5 yrs, 20-24 wks	BP ≥ 140/90 mmHg or rise SBP ≥ 30 mmHg or DBP ≥ 15 mmHg twice ≥ 6 hrs apart Prot. ≥ 0.3 g/ 24 hrs or ≥ 1+ dipstick, 7.8%	n.r. ≤ 0.229 (mg/dL:mg/dL)	Sens: 75% Spec: 77.7% PPV: 20.7% NPV: 97%	Single urine calcium to creatinine ratio may be an effective method for screening women at the greatest risk of pre-eclampsia.
Baker, 1994, UK, EL II, A prospective, non-interventional study	500, IN: Normotensive nulliparas EX: renal disease, chronic hypertension Median 27 yrs (range 24-31), 18-19 wks	DBP ≥ 90 mmHg twice ≥ 4 hrs apart Prot. ≥ 0.3 g/ 24 hrs, 2.6%	Perspective analyzer (colorimetric)/ Monarch centrifugal analyzer (kinetic) n.r.	Sens: 31% Spec: 55% (correctly predicted 71%)	

Table 6 Bilateral Notches

Author, Year, Country, Evidence level, Study design	No. of women analysed, Inclusion/ Exclusion criteria, age, gestational age at test	Reference standard used, Incidence of PE (%)	Index test	Results	Conclusions/ Comments
Papageorghiou, 2001, UK, EL II, Cohort study	7851, IN: singleton pregnancies, routine antenatal care. EX: foetal abnormalities 29.7 (16-47) yrs, 22-24 wks	DBP ≥ 90 mmHg twice > 4h apart, prot. ≥ 0.3 g/24h or ≥ 2+ dipstick twice if no 24h collection available, 1.4%	CD + PW, transvaginal Acuson SP-10, Aloka 5000, Aloka 17000, ATL HDI 3000, ATL Hdi 3500, Hitachi, Toshiba, Siemens	Sens: 25.4% Spec: 90.9% PPV: 2.5% NPV: 99.3% +LR: 8.87 -LR: 0.62	
Harrington, 1997, UK, EL II, Cohort study	626, IN: Singleton pregnancies, unselected 15-49 yrs, 12-16 wks	SBP ≥ 140 or DBP ≥ 90 mmHg, prot > 0.3g/24h, 4.8%	CD + PW, transvaginal Acuson 128	Sens: 92.9% Spec: 85.1% PPV: 23.6% NPV: 99.5%	
Marchesoni, 2003, UK, EL II, Case control study	895 (177 cases and 718 controls) Unselected women 31.7 ± 5.3 yrs, 20 wks, 24 wks	BP > 140/90 mmHg, prot. > 0.3g/24h, 2.9%	CD Acuson Sequoia	Sens: 72% Spec: 94% PPV: 26% NPV: 99%	
Schwarze, 2005, Germany, EL II, Prospective study	346 women (19-22 wks- 215 women) (23-26 wks-131 women), EX: essential hypertension, DM, autoimmune disorders, history of PE, IUGR, IUD, placental abruption; multiple pregnancies, foetal abnormalities 31.4 (17-46) yrs, 19-22 wks, 23-26 wks	RR ≥ 140/90 mmHg, prot. ≥ 0.3g/24h, no UTI, 4.9%	CD Elegra (Siemens), Acuson 128 XP10	19-22 wks vs 23-26 wks Sens: 40% vs 67% Spec: 82% vs 84% PPV: 10% vs 17% NPV: 97% vs 98%	The predictive value of uterine artery Doppler for adverse pregnancy outcome in a low-risk population is of limited diagnostic value. Performing uterine artery Doppler studies at 23-26 weeks' gestation increases the predictive value for adverse pregnancy outcomes.

Table 7 Integrated Doppler test with serum markers

Author, Year, Country, Evidence level, Study design	No. of women analysed, Inclusion/ Exclusion criteria, age, gestational age at test	Reference standard used, Incidence of PE (%)	Index test cut off	Results	Conclusions/ Comments
Emine,2005, Turkey, EL II, Prospective study	178, EX: multiple pregnancies, hypertension before 26 wks, diabetes or pregnancy with prenatal and postnatal diagnosis of a chromosomal/ structural abnormality, previous pregnancy complicated by pre-eclampsia, 28.8 ± 5.1 30.6 ± 4.3, 16-18 wks 24-26 wks	BP ≥ 140/90 mmHg and first Dx after 20 wks, proteinuria ≥ 300mg/24hr 7.9%	Two site enzyme immunoassays, immunometric assays, two site chemiluminescent immunometric assay, ultrasound machines	Bilateral notch Sens:85.7% Spec: 97.6% Bilateral notch + serum activin Sens: 78.6% Spec: 100% Bilateral notch + serum inhibin Sens: 71.4% Spec: 100% Bilateral notch OR serum activin Sens: 100% Spec: 86%	Maternal serum inhibin A and activin A levels and uterine artery Doppler appear to be uselful screening tests during the second trimester for pre-eclampsia. However the addition of these hormonal markers to Doppler velocimetry only slightly improves the predictive efficacy.
Audibert, 2005, France, EL II, Cohort study	2615, EX: multiple pregnancies, without ultrasound between 10-14 wks, women refered for nuchal translucency, structural anomalies, chromosomal abnormalities, 30.9 ± 4.5 years, 14-18 wks 18-26 wks	SBP ≥140 mmHg or a DBP ≥90 mmHg twice, proteinuria > 0.3 g/24hr or at least 2+ protein on urine dipstick, Prevalence of PE 1.95%	Amerlite kit,	Bilateral notch Sens: 21.56% Spec: 95.94% History of pre-eclampsia or bilateral notch or hCG > 2.5 MoM Sens: 41.17% Spec: 91.61%	Combination of serum markers and abnormal uterine Doppler ultrasound improves the identification of women at risk for subsequent pregnancy complications. The care providers should be encouraged to perform a uterine Doppler ultrasound when serum markers are abnormal. However, the sensitivity of these tests is too low to provide an efficient generalized screening.

11.3 Preterm birth

Clinical question

What is the diagnostic value of the following screening methods in identifying women at risk of preterm labour?

- History
- Vaginal examinations
- USS – cervical length up to 22 weeks of pregnancy
- Oral health/dental health
- Swabs for bacterial vaginosis

Previous NICE guidance (for the updated recommendations see below)

Routine vaginal examination to assess the cervix is not an effective method of predicting preterm birth and should not be offered.

Although cervical shortening identified by TVS and increased levels of FFN are associated with an increased risk of preterm birth, the evidence does not indicate that this information improves outcomes; therefore neither TVS nor FFN should be used to predict preterm birth in healthy pregnant women.

Introduction and Background information

In the UK approximately 7% of births occur prior to 36 completed weeks gestation and 1.4% prior to 31 completed weeks *(figures for England, NHS Maternity Statistics 2003-2004)*. According to CEMACH, more than 70% of all neonatal deaths occur in pre-term babies, that is, birth of a baby before 37 weeks of completed gestational age. *(Perinatal mortality surveillance, 2004, England, Wales and Northern Ireland, CEMACH, http://www.cemach.org.uk/publications.htm)*. It is an important cause of major and minor morbidity such as necrotising enterocolitis, bronchopulmonary dysplasia, intraventricular haemorrhage, cerebral palsy and cognitive impairment during early years of life. Even after infancy, these babies are at increased risk of developing chronic diseases in adult life.

44 papers from 38 studies have been included in this review for evaluating diagnostic accuracy of the following twelve screening tests:

1. Previous history of spontaneous preterm birth (SPTB)
2. Clinical/digital examination
3. Cervico-vaginal fetal fibronectin (FFN) levels
4. Cervico-vaginal interleukin-6 (IL-6) levels
5. Cervico-vaginal interleukin-8 (IL-8) levels
6. Maternal serum alpha feto-protein levels (MSAFP)
7. Maternal serum beta-human chorionic gonadotrophin levels (MSHCG)
8. Maternal serum C reactive protein levels (CRP)
9. Asymptomatic bacteriuria
10. Bacterial vaginosis (BV)
11. Transvaginal sonography (TVS) for cervical length
12. Transvaginal sonography for funnelling of cervix.

Most of the studies included for this review are prospective cohort studies. High quality studies with Evidence level 1 were identified and included for evaluating diagnostic accuracy of the following screening tests - previous history of spontaneous preterm birth, cervico-vaginal FFN levels, bacterial vaginosis using Nugent's criteria for gram staining, and transvaginal ultrasound for cervical length and funnelling. For other screening tests, the evidence level of included studies was predominantly 2 or 3 due to two main reasons – absence of blinding and/or study population not being representative of the reference population. Only studies conducted on asymptomatic women (with no signs and symptoms of preterm labour) were considered for this review. Since most of the studies identified for cervico-vaginal IL-6, IL-8, and serum CRP tests

were conducted in symptomatic women (with threatened preterm labour), only a few quality studies remained for these tests for asymptomatic women.

Details of screening tests including timing, frequency and thresholds have been specified where possible. Outcome assessed was spontaneous preterm delivery less than 37 weeks (SPTD < 37 weeks), and efforts were made to calculate the diagnostic value of the tests after excluding cases of induced preterm delivery (PTD). Many studies had evaluated screening performance of various tests for outcome with different gestational age (for example < 32, 33 or 35 weeks), but for the sake of comparison results have been provided for commonly used thresholds and SPTD < 37 weeks as the outcome. Wherever possible, incidence of SPTD and prevalence of test positive have also been calculated.

Studies included in the review of each screening test have been tabulated in decreasing order of their evidence level. In case of those with similar evidence levels, priority is given to the study with a bigger sample size.

History of previous spontaneous preterm birth (SPTB)

Description of included studies

Three studies were included – two prospective cohort [EL Ib] and one retrospective cohort [EL II]. All were multi-centre studies with good sample size. Though the thresholds of screening tests were different in these studies and outcomes other than SPTD < 37 wks were also evaluated, results have been given for history of previous SPTB > 20 weeks as the screening test and outcome SPTD < 37 weeks only. (Table I)

Findings

In the three studies sensitivity (ST) and specificity (SP) ranged from 19 to 67% and 73 to 97% respectively. The test had high + LR of 5.78 (4.47-7.46) in one study (Kristensen et al), but – LR was 0.84 (0.80-0.89) and it was a study with EL 2. For the studies with EL 1, values of + LR ranged from 2.26 to 2.74 and - LR from 0.45 to 0.77. On meta-analysis, significant statistical heterogeneity ($p < 0.00001$) was observed for both the positive and negative LR. The summary + LR was 2.83 (2.53-3.16) and summary – LR was 0.76 (0.72-0.80) respectively. (Figure 1)

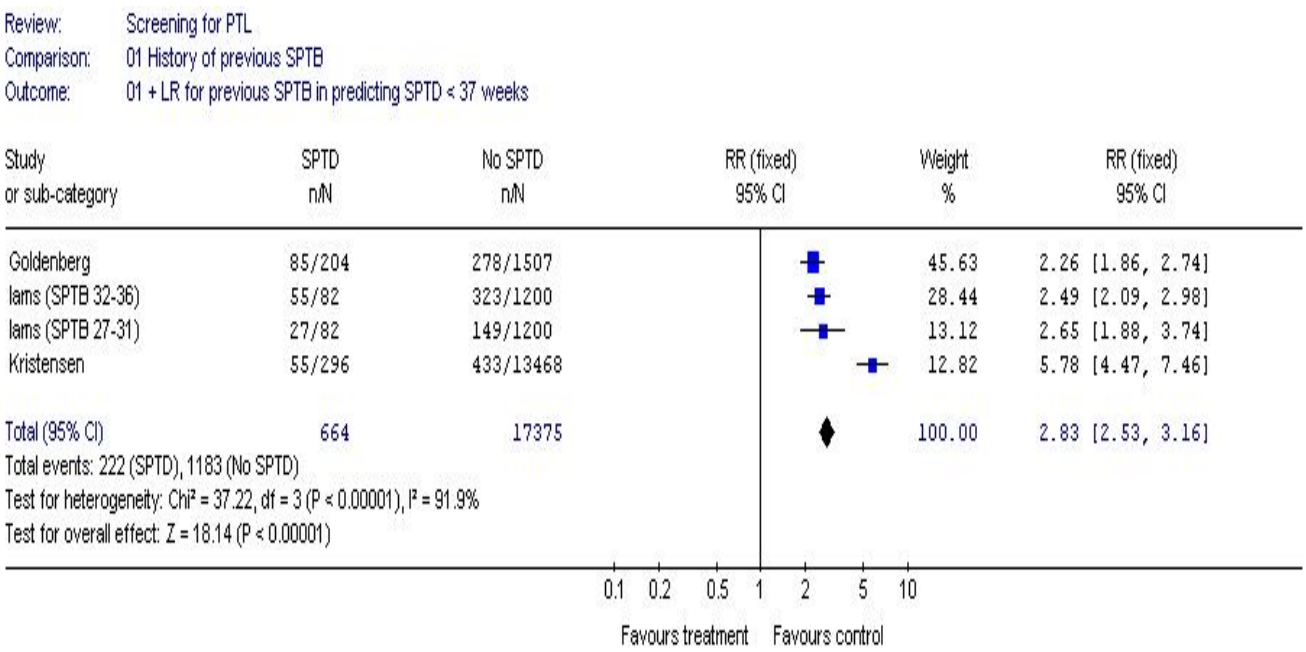
Evidence summary

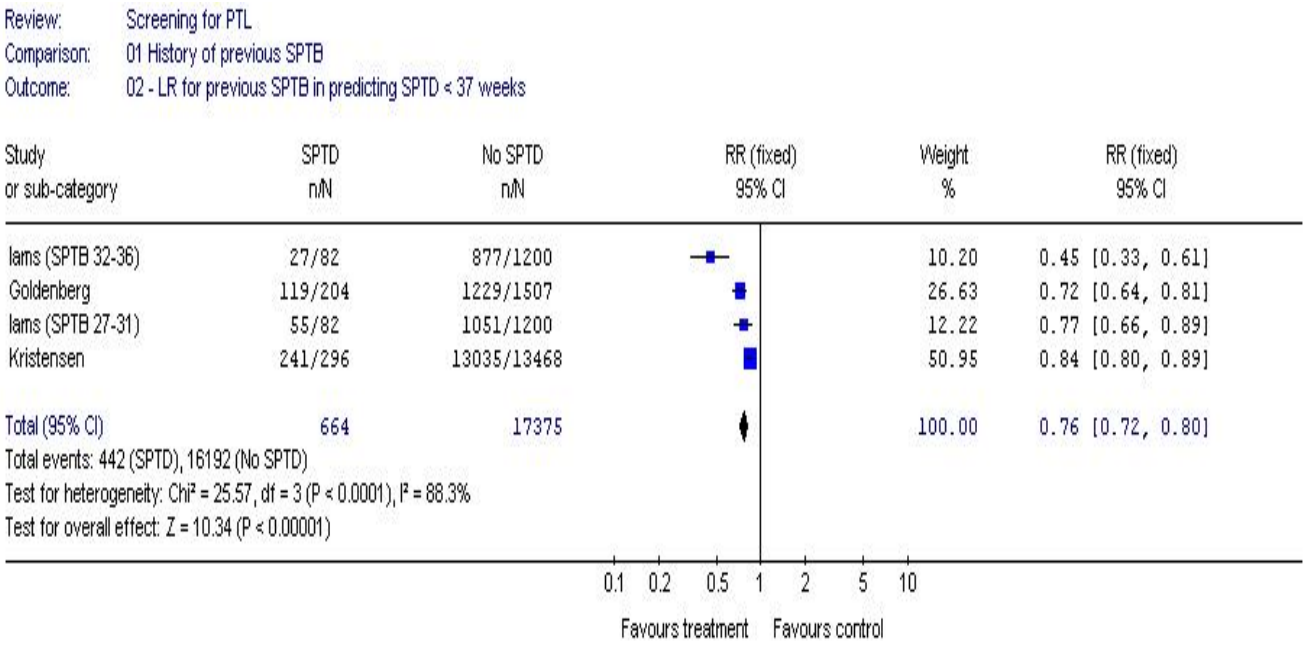
Evidence indicates that history of previous spontaneous preterm birth does not seem to have high diagnostic value in predicting and ruling out SPTD in the current pregnancy.

Table I Characteristics of included studies on diagnostic value of maternal H/O previous spontaneous preterm birth

Study and EL	***Study characteristics***	***Population characteristics***	***Sample size (% of study population)***	***Timing of screening test with threshold (prevalence of test positive)***	***Outcome in wks (incidence of SPTD)***	***Diagnostic value with 95% CI***
Goldenberg 1998 [880] (USA) EL 1b	Prospective cohort, multi-centre.	Singleton pregnancies. *Exclusions*: multiple gestations, cervical cerclage, placenta previa, major fetal anomaly.	1711 (58.4% - rest were primiparas)	H/O previous SPTB (20-37 weeks) at 22-24 weeks visit (21.2% in study population)	< 32 , < 35, and < 37 (11.9% at < 37)	*For SPTD < 37 weeks* ST - 0.42 (0.35-0.49) SP - 0.82 (0.80-0.83)
Iams 1998 [881] (USA) EL Ib	Prospective cohort, multi-centre.	Singleton pregnancies. (secondary analysis of data from Goldenberg study to measure risk of recurrent SPTB – lower limit of gest. age for SPTB reduced from 20 to 18 weeks)	1282	H/O previous SPTB at 18-26, 27-31, and 32-36 weeks.	< 35	*H/O previous SPTB at 27-31 wks* ST - 0.33 (0.23-0.44) SP - 0.88 (0.86-0.89) *H/O previous SPTB at 32-36 wks* ST - 0.67 (0.56-0.77) SP - 0.73 (0.70-0.76)
Kristensen 1995 [882] (Denmark) EL II	Retrospective cohort, multi-centre. (records from National Health Registers used	All women with permanent address in Denmark who gave birth to their first singleton infant in 1982 and a second in 1982-87	13967 (99.5%)	H/O previous SPTB at < 37 weeks (3.5% in study population)	< 37 (2.2% - SPTD, 3.5% all PTD)	*For SPTD < 37 weeks* ST - 0.19 (0.14-0.23) SP - 0.97 (0.96-0.97)

Figure 1


Review: Screening for PTL
Comparison: 01 History of previous SPTB
Outcome: 01 + LR for previous SPTB in predicting SPTD < 37 weeks
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Goldenberg 85/204 278/1507 45.63 2.26 [1.86, 2.74]
Iams (SPTB 32-36) 55/82 323/1200 28.44 2.49 [2.09, 2.98]
Iams (SPTB 27-31) 27/82 149/1200 13.12 2.65 [1.88, 3.74]
Kristensen 55/296 433/13468 12.82 5.78 [4.47, 7.46]
Total (95% CI) 664 17375 100.00 2.83 [2.53, 3.16]
Total events: 222 (SPTD), 1183 (No SPTD)
Test for heterogeneity: Chi² = 37.22, df = 3 (P < 0.00001), I² = 91.9%
Test for overall effect: Z = 18.14 (P < 0.00001)
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control


Review: Screening for PTL
Comparison: 01 History of previous SPTB
Outcome: 02 - LR for previous SPTB in predicting SPTD < 37 weeks
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Iams (SPTB 32-36) 27/82 877/1200 10.20 0.45 [0.33, 0.61]
Goldenberg 119/204 1229/1507 26.63 0.72 [0.64, 0.81]
Iams (SPTB 27-31) 55/82 1051/1200 12.22 0.77 [0.66, 0.89]
Kristensen 241/296 13035/13468 50.95 0.84 [0.80, 0.89]
Total (95% CI) 664 17375 100.00 0.76 [0.72, 0.80]
Total events: 442 (SPTD), 16192 (No SPTD)
Test for heterogeneity: Chi² = 25.57, df = 3 (P < 0.0001), I² = 88.3%
Test for overall effect: Z = 10.34 (P < 0.00001)
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

Clinical examination

Description of included studies

Five prospective cohort studies were included – one with [EL Ib] and four with [EL II], the reason being absence of blinding in these studies. In the study with [EL Ib], Bishop Score was used for screening and clinical examination carried out 4 times in each woman. In studies with [EL II], difference was observed in the frequency, timing and threshold of the screening test used. Due to existing heterogeneity, meta-analysis was not performed. Values for positive and negative LR have been presented separately for the two most commonly used signs at clinical examination – cervical dilatation (in 4 studies) and short cervix (in 2 studies) (Table II)

Findings

For cervical dilatation, ST and SP ranged from 13 to 57% and 57 to 98% respectively. Study by Leveno et al had a high + LR of 9.25 (3.91-21.85), but – LR was 0.46 (0.19-1.08). Chambers et al had moderate values for + LR and – LR of 2.16 and 0.76 respectively. LR's for the other two studies were not as good as those of the above two mentioned studies (Figure 2A)

ST for a short cervix diagnosed clinically ranged from 11 to 21% and SP from 89 to 95%. Chambers et al had a better – LR of 0.88 (0.81-0.97) of the included studies, but + LR was 1.96 (1.41-2.74) (Figure 2B)

Evidence summary

A wide variation in results of screening accuracy is observed for different clinical methods for predicting SPTD. Evidence shows that clinical examination has poor diagnostic value in predicting and ruling out SPTD.

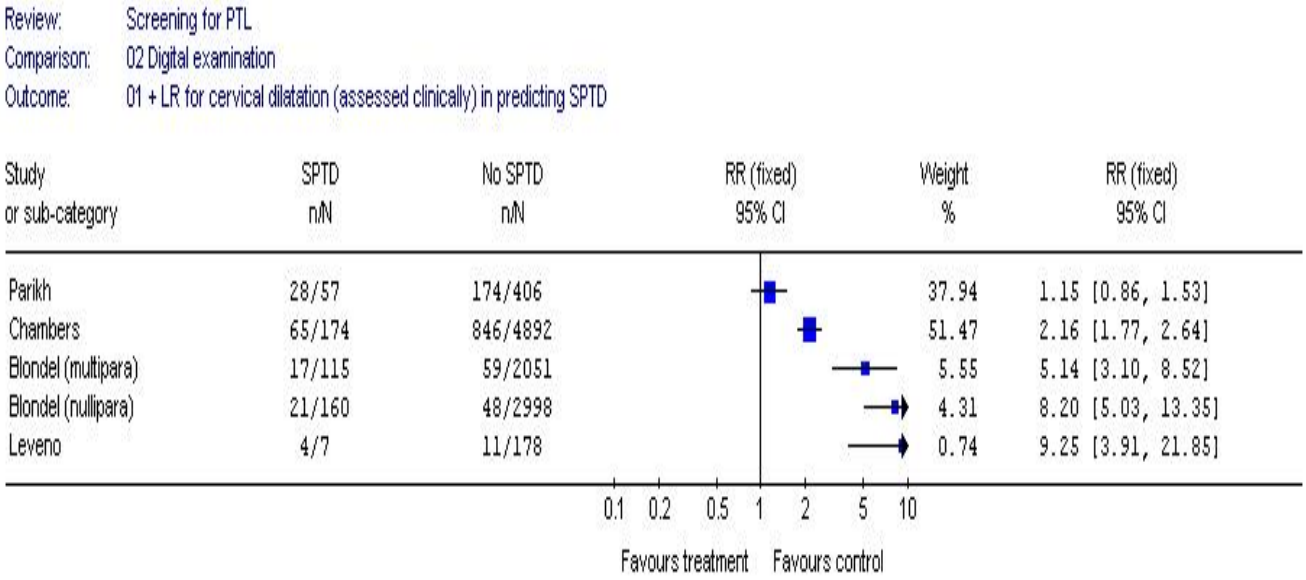
1 **Table II** Characteristics of included studies on diagnostic value of vaginal digital examination

2

Study and EL	***Study characteristics***	***Population characteristics (Low risk or high risk)***	***Sample size (% of study population)***	***Timing and frequency of screening test (with threshold)***	***Outcome in wks (incidence of SPTD)***	***Diagnostic value with 95% CI***
Iams 2001 [883] (USA) EL Ib	Prospective cohort, multi-centre, blinded	Nulliparous women and multiparous with no H/O previous SPTB or abortion. (low risk)	2107 (71.9)	Digital examination 4 times before 35 wks (Bishop score≥ 4)	< 35 (3.0% in sample population)	ST – 0.23 (O.13-0.33) SP – 0.93 (0.91-0.94)
Blondel 1990 [884] (France) EL II	Prospective cohort, in 2 centres, not blinded	Singleton pregnancies attending two outpatient clinics (both low & high risk)	6909 (90.4) nullipara 4025 and parous 2884	Clinical examination at 25-28 and 29-31 wks for 5 signs – (1 cm internal os dilatation, short cervix ≤1 cms, mid position of cervix, soft or firm cervix, expansion of lower uterine segment)	< 37 (For nullipara at 25-28 wks 5.0%, 29-31 wks 4.4%. For multipara at 25-28 wks 5.3%, 29-31 wks 4.1%)	*Examination at 25-28 wks* 1) Cervical dilatation ST nulli – 0.13 (0.08-0.19) ST multi – 0.15 (0.09-0.23) SP nulli – 0.98 (0.98-0.99) SP multi – 0.97 (0.96-0.98) 2) Short cervix ST nulli – 0.14 (0.09-0.20) ST multi – 0.11 (0.06-0.17) SP nulli – 0.95 (0.94-0.96) SP multi – 0.95 (0.94-0.96)

Chambers 1990 [885] (France) EL II	Prospective cohort, in 2 centres, not blinded	Pregnant women with at least 2 visits at < 28 weeks (both low & high risk)	5758 (study population not specified)	Once in 2 weeks (Length ≤1 cms before 28 wks for short cervix, dilatation ≥1 cms before 37 wks for open cervix)	< 37 (4.04%)	*For cervical dilatation* ST – 0.37 (0.30-0.45) SP – 0.83 (0.82-0.84) *For short cervix* ST – 0.21 (0.15-0.28) SP – 0.89 (0.88-0.90)
Parikh 1961 [886] (India) EL II	Prospective cohort, single centre, not blinded	Singleton pregnancies attending ANC clinic of a government hospital (both low & high risk)	463 (70.7)	Twice / week at 21-36 wks (admit digit at internal os for cervical dilatation)	< 37 (12.3% in sample population)	ST – 0.49 (0.36-0.63) SP – 0.57 (0.52-0.62)
Leveno 1986 [887] (USA) EL II	Prospective cohort, single centre, blinded	Consecutively enrolled singleton pregnancies (low risk)	185 (no exclusions specified)	Single examination at 26-30 wks. (>2cms dilated)	< 37 (3.8% in sample population)	ST – 0.57 (0.18-0.90) SP – 0.94 (0.89-0.98)

Figure 2 (A)


Review: Screening for PTL
Comparison: 02 Digital examination
Outcome: 01 + LR for cervical dilatation (assessed clinically) in predicting SPTD
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Parikh 28/57 174/406 37.94 1.15 [0.86, 1.53]
Chambers 65/174 846/4892 51.47 2.16 [1.77, 2.64]
Blondel (multipara) 17/115 59/2051 5.55 5.14 [3.10, 8.52]
Blondel (nullipara) 21/160 48/2998 4.31 8.20 [5.03, 13.35]
Leveno 4/7 11/178 0.74 9.25 [3.91, 21.85]
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

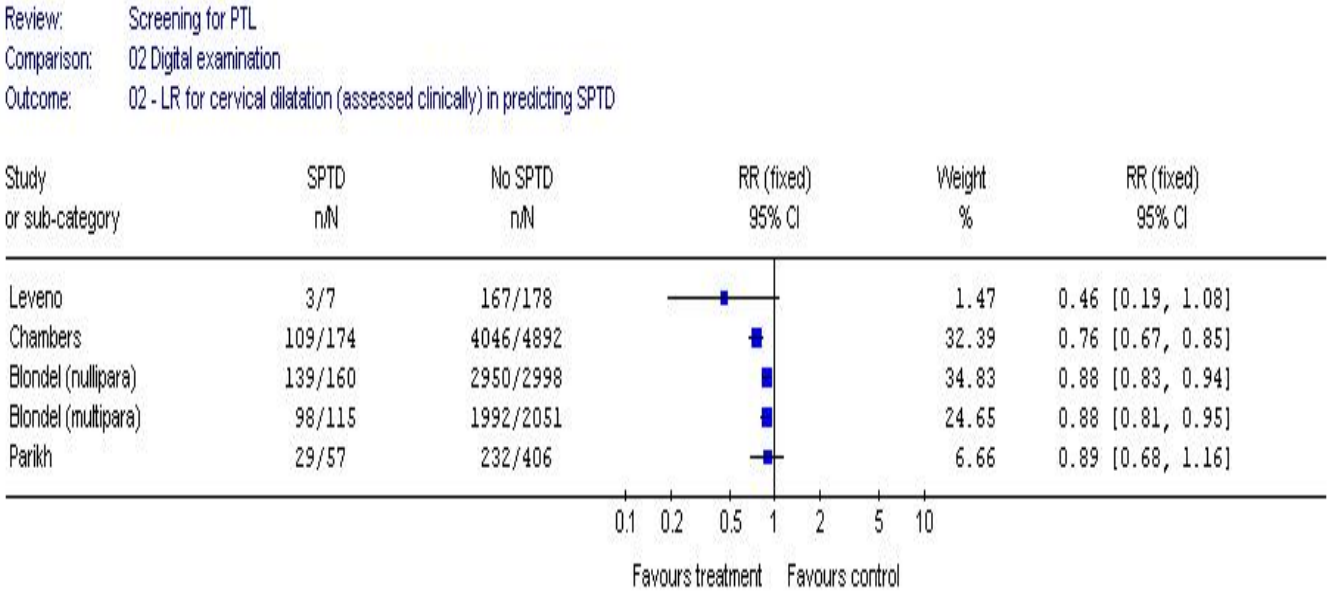
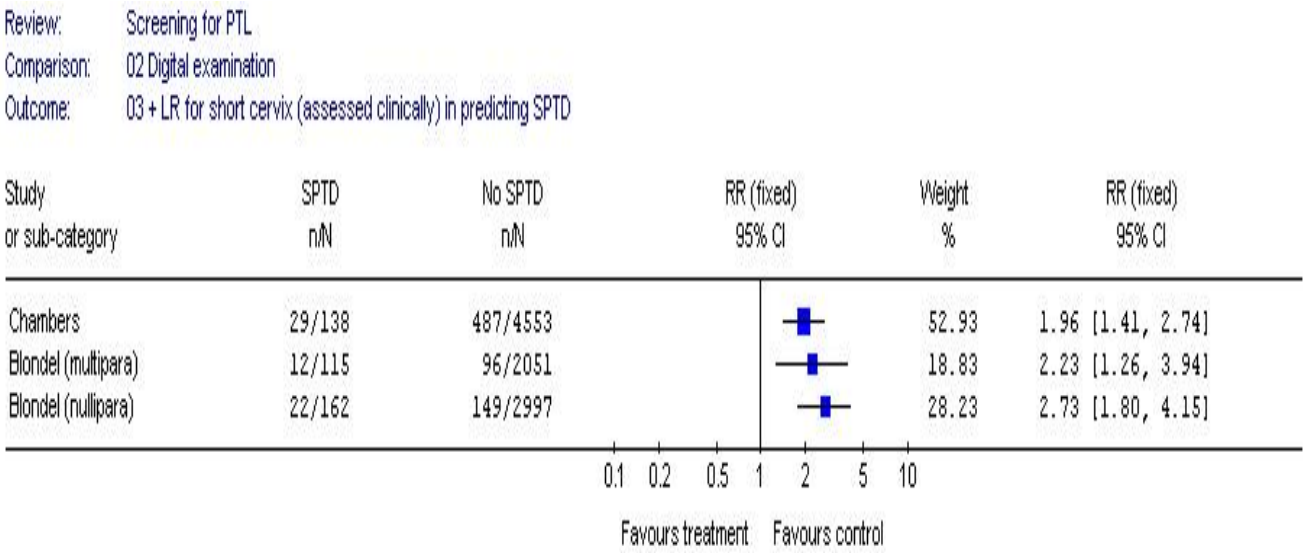
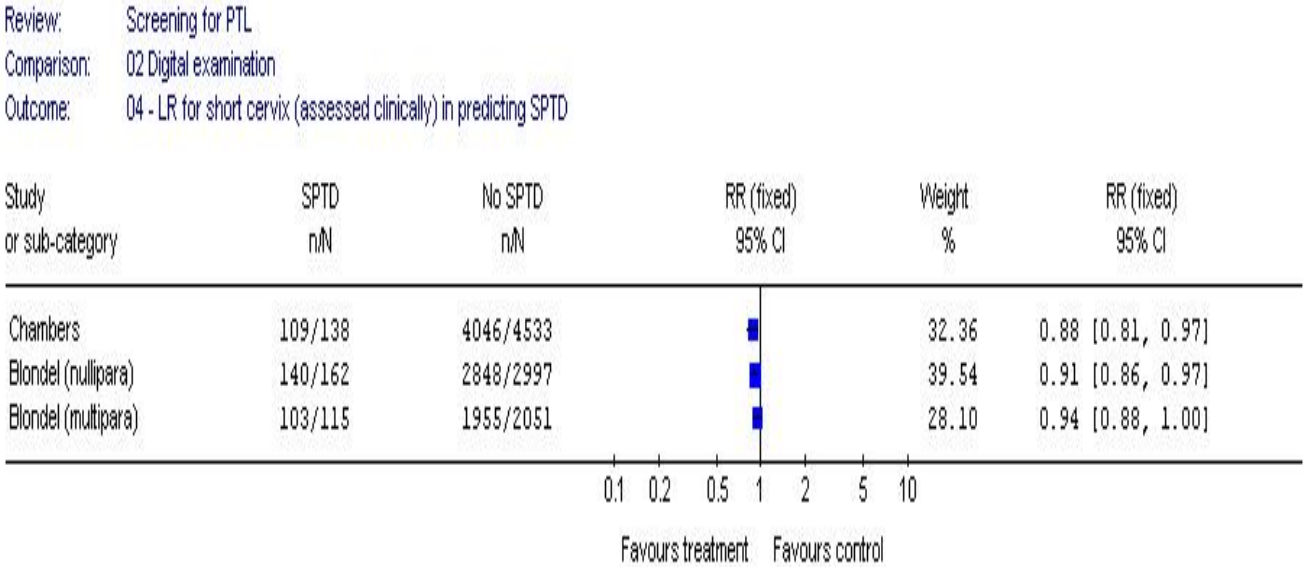

Review: Screening for PTL
Comparison: 02 Digital examination
Outcome: 02 - LR for cervical dilatation (assessed clinically) in predicting SPTD
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Leveno 3/7 167/178 1.47 0.46 [0.19, 1.08]
Chambers 109/174 4046/4892 32.39 0.76 [0.67, 0.85]
Blondel (nullipara) 139/160 2950/2998 34.83 0.88 [0.83, 0.94]
Blondel (multipara) 98/115 1992/2051 24.65 0.88 [0.81, 0.95]
Parikh 29/57 232/406 6.66 0.89 [0.68, 1.16]
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

Figure 2 (B)


Review: Screening for PTL
Comparison: 02 Digital examination
Outcome: 03 + LR for short cervix (assessed clinically) in predicting SPTD
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Chambers 29/138 487/4553 52.93 1.96 [1.41, 2.74]
Blondel (multipara) 12/115 96/2051 18.83 2.23 [1.26, 3.94]
Blondel (nullipara) 22/162 149/2997 28.23 2.73 [1.80, 4.15]
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control


Review: Screening for PTL
Comparison: 02 Digital examination
Outcome: 04 - LR for short cervix (assessed clinically) in predicting SPTD
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Chambers 109/138 4046/4533 32.36 0.88 [0.81, 0.97]
Blondel (nullipara) 140/162 2848/2997 39.54 0.91 [0.86, 0.97]
Blondel (multipara) 103/115 1955/2051 28.10 0.94 [0.88, 1.00]
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

Cervico-vaginal fetal fibronectin levels (FFN)

Description of included studies

The six studies concerning this test were prospective cohort studies and blinding was specified in all. In two studies [EL II] the dropout rate was more than 40% while rest were classified [EL Ib]. The population was low risk singleton pregnancies in all studies. A single swab in the second trimester at different gestational ages was taken usually from the posterior vaginal fornix, and the threshold used for a positive test was FFN levels $\geq$ 50ng/ml. Meta-analysis was performed for the predictive accuracy of a single test in second trimester with outcome SPTD < 37 wks. One good quality study was excluded from meta-analysis as it evaluated SPTD < 33 wks as the outcome. (Table III)

Findings

ST ranged from 13 to 55% and SP from 83 to 99% for the test in predicting SPTD < 37 wks. In the study that used < 33 wks as the time for the outcome, ST and SP were 33 and 97% respectively.

For the individual studies + LR ranged from 2.19 (1.08-4.47) to as high as 18.00 (3.21-100.86), and – LR from 0.92 (0.83-1.02) to a low of 0.53 (0.26-1.11). The study with the highest + LR (Chang et al) had a - LR of 0.84, but the confidence interval (CI) crossed unity. Similarly Crane et al had the best value for – LR but again the CI crossed unity.

No statistically significant heterogeneity was observed for both + LR and – LR on performing meta-analysis. The summary LR values for a positive test was 3.53 (2.78-4.49) and for the negative test 0.86 (0.82-0.90). *(Figure 3)*

Evidence summary

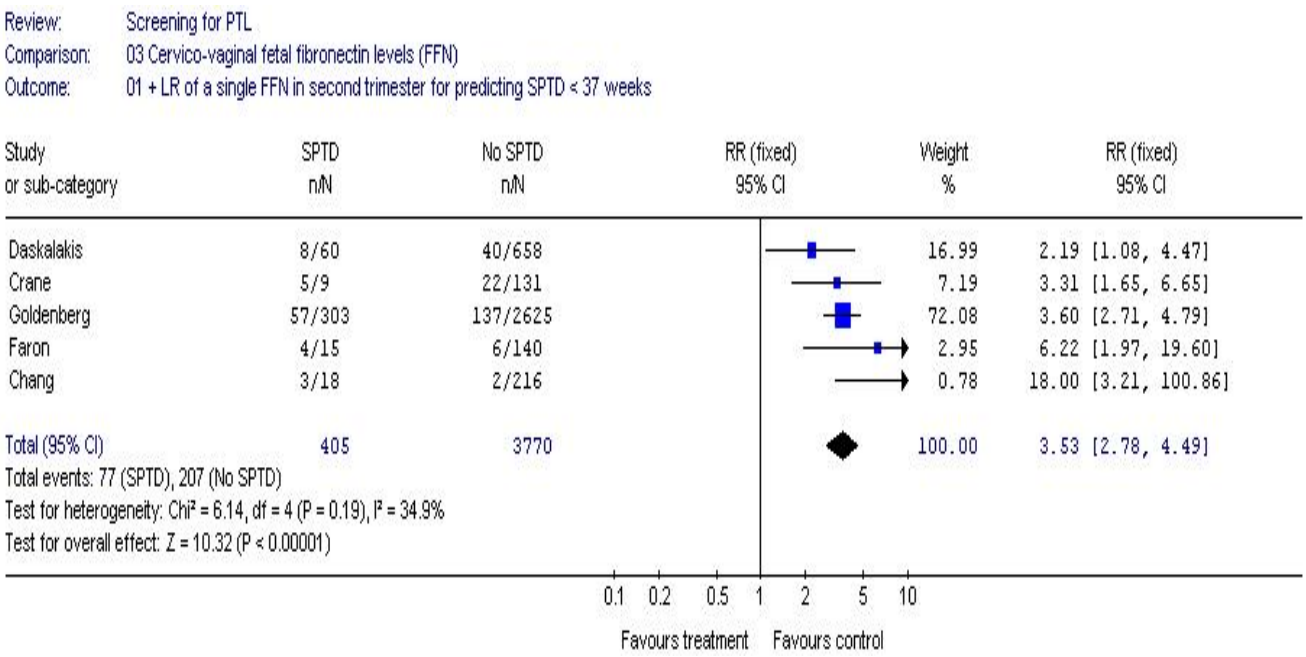
There is high quality evidence to show that a single second trimester cervico-vaginal swab with a positive result for fibronectin levels has moderate value in predicting SPTD < 37 weeks, but a negative result decreases the probability of SPTD only minimally.

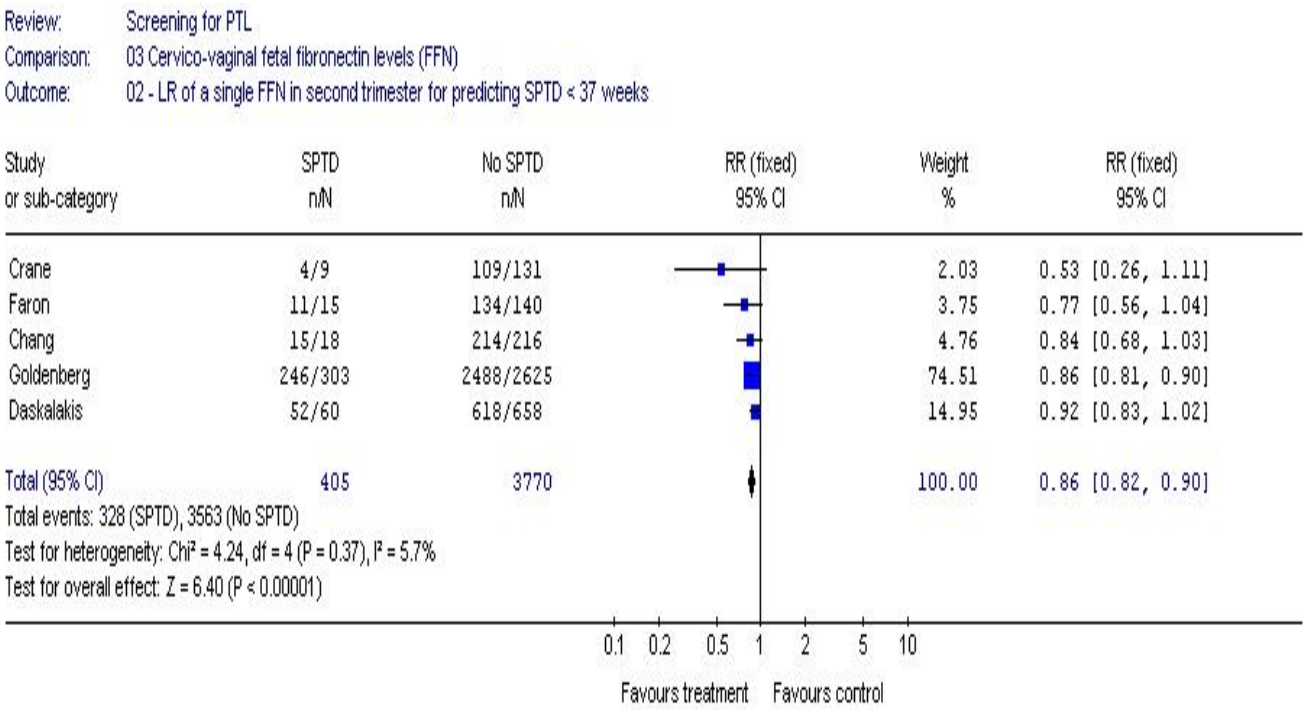
Table III Characteristics of included studies on diagnostic value of cervico-vaginal fetal fibronectin levels

Study and EL	***Study characteristics***	***Population characteristics (low or high risk)***	***Sample size (% of study population)***	***Timing of screening test with threshold (prevalence of test positive)***	***Outcome in weeks (incidence of SPTD)***	***Diagnostic value with 95% CI***
Heath 2000 [888] (UK) EL Ib	Prospective cohort, single fetal medicine unit, blinded.	Singleton pregnancies for routine anomaly US scan at 23 weeks. *Exclusions:* multiple gestations, fetal anomaly, cervical cerclage, previous SPTB < 33 wks (low risk)	5058 (98.5)	Single swab from posterior fornix at 22-24 weeks, threshold ≥ 50 ng/ml. (3.5% in sample population)	< 33 (0.85% in sample population)	ST - 0.33 (0.20-0.49) SP - 0.97 (0.96-0.97)
Goldenberg 1998 [880] (USA) EL Ib	Prospective cohort, multi-centre, blinded.	Singleton pregnancies. *Exclusions*: multiple gestations, cervical cerclage, placenta previa, fetal anomaly. (low risk)	2929 (95.3)	Single swab from posterior fornix at 24-26 weeks, threshold ≥ 50 ng/ml. (6.6% in sample population)	< 35 (4.4%) < 37 (10.3%)	*For SPTD < 37 weeks* ST - 0.19 (0.14-0.23) SP - 0.95 (0.94-0.95)
Chang 1997[889] (Singapore) EL Ib	Prospective cohort, single centre, blinded.	Singleton pregnancies with no risk factor for PTL. *Exclusions*: active vaginal bleeding, uncertain gestational age, hypertensive	234 (97.5)	Single swab from posterior fornix at 22-25 weeks, threshold ≥ 50 ng/ml. (2.1% in sample population)	< 34 (2.4%) < 37 (7.7%)	*For SPTD < 37 weeks* ST - 0.17 (0.04-0.41) SP - 0.99 (0.97-1.00)

		disease, PROM (low risk)				
Faron 1997 [890] (Belgium) EL Ib	Prospective cohort, single centre, blinded	Pregnant women attending ANC for routine care with known gestation *Exclusions*: vaginal bleeding (low risk)	155 (91.2)	Single swab from endocervix at 24-33 weeks, threshold ≥ 50 ng/ml. (6.5% in sample population)	< 37 (9.7% in sample population)	ST - 0.27 (0.04-0.49) SP - 0.96 (0.92-1.00)
Daskalakis 2006 [891] (Greece) EL II	Prospective cohort, single centre, blinded	Singleton pregnancies having anomaly scan at 22-25 weeks Exclusions: previous SPTB, multiple gestation, placenta previa, fetal anomalies, cervical incompetence or cerclage (low risk)	718 (55.8)	Single swab from posterior fornix at 22-25 weeks, threshold ≥ 50 ng/ml. (6.7% in sample population)	< 37 (8.3% in study population))	ST - 0.13 (0.05-0.23) SP – 0.94 (0.92-0.96)
Crane 1999 [892] (Canada) EL II	Prospective cohort, single centre, blinded	Singleton pregnancies at 20-24 weeks *Exclusions*: ruptured membrane, placenta previa, active bleeding, multiple gestations, cervical cerclage, fetal anomalies (low risk)	140 (59.7)	Swabs from both posterior fornix and cervix at 20-24 weeks, threshold ≥ 50 ng/ml. (19.2% for vaginal FFN, 25% for cervical FFN)	< 37 (6.4% in study population)	*For vaginal FFN* ST – 0.55 (0.24-0.84) SP – 0.83 (0.76-0.89)

Figure 3


Review: Screening for PTL
Comparison: 03 Cervico-vaginal fetal fibronectin levels (FFN)
Outcome: 01 + LR of a single FFN in second trimester for predicting SPTD < 37 weeks
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Daskalakis 8/60 40/658 16.99 2.19 [1.08, 4.47]
Crane 5/9 22/131 7.19 3.31 [1.65, 6.65]
Goldenberg 57/303 137/2625 72.08 3.60 [2.71, 4.79]
Faron 4/15 6/140 2.95 6.22 [1.97, 19.60]
Chang 3/18 2/216 0.78 18.00 [3.21, 100.86]
Total (95% CI) 405 3770 100.00 3.53 [2.78, 4.49]
Total events: 77 (SPTD), 207 (No SPTD)
Test for heterogeneity: Chi² = 6.14, df = 4 (P = 0.19), I² = 34.9%
Test for overall effect: Z = 10.32 (P < 0.00001)
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control


Review: Screening for PTL
Comparison: 03 Cervico-vaginal fetal fibronectin levels (FFN)
Outcome: 02 - LR of a single FFN in second trimester for predicting SPTD < 37 weeks
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Crane 4/9 109/131 2.03 0.53 [0.26, 1.11]
Faron 11/15 134/140 3.75 0.77 [0.56, 1.04]
Chang 15/18 214/216 4.76 0.84 [0.68, 1.03]
Goldenberg 246/303 2488/2625 74.51 0.86 [0.81, 0.90]
Daskalakis 52/60 618/658 14.95 0.92 [0.83, 1.02]
Total (95% CI) 405 3770 100.00 0.86 [0.82, 0.90]
Total events: 328 (SPTD), 3563 (No SPTD)
Test for heterogeneity: Chi² = 4.24, df = 4 (P = 0.37), I² = 5.7%
Test for overall effect: Z = 6.40 (P < 0.00001)
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

Cervico-vaginal interleukin (IL-6) levels

Description of included studies

There were three studies included for this test, all with [EL II] a prospective cohort study, and two nested case-control studies. All had a small sample size. Timing and frequency of screening tests, thresholds used for a positive test, and outcomes assessed were different in all the three studies. Meta-analysis was not conducted and results have been presented separately for each study (Table IV)

Findings

In the three studies, ST ranged from 9 to 50% while SP ranged from 84 to 90%. Best values for the LRs were obtained for the prospective cohort study (Lockwood et al). For the threshold > 250 pg/ml, it showed a + LR of 3.34 (1.96-5.70) and – LR of 0.59 (0.42-0.83). Results from the other prospective cohort study (Inglis et al) were in complete contrast. Values obtained in the study for + LR and – LR were poor; 0.56 (0.08-3.97) for + LR and 1.08 (0.87-1.35) for the - LR. In the nested case-control study, LR for a positive test was 2.08 (1.10-3.96) and for a negative test was 0.88 (0.80-0.98). *(Figure 4)*

Evidence summary

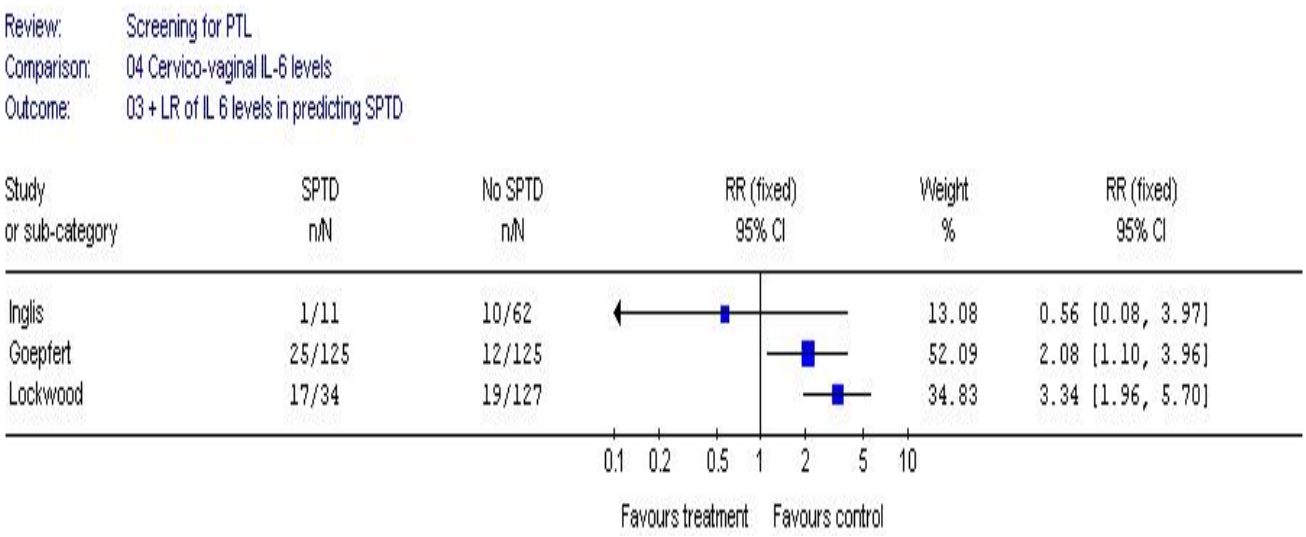
Though studies on diagnostic performance of cervico-vaginal IL-6 levels in asymptomatic women are limited, available evidence shows that it has poor screening accuracy for SPTD.

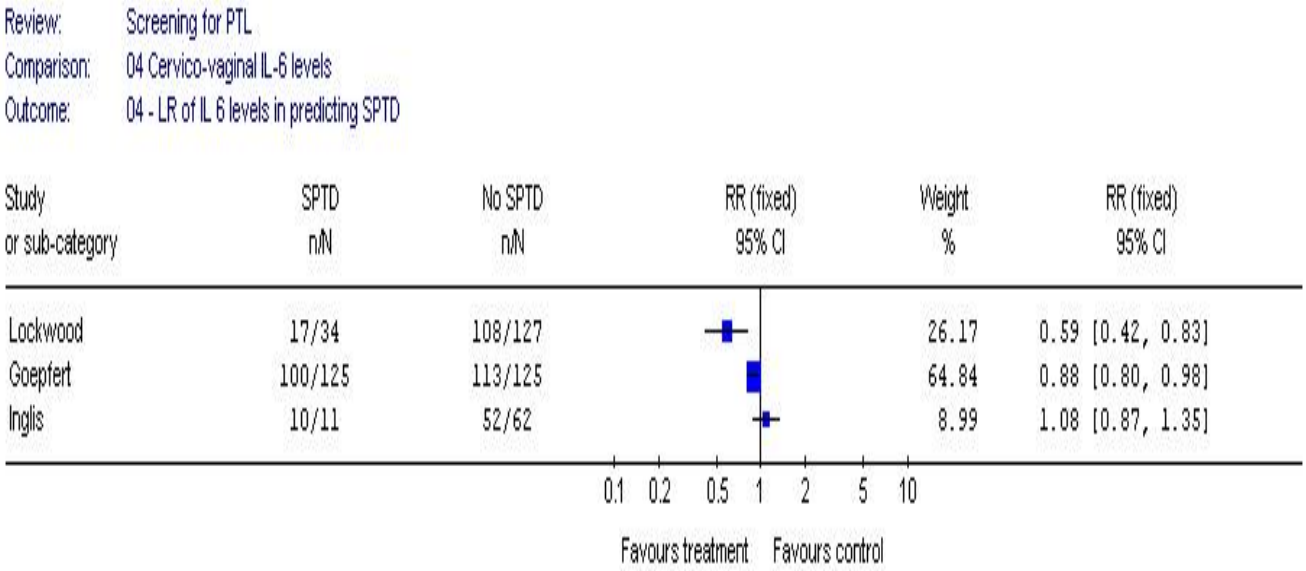
Table IV Characteristics of included studies on diagnostic value of cervico-vaginal IL-6 levels

Study and EL	***Study characteristics***	***Population characteristics (low or high risk)***	***Sample size (% of study population)***	***Timing of screening test with threshold (prevalence of test positive)***	***Outcome in weeks (incidence of SPTD)***	***Diagnostic value with 95% CI***
Lockwood 1994 [893] (USA) EL II	Nested case-control, single centre, blinded	Pregnant women attending single obstetric clinic *Exclusions*: placenta previa, unknown dates, hydatidiform mole, major congenital anomaly, serious maternal complications.	161 (not specified)	Serial testing every 3-4 wks from 24-36 wks Threshold 125 and 250 pg/ml from ROC curve.	< 37 (26.8% in sample population)	*For threshold > 250 pg/ml at 24-36 weeks* ST – 0.50 (0.33-0.67) SP – 0.85 (0.79-0.91)
Inglis1994[894] (USA) EL III	Prospective cohort, single centre, blinded	Singleton pregnancies (15 to 40 years) at < 37 wks with intact membranes. *Exclusions*: congenital anomalies, placenta previa, known genital or urinary infection, use of antibiotics within 7 days prior to entry to study. (low risk)	73 (65.8) after excluding women with threatened preterm labour.	Single test at 20-36 wks, Threshold 50 pg/ml. (15.06% in sample population)	< 37 (16.4% in sample population)	ST – 0.09 (0.00-0.41) SP – 0.84 (0.72-0.92)

Goepfert 2001 [895] (USA) EL III	Retrospective case-control nested within a multi-centre cohort study, blinded	*Cases*: women with SPTB < 35 wks and cervical specimen available for IL-6 assay. *Controls*: women with term deliveries pregnancies matched for race, parity and centre.	250 (cases 125, controls 125)	Single test at 22-24 wks. Threshold 305 pg/ml	< 32 < 35	*For SPTD < 35 weeks* ST – 0.20 (0.13-0.28) SP – 0.90 (0.84-0.95)

Figure 4


Review: Screening for PTL
Comparison: 04 Cervico-vaginal IL-6 levels
Outcome: 03 + LR of IL 6 levels in predicting SPTD
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Inglis 1/11 10/62 13.08 0.56 [0.08, 3.97]
Goepfert 25/125 12/125 52.09 2.08 [1.10, 3.96]
Lockwood 17/34 19/127 34.83 3.34 [1.96, 5.70]
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control


Review: Screening for PTL
Comparison: 04 Cervico-vaginal IL-6 levels
Outcome: 04 - LR of IL 6 levels in predicting SPTD
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Lockwood 17/34 108/127 26.17 0.59 [0.42, 0.83]
Goepfert 100/125 113/125 64.84 0.88 [0.80, 0.98]
Inglis 10/11 52/62 8.99 1.08 [0.87, 1.35]
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

Cervico-vaginal interleukin (IL-8) levels

Description of included studies

Two prospective cohorts were included – both with [EL II] and carried out by the same principal author in Japan. In both studies blinding was not specified. In the study with a bigger sample size, IL-8 was measured serially in the cervico-vaginal fluid – initially once at 20-23 weeks and then biweekly at 24-28 weeks. The threshold for a positive test was also different in both studies. Due to heterogeneity of the test timing, frequency and the threshold values, meta-analysis was not performed (Table V).

Findings

The larger study with serial testing showed ST and SP of 27 and 80% respectively. It had a + LR of 1.38 (1.04-1.82) and - LR of 0.91 (0.82-1.01) for predicting SPTD < 37 weeks. Another study with a smaller sample size showed better results for all values. ST was 42%, SP 85%, + LR 2.75 (1.68-4.52), and the - LR 0.67 (0.30-1.15). In both studies, CI for the – LR crossed unity *(Figure 5)*

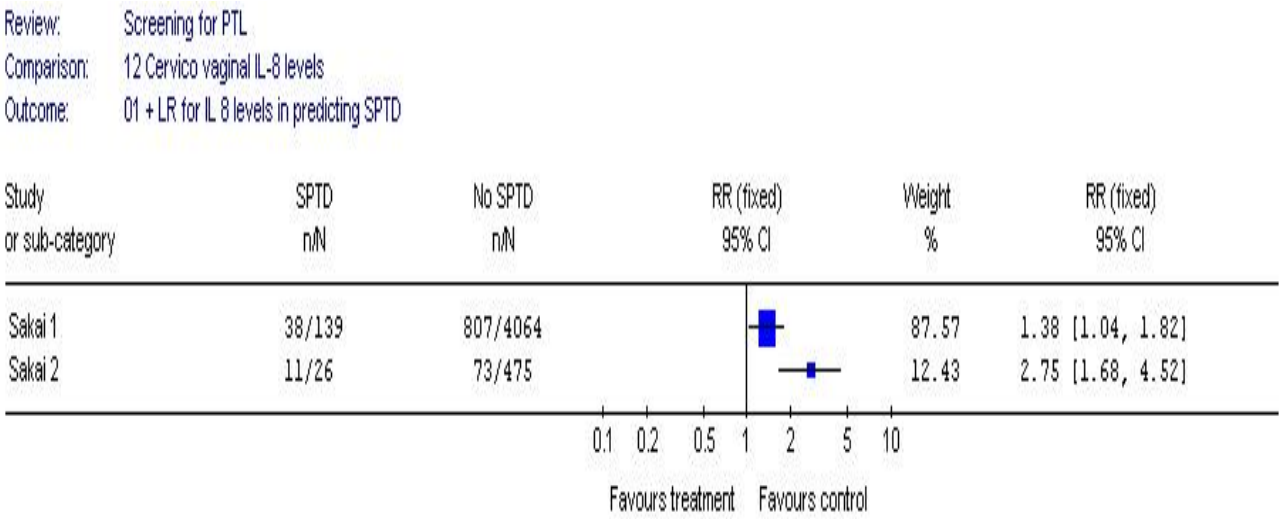
Evidence summary

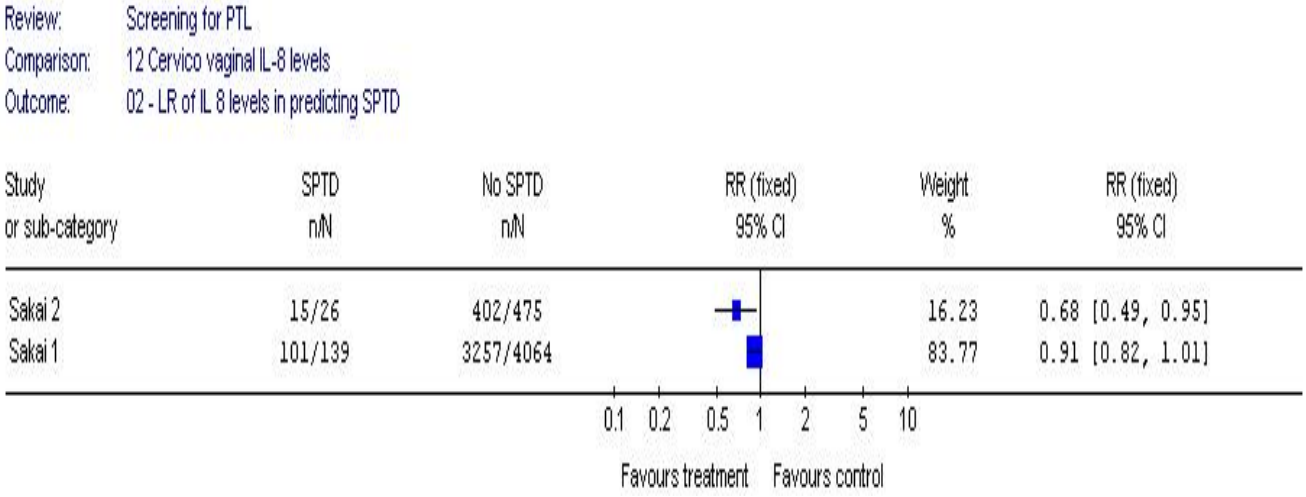
Though the evidence is limited, it shows that the likelihood of SPTD < 37 weeks is increased minimally with a positive test for cervico-vaginal IL 8 levels.

Table V Characteristics of included studies on diagnostic value of cervico-vaginal IL-8 levels

Study and EL	Study characteristics	Population characteristics (low or high risk)	Sample size (% of study population)	Timing and site of screening test with threshold	Outcome in wks (incidence of SPTD)	Diagnostic value with 95% CI
Sakai 2004 [896] (Japan) EL II	Prospective cohort, multi-center, not blinded.	Singleton pregnancies *Exclusions*: premature labour at < 20 wks, PROM, genital bleeding, abruptio placentae, placenta previa, pre-eclampsia, fetal anomalies.	4203 (95.4)	Serial testing – once a month in 20-23 wks and then once biweekly in 24-28 wks. Threshold 360 ng/ml (IL-8 positivity once in 19.1%)	< 32 (0.43%) < 34 (0.64%) < 37 (3.3%)	*For SPTB < 37 weeks* ST – 0.27 (0.20-0.36) SP – 0.80 (0.79-0.81)
Sakai 2004 [897] (Japan) EL II	Prospective cohort, single center, not blinded.	Singleton pregnancies *Exclusions*: premature births caused by fetal asphyxia, abruptio placentae, placenta previa, pre-eclampsia.	501 (study population not specified)	Single test at 20-24 wks. (377 ng/ml)	< 37 (5.2% in sample population)	ST – 0.42 (0.23-0.63) SP – 0.85 (0.81-0.88)

Figure 5


Review: Screening for PTL
Comparison: 12 Cervico vaginal IL-8 levels
Outcome: 01 + LR for IL 8 levels in predicting SPTD
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Sakai 1 38/139 807/4064 87.57 1.38 [1.04, 1.82]
Sakai 2 11/26 73/475 12.43 2.75 [1.68, 4.52]
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control


Review: Screening for PTL
Comparison: 12 Cervico vaginal IL-8 levels
Outcome: 02 - LR of IL 8 levels in predicting SPTD
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Sakai 2 15/26 402/475 16.23 0.68 [0.49, 0.95]
Sakai 1 101/139 3257/4064 83.77 0.91 [0.82, 1.01]
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

Maternal serum alpha fetoprotein levels (MSAFP)

Description of included studies

Three prospective cohort studies were included for this test but there was no blinding in two studies [EL II] where retrospective analysis of data was done. In all studies screening test was performed at 15-20 weeks as part of routine screening for Down's syndrome and neural tube defects. AFP levels $\geq$ 2.0 MoM was the threshold used in 2 studies. In two studies outcome was defined as SPTD $<$ 37 wks while the third looked at SPTD $<$ 32 wks. As studies had different thresholds and outcome, they were not combined and results are presented individually (Table VI)

Findings

The range of ST was from 2 to 19% and for SP from 80 to 99%. The study with the highest level of evidence had poor values for both + LR [0.97 (0.51-1.85)] and – LR [1.01 (0.86-1.17)]. Study by Dugoff et al had a high + LR of 6.80 (4.75-9.74) but the – LR was only 0.91 (0.87-0.95) for outcome less than 32 weeks *(Figure 6)*

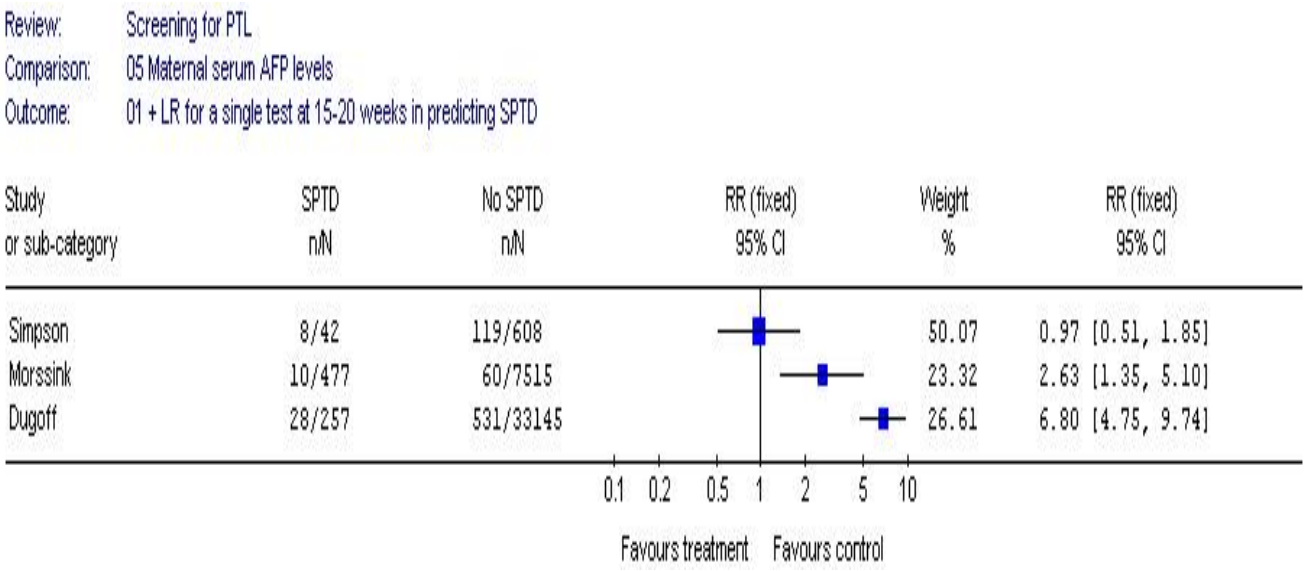
Evidence summary

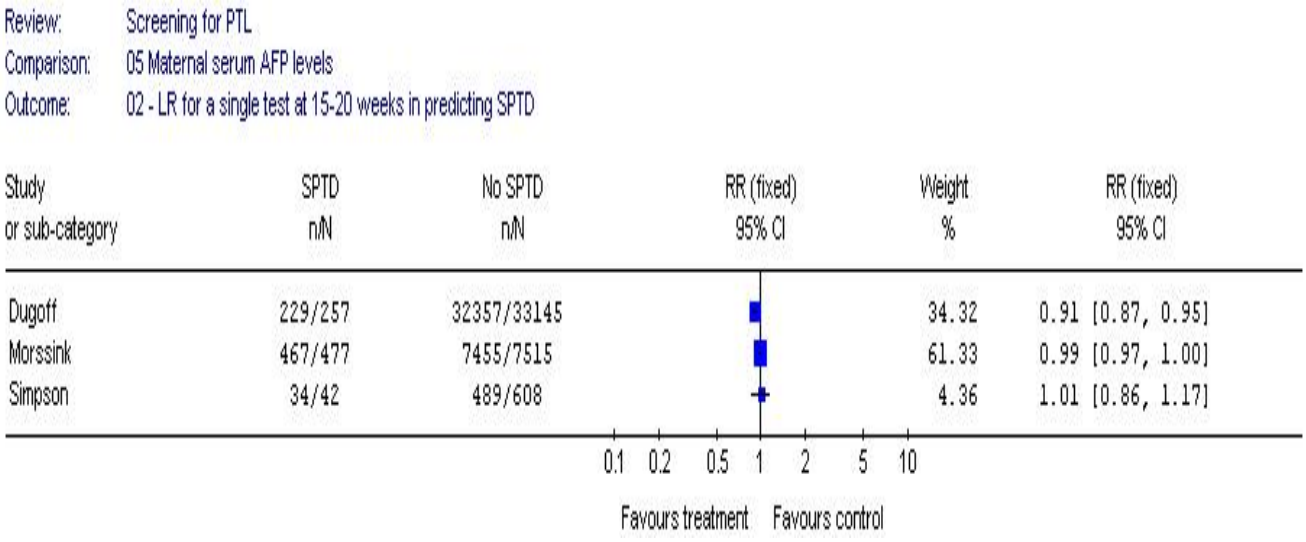
Positive and negative results of MSAFP at 15-20 weeks seem to have poor predictive accuracy for SPTD, though the evidence is limited.

Table VI Characteristics of included studies on diagnostic value of maternal serum AFP levels

Study and EL	***Study characteristics***	***Population characteristics (low or high risk)***	***Sample size (% of study population)***	***Timing of screening test with threshold (prevalence of screen positive)***	***Outcome in wks (incidence of SPTD)***	***Diagnostic value with 95% CI***
Simpson 1995 [898] (USA) EL Ib	Prospective cohort, single center, blinded.	Singleton pregnancies attending regional medical centre who provided both samples. *Exclusions*: multiple gestations, neural tube defects, other malformations(low risk)	650 (86.3)	Testing done twice – at 15-20 wks and 24-36 wks, threshold ≥ 2.0 MoM. (19.5% of sample population)	< 37 (6.5% in sample population)	*For sampling at 15-20 weeks* ST - 0.19 (0.05-0.34) SP – 0.80 (0.77-0.84)
Dugoff 2005 [899] (USA) EL II	Prospective cohort, multi-centre, not blinded (retrospective analysis of data)	Women ≥ 16 yrs age confirmed to have singleton pregnancies between 10-14 wks *Exclusions*: Fetal chromosomal and structural anomalies (low risk)	33145 (98.0)	Single test at 15-19 weeks, threshold ≥ 2.0 MoM (1.7% in sample population)	< 32 (0.77% in sample population)	ST - 0.11 (0.07-0.115) SP - 0.98 (0.98-0.99)
Morssink 1995 [900] (Netherlands) EL II	Prospective cohort, multi-centre, not blinded (retrospective analysis of data)	Singleton pregnancies who underwent screening for Down's or neural tube defects *Exclusions*: pregnancies with diabetes, congenital anomaly, SPTD < 25 weeks	7992 (87.6)	Single test at 15-20 wks, threshold ≥ 2.5 MoM (1.1% of study population)	< 37 but excluding infants with weight < 10^{th} centile (6.0% in sample population)	ST – 0.02 (0.01-0.02) SP – 0.99 (0.99-0.99)

Figure 6


Review: Screening for PTL
Comparison: 05 Maternal serum AFP levels
Outcome: 01 + LR for a single test at 15-20 weeks in predicting SPTD
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Simpson 8/42 119/608 50.07 0.97 [0.51, 1.85]
Morssink 10/477 60/7515 23.32 2.63 [1.35, 5.10]
Dugoff 28/257 531/33145 26.61 6.80 [4.75, 9.74]
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control


Review: Screening for PTL
Comparison: 05 Maternal serum AFP levels
Outcome: 02 - LR for a single test at 15-20 weeks in predicting SPTD
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Dugoff 229/257 32357/33145 34.32 0.91 [0.87, 0.95]
Morssink 467/477 7455/7515 61.33 0.99 [0.97, 1.00]
Simpson 34/42 489/608 4.36 1.01 [0.86, 1.17]
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

Maternal serum beta-human chorionic gonadotrophin levels (MSHCG)

Description of included studies

The three studies included were prospective cohort studies [EL II] without blinding. Data were analyzed retrospectively in two studies. In two studies the screening test was performed in the first trimester, while in the third it was done in the second trimester. The study population was low risk in all. The threshold of a positive test and outcome were different in all studies. (Table VII)

Findings

In the study with the largest sample size (Dugoff et al) carried out in the second trimester for predicting SPTD < 32 weeks, values for ST, SP, + LR and – LR were 17%, 94%, 2.87 (2.18-3.78), and 0.89 (0.84-0.94) respectively. In the other two first trimester studies, wide variation was observed in all the results. ST and SP ranged from 5 to 73% and 21 to 95% respectively. The CI of both the + LR and – LR included value of 1 and gave poor probability for the test results. *(Figure 7)*

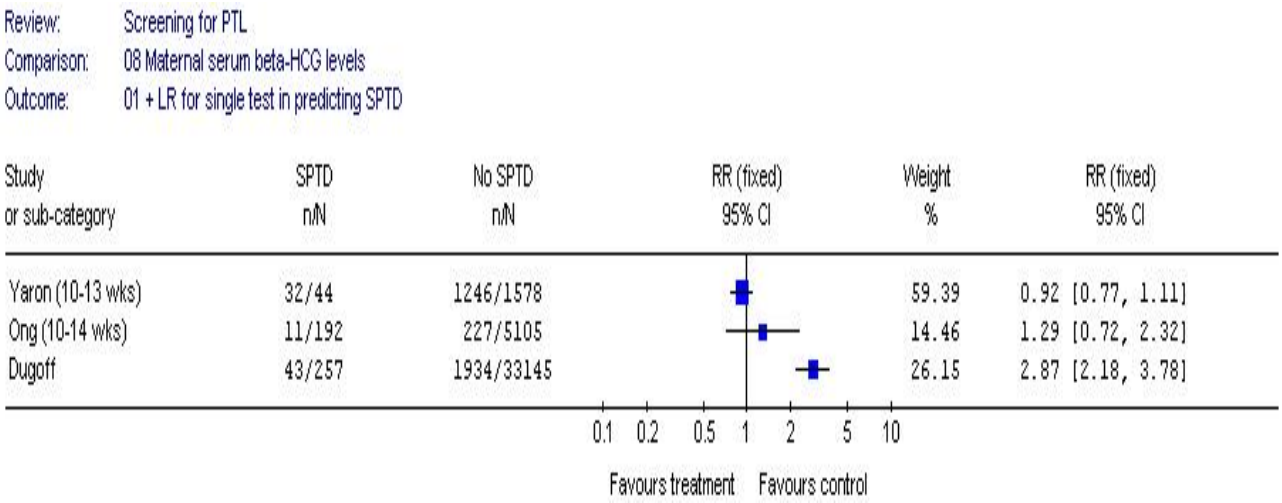
Evidence summary

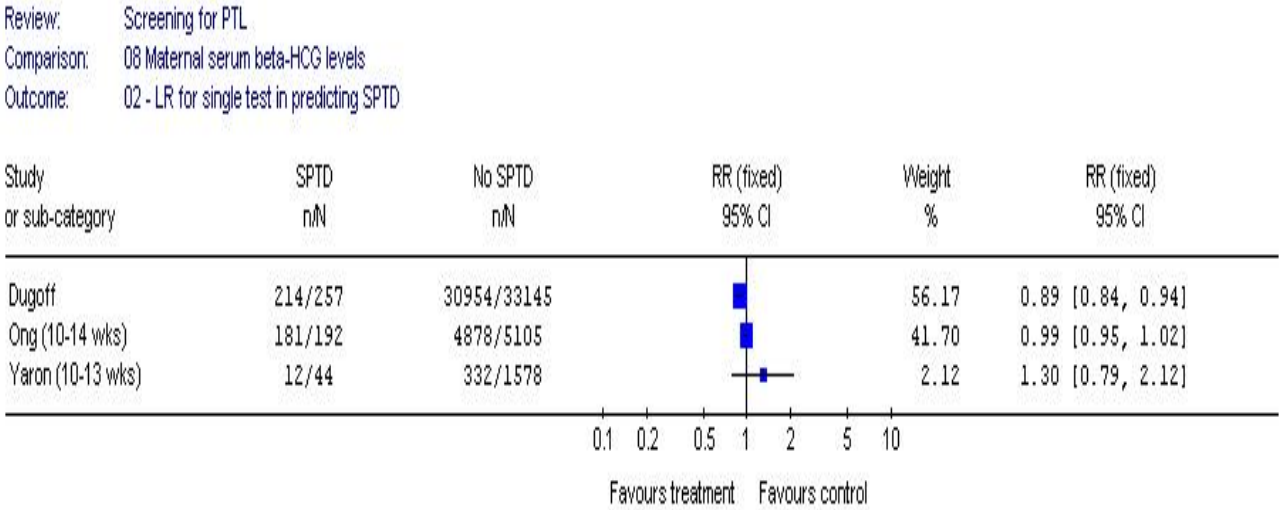
A positive test for a second trimester MSHCG is more useful in predicting SPTD < 32 weeks than a negative test in ruling it out, but the evidence is poor. Screening performance of first trimester MSHCG test is poor.

Table VII Characteristics of included studies on diagnostic value of maternal serum beta-hCG levels

Study and EL	***Study characteristics***	***Population characteristics (low or high risk)***	***Sample size (% of study population)***	***Timing of screening test with threshold (prevalence of test positive)***	***Outcome in wks (incidence of SPTD)***	***Diagnostic value with 95% CI***
Dugoff 2005 [899] (USA) EL II	Prospective cohort, multi-center, not blinded (retrospective analysis of data)	Women ≥ 16 yrs age confirmed to have singleton pregnancies between 10-14 wks *Exclusions*: Fetal chromosomal and structural anomalies (low risk)	33145 (98.0)	Single test at 15-19 wks, threshold ≥ 2.0 MoM (6.0% in sample population)	< 32 (0.77% in sample population)	*For threshold ≥ 2.0 MoM* ST - 0.17 (0.13-0.21) SP - 0.94 (0.94-0.94)
Ong 2000 [901] (UK) EL II	Prospective cohort, two centers, not blinded (retrospective analysis of data)	Singleton pregnancies without fetal & chromosomal anomalies (low risk)	5297 (94.9)	Single test at 10-14 wks, threshold < 5th and 10th centile (4.5% in sample population)	< 37 (3.6%) < 34 (0.9%)	*For threshold < 5th centile* ST – 0.05 (0.02-0.09) SP – 0.95 (0.95-0.96)
Yaron 2002 [902] (Israel) EL II	Prospective cohort, single center, not blinded	Singleton pregnancies undergoing first trimester screening for Down syndrome. *Exclusions*: Fetal and chromosomal anomalies (low risk)	1622 (91.5)	Single test at 10-13 wks, different thresholds - < 1.0, 1.01-2.0, 2.01-3.0, 3.01-4.0, 4.01-5.0, and > 5.01 MoM.	< 37 (2.7% of sample population)	*For threshold ≤ 2.0 MoM* ST – 0.73 (0.60-0.85) SP – 0.21 (0.19-0.23)

Figure 7


Review: Screening for PTL
Comparison: 08 Maternal serum beta-HCG levels
Outcome: 01 + LR for single test in predicting SPTD
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Yaron (10-13 wks) 32/44 1246/1578 59.39 0.92 [0.77, 1.11]
Ong (10-14 wks) 11/192 227/5105 14.46 1.29 [0.72, 2.32]
Dugoff 43/257 1934/33145 26.15 2.87 [2.18, 3.78]
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control


Review: Screening for PTL
Comparison: 08 Maternal serum beta-HCG levels
Outcome: 02 - LR for single test in predicting SPTD
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Dugoff 214/257 30954/33145 56.17 0.89 [0.84, 0.94]
Ong (10-14 wks) 181/192 4878/5105 41.70 0.99 [0.95, 1.02]
Yaron (10-13 wks) 12/44 332/1578 2.12 1.30 [0.79, 2.12]
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

Maternal serum CRP levels

Description of included studies

Two nested case-control studies without blinding [EL III] were identified. One study was conducted in the first trimester and used CRP levels greater than 4.3 ng/ml as the threshold for a positive test, while the other carried out in the second trimester used 7.6 ng/ml as the cut-off. Both evaluated SPTD < 37 weeks as outcome (Table VIII).

Findings

The first trimester study showed ST of 35% and SP of 78%. LR for a positive test was 1.55 (1.12-2.13) and that for a negative test was 0.84 (0.73-0.98). In the second trimester study ST and SP was 26 and 86%, and values for + LR and – LR were 1.81 (1.12-2.13) and 0.86 (0.76-0.99) respectively (Figure 8).

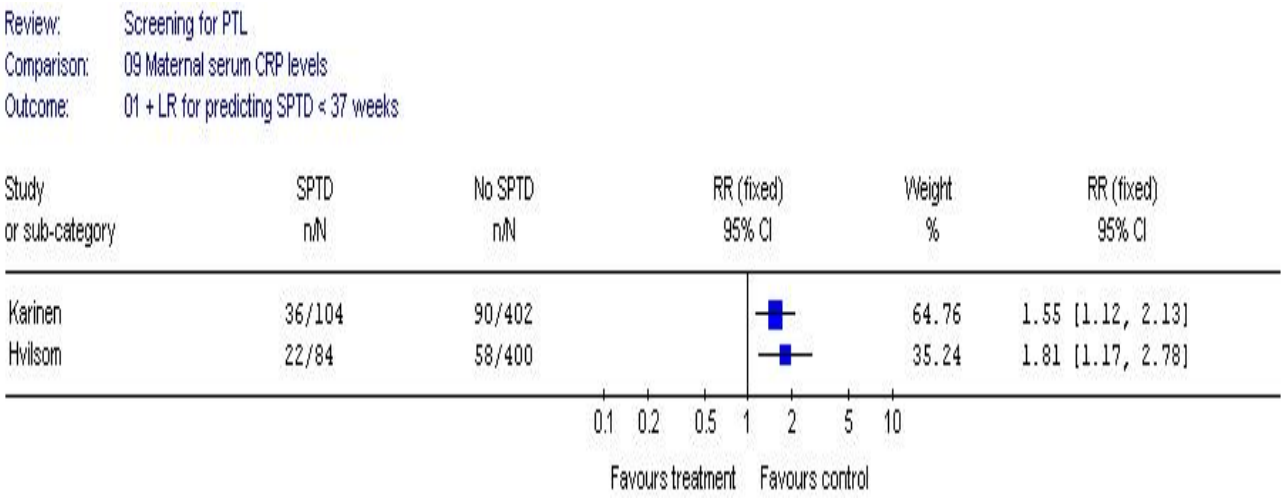
Evidence summary

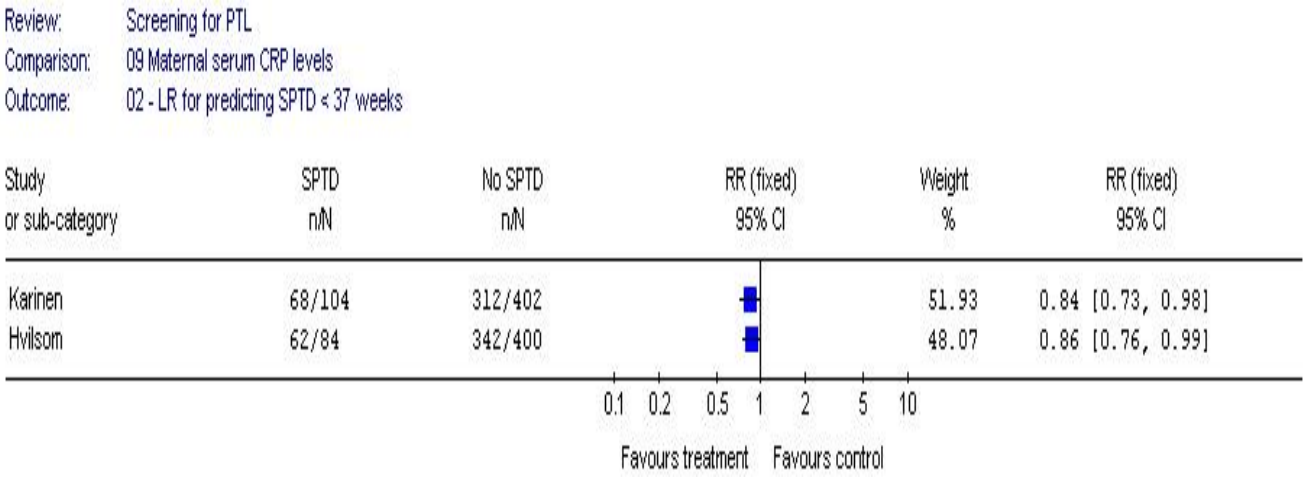
There is lack of good quality studies on the diagnostic value of maternal serum CRP levels. Evidence from level 3 studies shows that positive and negative results of maternal serum CRP have poor predictive accuracy for SPTD < 37 weeks.

Table VIII Characteristics of included studies on diagnostic value of maternal serum CRP levels

Study and EL	***Study characteristics***	***Population characteristics***	***Sample size (% of study population)***	***Timing of screening test with threshold***	***Outcome in wks***	***Diagnostic value (95% CI)***
Hvilsom 2002 [903] (Denmark) EL III	Nested case-control study, single center, not blinded.	*Cases*: women having idiopathic SPTD < 37 weeks. *Controls*: randomly selected women who had term delivery	484 (84 cases, 400 controls) from a cohort of 2846 singleton pregnancies	Single test at 14-19 wks (median 16.3 wks). Threshold 7.6 ng/ml	< 37	ST – 0.26 (0.17-0.36) SP – 0.86 (0.82-0.89)
Karinen 2005 [904] (Finland) EL III	Nested case-control study, from population based birth cohort, not blinded	*Cases*: women having idiopathic SPTD < 37 weeks *Controls*: randomly selected women who had term delivery matched on age and parity	506 (104 cases, 402 controls) from a cohort of 2309 singleton pregnancies.	Single test in first trimester (mean age 10.4 wks) Threshold - 4.3 ng/ml	< 37	ST – 0.35 (0.26-0.45) SP – 0.78 (0.73-0.82)

Figure 8


Review: Screening for PTL
Comparison: 09 Maternal serum CRP levels
Outcome: 01 + LR for predicting SPTD < 37 weeks
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Karinen 36/104 90/402 64.76 1.55 [1.12, 2.13]
Hvilsom 22/84 58/400 35.24 1.81 [1.17, 2.78]
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control


Review: Screening for PTL
Comparison: 09 Maternal serum CRP levels
Outcome: 02 - LR for predicting SPTD < 37 weeks
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Karinen 68/104 312/402 51.93 0.84 [0.73, 0.98]
Hvilsom 62/84 342/400 48.07 0.86 [0.76, 0.99]
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

Asymptomatic bacteriuria

Description of included studies

All the four prospective cohort studies with [EL II] included for this test did not specify blinding as a study criterion. Three of these studies were conducted in the 1960's. All of them used culture of mid-stream urine sample (MSU) as the screening test, and in two studies it was repeated after the first positive test to confirm asymptomatic bacteriuria. Outcome evaluated was SPTD < 37 weeks in all. In two studies the sample size was very small compared to the study population as treatment was started later during the study and that population was excluded. Meta-analysis was performed to calculate summary LR's for a positive and negative test taking results from the firstly performed urine analysis only where possible. (Table IX)

Findings

ST ranged from 7 to 30% and SP from 65 to 97%. Statistically no significant heterogeneity was observed for both the + LR and the – LR. The summary value of LR for a positive test was 1.97 (1.45-2.68) and the range in individual studies was from 0.89 to 2.63. LR for a negative test result had a summary value of 0.46 (0.31-0.67) and range of 1.19 to 0.31 *(Figure 9)*

Evidence summary

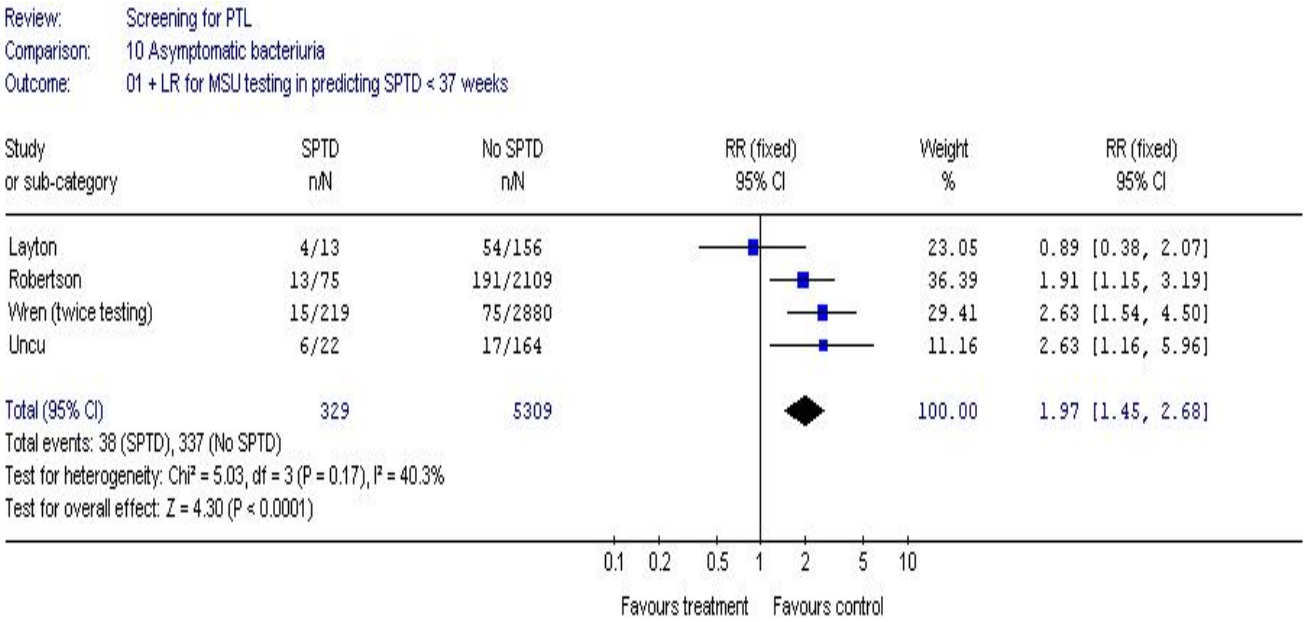
A negative result of a MSU sample for asymptomatic bacteriuria has good diagnostic value in ruling out SPTD < 37 weeks compared to a positive result for predicting it, but the evidence is not of high quality.

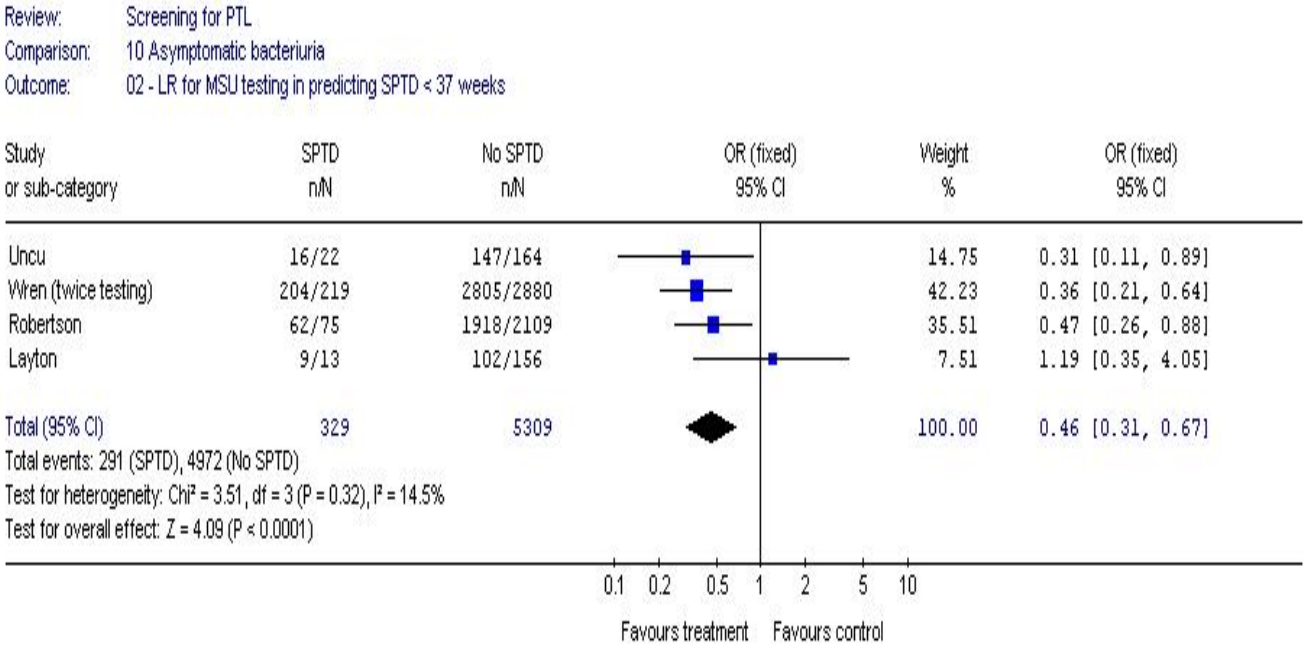
Table IX Characteristics of included studies on diagnostic value of asymptomatic bacteriuria by MSU

Study and EL	***Study characteristics***	***Population characteristics (low or high risk)***	***Sample size (% of study population)***	***Timing and site of screening test (prevalence of test positive)***	***Outcome in wks (incidence of SPTD)***	***Diagnostic value with 95% CI***
Wren 1969 [905] (Australia) EL II	Prospective cohort, single centre, not blinded.	All pregnant women booking at antenatal clinic. *Exclusions*: twin pregnancies, women who moved hospital (both low & high risk)	3009 (83.5) This is after excluding women who were treated.	MSU at first booking visit, repeated if positive. (4.9% in study population for both positive test)	< 37 (7.1% in sample population)	*For both test positive* ST – 0.07 (0.04-0.11) SP – 0.97 (0.97-0.98)
Robertson 1968 [906] (UK) EL II	Prospective cohort, single center, not blinded.	All pregnant women attending the booking antenatal clinic *Exclusions*: twin pregnancies, abortions, symptomatic at first visit, women who moved hospital. (both low & high risk)	2184 (26.4) Later in the study women were given treatment, hence small sample for untreated.	Single MSU at booking visit. (6.2% in study population)	< 36 (3.4% in sample population)	ST – 0.17 (0.08-0.26) SP – 0.91 (0.90-0.92)
Uncu 2001 [907] (Turkey) EL II	Prospective cohort, single centre, not blinded.	All pregnant women < 32 weeks seen at outpatient ANC clinic. *Exclusions*: existing renal disease or bacteriuria, on antibiotics.	186 (68.9)	Single MSU at < 32 wks (9.3% in study population)	< 37 (11.8% in sample population)	ST – 0.27 (0.09-0.46) SP – 0.90 (0.86-0.95)

Layton 1964 [908] (UK) EL II	Prospective cohort, single centre, not blinded	All pregnant women attending antenatal clinic < 32 weeks	169 (??)	MSU at < 32 weeks, repeated if positive. (8.8% in sample population)	< 37 (7.7% in sample population)	ST - 0.30 (0.05-0.55) SP – 0.65 (0.58-0.73)

Figure 9


Review: Screening for PTL
Comparison: 10 Asymptomatic bacteriuria
Outcome: 01 + LR for MSU testing in predicting SPTD < 37 weeks
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Layton 4/13 54/156 23.05 0.89 [0.38, 2.07]
Robertson 13/75 191/2109 36.39 1.91 [1.15, 3.19]
Wren (twice testing) 15/219 75/2880 29.41 2.63 [1.54, 4.50]
Uncu 6/22 17/164 11.16 2.63 [1.16, 5.96]
Total (95% CI) 329 5309 100.00 1.97 [1.45, 2.68]
Total events: 38 (SPTD), 337 (No SPTD)
Test for heterogeneity: Chi² = 5.03, df = 3 (P = 0.17), I² = 40.3%
Test for overall effect: Z = 4.30 (P < 0.0001)
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control


Review: Screening for PTL
Comparison: 10 Asymptomatic bacteriuria
Outcome: 02 - LR for MSU testing in predicting SPTD < 37 weeks
Study or sub-category
SPTD n/N
No SPTD n/N
OR (fixed) 95% CI
Weight %
OR (fixed) 95% CI
Uncu 16/22 147/164 14.75 0.31 [0.11, 0.89]
Wren (twice testing) 204/219 2805/2880 42.23 0.36 [0.21, 0.64]
Robertson 62/75 1918/2109 35.51 0.47 [0.26, 0.88]
Layton 9/13 102/156 7.51 1.19 [0.35, 4.05]
Total (95% CI) 329 5309 100.00 0.46 [0.31, 0.67]
Total events: 291 (SPTD), 4972 (No SPTD)
Test for heterogeneity: Chi² = 3.51, df = 3 (P = 0.32), I² = 14.5%
Test for overall effect: Z = 4.09 (P < 0.0001)
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

Bacterial vaginosis (BV)

Description of included studies

Five studies were included – all prospective cohort studies with [EL Ib] and two were conducted in more than 1 centre. The study population was low risk in 4 studies and risk status was not specified in the last study. In all studies swab (usually single) was taken from the posterior vaginal fornix in the late first or second trimester, and Gram staining with Nugent's criterion used to diagnose BV. In one study (Hillier et al) results were calculated only for those women who did not receive antibiotics. All the studies used SPTD < 37 weeks as the outcome. Meta-analysis was performed for LR of a single test in second trimester for predicting SPTD < 37 weeks (Table X)

Review findings

In the studies, BV had a ST ranging from 15 to 44% and SP from 76 to 93% respectively. For the LR's of individual studies, Purwar et al had the best results. It had a high + LR value of 5.31 (3.84-7.33) and a low – LR of 0.54 (0.42-0.71). When the results of all the included studies were combined, significant statistical heterogeneity was observed for both + LR and – LR, and the summary values obtained were not as good as those for individual studies. Summary + LR was 1.70 (1.49-1.94) and summary – LR was 0.88 (0.85-0.92) *(Figure 10)*

Evidence summary

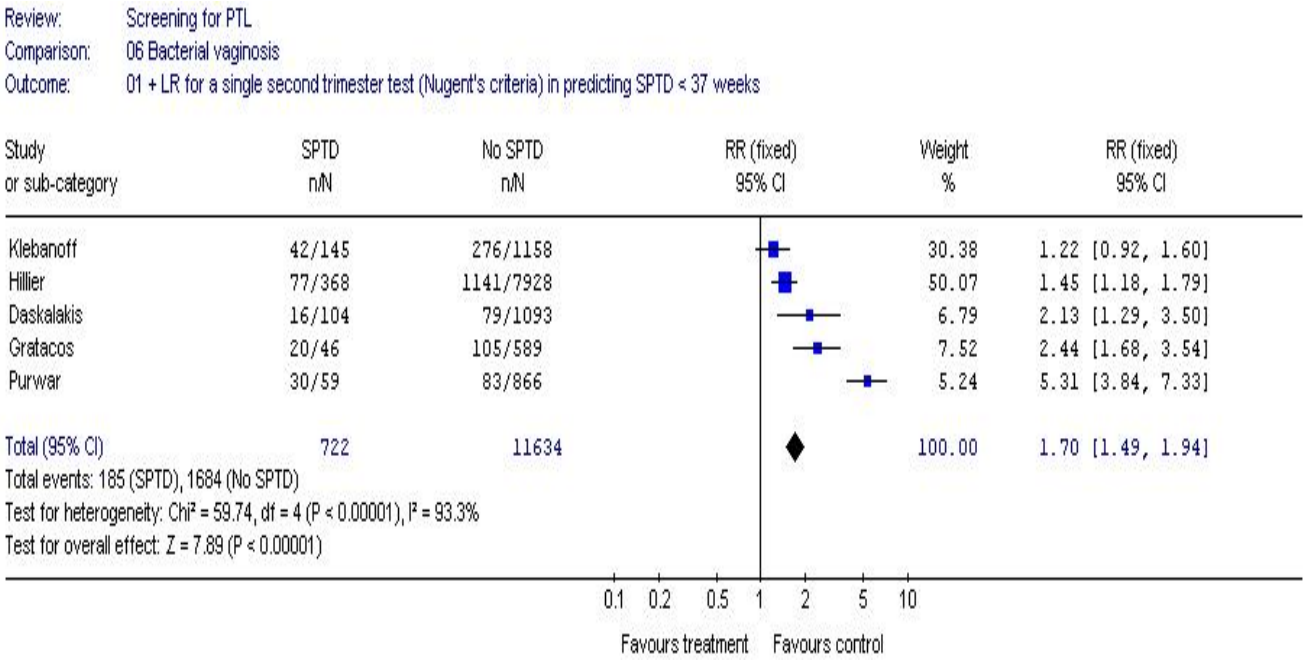
There is high quality evidence that a single second trimester vaginal swab for BV (using Nugent's criterion on Gram staining) has poor diagnostic value as a screening test for SPTD < 37 weeks.

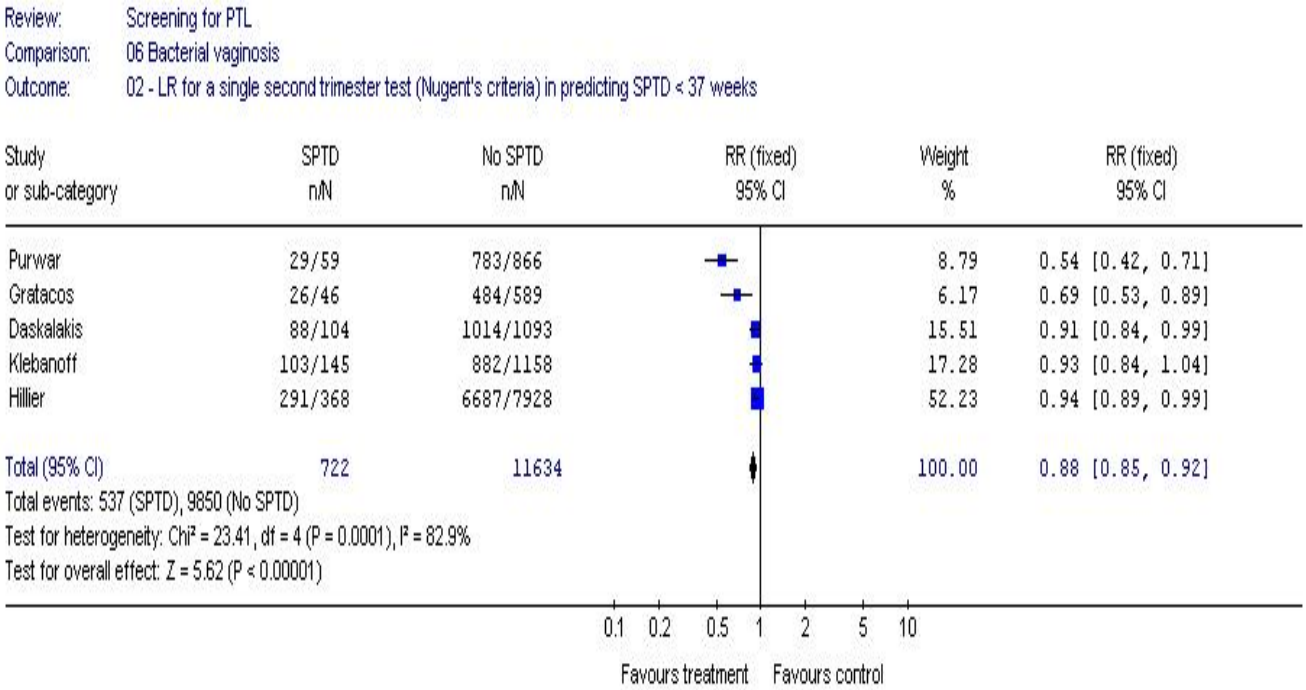
Table X Characteristics of included studies on diagnostic value of Gram staining (Nugent's criteria) for bacterial vaginosis

Study and EL	***Study characteristics***	***Population characteristics (low or high risk)***	***Sample size (% of study population)***	***Timing and site of screening test (prevalence of BV)***	***Outcome in wks (incidence of SPTD)***	***Diagnostic value with 95% CI***
Klebanoff 2005 [909] (USA) EL Ib	Prospective cohort, multi-centre, blinded.	Pregnant women with no major medical or obstetric complications, no symptoms of UTI, and not received any antibiotics within past 14 days. (Low risk)	12937 (81.5)	Single vaginal swab at < 13, 13-14, 15-16, 17-18, 19-20, or 21-22 wks. (34.4% in study population)	< 37 (11.4%)	*For vaginal swab at 21-22 weeks* ST – 0.28 (0.21-0.35) SP – 0.76 (0.74-0.78)
Hillier 1995 [910] (USA) EL Ib	Prospective cohort, multi-center, blinded.	Singleton pregnancies during routine prenatal visits after 23-26 wks. (Low risk)	10397 (74.7)	Single posterior fornix swab at 23-26 weeks (16% in study population)	< 37 and birth-weight < 2500 gms (4.8%)	*For women who did not receive antibiotics (N=8196)* ST – 0.21 (0.17-0.25) SP – 0.84 (0.83-0.85)
Purwar 2001 [911] (India) EL Ib	Prospective cohort, single centre, blinded.	Randomly selected asymptomatic singleton pregnancies without vaginal discharge. (Low risk)	938 (93.2)	Single vaginal swab at 16-28 wks (11.5% in study population)	< 37 (7.7% for PTD, 6.3% for SPTD)	*For SPTD* ST – 0.44 (0.33-0.55) SP – 0.90 (0.88-0.92)

Daskalakis 2006 [891] (Greece) EL Ib	Prospective cohort, single centre, blinded	Singleton pregnancies having anomaly scan at 22-25 weeks (Low risk)	1197 (93.0)	Single vaginal swab at 22-25 weeks (7.9% in sample population)	< 37 (8.7%)	ST - 0.15 (0.08-0.22) SP – 0.93 (0.91-0.94)
Gratacos 1998[358] (Spain) EL Ib	Prospective cohort, single centre, blinded	Singleton pregnancies at hospital clinic < 35 wks (risk not specified)	635 (92.3)	Twice sampling from posterior fornix - at < 24 and < 35 weeks. (19.6% in study population)	< 37 (7.2%)	*For sampling < 24 weeks* ST – 0.43 (0.29-0.57) SP – 0.82 (0.79-0.85)

Figure 10


Review: Screening for PTL
Comparison: 06 Bacterial vaginosis
Outcome: 01 + LR for a single second trimester test (Nugent's criteria) in predicting SPTD < 37 weeks
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Klebanoff 42/145 276/1158 30.38 1.22 [0.92, 1.60]
Hillier 77/368 1141/7928 50.07 1.45 [1.18, 1.79]
Daskalakis 16/104 79/1093 6.79 2.13 [1.29, 3.50]
Gratacos 20/46 105/589 7.52 2.44 [1.68, 3.54]
Purwar 30/59 83/866 5.24 5.31 [3.84, 7.33]
Total (95% CI) 722 11634 100.00 1.70 [1.49, 1.94]
Total events: 185 (SPTD), 1684 (No SPTD)
Test for heterogeneity: Chi² = 59.74, df = 4 (P < 0.00001), I² = 93.3%
Test for overall effect: Z = 7.89 (P < 0.00001)
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control


Review: Screening for PTL
Comparison: 06 Bacterial vaginosis
Outcome: 02 - LR for a single second trimester test (Nugent's criteria) in predicting SPTD < 37 weeks
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Purwar 29/59 783/866 8.79 0.54 [0.42, 0.71]
Gratacos 26/46 484/589 6.17 0.69 [0.53, 0.89]
Daskalakis 88/104 1014/1093 15.51 0.91 [0.84, 0.99]
Klebanoff 103/145 882/1158 17.28 0.93 [0.84, 1.04]
Hillier 291/368 6687/7928 52.23 0.94 [0.89, 0.99]
Total (95% CI) 722 11634 100.00 0.88 [0.85, 0.92]
Total events: 537 (SPTD), 9850 (No SPTD)
Test for heterogeneity: Chi² = 23.41, df = 4 (P = 0.0001), I² = 82.9%
Test for overall effect: Z = 5.62 (P < 0.00001)
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

Transvaginal sonography (TVS) for cervical length

Description of included studies

Of the five prospective cohort studies included for reviewing this test, four have [EL Ib] and one [EL II] because blinding was not a study criterion. In three studies the population was made up of both low and high risk pregnant women, while the other two studies had only a low risk population. TVS for measuring cervical length was carried out in all studies in the second trimester. The critical length used for labelling a cervix as 'short' was calculated by ROC curve in two studies, while in others the length varied. However all studies use a cervical length of $\leq$ 20 or 25 mm, and this length was used to conduct the meta-analysis. Outcome evaluated was SPTD $<$ 37 weeks for all but one study which assessed SPTD $<$ 34 weeks (Table XI)

Findings

ST ranged from 5 to 26% and SP from 93 to 100%. Fukami et al had the best LR's for a positive and negative test results compared to other studies, but it was a study with [EL 2]. Its LR for a positive test was 34.34 (16.18-72.88) and for a negative test was 0.51 (0.25-1.01). On conducting meta-analysis of studies using data for common thresholds, significant statistical heterogeneity was observed for both + LR and – LR. Summary LR for a positive test was 3.84 (3.12-4.17) and for a negative test was 0.85 (0.82-0.89) *(Figure 11)*

Evidence summary

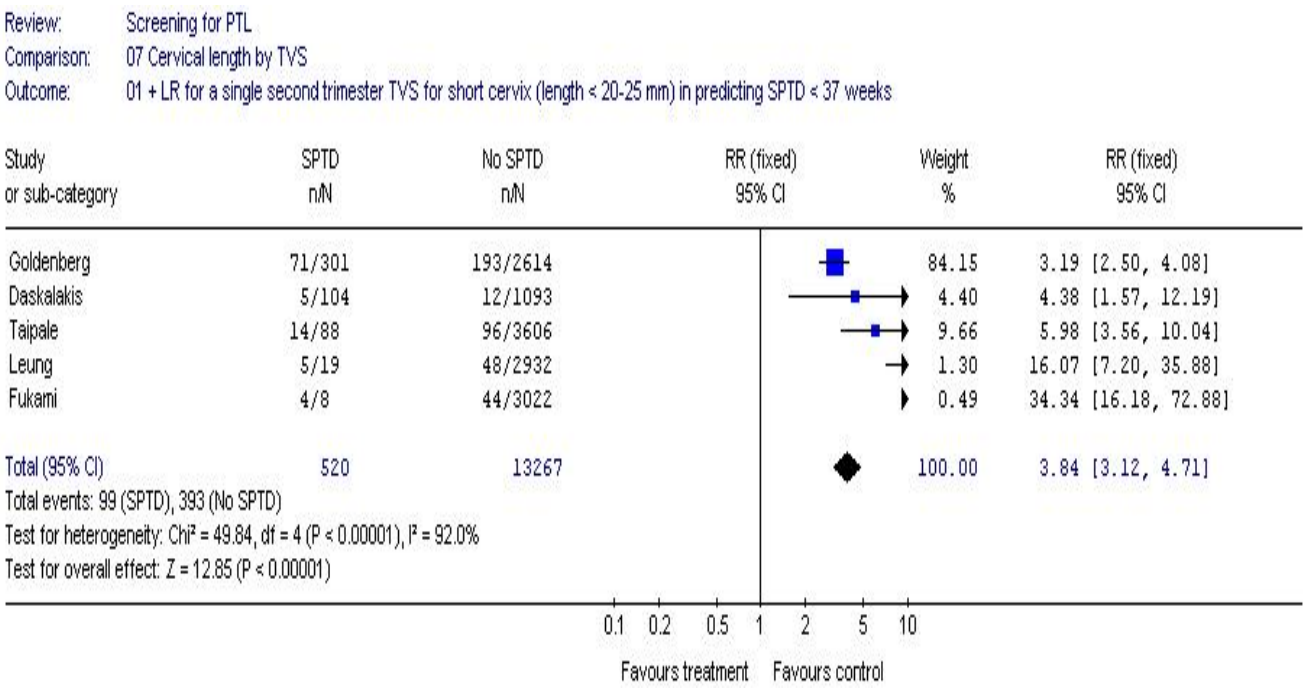
High quality evidence shows that a shortened cervix (length $\leq$ 25 mm) on TVS in the second trimester increases the likelihood of SPTD $<$ 37 weeks by a moderate value, but a cervical length of greater than 2.5 cm is poor at ruling it out.

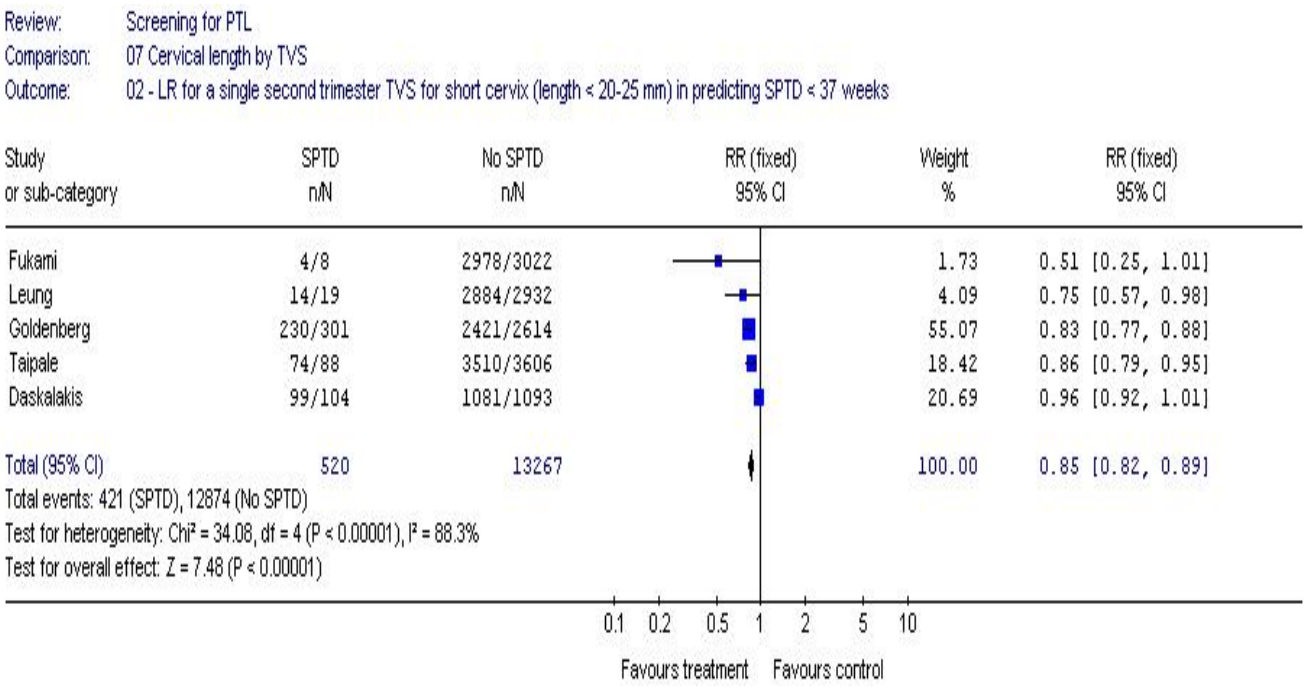
Table XI Characteristics of included studies on diagnostic value of cervical length by TVS

Study and EL	***Study characteristics***	***Population characteristics (low or high risk)***	***Sample size (% of study population)***	***Timing of screening test with threshold in mm (prevalence of test positive)***	***Outcome in wks (incidence of SPTD)***	***Diagnostic value with 95% CI***
Taipale 1998 [912] (Finland) EL Ib	Prospective cohort, single centre, blinded	Singleton pregnancies at 18-22 weeks for routine US anomaly scan. *Exclusions*: fetal anomalies, induced PTB, length of gestation beyond pre-specified limits. (low & high risk)	3694 (87.8)	Single TVS at 18-22 wks, Different thresholds but ≤ 29 mm best from ROC curve of study findings (3.0% in sample population)	< 37 (2.4% in sample population)	*Threshold ≤ 29 mm* ST – 0.16 (0.09-0.25) SP – 0.97 (0.97-0.98) *Threshold ≤ 25 mm* ST – 0.06 (0.02-0.13) SP – 1.00 (0.99-1.00)
Leung 2005 [913] (Hong Kong) EL Ib	Prospective cohort, single centre, blinded	Ethnic Chinese women with singleton pregnancies at 18-22 weeks *Exclusions*: fetal anomalies (both low & high risk)	2880 (97.6)	Single TVS at 18-22 wks. Different thresholds but ≤ 27 mm best from ROC curve of study findings	< 34 (0.7% in sample population)	*Threshold ≤ 27 mm* ST – 0.37 (0.15-0.58) SP – 0.96 (0.95-0.97) *Threshold ≤ 25 mm* ST – 0.26 (0.06-0.46) SP – 0.98 (0.98-0.99)
Goldenberg 1998 [880] (USA) EL Ib	Prospective cohort, multi-center, blinded	Singleton pregnancies. *Exclusions*: multiple gestations, cervical cerclage, placenta previa, fetal anomaly. (both low & high risk)	2929 (95.3)	Single TVS at 24 and 28 weeks Threshold ≤ 25, 26-35, > 35 mm.	< 32 < 35 < 37 (10.3%)	*For SPTD < 37 weeks and threshold ≤ 25 mm* ST – 0.24 (0.19-0.28) SP – 0.93 (0.92-0.94)

Daskalakis 2006 [891] (Greece) EL Ib	Prospective cohort, single center, blinded.	Singleton pregnancies having anomaly scan at 22-25 weeks *Exclusions*: H/O previous SPTB or abortion, fetus with anomalies, placenta previa, cervical cerclage or incompetence. (low risk)	1197 (93.0)	Single TVS at 22 to 25 weeks Threshold < 20 mm (1.4% in sample population)	< 37 (8.7% in sample population)	ST – 0.05 (0.01-0.09) SP – 0.99 (0.98-0.99)
Fukami 2003 [914] (Japan) EL II	Prospective cohort, single center, not blinded	Singleton pregnancies scanned between 16-19 weeks. *Exclusions*: chronic medical or obstetric problems that might lead to PTB, uterine or fetal anomalies, cervical cerclage. (low risk)	3030 (90.0)	Single TVS at 16 to 19 weeks Threshold ≤ 30 mm (1.6% in sample population)	< 32 and 32-36 weeks (2.9% in sample population)	*For 32-36 weeks outcome* ST – 0.18 (0.10-0.26) SP – 0.99 (0.99-0.99)

Figure 11


Review: Screening for PTL
Comparison: 07 Cervical length by TVS
Outcome: 01 + LR for a single second trimester TVS for short cervix (length < 20-25 mm) in predicting SPTD < 37 weeks
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Goldenberg 71/301 193/2614 84.15 3.19 [2.50, 4.08]
Daskalakis 5/104 12/1093 4.40 4.38 [1.57, 12.19]
Taipale 14/88 96/3606 9.66 5.98 [3.56, 10.04]
Leung 5/19 48/2932 1.30 16.07 [7.20, 35.88]
Fukami 4/8 44/3022 0.49 34.34 [16.18, 72.88]
Total (95% CI) 520 13267 100.00 3.84 [3.12, 4.71]
Total events: 99 (SPTD), 393 (No SPTD)
Test for heterogeneity: Chi² = 49.84, df = 4 (P < 0.00001), I² = 92.0%
Test for overall effect: Z = 12.85 (P < 0.00001)
0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control


Review: Screening for PTL
Comparison: 07 Cervical length by TVS
Outcome: 02 - LR for a single second trimester TVS for short cervix (length < 20-25 mm) in predicting SPTD < 37 weeks
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Fukami 4/8 2978/3022 1.73 0.51 [0.25, 1.01]
Leung 14/19 2884/2932 4.09 0.75 [0.57, 0.98]
Goldenberg 230/301 2421/2614 55.07 0.83 [0.77, 0.88]
Taipale 74/88 3510/3606 18.42 0.86 [0.79, 0.95]
Daskalakis 99/104 1081/1093 20.69 0.96 [0.92, 1.01]
Total (95% CI) 520 13267 100.00 0.85 [0.82, 0.89]
Total events: 421 (SPTD), 12874 (No SPTD)
Test for heterogeneity: Chi² = 34.08, df = 4 (P < 0.00001), I² = 88.3%
Test for overall effect: Z = 7.48 (P < 0.00001)
0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

Funnelling by TVS

Description of included studies

All the included studies were prospective cohorts (three with [EL Ib], one with [EL II]). Population was low risk in one study, both low and high risk in two studies, and not specified in the fourth one. TVS was carried out in all studies in the second trimester, but different thresholds were used to define 'funnelling'. Outcome evaluated was not the same in all studies. Due to heterogeneity in thresholds and outcome, meta-analysis was not performed (Table XII).

Findings

For the EL Ib studies, ST ranged from 9 to 32% and SP from 94 to 96%. The only study with EL 2 had a ST of 27% and SP of 97% respectively. On calculating the LR for a positive and negative test results, all the studies showed better results for + LR compared to – LR. Among EL 1 studies, Leung et al had the best results. It had a + LR of 5.32 (2.70-10.48) and – LR of 0.73 (0.54-0.99). The other two studies with EL 1 had a lower + LR and higher – LR value than the Leung study. In To et al study (EL 2), values for + LR and – LR were 7.91 (5.11-12.27) and 0.75 (0.65-0.88) respectively (Figure 12).

Evidence summary

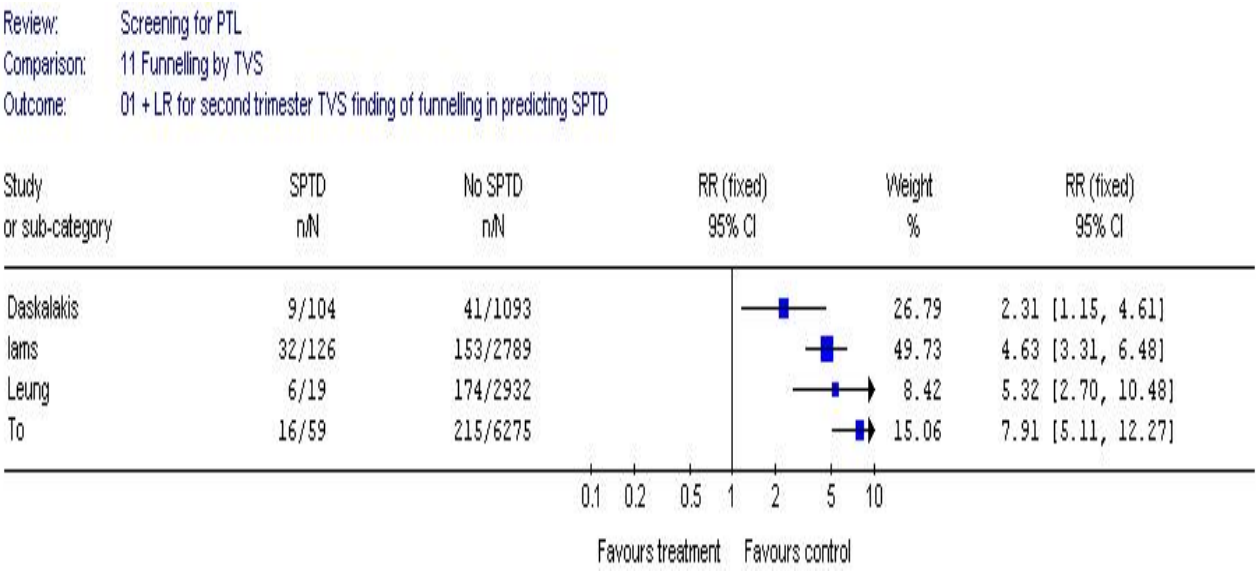
Funnelling detected by TVS in the second trimester seems to have moderate diagnostic value in predicting SPTD, but interpretation of the evidence is made difficult by variation in thresholds and outcome.

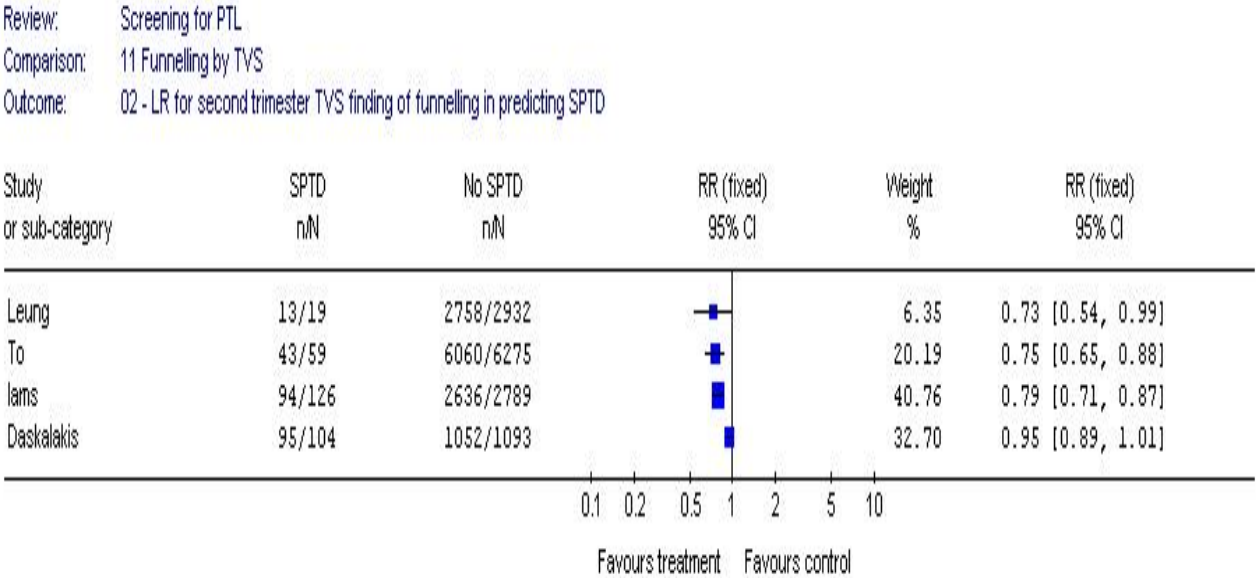
Table XII Characteristics of included studies on diagnostic value of cervical funnelling by TVS

Study and EL	***Study characteristics***	***Population characteristics (low or high risk)***	***Sample size (% of study population)***	***Timing of screening test with threshold in mm (prevalence of test positive)***	***Outcome in wks (incidence of SPTD)***	***Diagnostic value with 95% CI***
Leung 2005 [913] (Hong Kong) EL Ib	Prospective cohort, single center, blinded.	Ethnic Chinese women with singleton pregnancies at 18-22 weeks *Exclusions*: fetal anomalies (both low & high risk)	2880 (97.6)	Single TVS at 18-22 wks. Threshold - protrusion of amniotic memb. length > 5mm into the cervical canal.	< 34 (0.7% in sample population)	ST – 0.32 (0.11-0.52) SP – 0.94 (0.93-0.95)
Iams 1996[543] (USA) EL Ib	Prospective cohort, multi-centre, blinded	Singleton pregnancies. *Exclusions*: multiple gestations, cervical cerclage, placenta previa, fetal anomaly. (both low & high risk)	2915 (94.8) for 24 wks visit, 2531 (82.4) for 28 wks visit	Twice testing - at 24 and 28 weeks Threshold - protrusion of amniotic memb. length > 3mm into internal cervical os.	< 35 (4.3% in sample examined at 24 weeks)	*For testing at 24 weeks* ST – 0.25 (0.18-0.33) SP – 0.94 (0.94-0.95)
Daskalakis 2006 [891] (Greece) EL Ib	Prospective cohort, single center, blinded.	Singleton pregnancies having anomaly scan at 22-25 weeks *Exclusions*: H/O previous SPTB or abortion, fetus with anomalies, placenta previa, cervical cerclage or incompetence. (low risk)	1197 (93.0)	Single TVS at 22 to 25 weeks Threshold not defined	< 37 (8.7% in sample population)	ST – 0.09 (0.03-0.14) SP – 0.96 (0.95-0.97)

To 2001 [915] (UK) EL II	Prospective cohort, single center, not blinded.	Singleton pregnancies attending for routine ANC and undergoing 22-24 week cervical assessment using ultrasound scan. Exclusions: not described	6334 (92.9)	Single TVS at 22-24 weeks. Threshold – dilatation of internal os $\geq$ 5 mm in width. (4.3% of sample population)	< 33 (0.9% in sample population)	ST – 0.27 (0.16-0.39) SP – 0.97 (0.96-0.98)

Figure 12


Review: Screening for PTL
Comparison: 11 Funnelling by TVS
Outcome: 01 + LR for second trimester TVS finding of funnelling in predicting SPTD
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Daskalakis 9/104 41/1093 26.79 2.31 [1.15, 4.61]
Iams 32/126 153/2789 49.73 4.63 [3.31, 6.48]
Leung 6/19 174/2932 8.42 5.32 [2.70, 10.48]
To 16/59 215/6275 15.06 7.91 [5.11, 12.27]
0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control


Review: Screening for PTL
Comparison: 11 Funnelling by TVS
Outcome: 02 - LR for second trimester TVS finding of funnelling in predicting SPTD
Study or sub-category
SPTD n/N
No SPTD n/N
RR (fixed) 95% CI
Weight %
RR (fixed) 95% CI
Leung 13/19 2758/2932 6.35 0.73 [0.54, 0.99]
To 43/59 6060/6275 20.19 0.75 [0.65, 0.88]
Iams 94/126 2636/2789 40.76 0.79 [0.71, 0.87]
Daskalakis 95/104 1052/1093 32.70 0.95 [0.89, 1.01]
0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

GDG interpretation of evidence

The evidence does not justify the routine screening of low risk women for pre-term labour with, clinical examination, asymptomatic bacteriuria, vaginal swabs or ultrasound to assess cervical change. The evidence shows possible moderate specificity but very poor sensitivity.

Recommendation

Routine screening of low risk women for preterm labour should not be offered.

Research recommendation

There is need for future research investigating the value of transvaginal ultrasound to measure cervical length and funnelling to identify women at risk of preterm labor.

11.4 Placenta praevia

Placenta praevia occurs when the placenta covers the internal os and obstructs vaginal delivery of the fetus. A higher rate of pregnancy complications, including abruption placenta, antepartum haemorrhage and intrauterine growth restriction has been reported in women with low-lying placentas identified in the second trimester, despite apparent 'resolution' by the time of delivery.[547] [Evidence level 3]

Evaluation of transvaginal sonography for placental localisation has been shown to be safe in observational studies[599–550] [Evidence level 3] and more accurate than transabdominal sonography in one RCT.[551] [Evidence level 1b] Reported sensitivities range from 88% to 100% and false positives and false negatives are rare.[549,552] [Evidence level 3]

Using ultrasonography, placenta praevia may be detected early in pregnancy. However, many placentas that appear to cover the cervical os in the second trimester will not cover the os at term. In one cohort study (n = 6428 women), 4.5% of women were identified with a placenta extending over the internal os at 12 to 16 weeks of gestation with transvaginal sonographic screening and only 0.16% (10/6428) of these women had placenta praevia at birth. Eight of the ten women with placenta praevia had been identified prior to delivery and, in all eight of these women, the placenta extended 15 mm or more over the internal os at the initial scan.[553] [Evidence level 2b]

In another cohort study, among women scanned transvaginally at 18 to 23 weeks of gestation (n = 3696 women), 1.5% had a placenta extending over the internal os.[554] At delivery, 0.14% of women had placenta praevia and, again, the placenta covered the internal os by 15 mm or more at the time of the first scan for all five of the women. With a cutoff of 15 mm, 0.7% (27/3696) of women would have screened 'positive' and all five cases of praevia at delivery would have been identified (i.e., positive predictive value 19% and sensitivity100%). [Evidence level 2b]

Similarly, a cross-sectional study which examined 1252 women who underwent ultrasound examination from 9 to 13 weeks of gestation found that although 6.2% (77/1252) of women had a placenta extending over the internal cervical os at initial examination, only 0.32% (4/1252) of the cases persisted to delivery.[555] In all four cases, the edge of the placenta extended over the os by more than 15 mm during the first-trimester ultrasound examination. [Evidence level 3]

With regard to gestational age at the time of detection, later detection appears to be related to likelihood of persisting until delivery. A retrospective study demonstrated that, among women with placenta praevia at 15 to 19 weeks of gestation, 12% persisted until delivery compared with 73% among women in whom placenta praevia was identified at 32 to 35 weeks of gestation.[556] [Evidence level 3]

Symptomatic placenta praevia is associated with the sudden onset of painless bleeding in the second or third trimester. Women with placenta praevia are reported to be 14 times more likely to bleed in the antenatal period compared with women without placenta praevia.[557] Risk factors for symptomatic placenta praevia include prior history of placenta praevia, advancing maternal age, increasing parity, smoking, cocaine use, previous caesarean section and prior spontaneous or induced abortion.[558,559] [Evidence level 2a]

In the case of symptomatic placenta praevia, inpatient management has been recommended[560] [Evidence level 4] and no conclusive evidence contrary to this recommendation was located. A

Cochrane review of interventions for the management of placenta praevia compared home with hospitalisation and cervical cerclage with no cerclage.[561] Only three trials with a total of 114 women were identified and although a reduction of length of stay in hospital was observed no other significant differences were found to support inpatient or outpatient management. [Evidence level 1a] Three trials of such small size were considered insufficient evidence to support a change in practice.

RECOMMENDATION

Because most low-lying placentas detected at a 20-week anomaly scan will resolve by the time the baby is born, only a woman whose placenta extends over the internal cervical os should be offered another transabdominal scan at 36 weeks. If the transabdominal scan is unclear, a transvaginal scan should be offered. [C]

12 Fetal growth and wellbeing

Clinical question

What is the diagnostic value and effectiveness of the following screening methods in determining fetal growth?

- symphysio-fundal height measurement (SFH)
- ultrasound scanning (US)
- use of customized growth charts with SFH measurement
- use of customized growth charts with US scanning
- clinical judgement/abdominal palpation
- frequency

Previous NICE guidance (for the updated recommendations see below)

The use of umbilical artery Doppler ultrasound for the prediction of fetal growth restriction should not be offered routinely. [A]

The use of uterine artery Doppler ultrasound for the prediction of pre-eclampsia should not be offered routinely. [B]

The evidence does not support the routine use of ultrasound scanning after 24 weeks of gestation and therefore it should not be offered. [A]

The evidence does not support the routine use of antenatal electronic fetal heart rate monitoring (cardiotocography) for fetal assessment in women with an uncomplicated pregnancy and therefore it should not be offered. [A]

Auscultation of the fetal heart may confirm that the fetus is alive but is unlikely to have any predictive value and routine listening is therefore not recommended. However, when requested by the mother, auscultation of the fetal heart may provide reassurance. [D]

Routine formal fetal-movement counting should not be offered. [A]

Pregnant women should be offered estimation of fetal size at each antenatal appointment to detect small- or large-for-gestational-age infants. [A]

Symphysio–fundal height should be measured and plotted at each antenatal appointment. [Good practice point]

Future research

Further research on more effective ways to detect and manage small- and large-for-gestational age fetuses is needed.

Fetal presentation should be assessed by abdominal palpation at 36 weeks or later, when presentation is likely to influence the plans for the birth. Routine assessment of presentation by abdominal palpation should not be offered before 36 weeks because it is not always accurate and may be uncomfortable. [C]

Suspected fetal malpresentation should be confirmed by an ultrasound assessment. [Good practice point]

Introduction and background

The duration of pregnancy is 282 days from the first day of the last menstrual period and during this time, the fetus passes through various stages of growth and development during this period. Monitoring the growth of the fetus is of vital importance in identifying small and large-for-gestational age babies, both of whom are at an increased risk of the associated morbidity & mortality. The methods currently used to screen fetal growth are: abdominal palpation, symphysio-fundal height measurements, ultrasound scanning and fetal biometry, and customised growth charts. But the challenge is to identify these high risk pregnancies using the most effective screening methods.

Diagnostic value for predicting small for gestational age (SGA) babies

Twenty one studies have been reviewed under this section. Most of them are prospective cohort studies. Blinding has not been specified in most studies and these have been assigned [EL II] except for Doppler US of Umbilical Artery where all the included studies are of [EL Ib].

The population in these studies was either a low risk group of women with singleton pregnancies or an unselected group. Exclusions and number of women in the study population have been specified where information was available. Details of screening tests including timing, frequency and thresholds have been described if recorded. Many studies have evaluated screening performance of various tests at different thresholds and used different criteria for defining SGA. For the sake of comparison efforts have been made to calculate diagnostic value for commonly used thresholds (< 2SD or < 10th centile of reference curve/value) and outcome as BW < 10th centile for GA.

12.1 Clinical examination / abdominal palpation

Description of included studies

Two retrospective studies were identified – one using a database of a large geographical cohort[916] [EL II], and the other random selection of hospital records [917] [EL III]. Low risk singleton pregnancies with confirmed GA were included in both the studies, but blinding was not specified. Women were examined regularly after the 20th week in the first study and the diagnostic value of abdominal palpation calculated for SGA defined as BW < 10th centile. In the other study with a much smaller sample size, examination was done once a week from 33-36 wks, and last value of EFW taken. Based on 3 or more measurements, an EFW curve was also generated. Predictive accuracy was calculated for threshold < 10th centile in both parameters with BW < 9.4th centile as the outcome. *(Table 1)*

Findings

In the larger study (Bais et al, [916]) abdominal palpation had a ST of 0.21 and SP of 0.96 for predicting SGA babies. It had a +LR value of 5.19 (4.23-6.37) and – LR value of 0.82 (0.79-0.86).

In the second study [917], diagnostic value of both EFW value (single) and EFW curve was similar. EFW had ST of 0.45 and SP of 0.91, while EFW curve had ST of 0.38 and SP of 0.92 respectively. Wide variation was observed in confidence intervals due to the small sample size. LR for a positive test was 4.82 (2.69-8.78), while that of a negative test was 0.61 (0.48-0.77).

Evidence summary

There is lack of good quality evidence on the diagnostic value of clinical examination/abdominal palpation. Available evidence indicates that clinical examination/abdominal palpation does not have good diagnostic value for predicting SGA babies.

Table I Characteristics of included studies on diagnostic value of clinical examination

Study and EL	***Study characteristics***	***Population characteristics***	***Sample size (% of study population)***	***Timing of screening test with threshold/s (prevalence of test positive)***	***Outcome/s and its threshold (Incidence in %)***	***Diagnostic value with 95% CI***
Bais 2004 [916] (Netherlands) EL II	Retrospective analysis of database of a geographical cohort, blinding not specified.	All low risk singleton pregnancies with confirmed GA by US at 20 weeks *Exclusions:* women who delivered between 16-20 weeks, gave birth to infant < 500 gms, multiple pregnancies	6318 (93.9)	Abdominal palpation by midwives after 20 weeks till referral or delivery (frequency not specified) *Threshold:* clinical judgement	BW < 10th centile for SGA and < 2.3rd centile for severe SGA (8.5% SGA, 1.5% severe SGA)	*For SGA* ST – 0.21 (0.18-0.24) SP – 0.96 (0.95-0.96) + LR 5.19 (4.23-6.37) - LR 0.82 (0.79-0.86)
Secher 1990 [917] (Denmark) EL III	Retrospective cohort, single centre, blinding not specified.	Randomly selected singleton pregnancies with confirmed GA by US at 16-18 wks. *Exclusions*:	199 (Not specified)	Once a week from 33-36 weeks, study sample with more than 3 measurements. EFW calculated and	BW < 85% of expected for GA (or < 9.4th centile for GA).	*For EFW value < 10th centile* ST – 0.45 (0.32-0.58) SP – 0.91 (0.87-0.95) + LR 4.82 (2.69-8.78) - LR 0.61 (0.48-0.77)

		pregnancies complicated by diabetes or severe blood group incompatibilities.		EFW curve generated using modelling. *Threshold:* Last EFW value < 10th centile, and EFW curve < 10th centile.		*For EFW curve < 10th centile* ST – 0.38 (0.26-0.50) SP – 0.92 (0.88-0.96)

12.2 Symphysio-fundal height measurement (SFH)

Description of included studies

All the 5 studies included under this heading have [EL II]. Blinding was not specified in most of the studies. One was a retrospective cohort [918] and the other four were prospective cohort studies [919],[920],[921],[922]. In one study the population was made of a cohort of singleton pregnancies included in one arm of an RCT[920]. Two studies did not have well defined exclusion criterion. SFH was measured in all studies from 20 weeks onward till term, but exact timing, frequency and threshold of a positive test were different. All studies evaluated BW $< 10^{th}$ centile as the outcome. Meta-analysis was not performed due to existing heterogeneity. *(Table II)*

Findings

There was wide variation in the results. Results from the two studies with smaller sample size showed better values of Positive LR and Negative LR compared to the other studies. Best results were seen in Grover study [921] with a Positive LR of 12.42 (7.66-20.13) and a Negative LR of 0.21 (0.14-0.31). But the study with largest sample size (Persson et al, [919]) showed poor values for Positive LR (2.22, 1.77-2.78) and Negative LR (0.83, 0.77-0.90). *(Figure 1)*

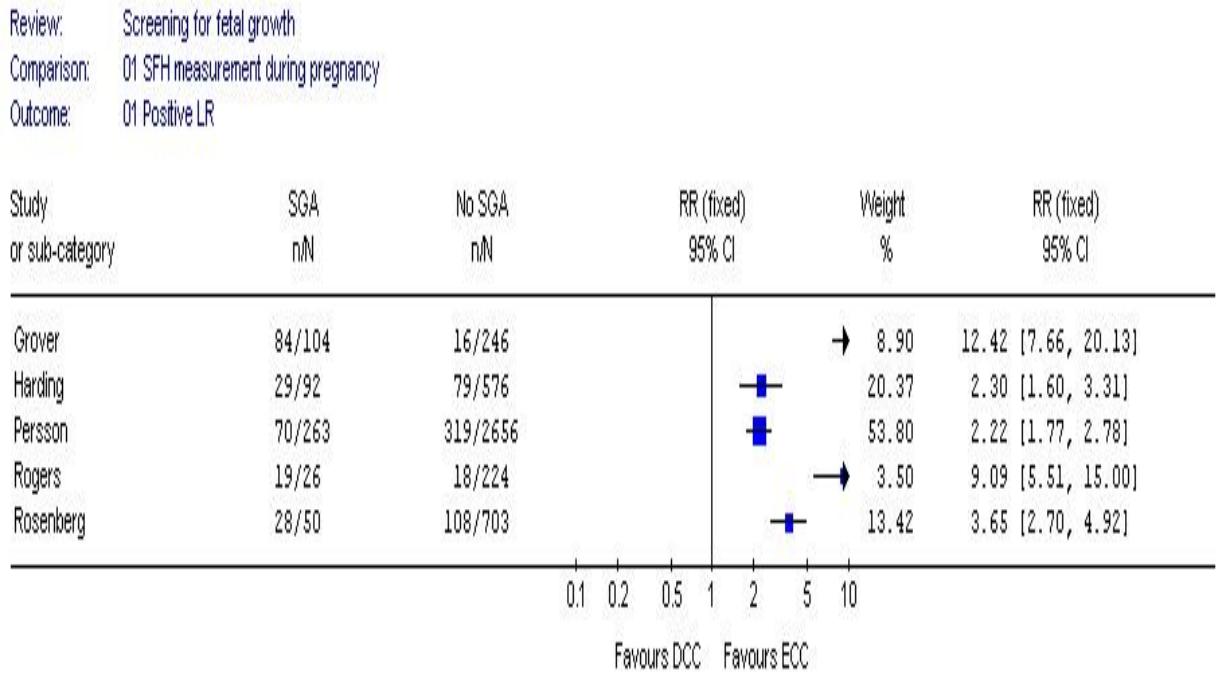
Evidence summary

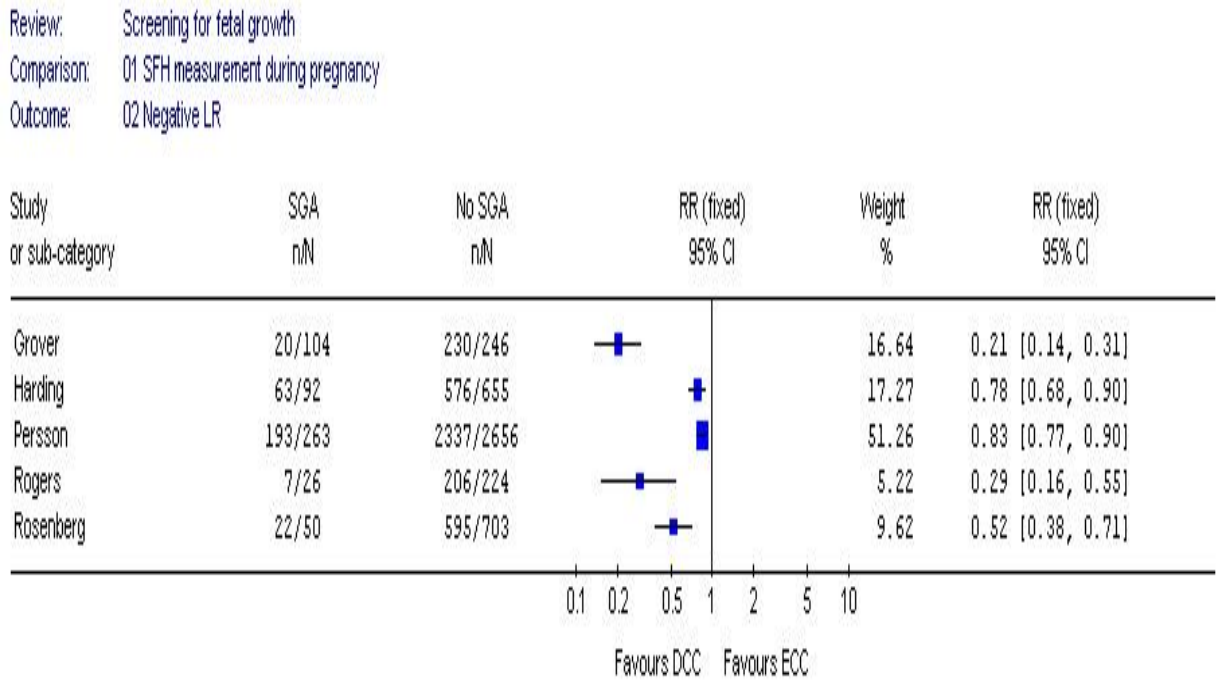
A wide variation in the results was observed for predictive accuracy of SFH measurement during pregnancy. Results from a multi-centre study shows that it does not have good diagnostic value for predicting and ruling out SGA babies.

Table II Characteristics of included studies on diagnostic value of SFH measurement

Study and EL	***Study characteristics***	***Population characteristics***	***Sample size (% of study population)***	***Timing of screening test with threshold/s (prevalence of test positive)***	***Outcome/s and its threshold (Incidence in %)***	***Diagnostic value with 95% CI***
Persson 1986 [919] (Sweden) EL II	Prospective cohort, multi-centre, blinding not specified.	Singleton pregnancies with regular menstrual cycles and known LMP. *Inclusions*: multiple gestation, mothers with more than 1 infant during study period or lack of registration in Medical Register.	2919 (91.3)	15 times approx. during the entire pregnancy. *Threshold*: SFH value < 2 SD of Reference Curve generated from 1350 healthy pregnant women.	BW < 10th centile for GA and sex (9.0% in sample population)	ST - 0.27 (0.22-0.32) SP - 0.88 (0.87-0.89)
Harding 1995 [920] (Australia) EL II	Prospective cohort, single centre, single blinded. (cohort was a group of women in one arm of RCT)	Randomly selected pregnant women who had approx. 5 scans between 18-38 weeks. *Exclusions*: multiple pregnancies, pre-existing HT, DM, maternal renal disease, fetal anomalies	747 at 28 weeks, 913 at 34 weeks. (65.8% at 28 wks and 80.4% at 34 weeks)	5 times at 18-20, 24, 28, 34, and 38 weeks. *Threshold:* Single SFH value < 10th centile for sample population and best cut-off from ROC curve.	BW < 10th centile for GA. (12.3% at 28 wks, 11.8% at 34 wks)	*Threshold < 10th centile(28 wks)* ST - 0.32 (0.23-0.40) SP - 0.88 (0.86-0.90) *Threshold < 10th centile(34 wks)* ST - 0.31 (0.22-0.40) SP - 0.87 (0.85-0.89)
Rosenberg1 982 [918] (UK) EL II	Retrospective cohort, single centre, blinding not specified.	Singleton pregnancies with known GA at < 26 weeks gestational age. *Exclusions*: multiple pregnancies, uncertain GA	753 (98.9)	From 20 weeks till delivery. *Threshold*: Two consecutive or three isolated SFH values < 10th centile of Reference Curve generated from 478 healthy pregnant women.	BW < 10th centile for GA (6.6% in sample population)	ST - 0.56 (0.42-0.70) SP - 0.85 (0.82-0.87)
Grover 1991 [921] (India) EL II	Prospective cohort, single centre, blinding not specified	Singleton pregnancies with known GA attending ANC. *Exclusions*: Not defined	350 (87.5)	SFH recording fortnightly till 30 wks then weekly till term. *Threshold*: SFH value < 1 SD of Reference Curve generated from 200 healthy pregnant women	BW < 10th centile for GA (29.7% in sample population)	ST – 0.81 (0.73-0.88) SP – 0.94 (0.91-0.97)
Rogers 1985 [922] (UK) EL II	Prospective cohort, single centre, blinding not specified.	Randomly selected pregnant women attending ANC of a hospital. *Exclusions*: not well defined	250 (study population not specified)	SFH measurements in the third trimester. *Threshold*: Single SFH value < 3 cms below mean of sample or 3 consecutive static or declining values.	BW < 10th centile for GA (10.4% in sample population)	ST – 0.73 (0.56-0.90) SP – 0.92 (0.88-0.96)

Figure 1 SFH measurement





12.3 Fetal biometry

Description of included studies

Four of the included studies were prospective cohort studies[923],[924],[925],[926] and one was a retrospective [927] – all with [EL II] and well defined exclusion criterion. Ultrasound was conducted in the third trimester and the diagnostic value calculated for a single measurement. All studies had used AC as a parameter, two had also used EFW based on Shepard's formula (using AC, BPD), and one used HC. Threshold for a positive test was similar in all ($< 10^{th}$ centile) and outcome assessed was BW $< 10^{th}$ centile for GA. Meta-analysis was performed for diagnostic accuracy of a single AC measurement in the third trimester. *(Table III)*

Findings

With AC as the only parameter used and threshold $< 10^{th}$ centile, ST ranged from 48 to 87% while SP ranged from 69 to 96%. Threshold values were not properly defined in the study by Hedriana et al [926]. On combining results of all the five studies, strong evidence of statistical heterogeneity was observed ($p < 0.00001$). Summary positive LR was 6.25 (5.60-6.97) and summary negative LR 0.55 (0.52-0.58). Values for positive LR ranged from 3.84 to 8.20 and those for negative LR from 0.16 to 0.78. *(Figure 2)*

Evidence summary

There is some evidence to indicate that a single measurement of fetal abdominal circumference in the third trimester has some diagnostic value in predicting the birth of SGA babies but the studies show statistical heterogeneity.

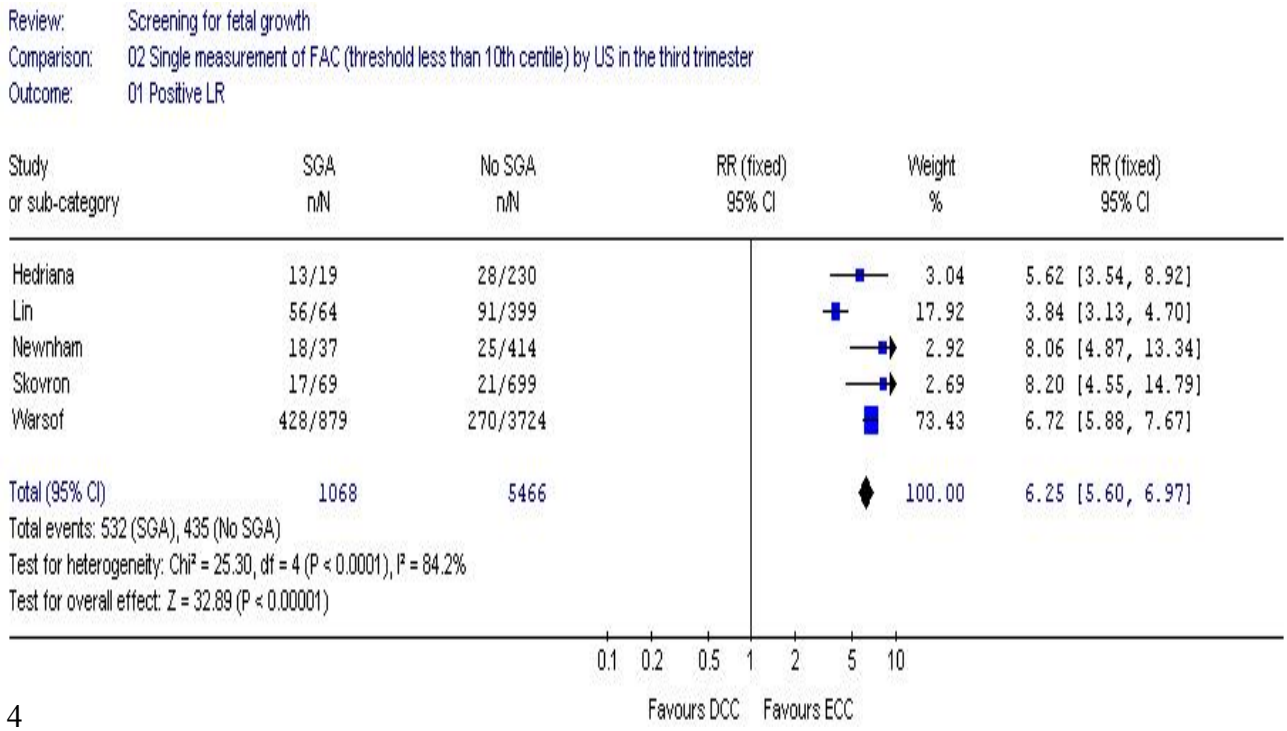
Table III Characteristics of included studies on diagnostic value of fetal biometry

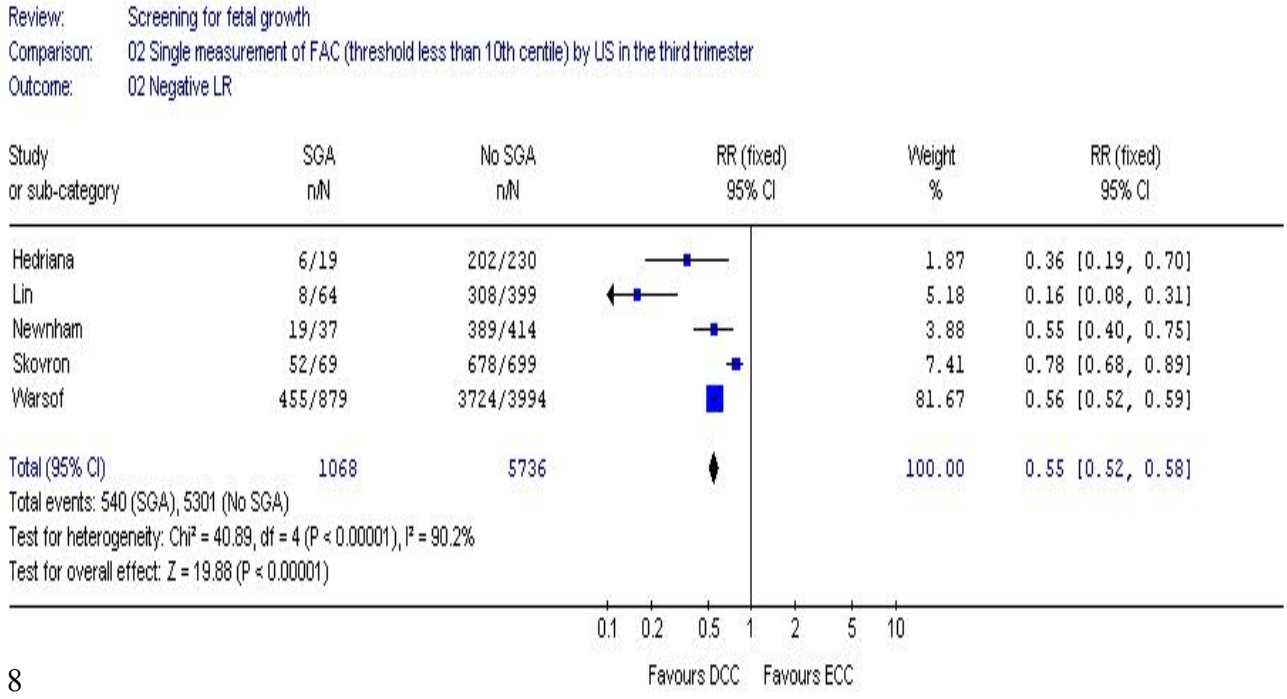
Study and EL	***Study characteristics***	***Population characteristics***	***Sample size (% of study population)***	***Timing of screening test with threshold/s (prevalence of test positive)***	***Outcome/s and its threshold (Incidence in %)***	***Diagnostic value with 95% CI***
Warsof 1986 [923] (UK) EL II	Prospective cohort, single centre, blinding not specified.	Ultrasonically confirmed singleton pregnancies before 24 weeks. *Exclusions*: lack of dating scan before 24 weeks.	3616 (79.9)	Once in third trimester at 28, 30, 32, 34 or 36 weeks. *Threshold:* BPD, HC and AC values < 25th centile or < 10th centile for GA.	BW < 10th centile for GA. (12.4% in sample population)	*Threshold < 25th centile* **For AC** ST – 0.79 (0.76-0.82) SP – 0.80 (0.79-0.81) **For HC** ST – 0.54 (0.50-0.58) SP – 0.78 (0.77-0.80) *Threshold < 10th centile* **For AC** ST – 0.48 (0.45-0.51) SP – 0.93 (0.93-0.94) **For HC** ST – 0.35 (0.32-0.39) SP – 0.91 (0.90-0.92)
Skovron 1991 [924] (USA) EL II	Prospective cohort, single centre, blinding not specified.	Singleton pregnancies *Exclusions*: gestational diabetes, placenta previa, premature labor, Rh sensitization, fetal	768 (77.1)	Once between 26 and 34 weeks. *Threshold*: AC and EFW (Shepard's formula) at < 10th and	BW < 10th centile for GA and sex (9.9% in sample population)	*Threshold < 25th centile* **For AC** ST – 0.83 (0.74-0.92) SP – 0.56 (0.52-0.60) **For EFW** ST – 0.51 (0.40-0.62) SP – 0.80 (0.77-0.83)

		anomalies.		< 25th centile for GA.		
Newnham 1990 [925] (Australia) EL II						*Threshold < 10th centile* **For AC** ST – 0.72 (0.62-0.83) SP – 0.69 (0.66-0.72) **For EFW** ST – 0.25 (0.15-0.35) SP – 0.97 (0.96-0.98)
Lin 1990 [927] (USA) EL II	Prospective cohort, single centre, not blinded for AC.	Singleton pregnancies with known GA at < 18 weeks gestational age. *Exclusions*: multiple pregnancies, gestational age > 20 wks, language difficulties, not pregnant, major fetal anomaly.	535 (87.0)	At 28 and 34 weeks. *Threshold*: AC < 5th centile for GA in the study population.	BW < 10th centile for GA (9.5% in sample population)	*At 28 weeks* ST - 0.27 (0.14-0.40) SP - 0.96 (0.94-0.98) *At 34 weeks* ST - 0.49 (0.33-0.65) SP - 0.94 (0.92-0.96)
	Retrospective cohort, single centre, blinding not specified	Singleton pregnancies undergoing obstetric US at a tertiary hospital. *Exclusions*: multiple gestation, ruptured membranes, uncertain	463 (study population not specified)	Twice in third trimester at interval of 2-4 weeks. *Threshold*: AC < 10th centile for GA in the study population.	BW < 10th centile for GA (13.8% in sample population)	ST - 0.87 (0.78-0.96) SP - 0.77 (0.73-0.81)

		dates, fetal anomalies.				
Hedriana 1994 [926] (USA) EL II	Prospective cohort, single centre, blinding not specified.	Ultrasonically confirmed singleton pregnancies. *Exclusions*: multiple gestation, maternal complications associated with severe intrauterine growth retardation, fetuses with anatomic defects.	249 (94.3)	Single and serial third trimester scans between 28 and 42 weeks. *Threshold*: Slope ± SD calculated for AC and EFW (Shepard's formula) centile using regression analysis. Exact values not specified.	BW < 10th centile for GA (7.6% in sample population)	*For single scan* **For AC** ST – 0.68 (0.47-0.89) SP – 0.88 (0.84-0.92) **For EFW** ST – 1.00 (1.00-1.00) SP – 0.76 (0.71-0.82)

Figure 2 Fetal Abdominal Circumference by US





12.4 Reduced amniotic fluid volume by ultrasound

Description of included studies

Three studies have been included – two cohort studies[920,927] with [EL II] (one prospective and another retrospective), and one case-control study [928] with [EL III] were included. Blinding was not specified in all but exclusions were well defined. Timing, frequency and threshold of a positive test were all different in the three studies. In one study (Lin et al, [927]), diagnostic performance of AC and reduced AF was calculated as a single test. *(Table IV)*

Findings

Values for positive LR and negative LR in the prospective cohort study (Harding et al, [920]) were poor - 1.02 (0.58-1.79) and 1.00 (0.93-1.07) respectively. Lin et al study [927] showed a high positive LR of 12.47 and negative LR of 0.77, but results from the third study were not consistent. *(Figure 3)*

Evidence summary

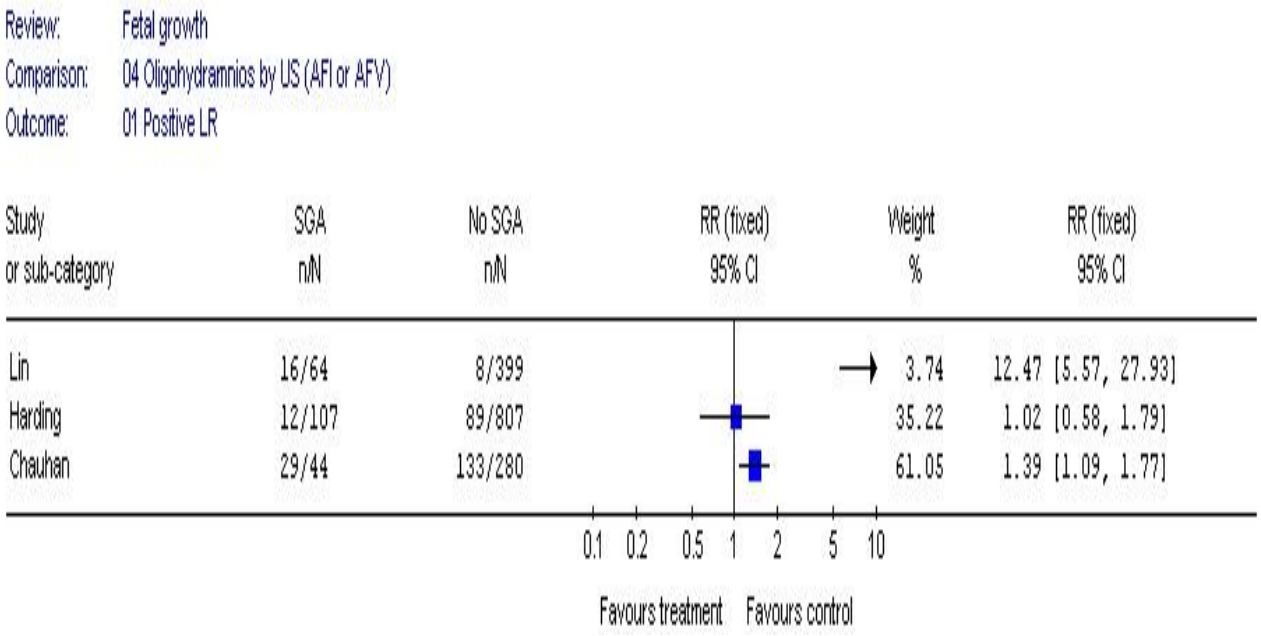
Evidence from 3 studies shows that reduced amniotic fluid volume diagnosed by US during pregnancy has poor diagnostic value in predicting and ruling out SGA babies.

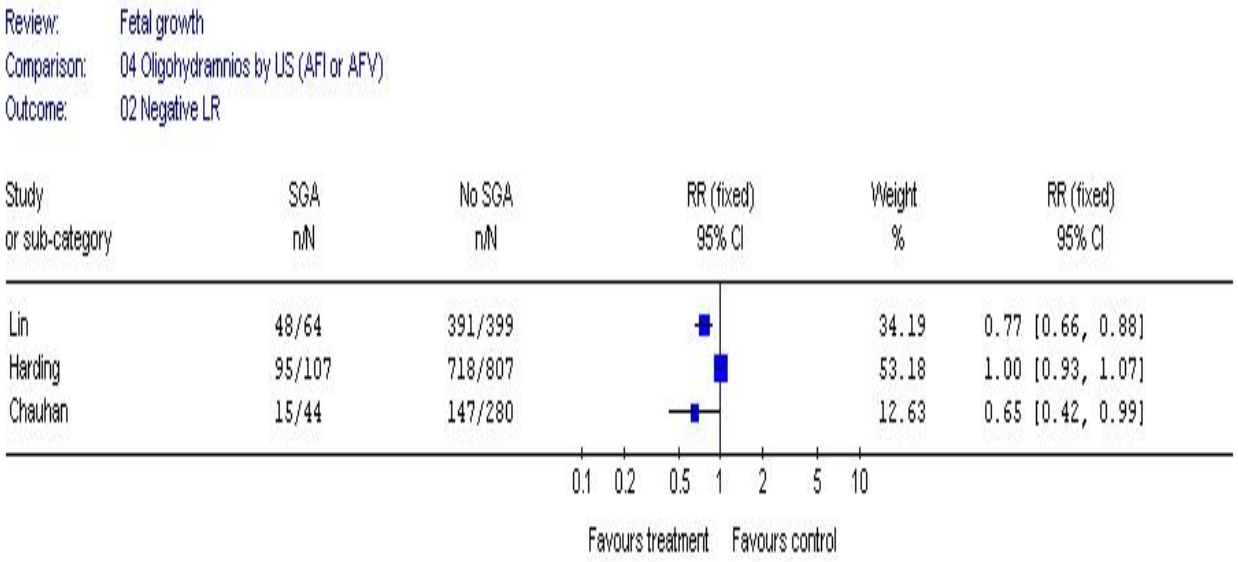
Table IV Characteristics of included studies on diagnostic value of reduced amniotic fluid volume (AFI or AFV) by US

Study and EL	***Study characteristics***	***Population characteristics***	***Sample size (% of study population)***	***Timing of screening test with threshold/s (prevalence of test positive)***	***Outcome/s and its threshold (Incidence in %)***	***Diagnostic value with 95% CI***
Harding 1995 [920] (Australia) EL II	Prospective cohort, single centre, not blinded for US measurements. (cohort was a group of women in one arm of RCT)	Randomly selected pregnant women who had approx. 5 scans between 18-38 weeks. *Exclusions*: multiple pregnancies, pre-existing HT, DM, maternal renal disease, fetal anomalies.	760 at 28 weeks, 914 at 34 weeks. (67.0% at 28 wks and 80.5% at 34 weeks)	5 times at 18-20, 24, 28, 34, and 38 weeks. *Threshold:* Single AFI value < 10th centile for sample population.	BW < 10th centile for GA. (12.6% at 28 wks, 11.7% at 34 wks)	*Threshold < 10th centile(28 wks)* ST - 0.21 (0.13-0.29) SP - 0.93 (0.91-0.95) *Threshold < 10th centile(34 wks)* ST - 0.11 (0.05-0.17) SP - 0.89 (0.87-0.91)
Lin 1990 [927] (USA) EL II	Retrospective cohort, single centre, blinding not specified	Singleton pregnancies undergoing obstetric US at a tertiary hospital. *Exclusions*: multiple gestation, ruptured membranes, uncertain	463 (study population not specified)	Twice in third trimester at interval of 2-4 weeks. *Threshold*: AC < 10th centile for GA in the study population and	BW < 10th centile for GA (13.8% in sample population)	*For AC < 10TH centile & Oligohydramnios* ST – 0.25 (0.15-0.36) SP – 0.98 (0.97-0.99)

		dates, fetal anomalies.		vertical diameter < 2 cms for largest pocket of amniotic fluid.		
Chauhan 1999 [928] (USA) EL III	Retrospective case-control, single centre, blinding not specified.	*Cases*: Singleton pregnancies, AFI ≤ 5 cms, reliable GA and no known anomalies. *Controls*: Next pregnancy with same GA and AFI between 5.1 to 23.9 cms.	324 (Cases - 162 Controls – 162)	Third trimester US for AFI within 72 hours of delivery. *Threshold*: AFI ≤ 5 cms .	BW < 10th centile for GA (13.6% in sample population)	ST – 0.66 (0.52-0.80) SP – 0.53 (0.47-0.58)

Figure 3 Reduced amniotic fluid volume by Ultrasound





12.5 Umbilical artery Doppler examination

Description of included studies

All of the 5 included studies were prospective cohort studies [EL Ib] with blinding [929,930,925,931,932] and one was conducted in more than one centre. Exclusion criteria have been well defined in four studies. Doppler US was conducted in either late second or third trimester. Three studies evaluated S/D (systolic/diastolic) ratio as a screening

parameter, one study used PI (pulsatility index), and fifth study evaluated both of them. Meta-analysis was performed for two different timings – 26 to 31 weeks (4 studies) and 32-36 weeks (3 studies) without taking into account the parameter used. One study was not included for meta-analysis as it did not provide data for calculation of their confidence intervals *(Table V)*

Findings

ST at both 26-31 weeks and 32-36 weeks ranged between 17 to 43 % while SP at both times was as high as 96%. There was not much variation in the values of positive and negative LR for individual studies.

At 26-31 weeks, positive LR ranged from 2.20 to 4.18 while negative LR ranged from 0.71 to 0.87. No evidence of statistical heterogeneity was observed for both positive and negative LR's. Summary values for positive LR and negative LR were 2.67 (2.02-3.53) and 0.84 (0.78-0.90) respectively. *(Figure 4a)*

At 32-36 weeks also there was no evidence of heterogeneity for both LR's. Summary positive LR was 3.34 (2.27-4.93) and positive LR ranged from 2.74 to 3.92 in individual studies. Negative LR ranged from 0.83 to 0.88 and its summary value was 0.85 (0.79-0.92). *(Figure 4b)*

Evidence summary

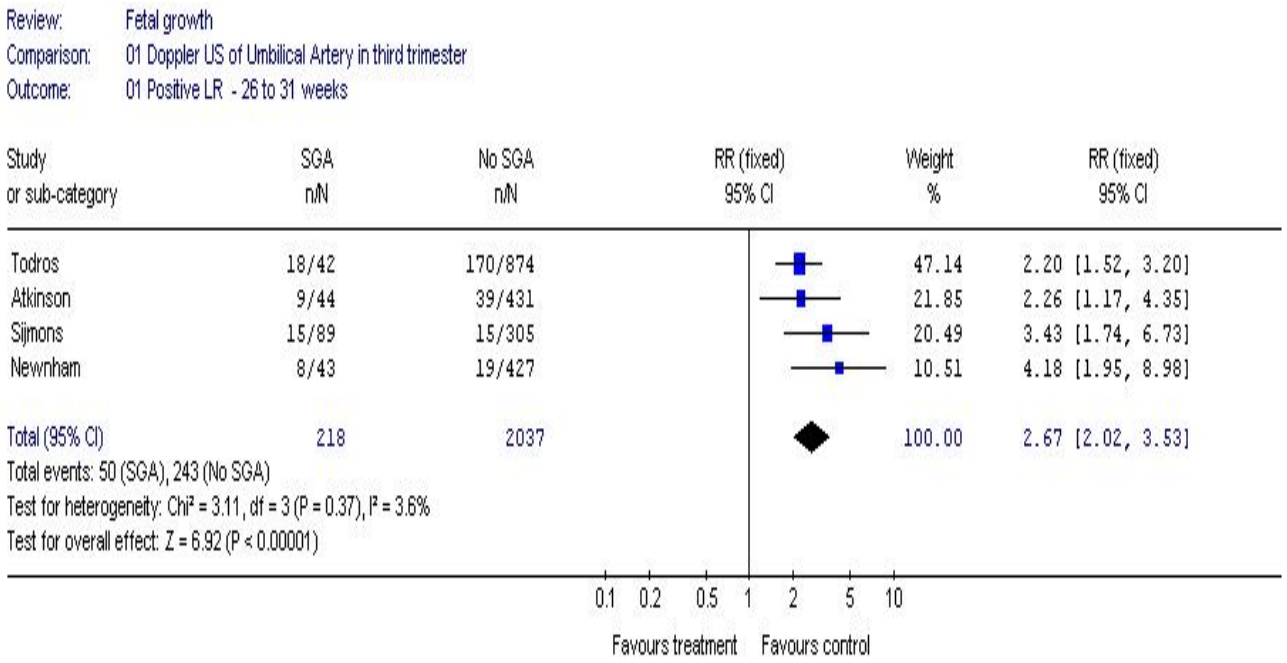
High quality evidence indicates that Umbilical Artery Doppler examination in the third trimester (at 26-31 wks and 32-36 weeks) has poor diagnostic value in predicting SGA births in a low risk population.

Table V Characteristics of included studies on diagnostic value of Doppler (Umbilical artery)

Study and EL	*Study characteristics*	*Population characteristics*	*Sample size (% of study population)*	*Timing of screening test with threshold/s (prevalence of test positive)*	*Outcome/s and its threshold (Incidence in %)*	*Diagnostic value with 95% CI*
Beattie 1989 [929] (UK) EL Ib	Prospective cohort, single centre, blinded.	Ultrasonically dated singleton pregnancies attending within 7 days of their 28th gest. week. *Exclusions*: private patients, late bookings, with altered dates who attended after 29 wks, late referrals.	2097 (62.0)	At 28, 34 and 38 weeks. *Thresholds:* Pulsatility index (PI), Systolic/diastolic (S/D) ratio and Resistance parameter - all > 90th centile for GA in the study population.	BW < 5th centile for GA. (values not given)	<u>*At 28 weeks*</u> For PI For S/D ratio ST - 28 31 SP - 89 90 <u>*At 34 weeks*</u> For PI For S/D ratio ST - 32 40 SP - 89 84
Todros 1995 [930] (Italy) EL Ib	Prospective cohort, multi- centre, blinded.	Singleton pregnancies with no obstetrical risk, pre-pegnancy pathologic condition or anomaly. *Exclusions*: women delivered at other hospitals	916 (95.2)	At 19-24 and 26-31 weeks *Threshold*: S/D ratio of 4.5 (at 19-24 wks) and 3.5 (at 26-31 wks) derived from ROC curve.	BW < 10th centile for GA (4.6% in sample population)	<u>*At 19—24 weeks*</u> ST – 0.45 (0.30-0.60) SP – 0.74 (0.71-0.77) <u>*At 26—31 weeks*</u> ST – 0.43 (0.28-0.58) SP – 0.80 (0.78-0.83)
Newnham 1990 [925] (Australia) EL Ib	Prospective cohort, single centre, blinded.	Singleton pregnancies with known GA at < 18 weeks gestational age. *Exclusions*: multiple pregnancies, gestational age > 20 wks, language difficulties, not pregnant, major fetal anomaly.	535 (87.0)	At 18, 24, 28 and 34 weeks. *Threshold*: S/D ratio > 95th centile for GA in study population.	BW < 10th centile for GA (9.5% in sample population)	<u>*At 28 weeks*</u> ST - 0.19 (0.07-0.30) SP - 0.96 (0.94-0.97) <u>*At 34 weeks*</u> ST - 0.17 (0.04-0.29) SP - 0.95 (0.93-0.97)
Sijmons 1989 [931] (Netherlands) EL Ib	Prospective cohort, single centre, blinded.	Randomly selected singleton pregnancies from a tertiary referral centre.	339 to 394 (84.5 to 98.5%) for different timing & outcomes	At 28 and 34 weeks *Threshold*: PI > 95th centile for GA in the study population.	1) BW < 10th centile for GA (22% in study population) 2) Ponderal index < 10th centile for GA	<u>*At 28 weeks*</u> 1) ST - 0.17 (0.09-0.25) SP - 0.95 (0.93-0.97) 2) ST - 0.19 (0.06-0.32) SP - 0.95 (0.93-0.97) <u>*At 34 weeks*</u> 1) ST - 0.22 (0.13-0.31) SP - 0.94 (0.92-0.97)

Study and EL	*Study characteristics*	*Population characteristics*	*Sample size (% of study population)*	*Timing of screening test with threshold/s (prevalence of test positive)*	*Outcome/s and its threshold (Incidence in %)*	*Diagnostic value with 95% CI*
						2) ST - 0.24 (0.09-0.39) SP - 0.93 (0.90-0.96)
Atkinson 1994 [932] (USA) EL Ib	Prospective cohort, single centre, blinded. (part of RCT for pre-eclampsia prevention)	Low risk nulliparaous women with singleton pregnancies. *Exclusions*: multiple gestation, H/O renal disease, collagen vascular disease, DM, hypertension.	475 (84.0) at 27-31 wks, 439 (77.7) at 32-36 wks	At 20-26, 27-31, 32-36 and 37-42 weeks Threshold: S/D ratio > 90th centile for GA in study population.	BW < 10th centile for GA (7.8% in study population)	<u>*At 27-31 weeks*</u> ST – 0.20 SP – 0.91 <u>*At 32-36 weeks*</u> ST – 0.24 SP – 0.91

Figure 4 (a) Doppler US of Umbilical Artery at 26-31 weeks



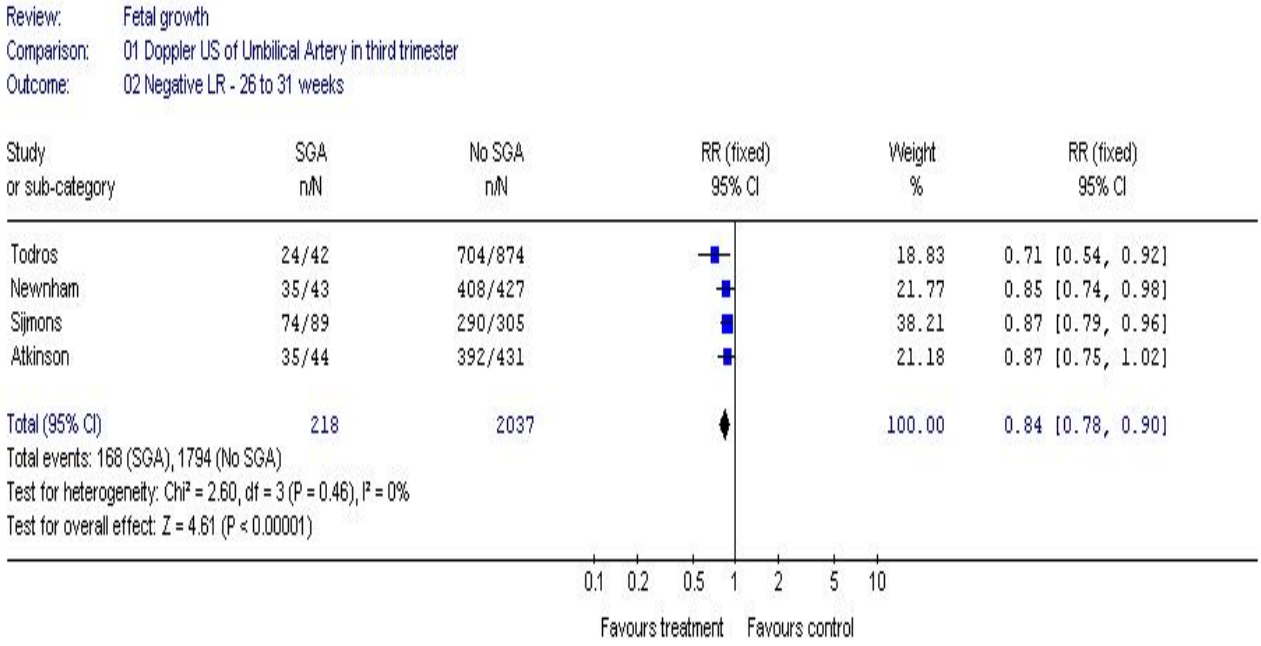
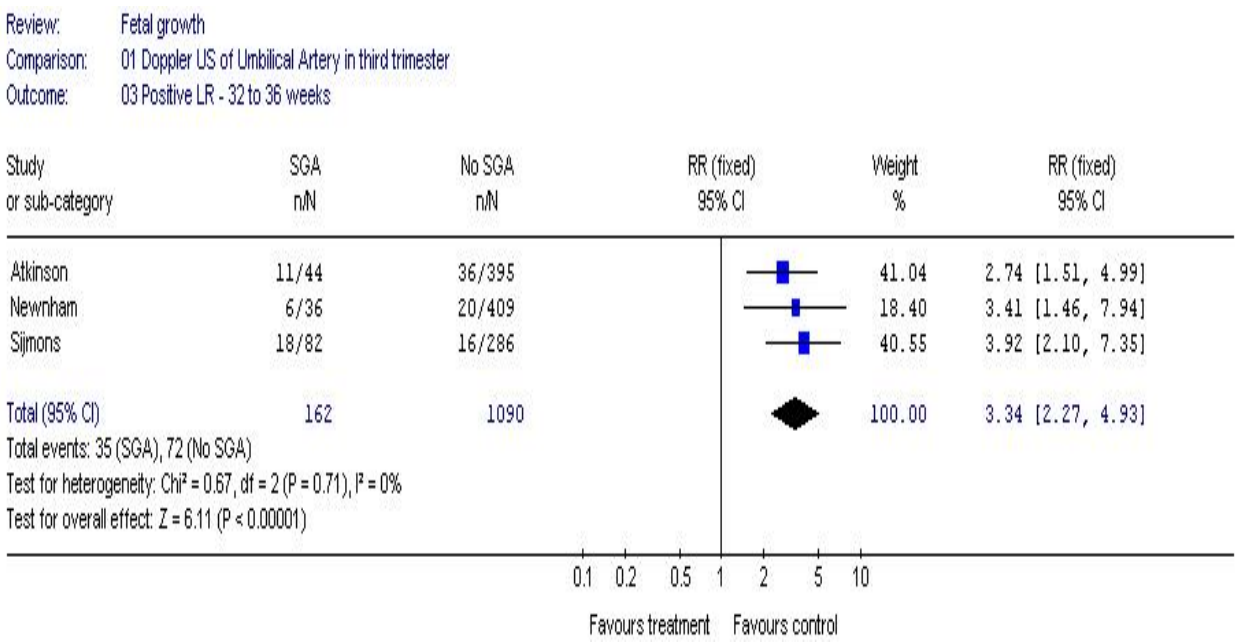
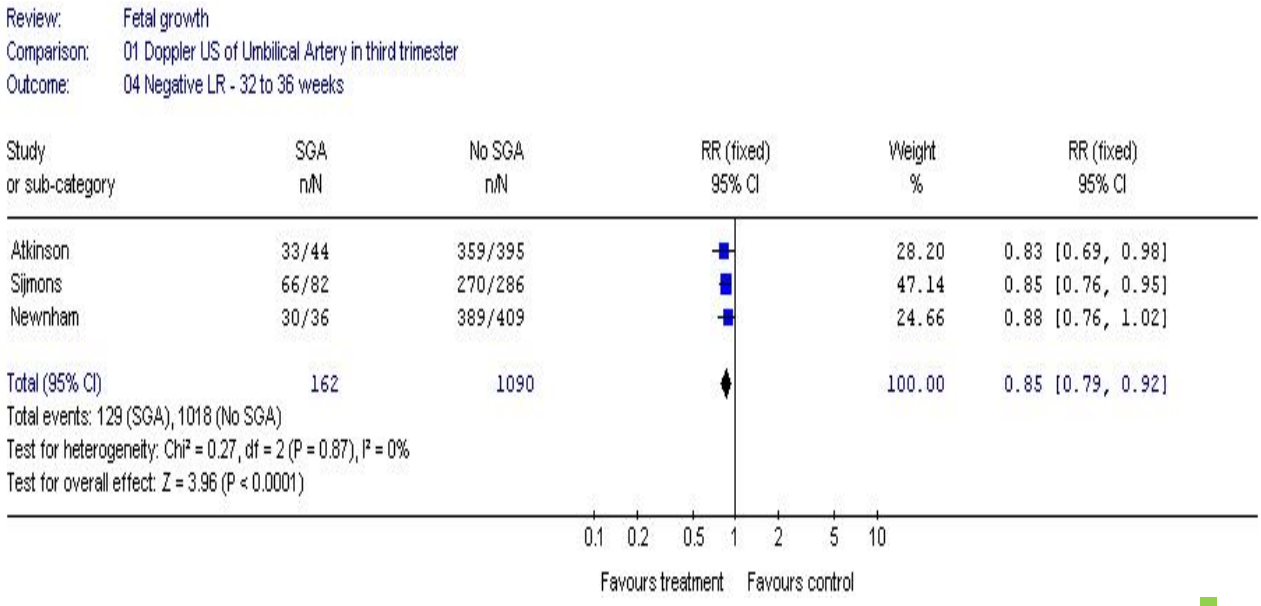


Figure 4 (b) Doppler US of Umbilical Artery at 32-36 weeks





12.6 Customized fetal growth charts (CFGC)

Description of included studies

A single prospective cohort study [933]with [EL II] was selected. Three more studies were identified for CFGC as a screening test but they did not provide data for calculating predictive accuracy. Third trimester US was conducted every 2 weeks to calculate EFW, and the last recording was used for calculating the customized weight centiles. Diagnostic value was assessed for three different outcomes including Ponderal index < 25th centile of the population. (*Table* 6)

Findings

ST of the test was 42% (range 26-58%) and SP 90% (range 86-94%). LR for a positive test was 4.20 (2.42-7.32) and that of a negative test was 0.65 (0.49-0.86)

Evidence summary

There is a lack of good quality studies on the predictive performance of customized fetal growth charts. Results from a single study shows that it has poor ability in predicting and ruling out birth of SGA infants.

Table VI Characteristics of included studies on diagnostic value of Customized fetal growth charts

Study and EL	***Study characteristics***	***Population characteristics***	***Sample size (% of study population)***	***Timing of screening test with threshold/s (prevalence of test positive)***	***Outcome/s and its threshold (Incidence in %)***	***Diagnostic value with 95% CI***
Owen 2003 [933] (UK) EL II	Prospective cohort, single centre, blinding not specified.	Singleton pregnancies with confirmed GA < 85 days. *Exclusions*: presence of recognized risk factors for accelerated /retarded fetal growth including H/O previous SGA baby, existing medical diseases or heavy smoking.	258 (82.4)	Third trimester US at 2 weekly intervals to calculate EFW (using BPD, abdominal area, FL) – the last EFW prior to delivery used for customized fetal weight centile. *Threshold:* Centile < 5^{th} and < 10^{th} for estimated values.	Ponderal index < 25^{th} centile. (14.0% in sample population) Also used were skinfold thickness < 10^{th} centile and mid-arm to occipito-frontal circumference ratio < 1SD.	*For customized estimated fetal weight < 10^{th} centile and outcome as Ponderal index < 25^{th} centile* ST – 0.42 (0.26-0.58) SP – 0.90 (0.86-0.94) + LR 4.20 (2.42-7.32) - LR 0.65 (0.49-0.86)

12.7 Diagnostic Value for Predicting Large for Gestational Age Babies (LGA)

No study was identified for diagnostic accuracy of four screening tests – clinical examination, amniotic fluid volume or polyhydramnios by US, Doppler US of umbilical artery and customized fetal growth charts. For the two remaining screening tests – SFH measurement and US biometry, all the 6 studies included are cohort studies with [EL II] (blinding not specified). Details of these studies have been tabulated. Meta-analysis could not be performed for both the screening tests due to heterogeneity in timing, thresholds and outcome assessed.

12.8 Symphysio-fundal height measurement for LGA babies

Description of included studies

All the three studies included were prospective cohort studies [919],[921],[934] . Two of them had also assessed diagnostic value of SFH in SGA babies [EL II]. None of the studies had specified blinding, and two did not specify the exclusion criterion. In all studies SFH measurements were made in the third trimester and plotted on a reference curve generated from a normal population of healthy pregnant women. One study did not specify exact values for diagnostic accuracy results [934] [EL III], and hence its diagnostic value is given as published without the corresponding confidence intervals. *(Table VII)*

Findings

The prospective cohort study with the largest sample size [919] did not show good values for ST – 38%, SP – 88%, Positive LR 3.09 (2.57-3.71) and Negative LR 0.71 (0.65-0.78). The other prospective cohort (Grover et al, [921]) showed very high LR for a positive test 16.63 (9.39-29.42) and low LR for a negative test 0.22 (0.13-0.38). However, this was a single centre unblinded study with a small sample size.

Evidence summary

There is wide variation in the results for the diagnostic accuracy of SFH measurements in prediction of LGA babies. Results from the largest study show that this measurement has poor diagnostic value in predicting and ruling out LGA babies.

Table VII Characteristics of included studies on diagnostic value of SFH measurement for LGA babies

Study and EL	***Study characteristics***	***Population characteristics***	***Sample size (% of study population)***	***Timing of screening test with threshold/s (prevalence of test positive)***	***Outcome/s and its threshold (Incidence in %)***	***Diagnostic value with 95% CI***
Persson 1986 [919] (Sweden) EL II	Prospective cohort, multi-centre, blinding not specified.	Singleton pregnancies with regular menstrual cycles and known LMP. *Inclusions*: multiple gestation, mothers with more than 1 infant during study period or lack of registration in Medical Register.	2919 (91.3)	15 times approx. during the entire pregnancy. *Threshold*: SFH value > 2 SD of Reference Curve generated from 1350 healthy pregnant women.	BW > 90th centile for GA and sex (9.5% in sample population.	ST - 0.38 (0.33-0.43) SP - 0.88 (0.87-0.89) + LR 3.09 (2.57-3.71) - LR 0.71 (0.65-0.78)
Grover 1991 [921] (India) EL II	Prospective cohort, single centre, blinding not specified	Singleton pregnancies with known GA attending ANC. *Exclusions*: Not defined	350 (87.5)	SFH recording fortnightly till 30 wks And then weekly till term. *Threshold*: SFH value > 1 SD of Reference Curve generated from	BW > 1SD according to national BW chart (13.7% in sample population)	ST – 0.79 (0.68-0.90) SP – 0.95 (0.93-0.98) + LR 16.63 (9.39-29.42) - LR 0.22 (0.13-0.38)

Okonofua 1986 [934] (UK) EL III	Prospective cohort, single centre, blinding not specified.	Singleton uncomplicated pregnancies attending a hospital ANC clinic and who were sure of their LMP. *Exclusions*: Not defined	100 (study population not specified)	200 healthy pregnant women SFH measurements and US biometry after 20 weeks in the third trimester. *Threshold*: Two consecutive SFH values > 90th centile of Reference curve generated from a sample of 30 healthy uncomplicated singleton pregnancies.	BW > 90th centile for GA (6.0% in sample population)	ST – 0.33 SP – 0.85

12.9 Fetal biometry for LGA babies

Description of included studies

Three studies were included – two prospective cohorts [926,934] and one retrospective [935]. Exclusions were not defined in one study. Wide variation was seen in the timing, frequency, parameters employed and the threshold used for a positive test, but all studies used BW > 90th centile as outcome for defining LGA. *(Table VIII)*

Findings

Two studies employing EFW by Shepard's formula showed ST of 48% and 74%, and similar SP values of 94%. Positive LR in one was 12.87 (8.22-20.15) while it was 8.09 (4.32-15.14) in the other. Values for negative LR were 0.28 (0.18-0.45) and 0.55 (0.42-0.73) respectively. Positive and negative LR values for AC measured in one study were 5.01 (3.12-8.07) and 0.51 (0.37-0.70) respectively.

Evidence summary

There is a lack of good quality studies for the diagnostic value of fetal biometry for detecting LGA babies. Results from one small study show that it might have some value in predicting and ruling out birth of LGA babies.

Table VIII Characteristics of included studies on diagnostic value of fetal biometry for LGA babies

Study and EL	***Study characteristics***	***Population characteristics***	***Sample size (% of study population)***	***Timing of screening test with threshold/s (prevalence of test positive)***	***Outcome/s and its threshold (Incidence in %)***	***Diagnostic value with 95% CI***
Hedriana 1994 [926] (USA) EL II	Prospective cohort, single centre, blinding not specified.	Ultrasonically confirmed singleton pregnancies. *Exclusions*: multiple gestations, maternal complications associated with severe intrauterine growth retardation, fetuses with anatomic defects.	249 (94.3)	Single and serial third trimester scans between 28 and 42 weeks. *Threshold*: Slope ± SD calculated for AC and EFW (Shepard's formula) centile using regression analysis. Exact values not specified.	BW > 90th centile for GA. (18.5% in sample population)	<u>*For single scan*</u> **For AC** ST – 0.54 (0.40-0.68) SP – 0.89 (0.85-0.93) + LR 5.01 (3.12-8.07) - LR 0.51 (0.37-0.70) **For EFW** ST – 0.48 (0.34-0.62) SP – 0.94 (0.91-0.97) + LR 8.09 (4.32-15.14) - LR 0.55 (0.42-0.73)
Okonofua 1986 [934] (UK) EL III	Prospective cohort, single centre, blinding not specified.	Singleton uncomplicated pregnancies attending a hospital ANC clinic and who were sure of their	100 (study population not	SFH measurements and US biometry after 20 weeks in the third trimester.	BW > 90th centile for GA (6.0% in sample population)	ST – 0.66 SP – 0.95

		LMP. *Exclusions*: Not defined	specified)	*Threshold*: Two consecutive values > 90th centile of BPD & AC reference curve generated from a sample of 30 healthy uncomplicated singleton pregnancies.		
Ott 1984 [935] (USA) EL III	Retrospective cohort, single centre, blinding not specified.	Pregnant women undergoing US examination within 72 hours of delivery. *Exclusions*: not defined.	595 (study population not specified)	BPD and AC measured within 72 hours of delivery and EFW (Shepard's formula) calculated. *Threshold*: EFW > 1.5 SD for the reference curve.	BW > 90th centile for GA (8.2% in sample population)	ST - 0.74 (0.62-0.86) SP - 0.94 (0.92-0.96) + LR 12.87 (8.22-20.15) - LR 0.28 (0.18-0.45)

12.10 Effectiveness studies

Nine studies were included – two Cochrane reviews, one controlled trial, four retrospective and one prospective cohort study, and one nested case-control study. Except three studies (2 Cochrane reviews and 1 controlled trial) which compared the effectiveness of screening tests, rest of the studies have compared the risk of adverse perinatal outcomes between pregnant women with positive test result and those with negative tests results.

The two Cochrane reviews were on effectiveness of symphysio-fundal height measurement and Doppler US respectively. Two cohort studies were selected for US biometry, and two studies (one cohort and one nested case-control) for amniotic fluid volume. No effectiveness study was identified for clinical examination of fetal growth. Three studies (one controlled trial and two retrospective cohorts) were identified for customized fetal growth charts, and the two retrospective cohort studies had analyzed the same Swedish birth cohort database but in a different manner.

12.11 Symphysio-fundal height measurement

Description of included studies

A Cochrane review[566] conducted to assess whether routine use of SFH measurement during antenatal care improves pregnancy outcome, compared to abdominal examination. It included all controlled trials of tape measurement of SFH during pregnancy compared with abdominal palpation method alone. Studies were identified using Pregnancy and Childbirth search strategy of the Cochrane group. One reviewer assessed the quality of included studies and extracted data. Analysis was done using Review Manager software. The primary outcomes were:

a) complications associated with FGR or IUGR - intrauterine death, intrapartum asphyxia and neonatal hypoglycaemia
b) complications associated with fetal macrosomia – CPD, caesarean section for failure to progress, shoulder dystocia
c) complications associated with multiple pregnancy – preterm delivery, perinatal mortality.

Secondary outcomes: other indices of maternal and perinatal mortality and morbidity, and indices of obstetric care including admission to hospital.

[EL 1 +]

Findings

A single trial enrolling 1639 participants was included. Pregnant women around 14 wks of pregnancy were randomly allocated to the experimental or control group using sealed, opaque and unnumbered envelopes. 21 women with twin pregnancies, 13 with uncertain dates and 60 with antenatal care somewhere else, were excluded from the study. SFH was routinely measured after 28 weeks and results plotted on a locally derived centile chart. Control group women had observations made with a fabric strip.

Peto Odds Ratio (OR) with 95% CI for main outcomes was:

Perinatal mortality		1.25 (0.38 - 4.08)
Labour induction for FGR	-	0.84 (0.44 - 1.59)
Caesarean section for FGR	-	0.72 (0.31 – 1.67)
Birthweight < 10th centile	-	1.34 (0.91 – 1.98)
Admission neonatal unit	-	1.07 (0.69 – 1.65)

No statistically significant difference was found for other outcomes (Apgar score less than 4 at 1 min. & 5 min., Umbilical artery pH < 7.15, and antepartum hospitalization for suspected FGR).

Evidence summary

Results from the single trial in the Cochrane review shows no evidence of improved outcome from SFH measurements.

12.12 Ultrasound biometry

Description of included studies

A retrospective cohort study [936] was carried out in a tertiary care hospital in the USA to determine whether fetal growth measured at serial US examinations can predict neonatal morbidity independent of whether gestational age is known. The study population (n = 321) was selected from a cohort of 1836 singleton pregnancies and included all those who underwent two or more US examinations 2-17 wks apart during the study period (July 1994 to March 1997). Excluded were women with 5 or more US examinations, twin pregnancies reduced to singleton, those who had undergone fetal surgery, those transferred for delivery and fetuses with major congenital and chromosomal anomalies. Results of US including fetal biometry measurements were obtained from the computerized database and EFW calculated using HC, AC and FL. Data from 236 women was used to construct a reference growth chart for EFW, and fetal growth < 10^{th} centile was defined as FGR while between 20^{th}-80^{th} centile was defined as Normal Fetal Growth (NFG). Information from Obstetric and Neonatal database was collected for the following outcomes: low birth weight (BW < 2500gms, < 2000 gms, < 1500 gms, < 5^{th} centile and < 3^{rd} centile for GA) and poor neonatal outcomes - preterm birth (< 37 wks), long hospital stay (> 4 days), admission in neonatal intensive care unit, and assisted ventilation required at birth. Risk of each outcome for FGR and NFG group was calculated in women with known GA only (n = 236), and relative risk (RR) with 95% CI computed. Multivariate analysis was then performed after adjusting for variable potential confounders (maternal age, height, weight, race, BMI, parity, fetal sex, H/O substance abuse and EFW). In the end gestational age was simulated for those with unknown GA and RR calculated for the whole sample. Blinding of investigator not specified. [EL 2 +]

A prospective cohort in Ireland [937] aimed to identify fetuses with US evidence of inadequate growth but born with BW > 10^{th} centile for GA; and to determine if these infants have high risk of obstetric interventions, intrapartum complications and neonatal morbidity compared to group with normal US for fetal growth. Study population was 285 unselected mothers with singleton pregnancies and confirmed GA by a second trimester scan referred for third trimester US examination. Cases with multiple pregnancies and fetal anomalies incompatible with life were excluded. Two scans were performed – in early third trimester and later at an average interval of 6 wks. Hadlock formula using HC, AC and FL was used to calculate EFW and its reference chart drawn using data from 40,004 singleton healthy pregnancies. Inadequate growth (IFG) was defined as fall in EFW centile > 20 between the two scans, and this group was compared with group not showing evidence of inadequate fetal growth (Adequate FG) for following complications: abnormal Doppler, induction of labour, meconium staining, need for intrapartum fetal blood sampling, operative vaginal delivery, caesarean section, Apgar score < 7 at 5 min and need for admission to neonatal ICU. [EL 2 -]

Findings

In the first study [936] there was no statistically significant difference in age, racial distribution, parity or substance abuse between the study population (n = 321) and total cohort (n = 1836). 71.9% of the study population underwent two second or third trimester US examinations while others had more than two.

Relative risk in women with fetuses of known gestational age is as follows (Sample size for FGR = 24, NFG = 212, Total = 236)

Outcome		FGR (in %)	NFG (in %)	RR (95%CI)
Low birth weight				
	BW < 2500gms	63	16	3.9 (2.5, 6.0)
	BW < 1500gms	25	3	8.8 (3.1, 25.2)
	BW < 5th centile	25	1	17.7 (4.7, 66.1)
Poor neonatal outcome				
	Preterm birth	50	22	2.3 (1.4, 3.7)
	Long neonatal hospital stay	50	19	2.6 (1.6, 4.2)
	Neonatal ICU admission	46	13	3.6 (2.1, 6.3)
	Assisted ventilation reqd.	21	5	4.0 (1.5, 10.6)

Fetuses with FGR had significantly increased risk of being low birth weight or having poor neonatal outcome compared to NFG group. In multivariate analysis after adjusting for potential confounding variables, fetal growth remained an independent predictor of low birth weight and poor neonatal outcomes with adjusted Odd Ratios ranging from 4.1 to 36.1. Moreover the risks of poor neonatal outcomes were very similar when analysis was done for the whole group using simulated gestational age.

In the second study [937] 89 women were excluded from the study population because their BW was either < 10th centile (n = 60) or > 90th centile (n = 29). Infants with BW < 10th centile had significantly increased incidence of intrapartum fetal blood sampling and admission to neonatal ICU ($p < 0.05$ for both with chi-square analysis) compared to infants with BW between 10th to 90th centile. Infants having BW > 90th centile had increased incidence of caesarean section ($p < 0.05$).

Of the remaining 196 fetuses, 75 showed evidence of inadequate growth (IFG group) while the remaining 121 formed comparator group (AFG group). Babies in the IFG group had a significantly higher incidence of admission to the Neonatal ICU (OR 3.1, 95% CI 1.19-8.52, p value < 0.05), and higher incidence of meconium staining but this was not statistically significant (OR 1.40, 95% CI 0.64-3.03, p value 0.36). No difference was observed between the two groups regarding all other outcomes.

Evidence summary

Inadequate fetal growth detected by US is associated with an increased risk of low birth weight and poor neonatal outcome.

Fetuses with evidence of inadequate growth on US but with BW appropriate for GA, have a similar risk of obstetric and neonatal complications as fetuses with adequate growth.

12.13 Ultrasound for Amniotic fluid volume

Description of included studies

The first cohort study conducted in USA [938] examined fetal growth and perinatal outcomes in pregnancies with isolated oligohydramnios by using data from the multicentre clinical trial of

Routine Antenatal Diagnostic Imaging with Ultrasound (RADIUS trial). The study population for this cohort (n = 7549) included English speaking women more than 18 years of age with singleton pregnancy, known LMP and GA < 18 wks in the screening arm of trial only, that is, those who underwent US screening twice at 15-22 and 31-35 weeks. Oligohydramnios (OH) was defined as AFI ≤ 5 cms and clinicians were blinded to the results. This cohort was use to describe the incidence and conditions associated with OH. Further to examine perinatal outcomes, women with OH were compared with those having normal AFI (Normal/N group, n = 7215). This comparison was made in both groups. GROUP 1 with associated maternal/fetal conditions (PROM, congenital malformations, HT, DM, IUGR, post-term) and GROUP 2 without any such condition. Isolated OH was defined as OH in women without any associated maternal/fetal condition. Chi-square test was used for comparison and RR with 95% CI calculated wherever appropriate. [EL 2+]

The other study is a nested case-control study from USA [939] carried out to determine whether hydramnios is associated with increased risk of adverse perinatal outcomes. Computerized records of all US examinations carried out from 1986-1996 were reviewed to identify singleton pregnancies in which AF volume was assessed. Cases were defined as pregnancies complicated by hydramnios after 20 wks gestation and controls included all singleton pregnancies having normal AF volume on US after 20 weeks. Hydramnios was taken as AFI ≥ 25 cms or depth more than 8 cms measured in a single vertical pocket or sonographers subjective impression. Multiple gestations and OH cases were excluded. Blinding is not specified. Comparison was made for adverse perinatal outcomes using chi-square test / Fischer exact test for dichotomous variables and Student 't' test for continuous variables. Confounding variables known to influence perinatal outcomes were analyzed in a multiple logistic regression model. [EL 2 +]

Findings

In the cohort study OH was diagnosed in 113/7549 of the study cohort and among these, 47% had certain associated maternal/fetal conditions leaving 60 cases with isolated OH. To compare perinatal outcomes, all cases of OH including those from the other arm of trial (n = 164) were used. OH in pregnancies associated with unfavourable maternal/fetal conditions (GROUP 1) had higher risk of adverse perinatal outcomes, but Isolated OH (in GROUP 2) had perinatal outcomes similar to those with normal AFI.

Values in table below are given as percentage.

Outcome	GROUP 1			GROUP 2		
	OH (n=78)	N (n=644)	RR (95%CI)	OH (n=86)	N (n=6571)	RR (95%CI)
Preterm delivery	24.4	13.2	1.9 (1.2-3.1)	3.5	4.1	0.9 (0.3-2.7)
Caesarean	24	29	0.9 (0.6-1.3)	19	14	1.4 (0.8-2.4)
Apgar < 7 (5 min)	7.7	3.1	2.2 (1.1-4.7)	1.2	1.2	1.0 (0.1-7.0)
Perinatal mortality	5.1	1.2	4.1 (1.3-13.4)	0	0.5	0
Severe morbidity	7.7	5.3	1.5 (0.5-3.8)	1.2	0.8	1.4 (0.2-10.3)
Moderate morbidity	6.4	5.9	1.1 (0.3-2.9)	1.2	2.2	0.5 (0.1-3.8)

Severe morbidity included grade IV ROP, BPD, ventilation more than 48 hours, intestinal perforation due to NEC, grade III or IV of IVH, subdural/cerebral haemorrage, neonatal seizures, chest tube insertion, documented neonatal sepsis, special care nursery stay ≥ 30 days.

Moderate morbidity included presumed neonatal sepsis, Oxygen requirement > 48 hours, NEC without perforation, IVH grade I or II, fracture of clavicle or other bone, facial nerve or brachial plexus injury, special care nursery stay ≥ 5 days.

In the nested case-control study US examinations were done in 40,065 women during the study period. After exclusion, 370 cases with hydramnios and 36,426 controls with normal AF volume were identified. Perinatal mortality rate (PMR) was more than 3 times higher, fetal anomalies 25

times higher, rate of caesarean section 3 times higher and diabetes 6 times higher in cases compared to women with normal AF volume.

Outcome	Cases	Controls	RR (95% CI)
PMR (per 1000 births)	49	14	3.4 (2.2-5.4)
Fetal anomalies (in %)	8.4	0.3	25.4 (17.4-37.2)
FGR (in %)	3.8	6.7	0.6 (0.3-0.9)
Caesarean (in %)	47	16.4	2.9 (2.6-3.2)
Diabetes (in %)	19.5	3.2	6.0 (4.9-7.5)

After controlling for confounding variables in a regression model, women with hydramnios still had increased risk of perinatal mortality (RR 3.8, 95%CI 1.9-7.3) and fetal anomalies (RR 18.2, 95%CI 8.7-38.2).

Evidence summary

Pregnancies with reduced amniotic fluid volume and no associated maternal or fetal conditions do not show an increased incidence of obstetric interventions and adverse perinatal outcomes. However oligohydramnios in the presence of pregnancy complications is associated with an increased risk of preterm delivery and perinatal death.

Increased amniotic fluid volume in pregnancies is associated with increased risk of maternal diabetes, fetal anomalies and perinatal mortality.

12.14 Doppler Ultrasound

Description of included studies

A Cochrane review[575] was carried out to assess the effectiveness of routine Doppler US on obstetric practice and pregnancy outcomes in unselected and low risk pregnancies. It included all randomized and quazi-randomized controlled trials where routine Doppler US of umbilical artery and/or uterine artery was done in both unselected and low risk pregnant women. Primary outcome measures were induction of labour, caesarean section, preterm delivery < 28 and < 34 weeks, all deaths (perinatal, neonatal, and infant), neurodevelopment at 2 years of age, and maternal psychological effects. The Cochrane Pregnancy and Childbirth Group Specialized Register and Cochrane Controlled Trial Register were searched. Two independent reviewers evaluated the trials for methodological quality and inclusion criterion. Additional information was sought from authors of two trials by personal communication. Data was extracted by both reviewers independently and double checked for discrepancies. Statistical analysis was performed using RevMan software and stratified analysis was planned for single, multiple and Doppler in all versus no Doppler/selective Doppler. [EL 1++]

Findings

Five trials were included – two studied unselected population and three only low risk populations. A total of 14,338 pregnant women were recruited. Three trials evaluated umbilical artery Doppler only and used sealed envelopes for randomization. The other two evaluated both umbilical and uterine artery waveforms and in addition used serial US or serial Doppler for the population. The methodological quality of all included studies was generally good. No data were available for prespecified outcomes of acute neonatal problems, long term neurodevelopment and maternal psychological effects. Due to the small number of included trials, no stratified analysis was performed.

Routine Doppler US (umbilical and/or uterine) versus no/concealed/selective Doppler US

Meta-analysis of four trials showed no differences between the two groups in antenatal admissions or other tests of fetal well being, induction of labour, instrumental deliveries, caesarean section,

neonatal interventions and overall perinatal mortality. 3 trials reported perinatal mortality for fetuses/neonates without congenital anomalies, but there was heterogeneity of results (chi-square 10.44, $p < 0.025$) with one trial finding increased perinatal mortality in the screened group (OR 3.31, 95%CI 1.37-2.53).

Serial US and Doppler US versus selective US

A single trial compared the two groups and no difference was found between them for all the primary outcomes. More babies in the screened group were of BW < 10th and < 3rd centile.

Evidence summary

Existing evidence shows that routine use of Doppler US (umbilical and/or uterine) in low risk or unselected populations does not seem to be beneficial either for mother or baby.

12.15 Customized fetal growth charts (CFGC)

Description of included studies

A prospective non-randomized controlled trial in UK[567] was carried out to evaluate the effect of a policy using serial SFH measurements plotted on CFGC compared with routine antenatal care policy of recording SFH against women's GA. Two similar catchment areas (in terms of distance from hospital, ethnicity and socio-economic background of population, number of referrals per year) of a tertiary level hospital served by separate and non-overlapping groups of community midwives and GP's were selected as the study and control group. The study commenced in May 1994 and ended in March 1995. Study group comprised all singleton pregnancies (n=734) booked before 22 weeks GA and issued CFGC, but 67 were excluded due to miscarriage or migration to other areas before delivery. The control group included 605 consecutive singleton pregnancies booked before 22 wks and delivered in the hospital. Primary outcomes measured were the number of SGA (< 10th centile) and LGA (> 90th centile) babies detected antenatally in each group. Secondary outcomes were the total number of investigations performed in each group including referrals to US department/pregnancy assessment unit, and admissions to the ward. Sample size was calculated to detect an increase of 25% detection of SGA at significance level of 5% and power of 80%. Blinding of outcome investigator and concealment of allocation was not possible due to the study design. [EL 1 -]

The second study was a population-based cohort study [940] using the Swedish Birth Register. Two standards for estimating birthweight were constructed from the database – a fixed population one based on gender and gestational length, and an individually customized one with further adjustment for maternal height, weight, parity and ethnic group. SGA determined by the population standard was termed SGA (pop.), by the customized standard as SGA (cust.), and by both standards as SGA (both). In both the groups, SGA was defined as the lowest 10%, 5% or 2.5% of birth-weights in the population. Risks of stillbirth, neonatal death and Apgar score below 4 at 5 minutes were then compared in infants classified as SGA by the two standards to that of non-SGA infants (classified using both standards). The cohort included all recorded births from 1992-95 and the study sample excluded multiple births, those with congenital malformations, unknown gestation and those with missing values for the required parameters. All the outcomes were adequately defined, but confounding factors were not controlled for. [EL 2 +]

In the last study [941] the same Swedish database as the one used in the second study, was analyzed retrospectively to examine the potential biases underlying the use of customized standards of birthweight for gestational age. It included all recorded births with complete data for a period of 10 years (1992-2001). Apart from using the same exclusion criterion as the one used earlier, this study also excluded births with GA < 28 weeks in order to ensure comparability between the two groups. After classifying the births as non-SGA (both standards), SGA (cust.), SGA (pop.), and SGA (both), the same outcomes as used in the earlier study were compared. In addition to it, logistic regression models were used to examine the association between the two standards and different outcomes taking into account the effect of potential confounding variables. [EL 2+]

Findings

The baseline characteristics including those related to pregnancy were similar in the two groups in the controlled trial.[567] 96.3% of the issued CFGC were retrieved after birth and most of them had between 3 to 7 measurements plotted.

A significantly higher proportion of SGA infants in the study group were suspected antenatally compared to the control group (47.9% versus 29.2%; OR 2.23, 95% CI 1.12-4.45). Moreover higher numbers of LGA babies were detected before birth in the study group (45.7% versus 24.2%; OR 2.63, 95% CI 1.27-5.45).

No difference was observed between the two groups for obstetric interventions (induction of labour, caesarean section, and instrumental delivery), preterm delivery, admission to special care baby unit, fetal abnormality and resuscitation at birth.

There were significantly fewer referrals from the study group to a pregnancy assessment centre, both in numbers of women referred and total number of visits. Also the number of women admitted to antenatal ward was significantly lower in the study group.

The study sample in the second study [940] was 326,377, and the rates of adverse outcomes were similar between the study group and the excluded group.

Based on the population standard, maternal age < 19 years, primiparity, BMI < 19.9, and maternal height < 154 cms were found to be the risk factors for SGA babies while BMI > 30 and maternal age more than 35 years were the risk factors found with customized standard.

Following is the comparison of risks (Odds ratio) between the two groups using births that are non-SGA by both standards as the reference category.

	Stillbirths	Neonatal death	Apgar < 4
SGA (pop)/non-SGA (cust)	1.2	0.9	1.2
SGA (cust)/non-SGA (pop)	6.1	4.1	2.2
SGA (cust)/SGA (pop)	5.1	3.4	2.0

Compared with births that were non-SGA by both standards, births classified as SGA (cust) had 5-6 times higher risk of stillbirth regardless of whether they were also small by the population standard. In contrast SGA classified by population standard only did not show an elevated risk. For the other two adverse outcomes a similar pattern of increased risk was seen among babies classified as SGA by the customized standard. They had an increased risk of neonatal death (OR 3.4, 95% CI 2.4 to 4.8) and low Apgar score < 4 (OR 2.0, 95% CI 1.7 to 2.3) compared to SGA babies classified by the population standard.

In the third study [941], a total of 782,303 singleton pregnancies at ≥ 28 weeks were included. There was substantial agreement in the classification by the two standards with 95% births classified as SGA or non-SGA by both standards. Analysis of the database showed increased risks of stillbirths (crude OR = 7.8) and neonatal death (crude OR = 6.7) among the SGA (cust.) babies, compared to marginally increased risks for SGA (pop.) births (crude OR 1.4 and 1.3 respectively). The risk among SGA (cust.) babies was even higher than that of SGA classified by both standards (crude OR 5.7 for both outcomes). These results were similar to those of the previous study.

However after controlling for gestational age as the potential confounder, the risk of adverse outcomes in SGA (cust.) babies (adj. OR 2.4 and 2.1) became less than that of SGA by both standards (adj. OR 4.8 and 4.9), and slightly higher to that of SGA (pop) babies (adj. OR 1.6 and 1.5). A substantial number of babies classified as SGA (cust) were born at < 37 weeks compared to the other groups (16.6% versus 7.0% for SGA both standards, 3.4% for SGA pop, and 4.2% for non-SGA). Among the stillbirths and neonatal deaths, the mean gestational age among SGA (cust) births was 234 days and 239 days respectively. This is much lower than that of SGA (both) – 257

and 258 days, and SGA (pop) births – 273 days for both groups. Similar results were seen after controlling for another confounding variable – maternal pre-pregnancy BMI. The authors concluded that the increased perinatal mortality risk among SGA (cust) babies is an artefact due to inclusion of more preterm babies.

Evidence summary

Customized fetal growth charts appear to lead to the antenatal detection of a higher proportion of SGA and LGA babies compared to routine SFH charts, but do not decrease obstetric interventions and adverse perinatal outcomes. However, there is conflicting evidence on the effect of CFGC in identifying SGA babies at increased risk of perinatal mortality. Results from a retrospective analysis of a database indicate that babies with poor delivery outcome are more likely to be categorized as SGA on a customized fetal growth chart compared to a population based standard. Another study using the same population database has attributed these results to confounding variables – preterm babies and mother's BMI. The increased risk was lowered substantially after adjusting for these two factors.

12.16 Health economics evidence

A systematic review of the evidence found no studies concerned with the cost-effectiveness of fetal growth monitoring and so it was decided that a decision analyses model would be developed. For full details of the review and the model, please refer to Appendix B. The GDG felt that through the identification of babies that are small for gestational age, approximately 185 - 225 perinatal deaths could be prevented. Cost-effectiveness analysis showed that if this were the case then SFH measurement followed by ultrasound monitoring of fetal growth would be a cost-effective intervention.'

GDG interpretation of evidence

SGA babies

1. Abdominal palpation is not useful in identifying fetuses at risk.
2. SFH measurement may have limited use in identifying SGA babies but good quality evidence is lacking. Although SFH measurements have limited value in detection of SGA babies, there is no evidence to suggest a change in current practice. There is no evidence to suggest that there is any benefit in measuring SFH prior to 24 weeks
3. Measurement of FAC has some diagnostic value in identifying SGA babies but the studies show statistical heterogeneity.
4. AFI is a poor predictor of SGA babies
5. Doppler examination has limited diagnostic value in the low risk population
6. There is a lack good quality evidence to support the use of customised growth charts in identifying SGA babies

LGA babies

1. SFH - Evidence suggests SFH measurements are not good at predicting LGA babies -
2. There is lack of good quality evidence for the diagnostic value of fetal biometry for LGA. One small study suggested that fetal biometry may be of some value in identifying LGA babies.

Recommendations

Symphysio-fundal height should be measured and recorded at each antenatal appointment from 24 weeks gestation.

A fetal growth scan to detect small-for-gestational-age unborn babies should be offered to women if the symphysio-fundal height measurement is 3 centimetres greater or less than the gestational age in weeks.

Ultrasound estimation of fetal size for suspected large-for-gestational-age unborn babies should not be undertaken in a low-risk population.

Doppler ultrasound should not be used to monitor fetal growth during pregnancy.

Customized fetal growth charts should not be used for screening for small-for-gestational-age babies.

Research recommendations

Further prospective research is required to evaluate the diagnostic value and effectiveness (both clinical and cost-effectiveness) of:

1.customized fetal growth charts,

2.Symphisio-fundal height measurement

3. routine ultrasound in the third trimester in predicting small or large for gestational age babies.

13 Management of specific clinical conditions

13.1 Pregnancy after 41 weeks

Data from one cohort[577] [Evidence level 2a] revealed that, at 40 weeks of gestation, only 58% of women had delivered. This increased to 74% by 41 weeks and to 82% by 42 weeks. Population studies indicate that in women who are healthy and have otherwise uncomplicated pregnancies perinatal mortality and morbidity is increased in pregnancies of longer duration than 42 weeks. The risk of stillbirth increases from 1/3000 ongoing pregnancies at 37 weeks to 3/3000 ongoing pregnancies at 42 weeks to 6/3000 ongoing pregnancies at 43 weeks.[577] [Evidence level 2a] A similar increase in neonatal mortality is also reported.

Ultrasound assessment of fetal size is associated with a reduction in rates of intervention for post-term pregnancies. One systematic review of nine RCTs found routine ultrasound scanning before 24 weeks to be associated with a reduction in the rate of induced labour for post-term pregnancy when compared with selective use of ultrasound (Peto OR 0.61, 95% CI 0.52 to 0.72). A systematic review evaluated interventions aimed at prevention or improvement of outcomes of delivery beyond term.[578] [Evidence level 1a]

Membrane sweeping

Sweeping the membranes in women at term reduced the delay between randomisation and spontaneous onset of labour, or between randomisation and birth, by a mean of 3 days. Sweeping the membranes increased the likelihood of both spontaneous labour within 48 hours (63.8% versus 83.0%; RR 0.77, 95% CI 0.70 to 0.84; NNT 5) and of birth within 1 week (48.0% versus 66.0%; RR 0.73, 95% CI 0.66 to 0.80; NNT 5). Sweeping the membranes performed as a general policy from 38 to 40 weeks onwards decreased the frequency of prolonged pregnancy: more than 42 weeks: 3.4% versus 12.9%; RR 0.27, 95% CI 0.15 to 0.49; NNT: 11; more than 41 weeks: 18.6% versus 29.87%, RR 0.62; 95% CI 0.49 to 0.79; NNT: 8.[579] [Evidence level 1a]

Membrane sweeping reduced the frequency of using other methods to induce labour ('formal induction of labour'). The overall risk reduction in the available trials was 15%. This risk reduction of a formal induction of labour was 21.3% versus 36.3% (RR 0.59, CI 0.50 to 0.70; NNT 7). The risk of operative delivery is not changed by the intervention. There was no difference in other measures of effectiveness or adverse maternal outcomes. Sweeping the membranes was not associated with an increase in maternal infection or fever rates (4.4% versus 4.5%; RR 0.97, 95% CI 0.60 to 1.57), Similarly, there was no increase in neonatal infection (1.4% versus 1.3%; RR 0.92, 95% CI 0.30 to 2.82). No major maternal side effects were reported in the trials.[579] [Evidence level 1a]

A trial that systematically assessed minor side effects and women's discomfort during the procedure, found women in the 'sweeping' group reported more discomfort during vaginal examination. Median pain scores were higher this group. (Pain was assessed by the Short Form of the McGill Pain Questionnaire, that included three scales: a visual analogue scale (0–10 cm), the present pain index (0–5) and a set of 15 descriptors of pain scoring 0–3). In addition, more women allocated to sweeping experienced vaginal bleeding and painful contractions not leading to onset of labour during the 24 hours following the intervention.[580]

There was no difference in any fetal outcome between the membrane sweeping and the non-membrane sweeping groups. These results must be interpreted with caution due to the presence of heterogeneity. The trials included in this review did not report in relevant clinical sub-groups.

Induction of labour after 41 weeks

The benefit of active induction of labour compared with expectant management is derived from trials of routine induction of labour after 41 weeks. With routine induction, perinatal death was reduced (Peto OR 0.23, 95% CI 0.06 to 0.90) and the rate of caesarean section was reduced (Peto OR 0.87, 95% CI 0.77 to 0.99).[578] [Evidence level 1a] There was no effect on instrumental delivery rates, use of epidural analgesia or fetal heart rate abnormalities during labour with a routine policy of induction of labour.[578] [Evidence level 1a] There was a reduction in meconium staining of the amniotic fluid with routine induction (Peto OR 0.74, 95% CI 0.65 to 0.84). However, this finding is probably related to the increase in meconium-stained liquor seen with increasing gestation in the conservative management arm of these trials.[578] [Evidence level 1a] No difference in maternal satisfaction as measured by one trial with either active management or expectant management was found (Peto OR 0.84, 95% CI 0.57 to 1.24).[578] [Evidence level 1a]

Alternative policy of screening pregnancies from 42 weeks

The systematic review included data on one trial comparing complex antenatal fetal monitoring (computerised cardiotocography, amniotic fluid index and assessment of fetal breathing, tone and gross body movements) to simpler monitoring (standard cardiotocography and ultrasound measurement of maximum pool depth) for identification of high-risk pregnancies from 42 weeks. There was no difference between the two policies with respect to perinatal mortality or caesarean section. However, the number of pregnant women included in this trial was small (n = 145) and, hence, the trial was underpowered to detect any significant differences in perinatal mortality.[578] [Evidence level 1a]

Offering routine early pregnancy ultrasound reduces the incidence of induction for perceived prolonged pregnancy. A policy of offering routine induction of labour after 41 weeks reduces perinatal mortality without an increase in caesarean section rates. The type of antenatal monitoring in the identification of high-risk pregnancies beyond 42 weeks is uncertain (but the simpler modalities used have been as effective as the more complex). There has been no detectable difference in effect of simpler modalities compared with more complex modalities.

Comprehensive information on the induction of labour can be found in the RCOG Evidence-based Clinical Guideline Number 9 (June 2001)[612] and in the NICE Induction of Labour guideline (to be published June 2008).

RECOMMENDATIONS

Prior to formal induction of labour, women should be offered a vaginal examination for membrane sweeping. [A]

Women with uncomplicated pregnancies should be offered induction of labour beyond 41 weeks. [A]

From 42 weeks, women who decline induction of labour should be offered increased antenatal monitoring consisting of at least twice-weekly cardiotocography and ultrasound estimation of maximum amniotic pool depth. [Good practice point]

See also Section 4.6 Gestational age assessment.

13.2 Breech presentation at term

Evidence from the National Sentinel Caesarean Section Audit indicates that about 4% of singleton pregnancies are breech presentation: 3% of term infants, 9% of those born at 33 to 36 weeks of gestation, 18% of those born at 28 to 32 weeks and 30% of those born at less than 28 weeks.[581]

Breech presentation, but not breech delivery, has been associated with cerebral palsy and handicap, due principally to the association with preterm birth and congenital malformations.[582,583]

Interventions to promote cephalic version of babies in the breech position include external cephalic version (ECV), moxibustion and postural management.

ECV involves applying pressure to the pregnant woman's abdomen to turn the fetus in either a forward or backward somersault to achieve a vertex presentation. Recognised complications of ECV attributable to the procedure (and incidence) include:

- fetal heart rate abnormalities: the most common is transient bradycardia (1.1% to 16%)[584–587]
- placental abruption (0.4% to 1%)[584,586]
- painless vaginal bleeding (1.1%)[586]
- admission for induction of labour (3%).[587]

Success rates for cephalic presentation at delivery following ECV in nulliparous women range from 35% to 57% and from 52% to 84% in parous women.[584–586,588] Caesarean section rates as a complication resulting from the procedure range from 0.4% to 4%.[584,588]

Two systematic reviews identified nine RCTs that examined the effect of ECV for breech at term and before term.[589,590] The trials excluded women with uterine scars or abnormalities, multiple gestations, fetal compromise, ruptured membranes, vaginal bleeding or medical conditions, and those in labour.

ECV before 37 weeks of gestation did not make a significant difference to the incidence of noncephalic births at term (three RCTs, n = 889 women, RR 1.02, 95% CI 0.89 to 1.17) nor to the rate of caesarean section (two RCTs, n = 742, RR 1.10, 95% CI 0.78 to 1.54).[589] [Evidence level 1a] Performing ECV at term (defined as 37 weeks of gestation or more in three RCTs, at least 36 weeks of gestation in two RCTs and between 33 and 40 weeks in one RCT) reduced the number of noncephalic births by 60% when compared with no ECV (six RCTs, n = 612 women, RR 0.42, 95% CI 0.35 to 0.50).[590] [Evidence level 1a] A significant reduction in caesarean section was also observed in the ECV group when compared with no ECV (six RCTs, n = 612, RR 0.52, 95% CI 0.39 to 0.71). Five of the trials used tocolysis routinely or selectively[585,588,591–593] and in one of them,[586] no tocolysis had been used. [Evidence level 1a]

Various interventions have been tried to increase the success rates of ECV. These include the routine or selective use of tocolysis, the use of regional analgesia, the use of vibroacoustic stimulation and amnioinfusion. A systematic review of six randomised and quasi-randomised trials comprising 617 women with a breech presentation at term was identified.[594] Routine tocolysis with betamimetic drugs was associated with a 30% increase in the chances of successful ECV (RR 0.74, 95% CI 0.64 to 0.87). This review also showed that the rate of caesarean section was reduced in the group of women who had tocolysis (RR 0.85, 95% CI 0.72 to 0.99). No differences, however, were reported in rates of noncephalic births at term (RR 0.80, 95% CI 0.60, 1.07). [Evidence level 1a] None of the RCTs used newer tocolytics and the effectiveness of these is uncertain. There is also not enough evidence to evaluate the use of fetal acoustic stimulation in midline fetal spine positions, or epidural or spinal analgesia.

An RCT[595] conducted in the USA evaluated the value of performing pelvimetry in predicting who would deliver vaginally compared with using clinical examination.[235] Women with a breech presentation at term were studied. In the first group, pelvimetry results were revealed to the obstetricians and used as a basis for the decision on mode of delivery. In the second group, pelvimetry results were not disclosed and mode of delivery was decided clinically. Main outcome measures (a priori) were the rates of elective and emergency caesarean section and the early neonatal condition. There was no effect of pelvimetry on the vaginal delivery rate or the overall caesarean section rate but use of pelvimetry lowered the emergency caesarean section rate by half (RR 0.53, 95% CI 0.34 to 0.83). [Evidence level 1b]

It is not certain from this evidence whether magnetic resonance imaging pelvimetry selects cases accurately for vaginal delivery or whether knowledge of pelvic adequacy gives the obstetrician confidence in allowing a trial of vaginal delivery.[596]

ECV at term for women with a singleton breech presentation reduces the number of noncephalic births. When ECV is carried out, tocolysis reduces the chances of failed external cephalic version. ECV is associated with adverse maternal and fetal outcomes, which can be minimised by fetal monitoring during the procedure.

Postural management to promote cephalic version entails relaxation with the pelvis in an elevated position. This is usually achieved either in a knee-to-chest position or in a supine position with the pelvis elevated by a wedge-shaped cushion. Maternal postural techniques have been assessed in a

systematic review of RCTs.[597] The size of all the trials was small and no effect on the rate of noncephalic births from postural management was detected between the intervention and control groups (five RCTs, n = 392, RR 0.95, 95% CI 0.81 to 1.11). Nor were any differences detected for caesarean section (four RCTs, n = 292, RR 1.07, 95% CI 0.85 to 1.33). [Evidence level 1a]

Further guidance on ECV and postural management may be found in the RCOG guideline on the management of breech presentation.[631]

Moxibustion refers to the burning of herbs to stimulate the acupuncture points beside the outer corner of the fifth toenail (acupoint BL 67). Two RCTs on moxibustion were located. One trial assessed the efficacy and safety of moxibustion.[598] The other trial assessed efficacy only.[599] In the first trial,[598] primigravidae in the 33rd week of gestation with breech presentation were identified by ultrasound. In the intervention group (n = 130), women were treated with moxibustion for one week and an additional week for those in whom ECV had not yet occurred. Women in the control group (n = 130) received no interventions for breech presentation. All women with persistent breech presentation after 35 weeks of gestation could undergo ECV. At an ultrasound check at the 35th week of gestation, 75% of babies were cephalic in the intervention group compared with 48% in the control group (RR 1.58, 95% CI 1.29 to 1.94). One woman in the intervention group and 24 in the control group underwent ECV after the 35th week of gestation. Version was not obtained in the woman from the intervention group but was obtained in 19 of the women from the control group. Nevertheless, babies in the moxibustion group were still significantly more likely to be cephalic at delivery compared with babies in the control group (RR 1.21, 95% CI 1.02 to 1.43). [Evidence level 1b]

RECOMMENDATIONS

All women who have an uncomplicated singleton breech pregnancy at 36 weeks of gestation should be offered external cephalic version (ECV). Exceptions include women in labour and women with a uterine scar or abnormality, fetal compromise, ruptured membranes, vaginal bleeding and medical conditions. [A]

Where it is not possible to schedule an appointment for ECV at 37 weeks of gestation, it should be scheduled at 36 weeks. [Good practice point]

Future research

Further research is necessary to determine if tocolysis improves the success rate of ECV.

14 Assessment tool

14.1 The development of an assessment tool

Background

The CEMACH 'Why Mothers Die 2000-2002'[942] report suggested that 'A national guideline for a booking clinic 'risk assessment' chart should be developed to identify those pregnant women for whom midwifery-led antenatal care and birth can be advised, and those for whom specialist or joint care is more appropriate'. The report recommended that every woman should be 'offered the type of care that most suits her own particular requirements'.

This view was supported by the National Service Framework's guidance on maternity services[943] which sets the standard of giving women '…easy access to supportive high quality maternity services designed around their individual needs and those of their babies'.

Introduction

The National Collaborating Centre for Women's and Children's Health (NCC-WCH) was commissioned by the National Institute for Health and Clinical Excellence (NICE) as part of the Antenatal Care Guideline update to develop an Assessment Tool for midwives to use at a first antenatal booking appointment.

Method

The aim was to highlight those items which would identify women as requiring obstetric input into their antenatal care. Given the lack of clinical evidence in this area, it was felt that consensus methodology should be undertaken to decide the content of the assessment tool. The approach adopted was that of a modified Delphi. Delphi participants are generally specifically chosen for their particular expertise in a particular area in our survey they were self-selecting, although we specified that all respondents to the original survey should have an involvement with maternity care; individual specialists were not selected.

Development of an Online Survey

Drawing up the questions:

The possible topics for inclusion were drawn from three sources. Firstly, expert opinion was sought from the Antenatal Care Update Guideline development group (which consists of 2 midwives, 2 obstetricians, 1 GP, 2 service user representatives, 1 ultrasonographer and 1 public health specialist). Further topics were identified through a systematic review of the literature. Additional topics were then taken from a sample of antenatal booking notes (n = 16). In total, 203 topics for possible inclusion in the tool were drawn up. These topics were then subdivided into six areas: Previous Pregnancies (n = 61), Family Medical History (n = 21), Past and existing medical problems (n = 45), Current Pregnancy (n = 18), Social Factors (n = 35) and Personal Factors (n = 23).

1st Consensus Round

The first round of consensus work consisted of an anonymous online survey accessible from the NCC-WCH website. We used online software at www.surveyconsole.com. The survey was aimed at all relevant stakeholder groups. This included midwives, obstetricians, service user representatives, paediatricians, and health visitors.

Publicity

The survey was publicised to the stakeholder groups through various channels:

- via letter to all of the Antenatal Care update Guideline Stakeholders
- letters to some heads of midwifery along with all of the board members of the NCC-WCH.
- adverts in BJOG, the RCOG newsletter and the RCM journal (Midwives).

- online advertisements on the corresponding websites to the journals, as well as on theRCN, NCC-WCH and NICE websites.
- publicised through NICE's Patient & Public Involvement Programme.

The online survey

The survey was accessible on-line for four weeks. Respondents to the survey were asked to rate each of the topics on a scale from 1 to 9 in terms of relative importance in deciding whether a woman required obstetric or midwife-led care, and thus whether the item ought to be included in an antenatal assessment tool. A score of 1 indicated that the respondent considered the topic 'not at all important' whilst a score of 9 was 'very important'. If a respondent felt unsure about a question or unable to answer, they moved on to the next question. To avoid exhaustion bias, the question order was randomised daily.

All respondents to the survey were given the chance to apply online to attend the second round of consensus work. In this way, we ensured that the second consensus sample was a sub-sample of the first.

Before conducting the survey, it had been decided that an overall median score of 1-3 for a topic would indicate consensus that it should not be included, a score of 7-9 that it should be included and a score of 4-6 that there was no overall consensus. However, analysis of the frequency distribution of the median scores from the survey showed a skew towards higher scores and so it was decided that a score of 8-9 would indicate consensus on inclusion, 1-3 would indicate consensus on exclusion, 5-7 would indicate no overall consensus and a score of 4 would be taken to an advisory panel.

The topics with median score 4 (n = 14) were taken to the Antenatal Care update Guideline Development Group at the NCC-WCH – a panel of nine members. Each was asked to rate the topics in the same manner as the survey. It was decided previously that a median score of 1-3 would indicate consensus that the tool should not be included whilst any other score would indicate that the question should be taken to the second round of consensus work. 8 topics were excluded and 6 were taken forward to be voted on in the second round.

Results from the first consensus round

We received 731 online questionnaires which were at least partially complete, of which 566 were fully complete. 48% of the respondents were midwives, 19% healthcare consumers/consumer representatives, 16% medical staff including obstetricians (8.6% of total) and 17% other (which includes health visitors, antenatal teachers etc.) The overall completion to started rate was 48.1%.

Consensus on inclusion was reached on 78 of the topics and consensus on exclusion was reached on 19 of the topics. This left 106 topics to take forward to the consensus conference.

2nd/3rd Round

The second and third round of consensus voting took place during a one day conference consisting of survey respondents who had applied to attend (120 applied, 56 attended).

Selection Procedure

Applicants who wished to apply to attend the conference were asked to complete an online application form. As well as providing contact details, applicants were also asked to provide a supporting statement detailing their current involvement with maternity care. Participants were selected both on the basis of their supporting statement and their geographical location to ensure that as many regions of England and Wales as possible were represented. Originally, it was felt that the delegates should be made up of an equal number of midwives, obstetricians and healthcare consumers. However, after conducting sub-group analysis on the responses to the first round of voting, there was no statistical difference in median scores between the three groups. To confirm this, a randomised sample of the median scores of obstetricians and midwives was compared with the median scores from healthcare consumers. By inspection, there was no statistical difference between the results for the different groups. As a result, more midwives were invited (as many more midwives applied to attend than the other groups).

Voting procedure

At the conference, delegates were presented with those topics where consensus had not been reached in the first round and asked to vote on each in turn using an electronic voting system (supplied by Groupdynamics – www.groupdynamics.co.uk). After the questions were displayed and read out, delegates were given 8 seconds to record their vote. As well as voting electronically, participants were also asked to vote on a paper version so that they could compare their score with the median for the group. The results of the vote on each question were displayed along with the median score. After each topic had been voted on, a frequency distribution of the median scores was analysed. It showed a skew towards lower scores and so it was decided that a median score of 7-9 indicated consensus on inclusion, 1-2 indicated consensus on exclusion and 3-6 indicated no overall consensus. The delegates were then asked to vote on those remaining topics where no consensus had been reached (n = 39). In this round, each vote was preceded by a discussion amongst the delegates in an attempt to achieve consensus.

Results from the 2nd/3rd Round

We reached consensus for inclusion on 14 topics, consensus for exclusion on 83 topics and no overall consensus on 10 topics. From the discussion which followed, it became apparent that further work should be conducted into further developing the tool in order to define a care pathway for women with social risk factors who may benefit from the input of specialists other than an obstetrician.

Evidence statement

This approach showed that it was possible to gain consensus on a range of potential risk factors derived from a number of sources, including systematic reviews, to allow the development of an assessment tool.

Interpretation of evidence

Although it has been possible to agree the basis of an assessment tool it requires further refinement and validation before it can be applied in practice.

Research Recommendation

Multi-centred validation studies are required in the UK to assess the use of the Antenatal care assessment tool. Using structured questions the tool aims to support the routine antenatal care of all women by identifying women who may require additional care. The tool identifies women who:

- can remain within or return to the routine antenatal pathway of care
- may need additional obstetric care for medical reasons
- may need social support and/or medical care for a variety of socially complex reasons.

15 Auditable standards

Criterion	Exception	Definition of terms
A pregnant woman has the offer of an HIV test documented in her notes	A woman known to have HIV infection	
A pregnant woman has the offer of a hepatitis B virus test documented in her notes	A woman known to have hepatitis B viral infection	
A pregnant woman has the offer of a syphilis serology test documented in her notes		
A pregnant woman has the offer of a rubella susceptibility test documented in her notes		
A pregnant woman has the offer of a Down's syndrome screening test documented in her notes		An acceptable test is currently one with a minimum detection rate of 60% and a false positive rate no greater than 5% (see guideline recommendation in Section 9.2)

Appendix A

Declaration of interests

Name	Description (industry/organisation)				
	Personal		Non-personal		Non-current interests
	Specific	Non-specific	Specific	Non-specific	
GDG members					
Jane Anderson					
Chris Barry					
Marie Benton					
Jennifer Elliott					
Rhona Hughes					
Nina Khazaezadeh					
Rachel Knowles					
Anne Longton					
Tim Overton	Treasurer to the British Maternal and Fetal Medicine Society				
Katie Yiannouzis					
NCC-WCH staff					
Rupert Franklin					
Eva Gautam-Aitken					
Paul Jacklin					
Rajesh Khanna					

Name	Description (industry/organisation)				
	Personal		Non-personal		Non-current interests
	Specific	Non-specific	Specific	Non-specific	
Rintaro Mori	Part-time lecturer (since July 2005) – School of public Health, Kyoto University. GBP 125 per day of work. External Supervisor (Seasonal June-November every year) London School of Hygiene and Tropical Medicine. GBP 300 per project plus expenses. Non-pecuniary: Director of CRIPH: Collaboration for Research in International Perinatal Health; Overseas Advisor: Health Policy Unity, the Japan Pediatric Society	Personal family interests: Dr Kyoko Mori (wife). Chief Investigator for Research Fund - Promoting welfare of disabled children: Parental stress of autistic spectrum disorder. GBP 1,240 – T&D Holdings inc.	Supervisor (Principal Investigator: Dr Shuko Nagai) Research Educational Fund. Promoting Neonatal Survival in Developing Countries: a randomised control trial of early skin-to-skin contact between low birth weight infants and their mothers in Madagascar. January 2007 – December 2007. GBP 20,700. Foundation for Advances Studies on International Development Co investigator (Chief Investigator: Professor Takeo Nakayama) Research Fund. Patient Involvement in Guideline Development. April 2007 to March 2010. GBP 124,400. Ministry of Health, Labour and Welfare – the Japanese Government. Co-investigaator (Chief Investigator: Dr Masanori Fujimura) Research Fund. Development of perinatal healthcare network: A comparative study of healthcare professionals' attitudes towards care of extremely premature babies between UK and Japan. April 2007 to March 2010. GBP 165,000. Ministry of Health, Labour and Welfare – the Japanese Government.		
Francesco Moscone					
Debbie Pledge					
Jeff Round					
Anuradha Sekhri					
Roz Ullman					
Martin Whittle	Non-pecuniary: Chair of Steering Group on Ultrasound Screening				
External advisers					
Fiona Ford					
Jane Hawdon	Non-pecuniary: Ad hoc advice and invited lecturer for BFI	Non-pecuniary: Ad hoc advice and host of visits to the UCLH neonatal unit – Bliss			
Anne Longton					

Name	Description (industry/organisation)				
	Personal		Non-personal		Non-current interests
	Specific	Non-specific	Specific	Non-specific	
Guy Rooney Personal pecuniary – specific:	Contacted to speak on behalf of Johnson&Johnson about their new anti HIV drug 'PREZISTA'. The fee includes training/education expenses on presentation. Fee £1000 Contacted to speak on a new vaccine to prevent Human Papilloma virus infection – 'GARDASIL:'. Fee - £265. Merck				

Appendix B

Economic considerations: economic models

B.1 Asymptomatic bacteriuria screening programme

The purpose of the model was to compare the cost effectiveness and cost consequences of two different methods for detecting the presence of asymptomatic bacteriuria (ASB). A decision analytic model was created to compare the two strategies:

1. screening with urine culture
2. screening with leucocyte esterase-nitrite dipstick.

These methods have different sensitivities and specificities and associated costs. Untreated ASB can lead to pyelonephritis, which can lead to increased rate of preterm birth. Screening for ASB can lead to the treatment of women for ABS, prevent cases of pyelonephritis and prevent the costs and consequences of preterm birth. The cost consequences of preterm birth by missing one case of ASB have not yet been included in other economic evaluations and may be extremely high. Therefore a model was constructed to include this parameter.

Literature review

Thirteen papers were identified by the search strategy and the abstracts were reviewed. All the papers were retrieved and reviewed using the standard economic evaluation checklist. Of the 13, four papers contained data that were relevant for the economic model. One study[45] considered the cost consequences of preterm birth.

Designing the model

The clinical effectiveness data needed to construct the model were obtained from the guideline. Additional data that had to be collected to construct the model were the prevalence of pyelonephritis and the prevalence of preterm birth. Data on these parameters were derived from a review showing a range of values that were used in the model and subjected to sensitivity analysis.[351] A meta-analysis was also undertaken by the systematic reviewer on the guideline to provide relevant estimates used in the model.

The cost data included in the model were reported for three levels of analysis:

- screening and treatment for asymptomatic bacteriuria
- screening and treatment for asymptomatic bacteriuria and for treatment for pyelonephritis
- screening and treatment for asymptomatic bacteriuria, treatment for pyelonephritis and the cost of preterm birth.

The model reported the cost effectiveness of the two screening options in the following ratios:

- average cost of screening and treating for asymptomatic bacteriuria per person screened
- average cost of screening and treating for asymptomatic bacteriuria and pyelonephritis per person screened
- average cost of screening and treating for asymptomatic bacteriuria, pyelonephritis and the cases of preterm birth per person screened
- total cost per case of pyelonephritis averted
- total cost per case of preterm birth averted
- incremental cost of moving from dipstick test to a culture test screening programme.

Cost data

The cost data used are shown in Table B.1. All costs apart from the costs of preterm birth were originally reported in US dollars and transformed to UK pounds sterling at the year 2002, using

the Purchasing Power Parity Index taken from the website: www.oecd.fr/dsti/sti/it/stats/ppp.htm, and were inflated to year 2002 prices using the Retail Price Index for Health Services.

The baseline model

The sensitivity of the dipstick was assumed to be 0.72 and the sensitivity of the culture method was assumed to be close to 100%. The value used for the prevalence of pyelonephritis in the treatment was 0.04, while the value used for the prevalence of pyelonephritis without treatment was 0.19. The prevalence of preterm birth for the treatment group was 0.088 and for the untreated group 0.155.

The cost of preterm birth was taken from a UK study[601] and was estimated to be around £14,200. This value was subjected to sensitivity analysis. The incremental cost effectiveness analysis shows that, when taking the cost of treating the cases of preterm birth into account, the dipstick screening method would cost an extra £32,357 for each case of preterm birth averted.

Sensitivity analysis

The parameters examined in the model were the sensitivity of the dipstick method, the prevalence of pyelonephritis among women who are treated for ASB, the cost of preterm birth and the prevalence of preterm birth. Increasing the sensitivity of the dipstick by 10% (from 0.72 to 0.82) led to a reduction in the overall difference in costs between the screening tests (savings reduced to £4 to £5 per test). Threshold sensitivity analysis was undertaken to establish the sensitivity of the dipstick test that would have to be reached in order for both the culture and the dipstick test to have equivalent overall costs when taking all costs (screening, treatment and preterm birth) into account. The threshold was 0.91. A greater sensitivity than this for the dipstick test would make it the preferred method of screening. In reality, such sensitivity is considered to be extremely high and reported only in one study (see Section 10.1).

Overall, preterm birth should be included in the analysis, since the relative cost effectiveness of the tests is sensitive to even one additional case of preterm birth at the higher and lower value of the baseline cost. This has not been explored in economic models published in the literature to date and should be explored further in future studies, alongside more robust UK-based estimates of the long-term costs of preterm birth. Increasing and decreasing the cost estimates of preterm birth by as much as 50% did not change the overall results (favouring the culture method).

B.2 Modelling streptococcus group B screening programme

The purpose of the model was to compare the cost effectiveness and cost consequences of two screening programmes, namely bacteriological screening compared with risk factor screening.

Literature review

Forty-three papers were identified by the search strategy and the abstracts were reviewed. Of these, 19 full papers were retrieved and reviewed using the Drummond checklist. Two unauthored reports were also reviewed.

Tabl B.1 Cost data used in the ASB model

Cost item	Range of values used in the model (£)
Cost of screening[600]	1,242 (sensitivity analysis ± 10% of this value)
Cost of pyelonephritis[600]	1,930 sensitivity analysis (± 10% of this value)
Cost of preterm birth[45]	14,000 to 21,000

None of the economic papers was in a UK setting and the majority of them were from a US setting. Sources of effectiveness data and the evidence for the clinical outcomes and all the ranges of their values were based on the clinical effectiveness data of the guideline using the best available data from the literature and expert opinion.

The lack of some definitive effectiveness data, such as the prevalence of early-onset group B streptococcus among positively screened women makes the completeness of the model

problematic and therefore no conclusion can be reached from this model as far as the two screening procedures are concerned.

Future cost effectiveness research should include these parameters in order for a model to be estimated.

B.3 Modelling syphilis screening programme

The purpose of the model was to compare the cost effectiveness and cost consequences of two screening programmes, namely universal screening versus selective screening. The reason for this specific comparison was to consider a change in policy from the current practice of universal screening towards a more limited and potentially more cost effective approach. This is because the prevalence of syphilis is the UK is very low and, in addition, there maybe identifiable groups of women who are at higher risk of contracting syphilis. A programme of selective screening could significantly reduce the number of women screened,[602] while at the same time identifying a relatively high proportion of carriers of the disease (100% for universal versus 70% to 78% for selective).

Literature review

In all, 47 papers were identified by the search strategy and the abstracts were reviewed. Of these, 25 full papers were retrieved and reviewed using the Drummond checklist. All the papers had some useful background information and contributed to the general structure of the model.

Data were extracted from one paper only, as it used UK-based cost data, post-1995, and UK effectiveness data, and considered the same screening alternatives.[602] This study identified possible screening strategy for the programme to compare their effectiveness and cost effectiveness to assess whether screening for syphilis is still necessary. Three possible strategic options for antenatal screening were examined:

- to continue the current universal screening programme
- to target the screening programme to pregnant women in high-risk groups
- to stop the screening programme entirely.

The study population comprised pregnant women in the UK, from which three high-risk groups were identified when considering screening strategy options: pregnant women in the Thames region, women from non-white ethnic groups and women born outside the UK.

Although the incremental cost per case detected of universal screening was high and although selectively screening groups by country of birth or by ethnic group could detect at least 70% of cases, this could be politically and practically difficult. Targeting by region would also be effective but difficult to implement.

The published evidence from this study is not ideal because the validity of estimate of measure of effectiveness was not reported. Also, the analysis did not include any cost to pregnant women such as anxiety or time taken to attend clinics and to set up partner notification services. Furthermore, the cost for the treatment of a woman's sexual partner was not calculated.

Designing the model

Because of the lack of data on the parameters discussed above, a model approach similar to the above study was adopted in this guideline. The model set out to estimate the total costs of screening and cost of syphilis treatment in pregnant women positively screened, cost of preterm birth, lifetime cost of congenital syphilis, and cost of spontaneous fetal loss.

Cost data

The cost data used are shown in Table B.2.

Table B.2 Cost data used in the syphilis model

Cost item	Range of values used in the model (£)
Cost of screening[602]	0.9 to 2.85

Cost of preterm birth[601]	14,000 to 145,000
Lifetime cost of congenital syphilis	Arbitrary value due to lack of literature data (arrived at through consensus with the Guideline Development Group)
Cost of treatment[602]	519 to 1,364

The evidence for the clinical outcomes and all the ranges of their values were based on the clinical effectiveness data of the guideline using the best available data from the literature and expert opinion.

Baseline results of the model

The model indicated that selective screening could detect from 70% (worse case scenario) to 78% of women affected by syphilis and that it is more cost effective even if preterm birth and lifetime costs of congenital syphilis cases are included. This model did not consider the value forgone of a programme that results in more cases of preventable congenital syphilis. This may be very high and therefore the selective screening programme may not be acceptable because of these losses.

Sensitivity analysis

Parameters examined in the sensitivity analysis were rate of transmission of congenital syphilis from the mother to the fetus (5%, 10%, 15%, 20%, 30%). Keeping all parameters constant, a rate of transmission more than 20% made the universal screening a more cost effective option in comparison with selective screening. The results are found to be insensitive to the sensitivity of the screening test.

B.4 Structural anomalies

Economic evaluation of screening for congenital cardiac malformations using a four chamber ultrasound scan versus the four chamber with outflow tract view

As part of the guideline on Diabetes in Pregnancy, a decision tree model was developed in Microsoft Excel® to assess the cost-effectiveness of mid-trimester screening for congenital cardiac malformations in pregnant women. It was felt that this model was of relevance within the context of the antenatal care guideline and therefore the model has been adapted for use with the antenatal population. Current UK practice is to screen pregnant women using a four chamber ultrasound scan at a gestational age of 20 weeks but using a four chamber view plus the outflow tract (the so called five chamber view) may allow the detection of some abnormalities, such as transposition of the great arteries (TGA) and tetralogy of Fallot, which are not usually visible with a four chamber view.

There are two principal reasons why it may be beneficial to screen for congenital cardiac malformations:

i. It allows the mother to consider termination of pregnancy, and
ii. Improved outcomes maternal and neonatal outcomes.

There are difficulties in considering the cost-effectiveness of screening using termination as a 'desirable outcome' and the evidence that screening produces a survival advantage is limited [944]. Nevertheless, there is some evidence suggesting that an antenatal diagnosis of TGA may reduce mortality. This is important for this analysis because TGA is an anomaly that would not normally be identifiable with a four chamber view but can be with an additional outflow tract (five chamber) view and therefore, the model particularly focuses on the cost-effectiveness of antenatal diagnosis of TGA.

The basic decision tree structure is illustrated in Figure B1. At 20 weeks women either receive a four chamber view ultrasound scan or a five chamber view ultrasound scan. Women with a positive scan result will then be sent for foetal echocardiography to confirm diagnosis and guide subsequent treatment. If this result is also positive women have the option to either terminate or proceed with the pregnancy. If they continue with the pregnancy they either give birth to a live baby or suffer a pregnancy loss. A proportion of babies born with cardiac malformations will have TGA and they may either survive or die.

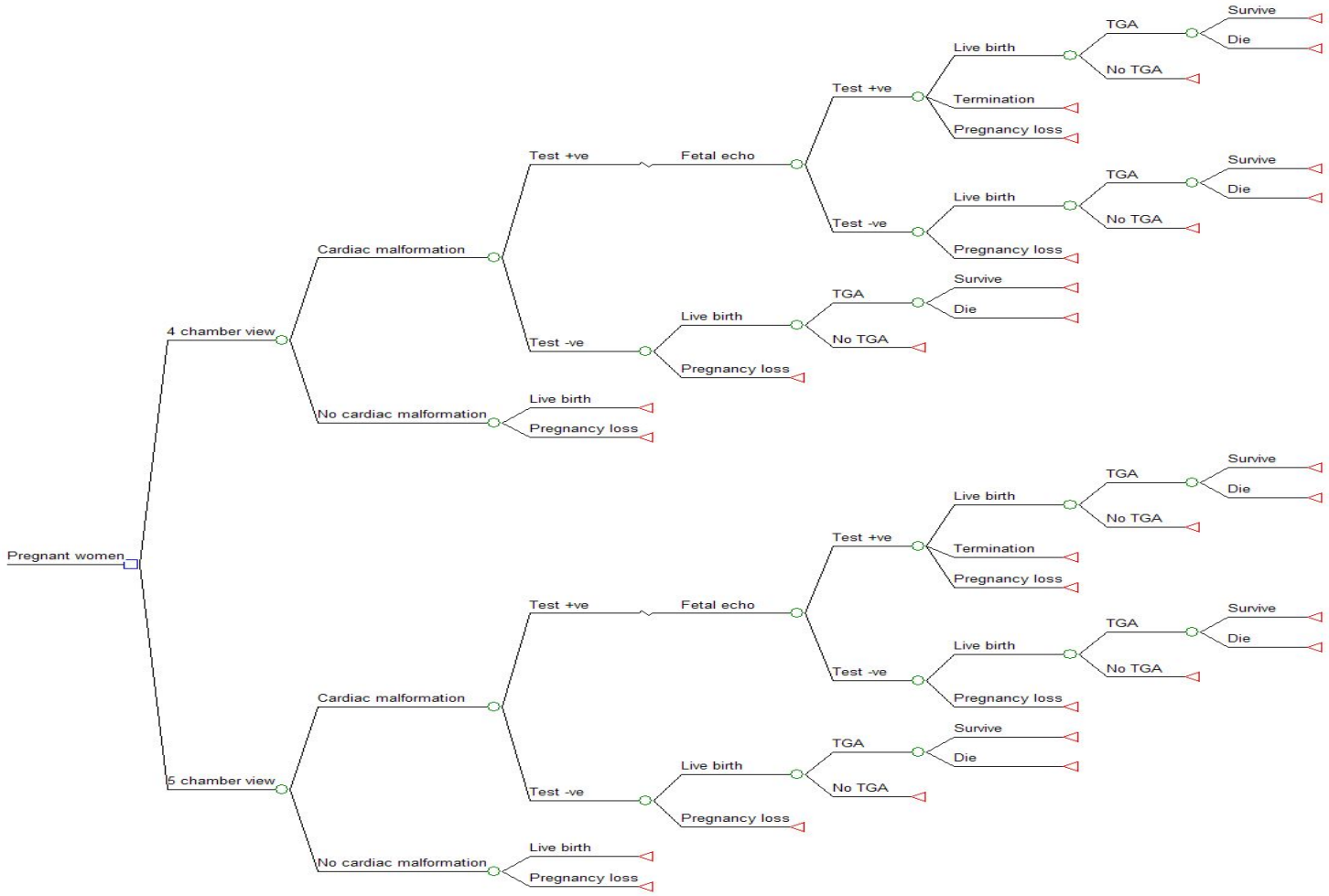


Figure B1 The decision tree structure

Model parameters

Table 1 Population characteristics

Characteristic	Value	Source	Notes
Population	1,000		Event data is often given as a rate per 1,000 and the ICER from the model is not affected by population size.
Prevalence of cardiac malformations at 20 weeks	0.0056	Wren et al. (2000)[945]	Value is for prevalence at birth[1]
Proportion of cardiac malformations that are TGA	0.043	Wren et al. (2003)[945]	
Pregnancy loss post 20 weeks (no cardiac malformations present)	0.0115	Ritchie et al. (2004) [804] www.nhshealthquality.org/nhsqis/files/Ultrasound%20CAR.pdf	Derived from survival probability from 2nd trimester to birth
Pregnancy loss post 20 weeks (cardiac malformations present)	0.0405	Ritchie et al. (2004)[804]	Derived from survival probability from 2nd trimester to birth

Table 2 Costs

Characteristic	**Cost**	**Source**	**Notes**
four chamber view scan	£34	NHS Ref Costs 2005-06	Mean value for a maternity ultrasound
five chamber view scan	£46	GDG	Based on estimate that appointment slots would be 20 minutes, compared to 15 minutes for a four chamber view[2].
Fetal echocardiography	£62	NHS Ref Costs 2005-06	Mean value for an echocardiogram
Termination of pregnancy	£492	NHS Tariff 2006/07	Value for a surgical termination
Birth	£3,000	NHS Ref Costs 2003; NHS General Medical Services Revised Fees and Allowances 2003-04	A weighted average including birth, GP fees, other maternity events, outpatient visits, neonatal care, tests

Table 3 Test characteristics

Characteristic	Value	Source	Notes
four chamber view sensitivity	0.73	Smith RS et al (1997)[946] http://www.d4pro.com/IDM/site/idm4cr.pdf	
four chamber view specificity	1.00	Smith RS et al (1997) [946]	

[1] The prevalence of cardiac malformations at 20 weeks may be slightly higher than at birth if we consider that terminations and foetal death are higher in affected pregnancies than non-affected. This is likely to represent a small bias in the model against the five chamber view but this is not important if the five chamber view is shown to be cost-effective

[2] The five chamber view cost does not take into account the fact that the number of equivocal scans is likely to increase

five chamber view sensitivity	0.82	Smith RS et al (1997) [946]	
five chamber view specificity	1.00	Smith RS et al (1997) [946]	
TGA proportion of defects only detectable on five chamber view	0.36	Ogge G et al (2006) [947]	In 58 cases of congenital cardiac defects, 14 were only usually diagnosable with outflow-tract view. Of these, 5 were TGA[3]
Foetal echocardiography sensitivity	0.92	http://www.unepsa.org/china/ab/1327.HTM - accessed 30/08/2006	
Foetal echocardiography specificity	0.95	http://www.unepsa.org/china/ab/1327.HTM - accessed 30/08/2006	
Termination of pregnancy rate diagnosis of cardiac malformation	0.25	Ritchie et al. (2004)[804]	

Table 4 Outcomes and QALYs

Characteristic	Value	Source	Notes
Life expectancy if TGA successfully treated (yrs)	76	Office of National Statistics, 2006	UK life expectancy at birth (2003-05) is 76.6 years for males and 81.0 years for females
TGA mortality antenatally detected	0.018	Wessex UK (1994-2005); Eurocat; Bonnet 1998-97, Bonnet 1998-2002; Kumar 1988-96;	Results reported in presentation by Wellesley et al. (4/226)
TGA mortality postnatally detected	0.166	Wessex UK (1994-2005); Eurocat; Bonnet 1998-97	Results reported in presentation by Wellesley et al. (70/422)
QALY weight successful TGA treatment	1.0		Assumes no long-term morbidity associated with successful TGA treatment
Annual discount rate	3.5%	NICE guidelines technical manual	

Results

With baseline results, the 4-chamber view is the cheapest strategy for screening for cardiac malformations due to the higher cost of the five chamber ultrasound scan. However, the higher sensitivity of the five chamber view results in 0.334 more live births per 1,000 pregnancies with antenatally detected cardiac malformations (table 6). A proportion of these, 36% at baseline, would be TGA and given the baseline assumption about lower mortality for TGA with an antenatal diagnosis, this leads to a concomitant 1.8 neonatal deaths averted per 100,000 pregnancies (table 7). Following on from these cost and effects the estimated incremental cost-effectiveness ratio for the five chamber view is £24,125 per QALY.

[3] Note only one TGA was actually detected giving a five chamber view sensitivity for detecting TGA of only 20%

Table 5 Costs of four chamber and five chamber strategies

Screening method	Cardiac scan	Foetal echo	Termination of pregnancy	Birth	Total cost	Cost per patient
4-chamber view	£34,000	£253	£463	£2,962,306	£2,997,022	£2,997
five chamber view	£46,000	£285	£520	£2,691,973	£3,008,777	£3,009

Table 6 Outcomes of four chamber and five chamber strategies

Screening method	Pregnancy loss	Termination of pregnancy	Healthy live birth	Live birth Cardiac malformation detected	Live birth Cardiac malformation not detected
4-chamber view	11.62	0.94	982.96	2.706	1.765
five chamber view	11.62	1.06	982.96	3.040	1.320

Table 7 Incremental cost-effectiveness of five chamber view

Screening method	Incremental values					
	Costs	Antenatal dx of cardiac malformations	Antenatal TGA dx	Neonatal deaths averted	QALYs	ICER
five chamber view	£11,755	0.33	0.12	0.018	0.487	£24,125 per QALY

Sensitivity analysis

A number of one-way sensitivity analyses were undertaken to assess to what extent uncertainty over certain parameter values was likely to be important in interpreting the baseline results. These sensitivity analyses are shown below[4]:

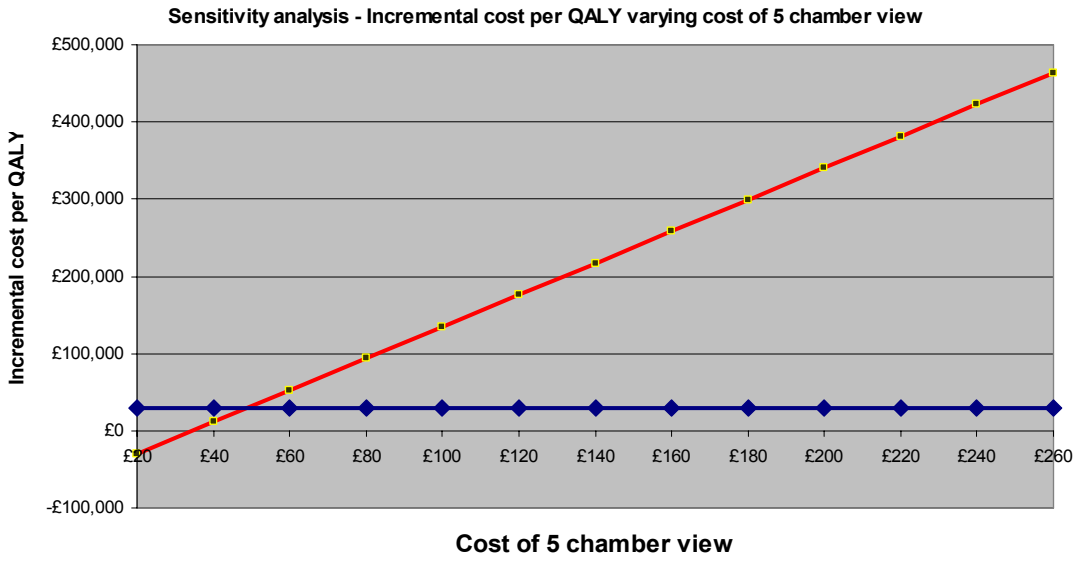


Figure B.2

[4] A £30,000 cost per QALY threshold is indicated in each of the figures

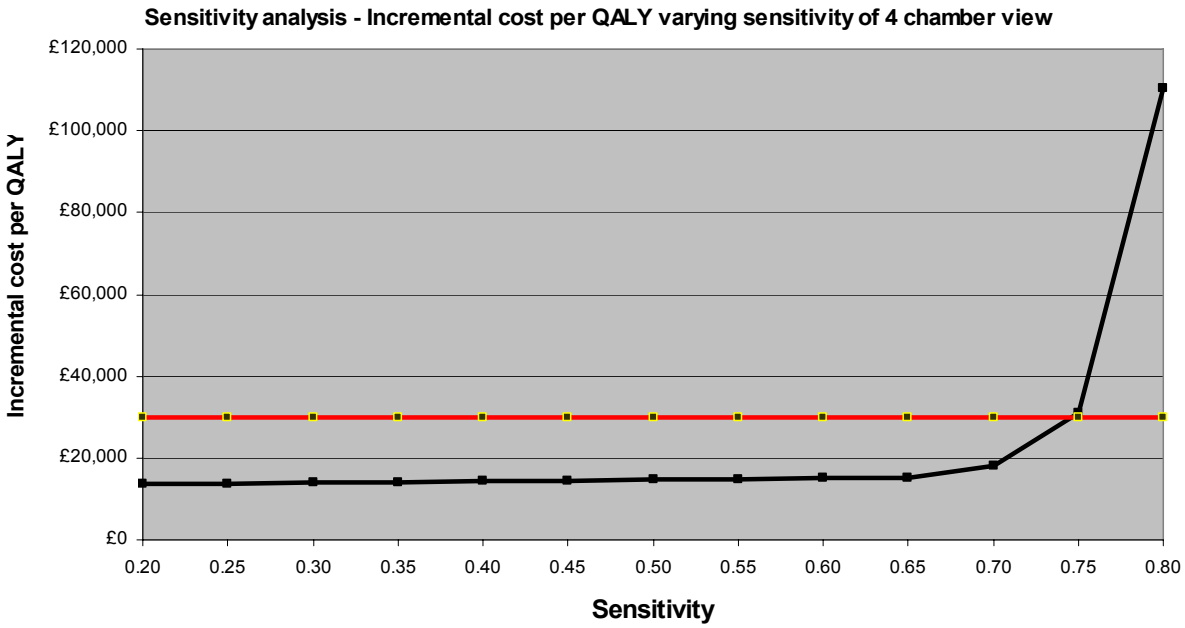


Figure 3

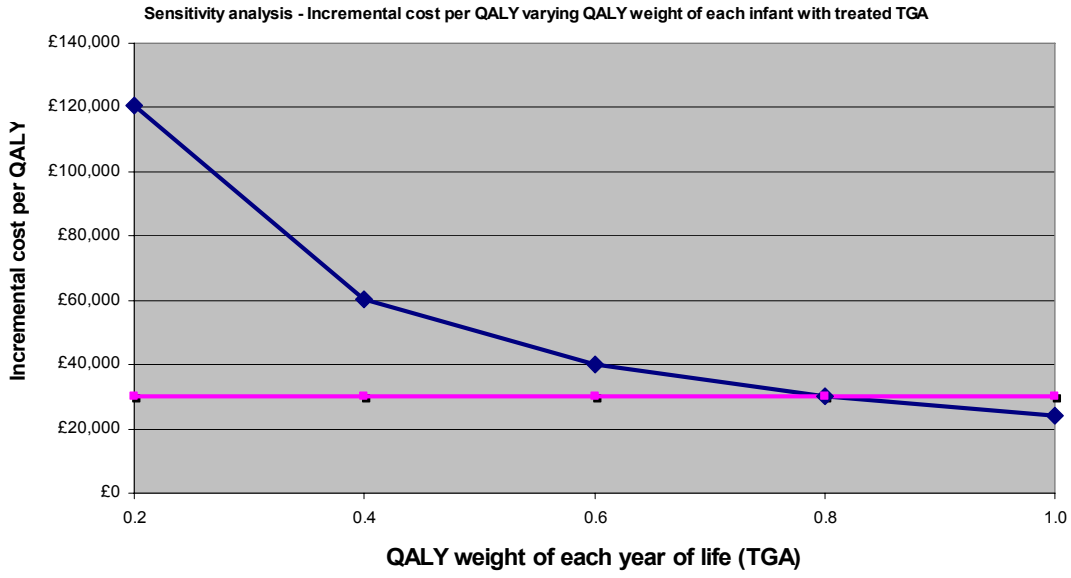
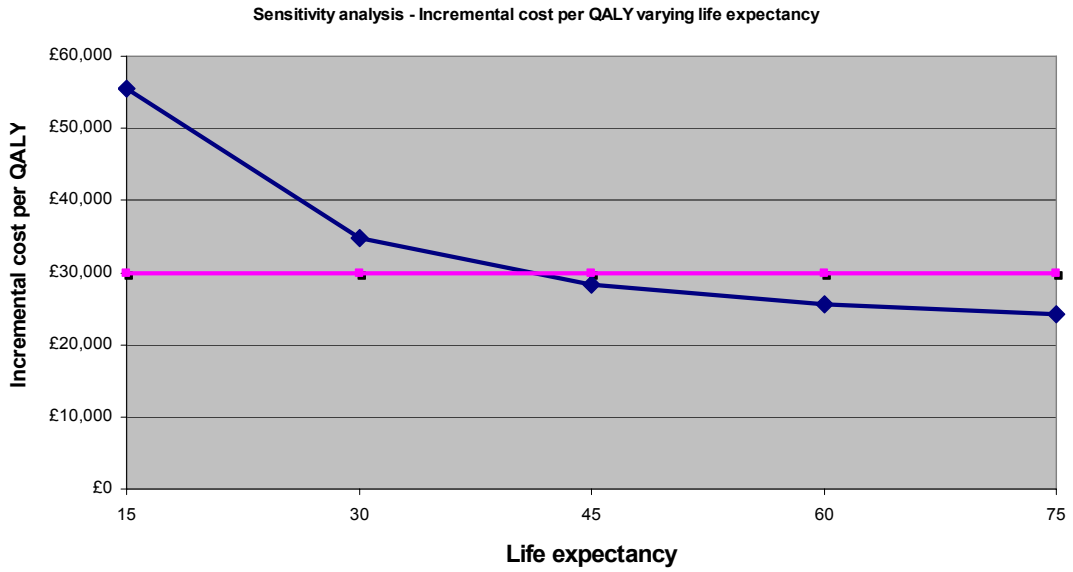
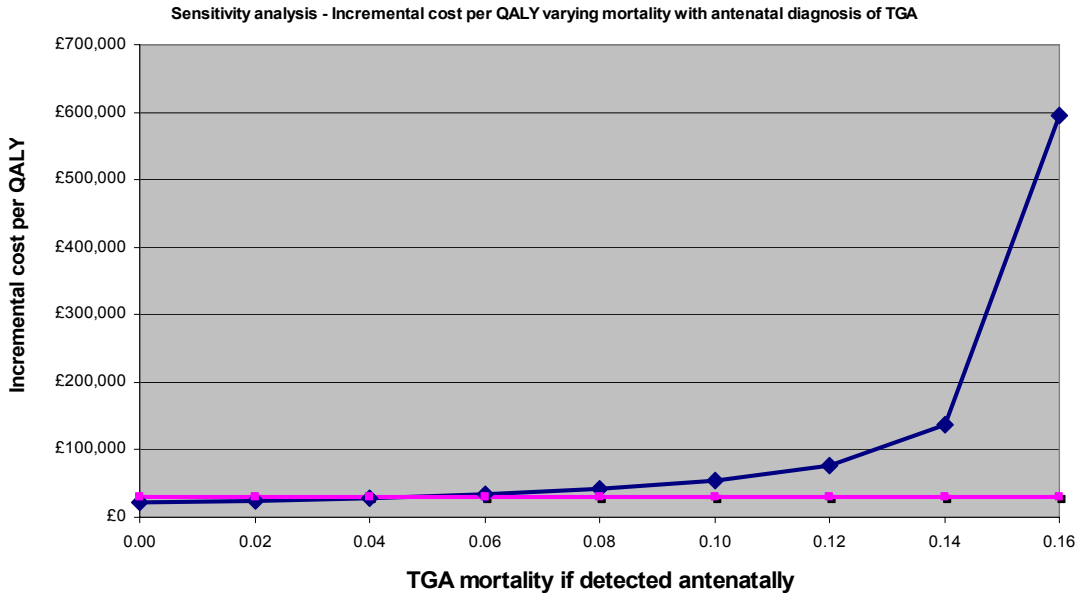


Figure 4


Sensitivity analysis - Incremental cost per QALY varying life expectancy
Incremental cost per QALY
£60,000
£50,000
£40,000
£30,000
£20,000
£10,000
£0
15
30
45
60
75
Life expectancy

1

2 **Figure 5**


Sensitivity analysis - Incremental cost per QALY varying mortality with antenatal diagnosis of TGA
Incremental cost per QALY
£700,000
£600,000
£500,000
£400,000
£300,000
£200,000
£100,000
£0
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.14
0.16
TGA mortality if detected antenatally

3

Figure 6

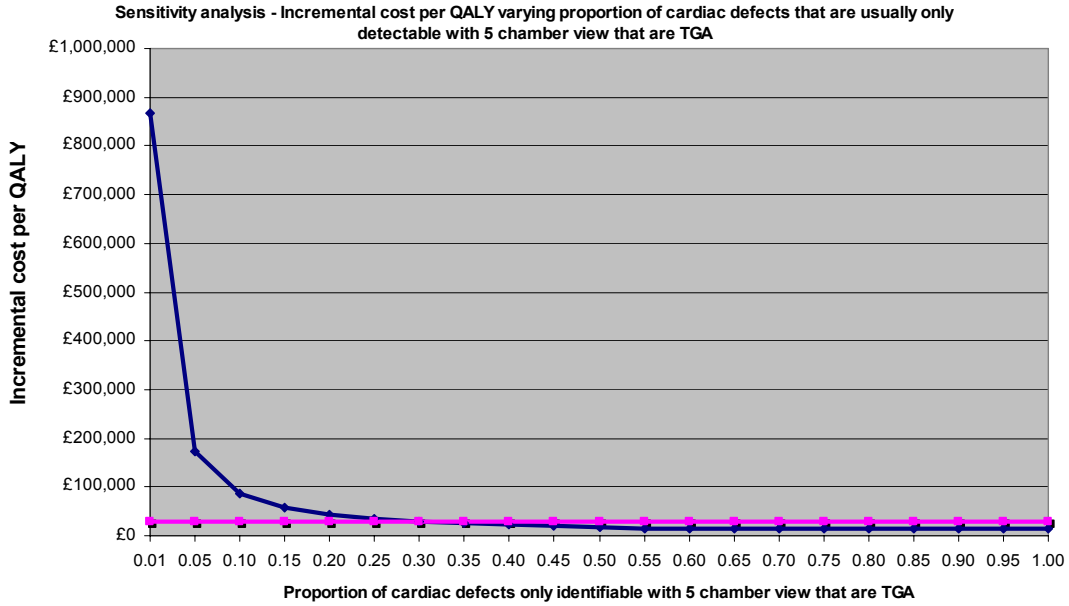


Figure 7

Discussion

With baseline values this model suggests that the five chamber view is borderline cost-effective for screening for cardiac malformations in pregnant women relative to the 4-chamber view. The higher costs of the five chamber view make it the more expensive option and the ICER of £24,125 is just above the £20,000 per QALY threshold used by NICE as a willingness to pay benchmark for cost-effectiveness[5]. However, it is likely that there are benefits of the five chamber view over and above those measured by the antenatal diagnosis of TGA.

The model assumes that TGA is the only cardiac malformation where an antenatal diagnosis confers a benefit in terms of improved health outcomes for infant and/or mother. The model's baseline parameter values give a TGA prevalence of approximately 0.24 per 1,000 pregnancies. With the model's baseline assumptions for TGA mortality detected and not detected antenatally, one neonatal death would be averted for every seven TGA malformations detected. If a five chamber view screen detected all TGA malformations then the number of pregnancies needed to screen with five chamber view to avert one neonatal death compared to 4-chamber view would be approximately 28,000.

The literature does not generally provide test sensitivity and specificity for individual cardiac malformations, instead giving a value for detecting any cardiac malformation. Hence, the improved sensitivity of the five chamber view compared to 4-chamber arises because it detects additional malformations that cannot be usually observed with

[5] NICE states that interventions with a cost per QALY of less than £20,000 should be considered cost-effective but there must be 'strong reasons' for accepting anything with a cost per QALY of greater than £30,000 per QALY as cost-effective

the 4-chamber view6. The model follows the literature in using overall sensitivities and specificities and it is this which generates the additional 0.33 antenatal diagnoses of cardiac malformations using the five chamber view. The model assumption is that these additional diagnoses are for malformations that would not normally be detectable with a 4-chamber view but would be detectable with an outflow-tract view. However, as TGA is not the only malformation falling into this category, the model does not assume that all additional antenatal diagnoses are TGA. It uses data presented by Ogge et al. (2006)[947] to estimate that 36% of these additional diagnoses would be TGA which leads to the model result that a five chamber screen would identify 0.12 TGA malformations per 1,000 pregnancies, approximately 50% of the total TGA malformations present in the population, five chamber view screening is still borderline cost-effective with this relatively low detection rate. However, it may be appropriate to assume a relatively low detection rate as the study by Ogge et al. (2006)[947] detected only one out of five TGA with a five chamber view. With the model's baseline detection rate it would be necessary to screen approximately 56,000 women with a five chamber view to avert one neonatal death.

The model's baseline result suggests that the detection rate threshold for TGA for five chamber view to achieve cost-effectiveness is quite low. The one-way sensitivity analyses indicate thresholds for cost-effectiveness for other parameter values. Figure 2 suggests that the test sensitivity for 4-chamber view would have to be greater than 75% for the ICER for the five chamber view to exceed £30,000 per QALY. Such test sensitivity would suggest there was only a very limited added-value in terms of cardiac malformations detected by using the five chamber view[7].

Figure 3, shows that the cost-effectiveness of five chamber view screening relative to 4-chamber is highly sensitive to the costs of screening[8]. five chamber view screening ceases to be cost-effective at screening costs of greater than £49, a cost only slightly higher than the baseline value.

Figures 4 and 5 generally show that the cost-effectiveness of five chamber view screening is not that sensitive to assumptions about QALYs or life expectancy within plausible ranges. Baseline values suggest that the incremental costs of five chamber view screening are £11,755 in a population of 1,000 pregnant women. Therefore, only 0.39 incremental QALYs are needed to generate a cost per QALY of £30,000. With baseline values this is approximately 21.7 QALYs per neonatal death averted. Life expectancy would have to be less than 40 years in order for the five chamber view to generate a cost per QALY of greater than £30,000. A QALY weight of less than 0.8 for TGA treatment would be necessary to produce a cost per QALY of £30,000 or more. Given the good outcomes and low morbidity from successfully treated TGA, these threshold values seem lower than what is plausible.

Figure 6 does show that the model's results are very sensitive to the assumptions made about the positive impact an antenatal diagnosis of TGA has on mortality. Antenatally detected TGA mortality must be lower than 5% (with undetected antenatally TGA mortality 16.6% - i.e. a difference of 11.1 percentage points9) to yield a cost per QALY of less than £30,000.

[6] The sensitivity of detecting TGA with the 4-chamber view is 0%

[7] The key point is the difference in test sensitivity between 4-chamber and five chamber view rather than the absolute value. The one-way sensitivity analysis of 4-chamber view sensitivity is undertaken holding the five chamber view sensitivity constant at 82%. The sensitivity analysis suggests that the five chamber view requires a sensitivity that is at least 4% better than 4-chamber view in order to achieve cost-effectiveness

[8] Again it is the difference between screening costs using 4-chamber and five chamber views that is important, rather than the absolute amount of one of the screening tests.

[9] The 95% confidence intervals for the reduction in percentage points mortality with antenatally detected TGA is 10.9% to 17.0%

Finally, figure 7 shows that cost-effectiveness is also sensitive to the proportion of additional cardiac malformations detected with the five chamber view that are assumed to be TGA. However, this also relates to the earlier discussion about the overall detection rate of TGA as, given the way the model is constructed, a lower proportion implies a lower detection rate. Here, TGA would have to account for less than 15% of the additional cardiac malformations detected for the five chamber screen ICER to exceed £30,000 per QALY.

The results of these sensitivity analyses suggest that considerable uncertainty about the cost-effectiveness of five chamber screening remains. However, the model only addresses cost-effectiveness of screening for cardiac malformations in terms of the impact an antenatal diagnosis of TGA has on improved health outcomes; it doesn't address the cost-effectiveness of such screening in providing information to inform decision making about termination of pregnancy.

B.5 Cost effectiveness model for screening and treatment of gestational diabetes

Systematic review

A systematic search of the literature identified 337 studies potentially related to the clinical question. After reviewing the abstracts 33 articles were retrieved for further appraisal and eight have been included in this section of the review. Two papers were identified in the literature that examined the cost-effectiveness of screening for and treating GD, six papers were identified that examined the cost-effectiveness of screening only for GD.

Screening and treatment of GD

A study conducted in France[948] examined three strategies for screening for GD using a decision analysis model. Under strategy one, women deemed to be at higher risk of GD based on a series of risk factors (family history of diabetes in a first degree relative, age over 35 years, BMI greater than 27, previous history of GD, pre-eclampsia, foetal death after 3 months gestation or previous macrosomia) were given a non-fasting 50g oral GTT. In strategy two all women were given the 50g oral GTT and in strategy three all women were given a 75g GTT. Data on costs were collected through a prospective study of 120 pregnancies and clinical data were taken from a review of published literature. Incremental analysis was reported in terms of cost per additional case prevented of macrosomia, prematurity, perinatal mortality or hypertensive disorder. All strategies were compared with a baseline of no screening for each outcome. The authors recommend strategy one, screening the population of high risk pregnant women using the 50g oral GTT based on it's favourable incremental cost-effectiveness ratio for preventing perinatal mortality (7871.55 Euros, compared with 8663.83 Euros and 29444.16 Euros for strategies two and three respectively).

A retrospective study conducted in Italy[949]examined the costs and outcomes for two groups of women. The first group had universal screening using a 50g GCT while the second were screened based on the presence of given risk factors (history of GD, previous macrosomia, family history of DM, age over 30 years and body mass). All women that tested positive in either screening group underwent a 100g GTT. Universal screening was found to be more costly than the selective screening approach per case of GD diagnosed (424 Euros and 406 Euros respectively) and that treatment cost 366 Euros. No incremental analysis was reported. The authors conclude that based on the savings from downstream interventions, such as caesarean section, associated with untreated GD that screening in some form was justified.

Screening for GD

A cost-utility analysis[950] examined four screening strategies for GD. The strategies were no screening, a 75g GTT, a 100g GTT and a sequential test (50g GCT followed by a

100g GTT). The authors concluded that the sequential testing strategy was cost-effective, though in a high prevalence population the 100g GTT may be an alternative cost-effective screening strategy. The study was conducted from a societal perspective, which could limit its applicability for decision making in an NHS setting, as this may overestimate costs. References are given for clinical and cost parameters but no specific details of these are reported. No detail was provided on what components comprised the total cost of each strategy and no unit costs were reported. Incremental analysis is undertake and outcomes are reported in QALYs, with maternal and infant outcomes reported separately. Sources for utility estimates are not provided. Given these draw backs the results of this study cannot be generalised to an NHS setting.

One study from the UK[951] examined the cost-per case of GD detected. Six screening strategies were considered: universal FPG, universal GCT with 7.8mmol/l cut-off, universal GCT with 8.2mmol/l cut-off, GCT with 8.2 mmol/l cut-off in women aged over 25, GCT with 8.2 mmol/l cut-off in women aged over 25 and risk factors, and universal GTT. The authors recommend the use of a universal FPG or giving a GCT to those over age 25 and with risk factors. The FPG detects an additional 6,009 cases at a cost of £489 per additional case detected when compare with GCT. A strategy of universal GTT is predicted to detect an additional 1,493 cases compared with the universal FPG, at a cost per additional case detected of £4,665.

Four studies reported in USD estimate the cost per case detected of GD[952], [953], [954], [955]. One study[952] examined the cost per case diagnosed of six different strategies. Incremental analysis is not reported. The authors recommend screening women aged over 25 years using a 50g 1hr glucose screening test. In a second study[953]the authors examined the cost per case diagnosed using different thresholds for the diagnosis of GD in a high risk population. The cost per case of GD identified by a 50g oral glucose screening test was 114USD at a cut-off of 7.2 mmol/L and 106USD at a cut-off of 8.3 mmol/L. The authors make no conclusion on the cost-effectiveness of either approach. A third study[953] examined the cost per case diagnosed of GD in two groups of women. Group 1 had historical or clinical risk factors for GD and Group 2 were offered routine screening. Screening was with a 50g GCT followed by a GTT for women with greater than 150mg/dl. The number of cases of GD diagnosed did not differ between groups. The cost per case diagnosed of the testing programme was 329USD. A fourth study[955] was conducted in Iran and reported in USD. Women were stratified into high, intermediate and low risk groups based on American Diabetic Association criteria. The Authors recommend universal screening in a high prevalence population such as theirs, with a cost per case diagnosed of 80.56USD. No incremental analysis was reported.

Introduction to model

The recently published Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) study demonstrated potential benefit of treatment for mild gestational diabetes. However, whilst clinical effectiveness is a necessary condition for cost-effectiveness it is not sufficient. Resources have competing uses and showing that resources yield a benefit does not demonstrate that an even greater benefit could not be produced if those resources were deployed in an alternative use. Furthermore, treatment requires identification of those affected by GD using some screening/diagnostic strategy which further reduces scarce resources available to other National Health Service patients. Therefore, the cost-effectiveness of treatment will partly be determined by the ability to identify patients for treatment via screening in a cost-effective fashion. Similarly, the cost-effectiveness of screening is predicated on an efficacious treatment which gives an acceptable cost per effect given the finite resources available.

The cost-effectiveness of screening and treatment for GD are highly inter-dependent. As a result a single cost-effectiveness model covering screening and treatment for GD was developed on behalf of both the Antenatal Care and Diabetes in Pregnancy guideline

development groups to enable them to make recommendations on this area of care for pregnant women.

The decision tree

The model utilises a decision analytic approach. In this approach competing alternatives represent the decisions. Then, by considering the probabilities of different scenarios under each decision, drawing on best available evidence, the expected costs and effects of each decision can be computed and compared.

At its most basic this cost-effectiveness model can be represented as the decision to screen and treat patients identified with GD versus no screening, as was the recommendation of the previous ANC guideline (Figure 1).

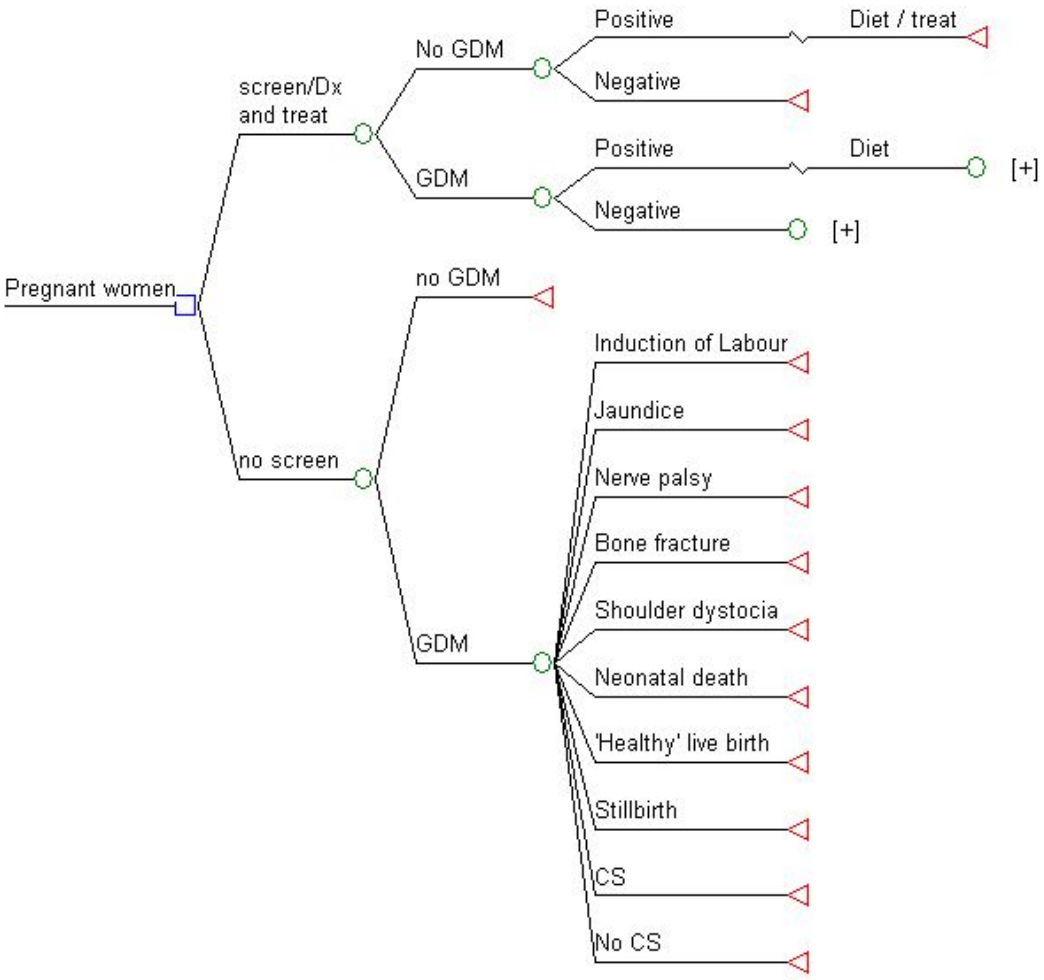


Figure 1 The basic decision tree structure

Note: + denotes that the tree is truncated, see figure ?? for the treatment sub-tree

Data from the ACHOIS Intervention Group was used to estimate the outcomes and associated costs of treating true positives. As ACHOIS was limited to those with 'mild'

GD the costs and effects may be an underestimate of the true costs and effects in the population under consideration. The outcomes and associated costs of false negatives were estimated from the Routine Care Group in ACHOIS. There is no need to consider the outcomes of women without GD (true negatives and false positives) in the screening arms as these do not differ from the population of otherwise healthy pregnant women, although it is necessary to consider the cost of providing treatment to women falsely diagnosed with GD (false positives).

In Figure 1 above the decision, for diagrammatic simplicity, is depicted as screen versus no screen. However, given an initial decision to screen there is then the decision of how to screen. The various screening options that have been considered in this model are described in the next section.

The key outputs of each screening strategy are the costs of screening and treating women and the number of women accurately diagnosed with GD. There are four possible outcomes when applying a diagnostic test:

- True positive - the patient is diagnosed as positive and has the condition/disease
- False positive - the patient is given a positive diagnosis but does not have the condition/disease
- True negative - the patient is not diagnosed with the condition/disease and does not have it, and
- False negative - the patient is not diagnosed with the condition/disease but does in fact have it.

The number of individuals diagnosed correctly is determined by the accuracy of the diagnostic test applied, known as its sensitivity and specificity and by the prevalence of the condition in the population being tested. The treatment and outcome sub-trees are identical for each screening strategy in this model but the costs and effects will vary according to the numbers diagnosed as having GD or not .

Screening strategies

Table 1 contains a list of the different strategies that have been considered as screening strategies for gestational diabetes (GD). All screening methods, including risk factor screening, screening blood tests and universal diagnostic tests, have been considered in isolation. Combinations of these tests have then been considered.

Where a strategy listed in Table 1 is more costly and less accurate at identifying patients with GD than an alternative strategy, then this is indicated in the results section (Table X). Not all possible strategies have been considered - particularly where they are clinically inappropriate, for example treating patients based on the presence of a risk factor alone. Some strategies have been excluded from further analysis after preliminary analysis showed them to be dominated by alternative strategies. Limitations in the data are discussed in greater detail later in this appendix.

Risk factors that have been considered:

- Age ≥ 30
- Age ≥ 25
- High-risk ethnic background (Ethnicity)
- BMI ≥ 27 (High BMI)
- Family history of diabetes

Screening blood tests that are considered:

- Fasting plasma glucose (FPG)
- Random blood glucose (RBG)
- 50g 1hr glucose challenge test (GCT)

Diagnostic blood test considered:

- 75g 2hr glucose tolerance test

Table 1 List of screening strategies

Strategy number	Risk factor	Screening blood test	Screening diagnostic test
1	-	-	GTT
2	ADA criteria[a]	FPG	GTT
3	ADA criteria	RBG	GTT
4	ADA criteria	GCT	GTT
5	ADA criteria	FPG	-
6	ADA criteria	-	GTT
7	ADA criteria	GCT	-
8	-	FPG	-
9	-	RBG	-
10	-	GCT	-
11	-	FPG	GTT
12	-	GCT	GTT
13	Age ≥ 30	FPG	GTT
14	Age ≥ 30	GCT	GTT
15	Age ≥ 25	FPG	GTT
16	Age ≥ 25	GCT	GTT
17	Age ≥ 30	-	GTT
18	Age ≥ 25	-	GTT
19	High-risk ethnicity	FPG	GTT
20	High-risk ethnicity	GCT	GTT
21	High-risk ethnicity	-	GTT

[a] Having one or more of the following risk factors – Age >25yrs; BMI>27kg/m^2; Family history of diabetes; High risk ethnic group

Assumptions

Decision analysis is used to help us make decisions about the best treatment or intervention to use, based on grounds of cost and clinical effectiveness. When developing a decision analysis model it is necessary to make simplifying assumptions to highlight what the important elements of the model might be and to reduce the complexity of the model. It is not possible to consider every possible potential outcome in a model and it is important to focus on those with the greatest relevance in answering the question at hand. The assumptions used in the model of screening strategies are given below.

1) A 75g 2hr Glucose Challenge Test is used as the gold standard diagnostic test (please refer to the Diabetes in Pregnancy guideline for details[636]) and is assumed to be 100% sensitive and specific.
2) It has not been possible to establish an accurate fertility rate in some population sub-groups. It is therefore assumed:

   - that the fertility rate among women with a high BMI is the same as the rate among women with a BMI within the normal range. This may overestimate the number of pregnancies in this group, as high BMI is associated with fertility problems[956].

3) The available data on BMI is not consistent. Population level data on BMI from the Office of National Statistics or the Health Survey for England is presented as Overweight and Obese with a BMI greater than or equal to 25. The data presented by Davies (2001) uses a BMI greater than or equal to 27 to define some at risk of GD based on BMI. It is assumed initially that the risk of those with a BMI greater than 25 is equal to that of those with a BMI greater than 27, though this will be explored in sensitivity analysis. If there is a genuine difference in the sub-populations, this

assumption may overestimate the number of cases of GD in the at risk population and lead to a greater number of false positive diagnoses of GD.

Input parameters

The parameters used to populate the model have been chosen based on the best available evidence, and are listed in Tables 2 – 4. Sources for each value are cited where appropriate.

Table 2 Accuracy of screening and diagnostic blood tests

Test	Sensitivity	Specificity	Source
Fasting plasma glucose	0.88	0.78	Reichelt[498]
Random blood glucose	0.48	0.97	Ostlund[837]
50g 1.0 hour glucose challenge test	0.80	0.43	Sesshiah
75g 2.0 hour glucose tolerance test	1.0	1.0	Gold standard

Table 2a Cost of screening and diagnostic blood tests

Variable	Cost	Source
Risk factor screening	£2	GDG estimate
Fasting plasma glucose	£5.39	Updated from Scott et al (2002)[483]
Random blood glucose	£5.39	Updated from Scott et al (2002)[483]
50g 1.0 hour glucose challenge test	£10.61	Updated from Scott et al (2002)[483]
75g 2.0 hour glucose tolerance test	£28.58	Updated from Scott et al (2002)[483]

Table 3 Risk factors for gestational diabetes - Age

Risk factor	% of population (Source)	Sensitivity (Source)	PPV (%)
Age ≥ 30	49.7 (ONS)	0.65 (Coustan)[957]	5.8
Age ≥ 25	74.2 (ONS)	0.85 (Coustan)[957]	4.5

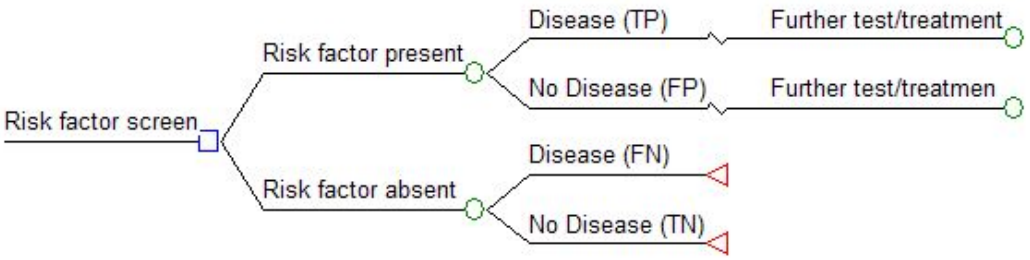
Table 4 Risk factors for gestational diabetes other than Age

Risk factor	% of population (Source)	% of women with GD (Source)	PPV (%)
GD in a previous pregnancy	3.5 (HES, 2005)	30 (Weeks, 1994)[958]	10.0
Family history of DM	10.0 (Davey and Hamblin, 2001)[831]	39.9 (Davey and Hamblin, 2001)[831]	14.0
High risk ethnic group	8.5 (Davey and Hamblin, 2001)[831]	68.7 (GDG opinion)	10.0
BMI ≥ 27	35.8 (ONS, 2001)	36.2 (Davey and Hamblin, 2001)[831]	3.5

Incorporating risk factors within the model

General overview

In terms of the decision tree for the GD screening/treatment model, risk factors can be thought of analogously to diagnostic tests:



Positives from a risk factor screen or screen/diagnostic test progress to the next stage of testing or treatment. Negatives do not progress.

The detection rate of a risk factor screen is given by the true positive rate[10] . This detection rate is an important component of the model, as treatment costs and effects are predicated on it. Its flip-side (false negatives) is also important because there may be 'downstream' costs associated with missed cases.

In the economic model of screening we are also concerned with the unnecessary costs of screening which is given by false negatives. The screening does not lead to improved outcomes in these patients and the scarce resources used in screening have an opportunity cost in terms of the benefit they could have achieved if used elsewhere in the healthcare system[11].

Therefore, the screening strategy with the highest detection rate is not necessarily the most cost-effective. There may be some desirable trade-off between detection and unnecessary testing and treatment.

The methodological problem

The data requirements for the model for any risk factor screening strategy are conceptually straightforward:

- What is the disease prevalence?
- What proportion of the population meets the risk criteria[12]?
- What proportion of cases is detected in the population who meet the criteria?

With answers to these questions the TP, FP, TN and FN branches of the decision tree can be completed.

The literature tends to focus on the detection rates of a particular risk factor (or more rarely combination of risk factors). Using ONS data in combination with the literature it is possible to estimate the TP, FP, TN and FN for a single risk factor screen at baseline prevalence. However, given data limitations it is much more difficult to derive these estimates for screening strategies based on combinations of risk factors.

[10] In our GDM model this is complicated by assumptions made about test acceptance.

[11] It isn't explicitly addressed in the model but an undesirable consequence of screening may be the unnecessary inconvenience and worry for false positives.

[12] This is two sides of the same coin as this information obviously also gives the proportion who don't meet the criteria

Prevalence varies across the country and this is potentially important in the cost-effectiveness of screening, as it influences the trade-off between detection and false-positives. Therefore, the model has been developed to explore how the conclusion may vary at different disease prevalence. To do this required that we model a relationship between changes in disease prevalence and the proportion classed at 'high risk'. This poses further methodological difficulties because of the complex and interdependent relationship between risk factors.

With sufficient patient level data, it is possible to envisage a multiple regression equation which would predict the change in prevalence arising from a change in the proportions with different risk factor combinations.

Prevalence = $a + bRF_1 + cRF_2 + dRF_3 \ldots\ldots\ldots + eRFn$

Such a model could be used to predict individual risk of disease.

However, in the model risk factor proportion is the dependent variable and it is likely that different combination of risk factors are consistent with the same overall disease prevalence. This means that the most cost-effective screening strategy may be determined by the demographic characteristics of a particular population rather than prevalence per se (although the latter is a function of the former).

Our approach to modelling risk factor screening

Due to the data limitations and methodological complexity, our approach involved certain simplifying assumptions and the accuracy of the model may ultimately depend on whether these give a sufficiently good approximation to the real world.

Each risk factor screening strategy involves dividing the population in two – those at 'high' risk and those at 'low' risk[13]. Logically, the disease prevalence is the weighted average of the respective prevalence in these two groups. The weights are the proportions in each of the groups.

Prevalence = (Proportion 'high risk' x 'high risk' prevalence) + (Proportion 'low risk' x 'low risk' prevalence)

The first step was to estimate a positive predictive value (PPV) for each risk factor screen – i.e. what proportion of the 'high risk' group had disease? This gives the disease prevalence for the 'high risk' group. Next a negative predictive value (NPV) is calculated – i.e. what proportion of the 'low risk' group didn't have disease. The prevalence in the 'low risk' group is given by 1-NPV. There may be some simplifying assumptions made in arriving at these estimates but as they use a combination of the literature and ONS data they are probably reasonably good at baseline[14].

We then assume that the PPV and NPV are independent of prevalence. In a hypothetical scenario where there was just one risk factor for a disease this would be correct. However, this linear relationship between risk factor proportion and prevalence is clearly a simplifying assumption in this case.

In practice what happens is as the proportion with a risk factor (e.g age) increases then there is also an increase in the proportion with multiple risk factors, which would change the PPV. This is even true for the ADA strategy, as clearly there is no reason why the proportion with multiple risk factors should be constant with respect to prevalence. Similarly, if the 'low risk' group have some risk factors then their disease prevalence (1-NPV) is also likely to change with changing disease prevalence.

[13] 'High' and 'low' risk should be interpreted as a comparison of two groups, where one has a higher level of risk than the other.

[14] ADA may be a slight exception because the paper we used to derive PPV and NPV values was based on a US population with a lower prevalence than baseline

The model does not capture the impact and interdependence of multiple risk factors. This means that the actual change in risk factor proportion to induce a certain change in prevalence is less than implied by the model.

Below we outline in more detail the assumptions that were made for each risk factor screening strategy used in the model.

Finally, it should also be noted that the model user can override the model relationship between prevalence and risk factors. If they choose this option, they themselves select the 'at risk' proportion and the proportion of cases that would exist in this population. This can be used to reflect better local data, if known, or to conduct sensitivity analysis. Such sensitivity analysis may indicate to what extent the simplifying assumptions drive the cost-effectiveness conclusions.

ADA (American Diabetic Association) criteria

ADA selective screening criteria exclude women who are:

- < 25 years
- <27 BMI
- Low prevalence ethnic group
- No 1st degree relative with history of DM

Sensitivity and specificity was estimated for estimated for the ADA criteria. Using a retrospective study by Danilenko-Dixon et al. (1999) which compared selective screening (using ADA criteria) versus universal screening. It was estimated only 10% would be exempt from screening in their population (of which 17.8% <25 years) – i.e. having none of the ADA risk factors. They found that 17/564 (3%) of GD cases were missed using ADA criteria[15]. The prevalence of GD in their population was 564/18,504 (3%). Using these numbers a sensitivity/specificity from the model baseline population was calculated as follows:

N	10,000
Prevalence	3.5%
GD cases	350
No GD	9,650
Then using the results reported by Danilenko-Dixon et al. (1999)	
Population screened used ADA criteria	90% (n=9,000)
GD cases in non-screened population	3%
Not screened population	
N	1,000
GD = 350*0.03	10.5
No GD = 1,000-10.5	989.5
Screened population	
N	9,000
GD = 350-10.5	339.5
No GD = 9,650-989.5	8,660.5
Sensitivity = 339.5 ÷ 350	97.0%
Specificity = 989.5 ÷ 9,650	10.3%

[15] Another study by Williams et al. (1999) suggested 4% of GDM cases would be missed by ADA criteria

Substituting the Danilenko-Dixion et. al study prevalence into the above calculations[16] then the sensitivity is unchanged and the specificity is 10.2%

In this case we needed to model the relationship between ADA parameters and prevalence even for our baseline analysis, because the calculations are taken from a population having different disease prevalence.

The key assumption in modelling a relationship for ADA criteria was to assume that the PPV and NPV were independent of disease prevalence. The PPV is essentially the disease prevalence in the 'High risk' group. The GD prevalence in the 'low risk' group is given by 1-NPV (0.92%).

The overall prevalence can then be seen as a weighted average of the 'high risk' and 'low risk' groups. For a given population GD prevalence, it is therefore possible to estimate the proportions in the 'high risk' and 'low risk' categories. The PPV in conjunction with the 'high risk' proportion gives the detection rate.

What is implied in this relationship for all population disease prevalence of ≥ 3.28% is that all the population would be 'high risk' as defined by ADA and therefore this is what our model assumes for the baseline prevalence (3.5%). This would not be the case in reality[17]. As the proportion with risk factors goes up, so does the proportion with multiple risk factors which will exert an upward pressure on prevalence over and above that of the single risk factor. Therefore, a smaller change in risk factor proportion than implied by the model is necessary to induce a certain change in disease prevalence.

Ethnicity

Here 'high risk' is defined as women in a 'high' prevalence ethnic group and 'low risk' is defined as women in a 'low' prevalence ethnic group.

The approach we used was similar to that used for the ADA criteria and is described below:

Proportion of 'high risk'	8.5%	ONS
Proportion of GD 'high risk' ethnic group	68.7%	Weeks[958]
Births	645,835	ONS
Births 'high risk' ethnic groups	54,896	Calculated
GD prevalence	3.5%	GDG
GD births	22,604	Calculated
GD births 'high risk' ethnic groups	15,529	Calculated
PPV (15,529 ÷ 54,896)	28.1%	Calculated
NPV (583,864 ÷ 590939)	98.8%	Calculated

Again it was assumed that PPV and NPV were independent of disease prevalence. As with ADA these provide prevalence in the 'high risk' and 'low risk' group with the

[16] Without varying the assumption that 10% of population of pregnant women would not be screened

[17] However, given the study on which our calculations were based; >90% proportion 'high risk' and >97% GDM detection might be considered 'realistic'

overall population prevalence being a weighted average of the two[18]. Therefore, it is possible to estimate the 'high risk' ethnic group proportion from any given population GD prevalence.

The model suggests that at a population prevalence of 2%, the 'high risk' ethnic proportion would be 2.98%. At a GD prevalence of 10% it predicts 32.6%. On the face of it these seem fairly plausible estimates but with the caveat that they are derived from a 'high risk' prevalence which is much higher than the literature would suggest.

BMI of 27 or greater

This strategy identifies high risk women as having a BMI of 27 or more and low risk women has having a BMI of less than 27. The proportion of 'high risk' women in this strategy at baseline was calculated as follows:

High risk BMI proportion	0.16	ONS
Low risk BMI births	542,501	Calculated
High risk BMI births	103,333	Calculated
GD prevalence	0.035	GDG
GD births	22,604	Calculated
High risk BMI prevalence	0.035	GDG
High risk BMI GD births	3,617	Calculated
Low risk BMI GD births	18,987	Calculated
Low risk BMI prevalence	0.035	Calculated
PPV	3.5%	Calculated19
NPV	96.5%	Calculated from ADA

We assume PPV and NPV are independent of disease prevalence and this enable us to calculate the change in 'high' and 'low' risk proportions which would give the model prevalence as the weighted average of the two risk groups.

Family history of diabetes

This strategy identifies high risk women as having a first degree relative with a history of diabetes and low risk women has having no first degree relative with a history of diabetes. The proportion of 'high risk' women in this strategy at baseline was calculated as follows:

High risk family history proportion	0.10	ONS
Low risk family history births	581,252	Calculated
High risk family history births	64584	Calculated
GD prevalence	0.035	GDG
GD births	22604.23	Calculated

[18] A prevalence of 28.1% for 'high risk' ethnic groups seems considerably higher than values quoted in the literature

[19] Prevalence = (proportion 'high risk' x PPV) + (proportion 'low risk' x (1-NPV):

Prevalence is given and PPV is the only unknown at baseline and hence can be calculated

High risk family history prevalence	0.14	Calculated
High risk family history GD births	9041.69	Calculated
Low risk family history GD births	13562.54	Calculated
Low risk family history prevalence	0.023	Calculated
PPV	2.3%	Calculated
NPV	97.6%	Calculated

The calculations in the different 'high' and 'low' risk proportions for different disease prevalence are done using the same method as for the risk screening strategy based on 'high' prevalence ethnicity and an age threshold of 25 years.

Age ≥ 25 years

This strategy identifies high risk women as 25 years of age or older and low risk women being 24 years of age or less.

At baseline this gives;

'High risk' proportion	74.2%
'Low risk' proportion	25.8%

The detection rate is then derived using a PPV, which is again assumed not to change with disease prevalence. The proportion of 'high risk' women in this strategy at baseline was calculated as follows:

Total births	645,835	ONS
Total births ≥ 25 years	478,738	ONS
GD prevalence	3.5%	GDG
GD births (0.035 x 645,835)	22,604	Calculated
Proportion detected ≥ 25 years	85%	Coustan[957]
GD detected (0.85 x 22,604)	19,214	Calculated
PPV (19,214 ÷ 478,738)	4.01%	Calculated

It should be noted that the model assumes that all the population is in the 'high risk' category for prevalence values of 4.3% and above.

Age ≥ 30 years

The method is the same as for ≥ 25 years, but this time formulating a relationship between 'high' and 'low' risk proportions group of the risk factor screen using ethnicity and an age threshold of 30 years.

'High risk' proportion	51.3%
'Low risk' proportion	48.7%

The detection rate is then derived using a PPV, which is again assumed not to change with disease prevalence.

Total births	645,835	ONS
Total births ≥ 30 years	314,390	ONS
GD prevalence	3.5%	GDG
GD births (0.035 x 645,835)	22,604	Calculated
Proportion detected ≥ 30 years	65%	Coustan[957]
GD detected (0.65 x 22,604)	14,693	Calculated
PPV (19,214 ÷ 478,738)	4.7%	Calculated

It should be noted that when the model assumes that all the population is in the 'high risk' category for prevalence values of 5.6% and above.

Treatment

The basic decision tree for treatment is depicted in Figure 2 below.

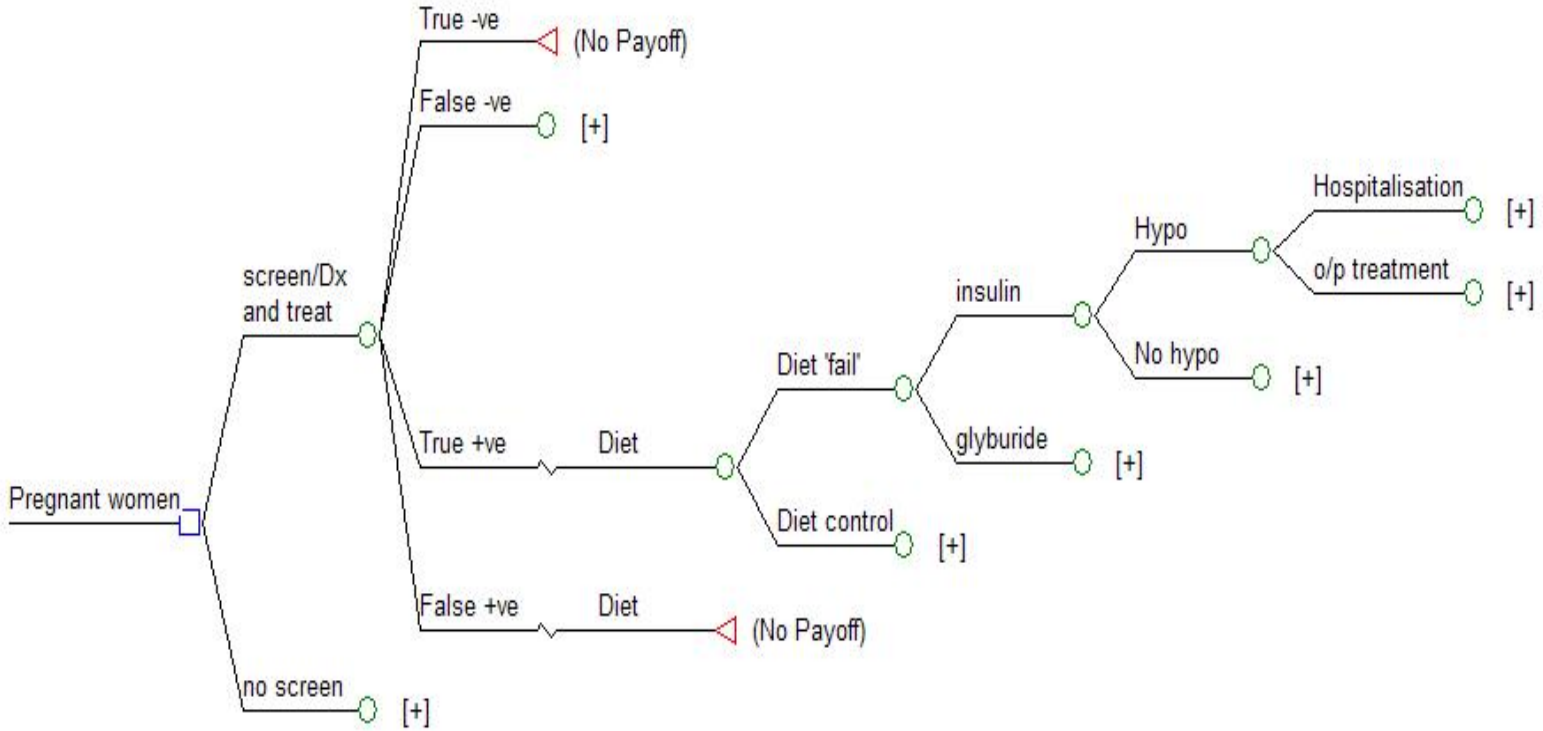


Figure 2 The basic treatment sub-tree

The screening part of the model produces an output of true positives, false negatives, false positives and true negatives and these numbers then inform the probabilities attached to given patient treatment pathways following a positive or negative diagnosis of GD.

As far as possible, treatment was modelled according to the ACHOIS protocol, as this is what the effectiveness data is based upon. It is assumed that patients would start treatment at a gestational age of 27 weeks and that this would continue for 90 days. The treatment protocol used in the model is outline below.

Diet

Initial treatment aims to control blood glucose using diet. This part of treatment consists of:

- 30 minutes individualised dietary advice from a qualified dietician
- 30 minutes instruction on self-monitoring blood glucose (SMBG) provided by a specialist nurse (band 5/6)
- SMBG, 4x daily
    - Costing of SMBG include one monitor, and assumes one lancet and one test strip per reading
- 5 minutes of assessment of control after 10 days on diet by a specialist nurse

At this 10-day assessment patients are judged to have achieved adequate control with diet or not. If they have achieved adequate control they remain on dietary control until the end of their pregnancy, with SMBG reduced to twice daily.

If women are deemed not to have achieved adequate control with diet, medical treatment (insulin analogue, glyburide, metformin) is then initiated.

Insulin analogue

- 45 minutes of instruction from a diabetic specialist nurse.
- Daily insulin dose: 20 units
- Pre-filled disposable injection device
- Twice daily injections (two needles per day of treatment)
- A proportion of patients will experience hypoglycaemia and a small proportion of these will be severe cases requiring an inpatient admission
- SMBG, 2x daily

Glibenclamide and metformin, two alternative oral hypoglycaemic treatments to analogue insulin, were also included in the model. A RCT of glyburide (glibenclamide) versus insulin for GD failed to find statistically significant differences in outcomes. Whilst, the effectiveness of metformin is currently being investigated as part of the ongoing MIG trial and is therefore a potential treatment option. The basic tree structure for an oral hypoglycaemic treatment, such as glibenclamide, would be as illustrated below (figure 3):

Glibenclamide

Daily dose: 15mg

Metformin

Daily dose: 1.5g

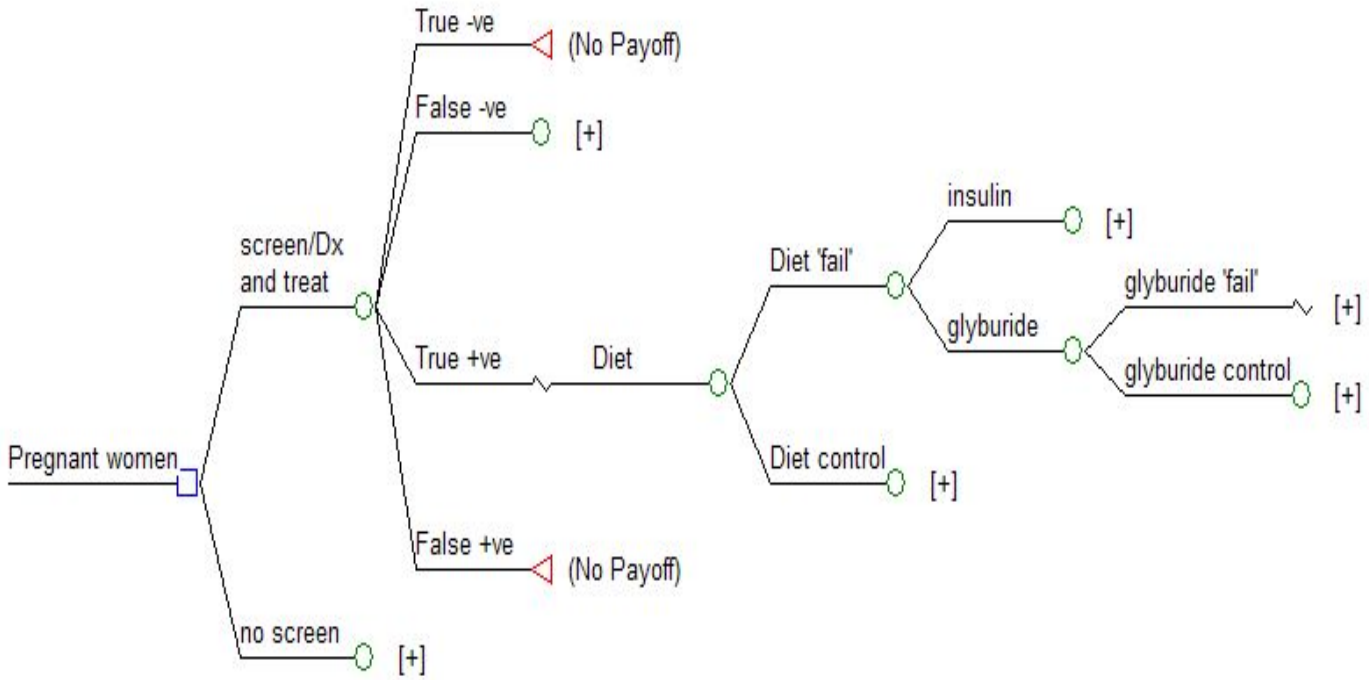


Figure 3 Glibenclamide treatment sub-tree

Outcomes and downstream costs

The model uses the following outcomes presented in the ACHOIS study to estimate the incremental QALY gain associated with screening and treatment of GD:

- Stillbirth
- Neonatal death
- Maternal health state utility

Furthermore, the following outcomes from ACHOIS are assumed to have 'downstream' cost implications. Costs are assigned to these outcomes and included in the evaluation of incremental costs:

- Neonatal death
- Shoulder dystocia
- Bone fracture
- Admission to neonatal nursery
- Jaundice requiring phototherapy
- Induction of Labour
- Caesarean section

We used the outcomes data of ACHOIS for 'serious perinatal complications' as the measure of the effectiveness in the model. The trial data allows this to be easily done for deterministic sensitivity analysis, with the different event rates giving well defined relative risks. In order to reflect the individual components of the composite measure a weighted cost and QALY was calculated for a serious perinatal complication based on the QALY and costs associated with each of the individual components. In order to calculate the weights it was assumed, based on the lack of statistical significance for any difference, that the proportion of serious perinatal complications accounted for by individual components did not differ according to whether they were treated for GD or not. Therefore, the data on individual events was pooled across both arms of the trial in order to estimate the weighting for individual components:

	Total	Weight
All serious perinatal complications	32	1.00
Stillbirth	3	0.09
Neonatal death	2	0.06
Shoulder dystocia	23	0.72
Bone fracture	1	0.03
Nerve palsy	3	0.09

Treatment model parameters

The tables below show the baseline parameter values for all model treatment inputs.

Table 5 Treatment timeframe (days)

Variable	Value (days)	Source	Notes
Treatment duration	90	DiP GDG	The DiP GDG consensus seemed to be that treatment would usually commence between a gestational age of 26-28 weeks. Taking the mid-point of 27 weeks, 90 days seem a reasonable approximation of the typical time to term
Exclusive diet	10	DiP GDG	The DiP GDG suggested that diet alone would be given 7-14 days to achieve adequate control

4 x daily SMBG	10	ACHOIS[824]	The actual ACHOIS protocol suggested that SMBG be done 4 x daily until glucose levels had been in the recommended range for 2 weeks

Table 6 Cost of professionals time

Variable	Time (mins)	Cost per hour	Source	Notes
Dietary advice	30	£28	Netten & Curtis (2006)[959]	Unit costs of a dietician for an hour of client contact
SMBG instruction	30	£63	Netten & Curtis (2006)[959] GDG estimate	Unit cost of a nurse specialist (community) for an hour of client contact
Control with diet Assessment/review	5	£63	Netten & Curtis (2006)[959] GDG estimate	Unit cost of a nurse specialist (community) for an hour of client contact
Insulin instruction	45	£63	Netten & Curtis (2006)[959] GDG estimate	Unit cost of a nurse specialist (community) for an hour of client contact
Risk factor screening questions	2		Netten & Curtis (2006)[959] GDG estimate	Unit cost of

Table 7 SMBG and treatment costs

Variable	Cost	Source	Notes
Blood Glucose monitor	£7.79	BNF 52	
Test strips	£0.31 each	BNF 52	Many makes, all similarly priced. £15.55 for a pack of 50 was the cheapest I found from a small sample
Lancets	£0.03 each	BNF 52	
Needles	£0.09 each	BNF 52	£8.57 for a pack of 100 needles
Insulin Analogue (Humalog®)	£0.39 per day	BNF 52	This is based on a dose of 20 units per day. A pre-filled disposable pen has 1500 units and costs £29.46
Glibenclamide	£0.16	BNF 52	Based on 15mg daily. A 5mg 28-tablet pack costs £1.50
Metformin	£0.10	BNF 52	Based on 1.5g daily. A 500mg 84-tablet pack costs £2.85
Treatment of severe hypoglycaemia	£500	Netten & Curtis (2006)[959] NHS Reference Costs 2005-06	Average cost per patient journey for paramedic ambulance £323 A&E admission with low cost investigation £80

Table 8 Downstream' outcome costs

Variable	Cost	Source	Notes

Admission to neonatal nursery	£1,676	NHS Ref Costs 2004	Assume 2 days of Neonatal intensive care at £838 per day
Induction of labour	£20	Davies & Drummond (1993)[960]	Updated to 2006 prices using Retail Price Index published by Office of National Statistics
Neonatal death	£2,568	NHS Tariff 2006 NHS Ref Costs 2004	From NHS Ref Costs 2004 FCE data assume that 25% of neonatal deaths are < 2 days (n = 974). NHS Ref Costs for this is £527 For remaining 75% assume 2 days of neonatal intensive care (£838 x 2) and Neonate with one major diagnosis which has an NHS Tariff of £1,572. £1,676 + £1,572 = £3,248
Shoulder dystocia	£629	NHS Tariff 2006	Cost for neonate with one minor diagnosis (HRG N03)
Bone fracture	£629	NHS Tariff 2006	Cost for neonate with one minor diagnosis (HRG N03)
Nerve palsy	£629	NHS Tariff 2006	Cost for neonate with one minor diagnosis (HRG N03)
Phototherapy	£629	NHS Tariff 2006	Cost for neonate with one minor diagnosis (HRG N03)
Emergency caesarean	£1,205	NHS Ref Costs 2004	Incremental cost over and above that of a normal vaginal birth
Elective caesarean	£822	NHS Ref costs 2004	Incremental cost over and above that of a normal vaginal birth

Table 9 Treatment pathway probabilities

Variable	Value	Source	Notes
Control with diet	0.86	Persson[505]	
Control with glibenclamide	0.96	Langer (2000)[961]	Data from Southampton indicates a higher failure rate (23%)
Control with metformin	0.96	-	Assumed the same as for glibenclamide
Hypoglycaemia on insulin therapy	0.20	Langer (2000)[961]	-
Hypoglycaemia on insulin analogue	0.202	-	Assumed the same as for insulin
Hypoglycaemia on glyburide	0.02	Langer (2000)[961]	-
Hypoglycaemia on metformin	0.02	-	Assumed the same as for glibenclamide
Severe Hypoglycaemia requiring hospitalisation	0.05	GDG estimate	-

Table 10 ACHOIS outcome probabilities

Variable	Treatment value	No treatment value	Source
Serious perinatal complications	0.014	0.044	ACHOIS[824]
Admission to neonatal nursery	0.706	0.613	ACHOIS[824]
Induction of Labour	0.374	0.286	ACHOIS[824]
Elective caesarean	0.142	0.116	ACHOIS[824]
Emergency caesarean	0.158	0.197	ACHOIS[824]

Jaundice (phototherapy)	0.087	0.092	ACHOIS[824]

Table 11 QALYs

Variable	QALY	Source	Notes
Averted death (stillbirth/neonatal)	25		This is the approximate lifetime QALYs from 75 years lived in perfect health with QALYS discounted at 3.5% per annum
Maternal QALY - treatment (During pregnancy)	0.72	ACHOIS[824]	It is assumed that this QALY gain persists throughout treatment
Maternal QALY - no treatment (During pregnancy)	0.70	ACHOIS[824]	It is assumed that this QALY gain persists throughout treatment
Maternal QALY – treatment (3 months post partum)	0.79	ACHOIS[824]	It is assumed that this QALY gain covers the entire 3 months post partum period
Maternal QALY – no treatment (3 months post partum)	0.78	ACHOIS[824]	It is assumed that this QALY gain covers the entire 3 months post partum period

Baseline result

The baseline results from the modelling exercise are given based on a population of 10,000 pregnant women and assume a baseline prevalence of GD of 3.5%. The total cost and QALYs generated for each strategy under the baseline assumptions are presented in Table X and are plotted on a cost-effectiveness plane in Figure X.

Table X Total QALY and cost for each screen strategy

Screening strategy	QALY	Cost
11	16.63	£146,206
1	17.48	£212,835
8	18.48	£304,773
9	18.70	£145,439
3	18.70	£126,949
13	19.46	£119,961
14	20.39	£191,551
19	20.56	£77,488
20	21.55	£89,782
12	21.96	£259,815
10	24.40	£838,588
15	25.45	£160,698
17	25.56	£203,930
16	26.66	£269,760
21	27.01	£99,370
2	29.94	£198,801
4	31.37	£345,966
5	33.26	£489,616
18	33.43	£286,799
7	34.85	£1,172,785
6	39.33	£367,052

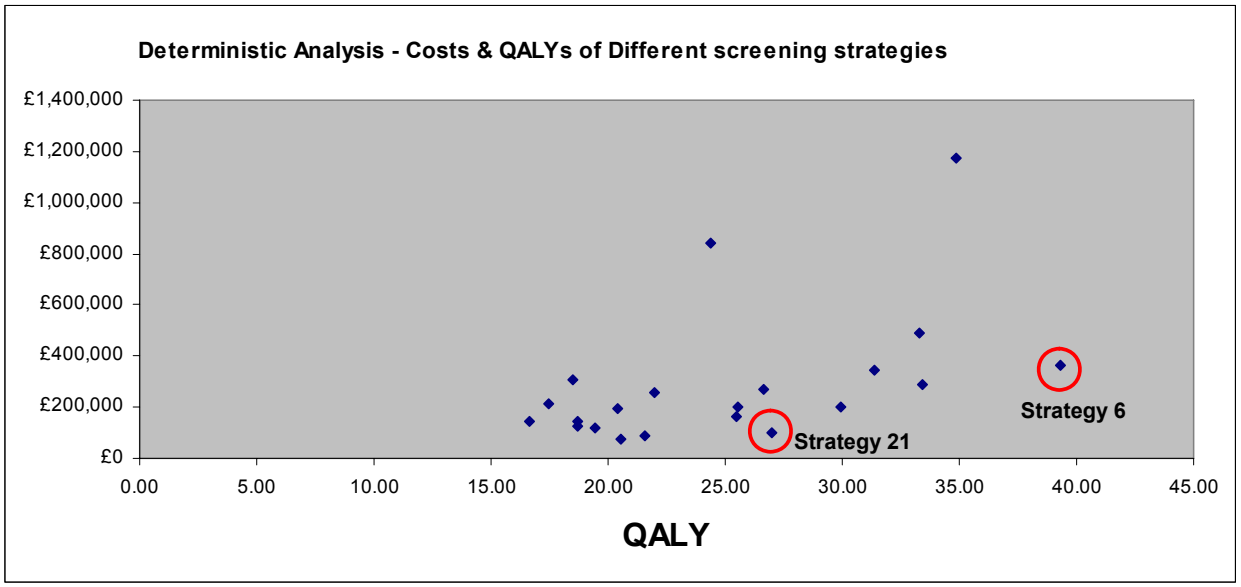


Figure X The Cost-effectiveness plane for the baseline analysis

Table 12 ICER for non-dominated strategies

Strategy	QALY	Cost	Incremental QALY	Incremental cost	ICER
21	27.01	£99,370	27.01	£99,370	£3,678
6	39.33	£367,052	12.31	£267,682	£21,739

The baseline analysis suggests that a strategy of offering women from a high risk ethnic background a diagnostic test (Strategy 21) would be cost-effective when compared to not offering a screening with an ICER of £3,678. The strategy of offering a diagnostic test to those women who are outwith the ADA criteria for a low risk population (Strategy 6) has an ICER of £21,739 when compared with Strategy 21. Though higher than the lower bound of the threshold of £20,000 per QALY stated is comfortable under the maximum willingness to pay per QALY of £30,000 and may be considered cost-effective under certain circumstances, for example if it is believed some salient piece of information falls outside of the model such as the identification of women at higher risk of developing type 2 diabetes in future. Thus it is possible that Strategy 6 reasonably could be argued to be cost-effective.

Sensitivity analysis

All decision analysis models are subject to uncertainty[962] and there are two common approaches to dealing with this uncertainty - making use of a reference case (that is, a standard of good practice) and sensitivity analysis. This model takes as its reference case the NICE guidelines manual standards for conducting economic evaluations. The methods and assumptions used in the model are highlighted above in detail and are tested using a second method of examining uncertainty, sensitivity analysis. In the following analyses we primarily use a series of one and multi-way sensitivity analysis to explore what happens when the value of one or more parameter is changed. This allows us to see what happens to the model results when these values are changed and the implications for our baseline results. The analyses that follow explore the uncertainty in a number of key areas, including:

- the reliability of the trial data on from the likelihood of an event occurring was based
- the prevalence of GD in the population
- the proportion of women that would undergo a screening or diagnostic blood test if it were offered, both when it is offered as first line test or when it is offered based on identification of a potentially high risk population

- the efficacy of using risk factors to define high and low risk populations, based on the presence of one or more of the risk factors highlighted in the ADA criteria (Age over 25, BMI greater than 27, family history of diabetes or from a high risk ethnic background)

Parameter uncertainty: outcomes

The primary outcome in ACHOIS was 'serious perinatal complication' but this was a composite outcome made of a number of secondary outcomes. ACHOIS found a statistically significant difference at the 5% level between the intervention and the control group for serious perinatal complications. However, it didn't find any statistically significant differences for any of the individual outcomes which made up the composite measure.

Ideally the output of the economic model would focus on the individual components of serious perinatal complications rather than the composite measure itself. This is because there is considerable difference in the seriousness of the individual components in terms of their impact on health related quality of life and downstream costs.

One solution would be simply to use the outcomes data of ACHOIS for the intervention and control for these individual components. However, the zero events for some of these individual outcomes in the intervention group are problematic. A zero event rate is likely to reflect the power of the study and lacks plausibility as a best point estimate. It also causes problems for subsequent probabilistic sensitivity analysis because the standard error for such a proportion would also be zero although PSA output also means that the lack of statistically significant differences would be reflected in the model's output.

Instead we used the outcomes data of ACHOIS for serious perinatal complications as the measure of the effectiveness in the model. The trial data allows this to be easily done for both deterministic and probabilistic sensitivity analysis, with the different event rates giving well defined relative risks and standard errors. In order to reflect the individual components of the composite measure a weighted cost and QALY was calculated for a serious perinatal complication based on the QALY and costs associated with each of the individual components. In order to calculate the weights it was assumed, based on the lack of statistical significance for any difference, that the proportion of serious perinatal complications accounted for by individual components did not differ according to whether they were treated for GD or not. Therefore, the data on individual events was pooled across both arms of the trial in order to estimate the weighting for individual components:

	Total	Weight
All serious perinatal complications	32	1.00
Stillbirth	3	0.09
Neonatal death	2	0.06
Shoulder dystocia	23	0.72
Bone fracture	1	0.03
Nerve palsy	3	0.09

The approach described above allows for modelling the outcomes associated with the ACHOIS trial. To explore the uncertainty in these results and the impact on the model results a one-way sensitivity analysis is undertaken. The outcome that has the greatest influence on the model results is the number of perinatal (still births and neonatal deaths). There is a potentially significant gain in QALYs to be made by preventing a perinatal death. In the ACHOIS trial group (those who received no ...) there were five perinatal deaths recorded (n=) while in the treatment arm there none (n=). This difference was not statistically significant. The number of deaths in the control group is similar to the number of perinatal deaths that would expected in the general population according to ONS data on perinatal mortality (in 2005 there were 5.4 still births, 2.6 early neonatal deaths and 3.4 late neonatal deaths per 1000 total births). The authors of the ACHOIS study highlight that at least one death in the control group was unrelated to GD.

The following tables show the results of the models if the number of perinatal deaths in each group were different than that reported in the trial. As the number of perinatal deaths decreases, the cost-effectiveness of the various strategies changes. When only four deaths in the trial group are attributed to GD, the ICERs of both Strategy 21 and Strategy 6 become less favourable and continue to do so until only one perinatal death is attributed to GD. Even when there is only a single death assumed, there is still a screening and treatment strategy that would be considered cost-effective - in this case Strategy 21. However, if no perinatal deaths are attributed to GD, then there is no strategy for screening and treatment that could be considered cost-effective.

This result demonstrates that the model is highly sensitive to the potential QALYs gained by preventing even a single perinatal death. The model also potentially underestimates the QALYs to be gained by preventing other adverse outcomes, such as shoulder dystocia or nerve palsy may therefore underestimate the cost-effectiveness of each strategy. However, the ICERs when no deaths are assumed are sufficiently large to suggest that the potential QALY gain from preventing some of these events would not be adequate for these strategies to be cost-effective.

What is clear from this analysis is that the potential benefits to the NHS with respect to QALYs gained form intervention are likely to be felt in the form of preventing perinatal deaths, and the cost effectiveness of screening and treatment strategies are highly influenced by this one particular adverse outcome.

Table 13 Four perinatal deaths attributable to GD

Strategy	QALY	Cost	Incremental QALY	Incremental cost	ICER
21	21.26	£99,520	21.26	£99,520	£4,682
6	30.95	£367,270	9.69	£267,750	£27,634

Table 14 Three perinatal deaths attributable to GD

Strategy	QALY	Cost	Incremental QALY	Incremental cost	ICER
21	15.80	£100,166	15.80	£100,166	£6,338
6	23.01	£368,210	7.20	£268,044	£37,211

Table 15 Two perinatal deaths attributable to GD

Strategy	QALY	Cost	Incremental QALY	Incremental cost	ICER
21	10.69	£100,316	10.69	£100,316	£9,388
6	15.56	£368,430	4.87	£268,113	£55,045

Table 15 One perinatal deaths attributable to GD

Strategy	QALY	Cost	Incremental QALY	Incremental cost	ICER
21	5.94	£100,478	5.94	£100,478	£16,914
6	8.65	£368,665	2.71	£268,187	£99,045

Table 15 No perinatal deaths attributable to GD

Strategy	QALY	Cost	Incremental QALY	Incremental cost	ICER
21	1.61	£101,074	1.61	£101,074	£62,857
6	2.34	£369,532	0.73	£268,458	£366,275

Single risk factors

The GDG expressed concerns over the number of women that would have to undergo a GTT if Strategy 6 were adopted. A large proportion of women tested would be tested based on age criteria alone - under the baseline assumptions as many as 90% might be offered the diagnostic test. This would lead to great inconvenience to a large number of women, only a small minority of whom will ultimately benefit from the testing process, as well putting strain on local service. As a result it was felt that the use of screening based on risk factors other than age should be considered.

Based on limitations in the available data the cost-effectiveness of using combinations of any of the single risk factors other than age is not possible - there is no way of telling how many patients would have one risk factor only and how many would have more than one. However, it may be the case that where single risk factors are cost-effective on their then any combination of these is also likely to be cost-effective. Therefore an analysis of the cost-effectiveness of each single risk factor, followed by a GTT test has been done, with each being risk factor plus GTT combination compared to a strategy of no screening or treatment. The results are presented in Table X.

Table X ICER for single risk factor strategies followed by a diagnostic test when compared with a strategy of no screening or treatment.

Strategy	QALY	Cost	ICER
Ethnicity	9.55	£66,237	£6,936
BMI	6.29	£80,116	£12,737
Family history	15.73	£81,932	£5,209

Any strategy where a single risk factor from the ADA criteria other age is applied alone, followed by a diagnostic test has an ICER that is below the threshold of £20,000 and in each case could be considered cost-effective on its own.

The above analysis established that screening and treatment of gestational diabetes generally is cost-effective in some populations. Below we consider the cost-effectiveness of different treatment options for gestational diabetes.

Cost analysis of different treatment options for GD

A systematic review of literature targeted at the guideline question on what is cost-effective treatment for gestational diabetes, identified a single paper for inclusion [963]. This paper described a cost model to compare the costs of an oral hypoglycaemic, glyburide, versus insulin for the treatment of gestational diabetes. The paper justifies what is essentially a cost minimisation approach on the basis that glyburide and insulin confer similar glycaemic control [961]. Their model based in a US setting excluded resource items that were identical to both treatments. Included in the costs for insulin were drug costs, costs of the consumables needed to administer the insulin and the cost of instructing patients on how to draw up the insulin and inject themselves. The cost of glyburide was based on the average wholesale cost of a milligram of drug multiplied by the weekly dose expected to be necessary for glycaemic control. In addition it was assumed that 4% of patients wouldn't achieve control with glyburide and would have to switch to insulin. Therefore, the model also incorporated a cost for glyburide failure. Patients switching also incurred the educational costs associated with insulin treatment. Finally, the model also included the 'downstream' costs of hypoglycaemia which was assumed to be more common in the insulin treated patients. In the baseline analysis glyburide was found to produce an average cost saving of $166 per patient. The authors report that most sensitivity analyses did not alter the direction of this finding. A threshold analysis suggested that insulin was only less costly than glyburide at the highest wholesale cost of $18.24 per week in conjunction with a daily dose of 18.9g which is considerably higher than what is believed to be necessary to achieve good glycaemic control. A similar cost model was developed to compare the cost of insulin analogue (lispro), and two oral hypoglycaemics (glibenclamide and metformin) in a UK context.

Introduction

A cost minimisation analysis can be considered to be a special case of cost-effectiveness analysis when the interventions being compared are equally efficacious. In such a scenario the cheapest option is unambiguously cost-effective as it dominates the alternatives, being cheaper and equally effective. A randomised study [961]failed to find significant differences in outcomes (maternal and neonatal) between glyburide and insulin treatment in women with gestational diabetes. It is on this basis, and in the absence of any conflicting evidence, that such a cost minimisation analysis might be justifiable to determine the cost-effectiveness of different GD treatments. Of course no evidence of a difference is not the same as evidence of no difference, however the p-values I this study were particularly large and the inference of no difference doesn't arise as a result of some outcomes being just the wrong side of an arbitrary 5% cut-off point for statistical significance.

Insulin analogue was used in this cost comparison rather than insulin as this is what would be offered to women with GD in the UK. Implicit in this is an assumption that outcomes with an analogue insulin would be equivalent to those with insulin. Metformin was additionally added into this analysis as an on-going study (MIG) is assessing its use in women GD and it could potentially be an important treatment option in the UK.

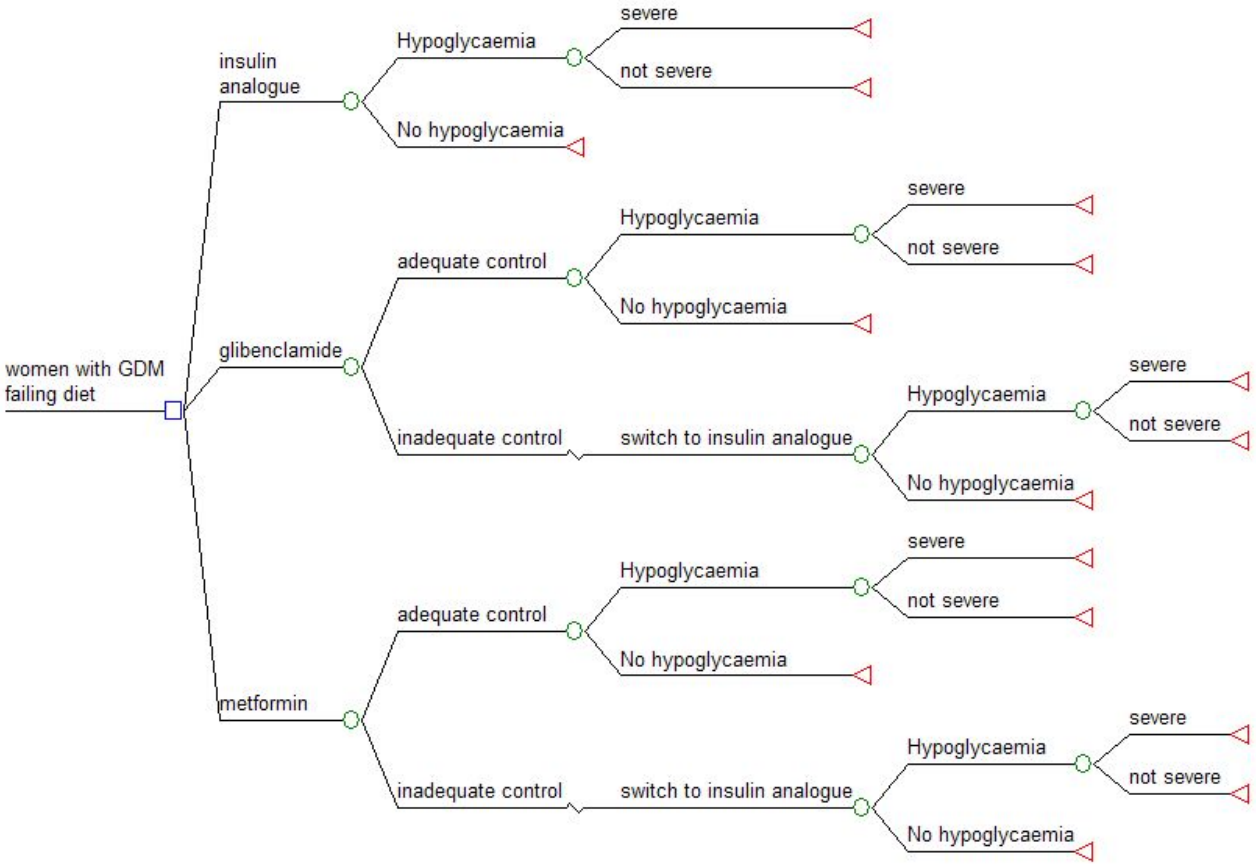


Figure 1 GD treatment cost model

Method

The basic structure of the cost analysis is shown in figure 1. It is assumed that a diagnosis of GD would be made at a gestational age of 27 weeks. As described in the screen/treat model patients would commence with dietary treatment. In patients who do not achieve adequate glycaemic control after 10 days, medical therapy would be commenced and this is the starting point for this cost comparison.

Costs which are common to all treatments, such as those associated with self-monitoring of blood glucose, are not included in the analysis. The costs for a woman taking insulin analogue include the time of a diabetic specialist nurse in providing instruction on how to administer the drug. Patients are assumed to use a pre-filled disposable injection pen (e.g. Humalog® Mix50) and to be on a daily dose of 20 units administered in twice daily injections. Therefore, they require two needles per day for their injection pen. The cost of glibenclamide is the drug cost based on a daily dose of 15mg. Similarly the cost of metformin is based on a daily dose of 1.5g.

In addition to the cost of treatment is important to also consider 'downstream' costs. Overall outcomes are assumed not to differ, but following the Langer study the model addresses a possible differential in the hypoglycaemia risk between the different treatments. It is additionally assumed at baseline that 5% of hypoglycaemic events will be 'severe' and it is these for which there will typically be an NHS resource implication. The cost of a 'severe' hypoglycaemic event is assumed to be the cost of a paramedic ambulance journey and an A&E admission.

The complete list of model parameters is given in Tables 1-3.

Table 1 Treatment timeframe (days)

Variable	Value (days)	Source	Notes
Treatment duration	80	DiP GDG	It is assumed a GD diagnosis would be made at a gestational age of 27 weeks. Patients would be given approximately 10 days to achieve control with diet and 80 days is a reasonable approximation of the typical time to term at the commencement of pharmacological treatment
Oral hypoglycaemic trial period	14	Langer??	

Table 2 Costs

Variable	Cost	Source	Notes
Insulin instruction	£47.25	Netten & Curtis (2006) GDG estimate	This is based on an instruction time of 45 minutes with instruction provided by a specialist nurse
Insulin analogue	£0.57 per day	BNF 52	This is based on a dose of 20 units per day. A pre-filled disposable pen has 1500 units and costs £29.46. It is further assumed that injections are twice daily requiring two needles at £0.09 each
Glibenclamide	£0.16	BNF 52	Based on 15mg daily. A 5mg 28-tablet pack costs £1.50
Metformin	£0.10	BNF 52	Based on 1.5g daily. A 500mg 84-tablet pack costs £2.85
Switching cost of oral hypoglycaemia failure	£0.00	GDG	It is assumed there is no additional cost over and above those incurred by all patients starting insulin analogue treatment
Treatment of severe hypoglycaemia	£403	Netten & Curtis (2006) NHS Reference Costs 2005-06	Average cost per patient journey for paramedic ambulance £323 A&E admission with low cost investigation £80

Table 3 Probabilities

Variable	Probability	Source	Notes
Control with glibenclamide	0.96	Langer 2000 [961] GDG estimate	A GDG member reports 0.77 for this parameter in his clinical practice
Control with metformin	0.96	Langer 2000 [961]	Assumed identical to glibenclamide
Hypoglycaemia on insulin analogue	0.202	Langer 2000 [961]	Assumed to be the same as Langer found for insulin
Hypoglycaemia on glibenclamide	0.02	Langer 2000 [961]	
Hypoglycaemia on metformin	0.02	Langer 2000 [961]	Assumed identical to glibenclamide
Proportion of hypoglycaemia that is 'severe'	0.05	GDG estimate	

Results

Table 4 shows the cost per patient of each of the three treatment options. These show the oral hypoglycaemics to be considerably cheaper than analogue insulin. Of the oral hypoglycamics metformin is the cheapest and, with the assumption of equal efficacy, the most cost-effective treatment.

Table 4

Treatment	Average cost per patient
Insulin analogue	£96.92
Glibenclamide	£16.32
Metformin	£11.68

Sensitivity analysis

A number of sensitivity analyses were undertaken to determine how robust the conclusion of the baseline result was to changes in model parameters where some uncertainty exists as to their 'true' value. For ease of exposition most sensitivity analyses focus on a comparison of glibenclamide and insulin analogue on the basis that, apart from a small difference in costs, these are assumed to be identical treatments in terms of both outcomes and 'downstream' costs.

However, threshold analyses were also undertaken which showed that, holding all other factors constant, metformin remained cheapest as long as control on metformin was at least 90.3% (with control on glibenclamide 96%) or control on metformin was at least 72.3% (with control on glibenclamide 77%).

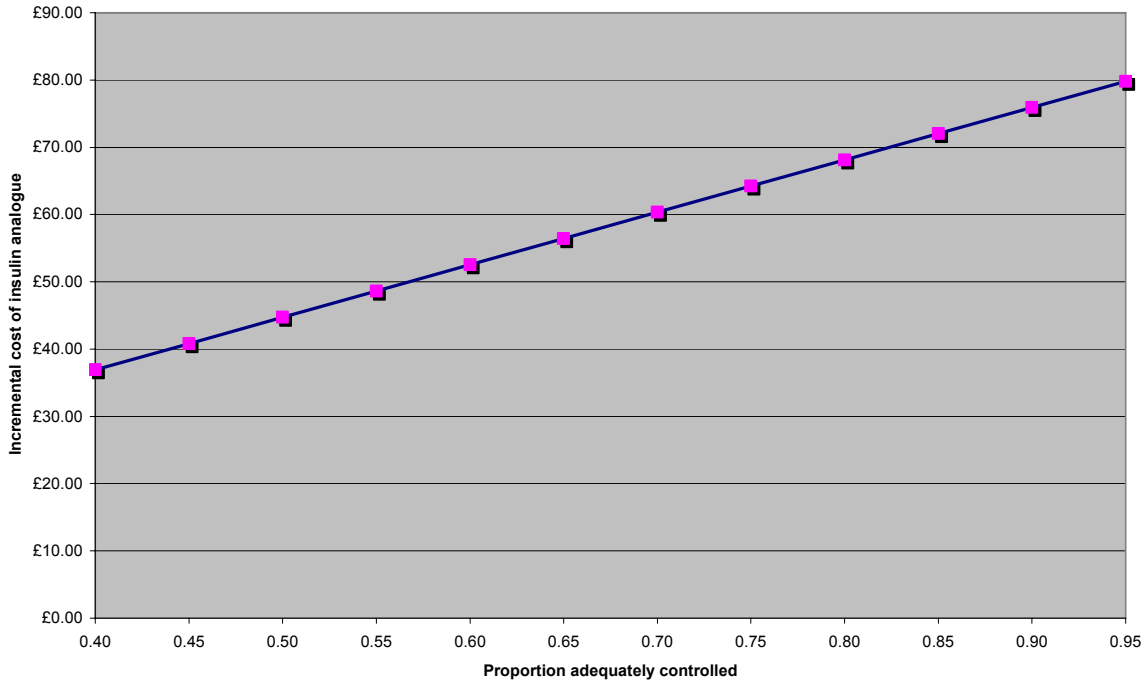


Figure 1 Incremental cost of insulin analogue as control on glibenclamide varies

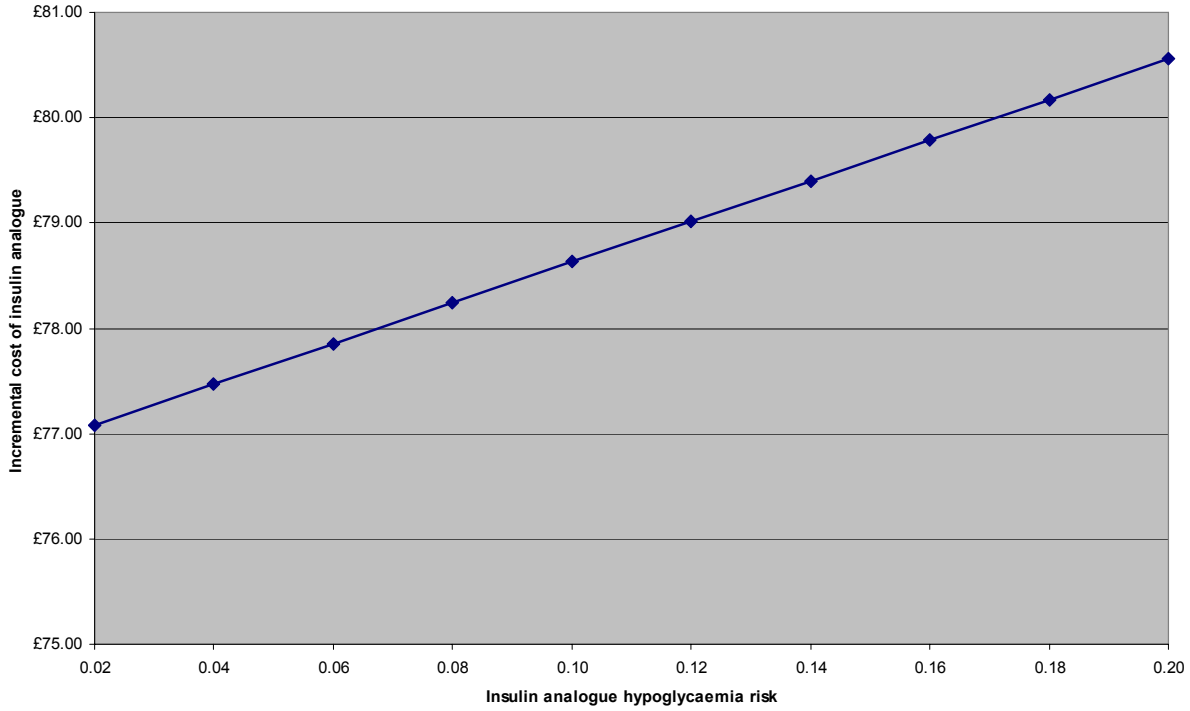


Figure 2 Incremental cost of insulin analogue as hypoglycaemia risk of insulin analogue varies

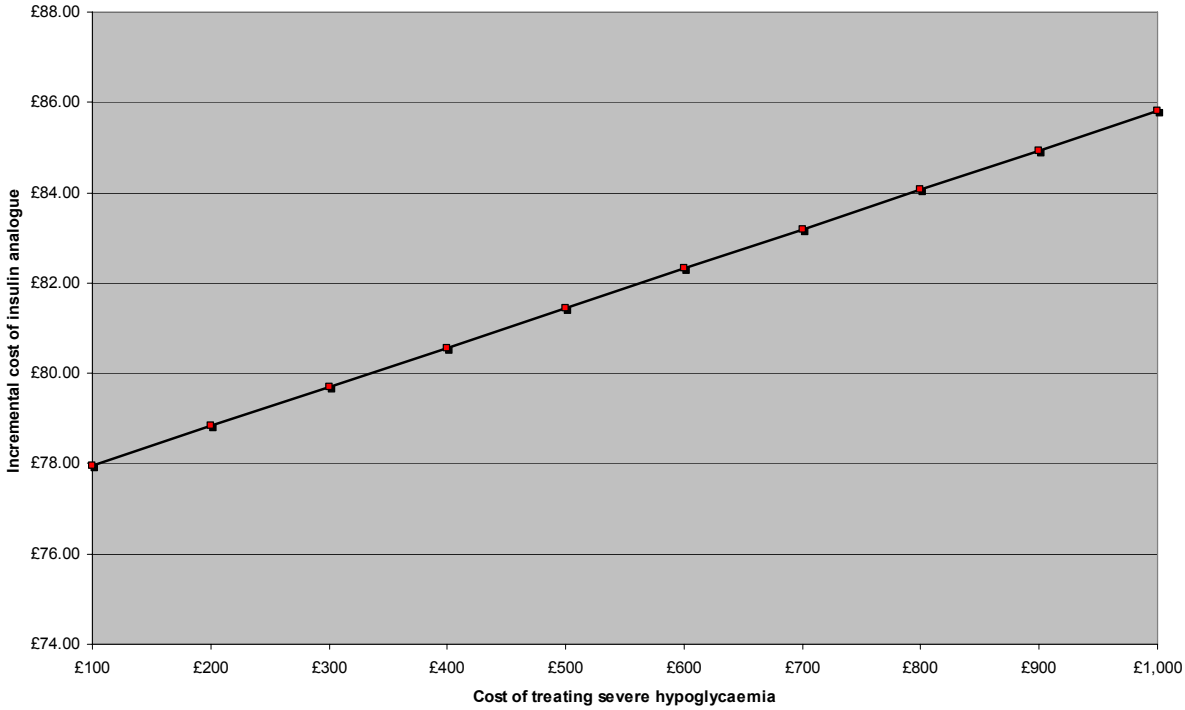


Figure 3 Incremental cost of insulin analogue as cost of treating severe hypoglycaemia varies

Discussion

Using the data from ACHOIS, this guideline has demonstrated that screening for GD and its treatment is cost-effective and that this finding is not contingent on the type of pharmacological treatment (insulin analogue or oral hypoglycaemic used). However, given that the treatments have different resource implications for the NHS it does not follow that all treatment is equally cost-effective. One study suggested [961] that 'among women with gestational diabetes, the degree of glycaemic control and the perinatal outcomes were essentially the same for those treated with glyburide and those treated with insulin. The lack of differences between the infants born to mothers in the two treatment groups corroborated the results in the mothers'. Therefore, if it argued on the basis of this study that glibenclamide is equally efficacious as insulin analogue and would have achieved similar outcomes to those observed with diet and insulin treatment observed in ACHOIS, then we can say that the results presented here suggest that glibenclamide is a more cost-effective treatment for GD than insulin analogue. Sensitivity analysis suggested that this conclusion was robust when model parameters were changed in a one-way fashion. Our GDG has suggested that the proportion of patients achieving control with glibenclamide may be lower in clinical practice than that observed by Langer at al. However, as the sensitivity analysis shows, glibenclamide continues to be cost-saving compared to insulin analogue even with a much smaller proportion achieving adequate control.

As yet there is not the evidence to justify a cost minimisation approach with metformin. However, if it too was shown to be as efficacious as insulin analogue then it would be the most cost-effective treatment of all.

One caveat to these findings is the assumption that there is no cost to the health service in switching patients from an oral hypoglycaemic to insulin analogue, other than those ordinarily incurred for patients taking insulin analogue. If there is a 'switching cost' then the cost-effectiveness of the oral hypoglycaemics would be less than that implied here.

B.6 Health economic model for fetal growth

Health economics evidence summary

A systematic search of the literature identified 42 articles potentially related to the economic evaluation of the measurement of fetal growth. The abstracts of all 42 papers were reviewed, but none met the inclusion criteria. All of the published economic evidence focused on the clinical aspects of fetal growth; few mentioned the importance of conducting a cost-effectiveness analysis. The lack of empirical evidence on economic evaluation is due, at least in part, to the paucity of robust clinical studies apart from the use of Doppler ultrasound of the umbilical artery and poor evidence of effectiveness of fetal biometry by ultrasound, as shown in the review of clinical evidence. Further, as ultrasound scanning is among the most common screening tests used in clinical practice, there is no clear alternative to compare ultrasound screening with and en economic evaluation requires a comparator (which can be 'do nothing') to examine alternative strategies.

Exploring the economic perspective of fetal growth

The lack of health economics studies in the area means that it is necessary to begin with a very general health economic framework. The object is to conduct a cost-effectiveness analysis of specific clinical strategies to identify and monitor babies that are small for gestational age (SGA). The aim is to help the GDG members to make a recommendation, on the basis of clinical and economic evidence, on what is the best strategy, if any, for monitoring fetal growth and identifying the SGA fetus, within the context of enabling the NHS to redistribute resources more efficiently across health care services.

The model focuses on a hypothetical population of pregnant women. The decision tree (Figure 1), depicts the decision pathway of the hypothetical cohort of patients (here pregnant women). The pathway starts with the decision whether to offer one of three strategies:

1) no measurement and monitoring of fetal growth
2) to measure and monitor fetal growth by ultrasound alone, and
3) to measure and monitor fetal growth by symphysio-fundal height and ultrasound.

Patient flow from this decision proceeds from left to right with the branches indicating all feasible pathways. The pathway of each pregnant woman is determined by the probability of an event occurring and these are represented in the model by chance nodes. Branches that originate from chance nodes indicate all possibilities that exist at such point in the pathway. The outcome of each terminal node (or end point) in the tree is birth by either caesarean section or by normal delivery.

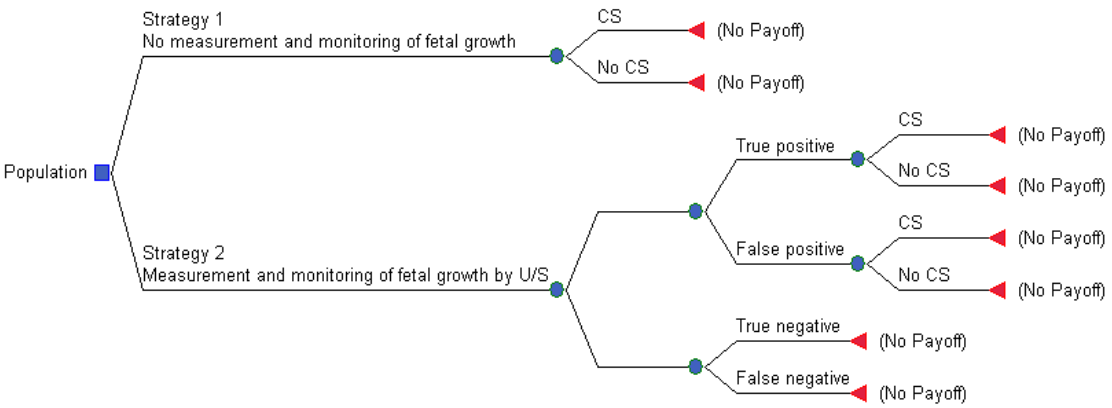


Figure 1 The decision tree

Assumptions underlying the model

1) The model that is presented here does not conform to the standard model of decision analysis. Under ideal circumstances, an economic model if a healthcare intervention would be based on the robust clinical data with an outcome that allows comparisons between alternative interventions, for example the quality adjusted life year (QALY). The approach taken towards answering this question is different, due to the lack of reliable clinical data, as highlighted above and in the systematic review of the clinical evidence (Chapter X). In this instance we look at what number of perinatal deaths attributable to being SGA would need to be prevented in order for the measurement and monitoring of fetal growth to be cost-effective.
2) In the absence of any reliable data on the accuracy of ultrasound scanning for the measurement of fetal growth, the initial assumption made in the analysis is that ultrasound scanning is 100% sensitive and 100% specific, giving perfect information on the size of the fetus and enabling healthcare professionals the opportunity to intervene where action will be of the greatest benefit. If the this intervention (strategy two, ultrasound screening) is not cost-effective when there is perfect information, then it would be unlikely to be cost-effective if we relax the assumption of perfect information with less accurate estimates of sensitivity and specificity. In any case, this strategy can act as a benchmark for comparison with other strategies (no fetal growth monitoring or monitoring using SFH measurement and ultrasound scanning).
3) Also assumed with the model is that fetal growth rates and SGA fetuses are well defined. There exist different definitions for normal fetal growth. Within the model normal fetal growth is defined as those fetuses falling within the 10^{th} and 90^{th} percentiles.
4) A number of parameter values used in the model are based on the expert opinion of the members of the GDG, drawing on the clinical experience of doctors, midwives, health visitors and patient representatives. However, this approach to populating the decision model introduces a great deal of uncertainty and this uncertainty is examined in sensitivity analysis.
5) An assumption has been made by the GDG that for every 1,000 known SGA fetuses, approximately 250 perinatal deaths can be prevented.

Model description

There are three main branches on the decision tree, representing the three different strategies for measuring and monitoring fetal growth. The tree is designed to highlight the differences in cost and effects of each strategy and to provide a basis for comparison.

Strategy 1: No measurement of fetal growth

In this strategy, fetal growth is not measured by any means and there is no subsequent monitoring. As with all strategies considered, there are two key maternal outcomes considered, caesarean section and normal birth. Rates of caesarean section and the costs associated with each outcome are given in Table 1. The key perinatal outcome is death.

Strategy 2: Measuring fetal growth by ultrasound

Under this strategy all women will be offered an ultrasound scan and at present we have assumed that all women will accept the offer, though there may be instances where a woman chooses not to undergo any fetal growth monitoring. Following the ultrasound, there are four possible diagnoses that the woman could receive:

1) True positive - the fetus is correctly identified as SGA following the ultrasound scan.
2) True negative - the fetus is correctly identified as not being SGA following the ultrasound scan
3) False positive - the fetus is incorrectly identified as SGA following the ultrasound scan when it is within the normal size range.
4) False negative - the fetus is incorrectly identified as not being SGA following the ultrasound scan when it is in fact in the bottom decile of fetal size.

Strategy 3: Measuring fetal growth by symphysio-fundal height and ultrasound

Under this strategy all women will be offered symphysio-fundal height (SFH) measurement to estimate the size of the baby. Where SFH measurement indicates that the fetus may be SGA, ultrasound scan monitoring of fetal growth is offered. The group offered further monitoring includes the true and false positive cases; the true and false negative cases will undergo no further monitoring. As in strategy two, at each stage of measurement there is a chance that the fetus will be

correctly or incorrectly diagnosed as SGA or not, that is there is a probability that the diagnosis is a true or false positive or true or false negative.

Clinical and cost data used in the model

Clinical data

The clinical parameters used in the model have been agreed with the GDG members and are shown in Table 1. These include the probability of a baby being SGA or non-SGA, the accuracy with which SFH measurement and ultrasound scanning can identify an SGA fetus and the probability of having a caesarean section or normal birth dependent on whether or not the fetus is considered SGA.

Table 1 Clinical parameters

Probability of key events and outcomes	Value	Range	Source
Probability of non-SGA	0.90	-	
Probability of SGA	0.10	-	
Probability of CS (Non-SGA)	0.25	-	HES statistics 2005/06
Probability of CS (SGA)	0.50	0.40 - 0.60	GDG opinion
Sensitivity of SFH measurement	0.27	0.10 - 1.0	Persson et al[919]
Specificity of SFH measurement	0.90	0.10 - 1.0	Persson et al[919]
Sensitivity of ultrasound scan of fetal size	0.48	0.10 - 1.0	Warsof et al[923]
Specificity of ultrasound scan of fetal size	0.93	0.10 - 1.0	Warsof et al[923]

Costs of fetal growth monitoring and birth

The perspective adopted for the economic evaluation conforms to that of the NHS, in line with NICE guidance on economic evaluations for guidelines. The cost parameters used in the model are shown in Table 2. These include the cost of ultrasound monitoring, cost of monitoring appointments and the cost of a normal birth or birth by caesarean section.

Table 2 Cost parameters

Cost of key events	Value	Source
Hospital birth (w/o cc)	£753	2007-08 Tariff
Hospital birth (w/cc)	£1,124	2007-08 Tariff
Caesarean section (w/o cc)	£1,404	2007-08 Tariff
Caesarean section (w/cc)	£1,926	2007-08 Tariff
SFH Measurement	£3.67	PSSRU 2006
U/S fetal growth scan	£34	NHS Reference costs 2006

Results

Comparing strategies

Having illustrated how the costs and benefits of the two strategies are generated, the next step is to compare them. The difference between the total cost of each strategy when compared with another gives the incremental cost. In this analysis, the incremental cost is then divided by the NICE willingness to pay per QALY to obtain the incremental effect needed to be achieved in order for the intervention to be considered cost-effective. In line with the NICE guidelines manual, the maximum willingness to pay is assumed to £20,000 per additional QALY. The number of QALYs per infant saved is assumed to be 25, based on the average life span of 76 years in the UK, discounted at 3.5% per annum and assuming a life lived in perfect health. Thus the additional effectiveness as

measured in perinatal deaths required to be prevented by adopting any given strategy compared to any other strategy is obtained by dividing the incremental effect in QALYs by 25.

The GDG estimated that the number of neonates that could be saved if they were to be identified through the measurement of fetal size and monitoring of fetal growth is approximately 200 - 250. This is based on the following assumptions from the GDG:

- There are ~ 6000 small for gestation age babies each year
- Just under one third of these (1805) will have intrauterine growth restriction.
- Of these, roughly 50% will not survive, regardless of any intervention
- Twenty to 25 per cent (~185 - 225) of the remaining number could benefit from intervention in the form of a perinatal death prevented.

If the above assumptions are correct then there will be a cost-effective strategy for measuring and monitoring fetal growth, based on the results presented below.

Perfect information

When the assumption about perfect information on fetal growth is held, the following results are obtained.

Strategy One compared with Strategy Two

The additional cost of Strategy 2 compared to Strategy 1 is £40.2 million, with an incremental effect (QALYs) to be cost-effective of 2,011. The additional neonatal deaths needed to advert to be cost-effective are 80.

Strategy One compared with Strategy Three

The additional cost of Strategy 3 compared to Strategy 1 is £20.7 million, with an incremental effect (QALYs) to be cost-effective of 1,037. The additional neonatal deaths needed to advert to be cost-effective are 41.

Strategy Two compared with Strategy Three

The additional cost of Strategy 3 compared to Strategy 2 is £19.5 million, with an incremental effect (QALYs) to be cost-effective of 974. The additional neonatal deaths needed to advert to be cost-effective are 39.

Imperfect information

In the above results, the absence of reliable data on the accuracy of ultrasound scanning for identifying led to a base-case analysis where all forms of fetal growth measurement were assumed to be 100% sensitive and 100% specific. In line with the GDG assumptions about the number of perinatal deaths that could be avoided given the knowledge that the fetus was SGA, it would be cost-effective to choose either Strategy 2 or Strategy 3 for fetal growth monitoring. However, in practice it is known that both SFH and ultrasound scanning are much less accurate than this. An estimate of the sensitivity and specificity of each method is estimated from the clinical data and the results are presented here.

Strategy One compared with Strategy Two

The additional cost of Strategy 2 compared to Strategy 1 is £45.7 million, with an incremental effect (QALYs) to be cost-effective of 2,286. The additional neonatal deaths needed to advert to be cost-effective are 91.

Strategy One compared with Strategy Three

Implementing Strategy Three would lead to additional costs of £4.9 million when compared with Strategy One with an incremental effect of 262. Ten additional perinatal deaths would need to be avoided for Strategy Three to be cost-effective when compared with Strategy One.

Strategy Two compared with Strategy Three

The additional cost of Strategy 2 compared to Strategy 3 is £40.7, with an incremental effect (QALYs) to be cost-effective of 2,039. Further, *Strategy 2 correctly diagnoses 35 more SGA babies than Strategy 3 per 1,000 births*. The additional neonatal deaths needed to advert for Strategy 2 to be cost-effective is 84.

Appendix C

Training and equipment standards for ultrasound screening in pregnancy

Sonography is not recognised as a speciality by the Health Act 1999, so there is no obligation for sonographers to be registered to practise. There is currently no statutory requirement for ultrasound practitioners to receive accredited training.

Many sonographers will have achieved a postgraduate certificate or diploma in clinical ultrasound. Well-established programmes leading to these qualifications are available in a number of universities in the UK and courses are accredited by the Consortium for the Accreditation of Sonographic Education (CASE). Members of the consortium include the British Medical Ultrasound Society, the Royal College of Radiographers (RCR), the Royal College of Midwives and the United Kingdom Association of Sonographers.

To achieve and attain CASE accreditation, an individual course must demonstrate that both its academic and clinical teaching programmes and its assessment methods are sufficiently rigorous to ensure that successful students are safe to practise in the ultrasound areas for which they have studied. Current postgraduate education certificates and diploma training programmes in obstetric ultrasound are designed with the provision of a safe, accurate and efficient screening service for fetal anomaly in mind.

With regard to the implementation of the National Down's Syndrome Screening Programme for England, all professionals involved in providing antenatal screening information & services should have received the appropriate education for their roles and responsibilities and any specific tasks required.

All health professionals undertaking an ultrasound scan must have an accredited certificate in obstetric ultrasound or equivalent and also attend an appropriate communication/counselling course.

(Extracted from Antenatal screening – working standards, National Down's Syndrome Screening Programme for England, (March 2004)) [964]

There is a need for practical competence tests at NHS trust level. The RCOG Working Party recommends that local departments monitor standards and keep checks on them.

Trusts should have a process for retraining and updating as required but at present there is little provision for this in trust budgets. Clinical governance provides a facilitating mechanism.

The RCOG is in the process of implementing Advanced Training Skills Modules (ATSM's) and all medical staff who undertake fetal anomaly scanning should hold the relevant ATSM. Skills should be maintained by performing detailed scans in at least one and preferably two sessions per week.

Medical and midwifery staff should not undertake scans of any sort if they have not been specifically trained.

A scan to perform a fetal structural survey demands the use of modern equipment (not more than 5 years old) of modest sophistication. The scanner must be capable of performing the necessary measurements and should provide good image quality. As always, regards for safety in the use of ultrasound is paramount and minimum output should be used in accordance with the ALARA principle: as low as reasonably attainable.

[Extracted from the recommendations of the Royal College of Obstetricians and Gynaecologists' Working Party on Ultrasound Screening for Fetal Abnormalities.[302]]

Appendix D

Further information

During the review process of this guideline, various topics were suggested by stakeholders and peer reviewers for inclusion in the guideline. The inclusion or exclusion of any subject not already contained in the guideline was carefully considered by the Guideline Development Group.

Topics that were not originally included in the scope of this guideline and for which guidance already exists are listed in this Appendix, with information on where further information can be obtained. All other topics raised by stakeholders or peer reviewers have been addressed in the main text of the guideline.

Cystic fibrosis	UK National Screening Committee [http://www.doh.gov.uk/nsc/]
Herpes	*Genital Herpes in Pregnancy: Management* (RCOG Guideline No. 30, March 2002). [www.rcog.org.uk/guidelines.asp?PageID=106&GuidelineID=39]
HTLV 1	The UK National Screening Committee position on HTLV1 (human T lymphocyte virus 1) is that screening should not be offered for pregnant women. (www.nelh.nhs.uk/screening/antenatal_pps/htlv1.html)
Thrombophilia	The UK National Screening Committee position on thrombophilia is that there is no evidence to support screening to identify those deemed at increased risk of venous thrombosis in pregnancy. [www.nelh.nhs.uk/screening/antenatal_pps/thrombophilia.html]
Varicella	*Chickenpox in Pregnancy* (RCOG Guideline No. 13, July 2001). [www.rcog.org.uk/guidelines.asp?PageID=106&GuidelineID=7]

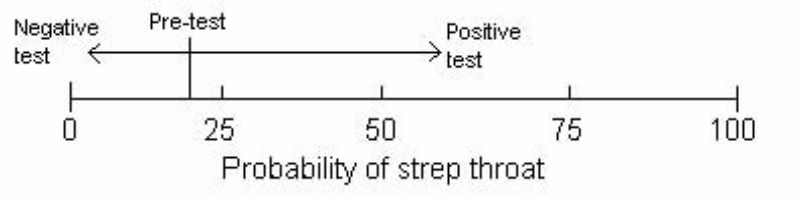
Note

RCOG Guidelines (also known as Green-top guidelines) are clinical guidelines produced by the Guidelines and Audit Committee of the Royal College of Obstetricians and Gynaecologists. Guidelines can be accessed online at: www.rcog.org.uk/guidelines.asp?PageID=106.

Appendix E

Likelihood ratios

When we decide to order a diagnostic test, we want to know which test (or tests) will best help us rule-in or rule-out disease in our patient. In the language of clinical epidemiology, we take our initial assessment of the likelihood of disease ('pre-test probability'), do a test to help us shift our suspicion one way or the other, and then determine a final assessment of the likelihood of disease ('post-test probability'). Take a look at the diagram below, which graphically illustrates this process of 'revising the probability of disease'.



Likelihood ratios tell us how much we should shift our suspicion for a particular test result. Because tests can be positive or negative, there are at least two likelihood ratios for each test. The 'positive likelihood ratio' (LR+) tells us how much to increase the probability of disease if the test is positive, while the 'negative likelihood ratio' (LR-) tells us how much to decrease it if the test is negative. The formula for calculating the likelihood ratio is:

$$LR = \frac{\text{probability of an individual } \textbf{with} \text{ the condition having the test result}}{\text{probability of an individual } \textbf{without} \text{ the condition having the test result}}$$

Thus, the positive and likelihood ratio are:

$$LR+ = \frac{\text{probability of an individual } \textbf{with} \text{ the condition having a positive test}}{\text{probability of an individual } \textbf{without} \text{ the condition having a positive test}}$$

$$LR- = \frac{\text{probability of an individual } \textbf{with} \text{ the condition having a negative test}}{\text{probability of an individual } \textbf{without} \text{ the condition having a negative test}}$$

You can also define the LR+ and LR– in terms of sensitivity and specificity:

LR+ = sensitivity/(1 – specificity)

LR– = (1 – sensitivity)/specificity

Let's consider an example:

In a study of the ability of rapid antigen tests to diagnose strep pharyngitis, 90% of patients with strep pharyngitis have a positive rapid antigen test, while only 5% of those without strep

pharyngitis have a positive test. The LR+ for the ability of rapid antigen tests to diagnose strep pharyngitis is:

$$LR+ = 90\%/(100\% - 95\%) = 90\%/5\% = 18$$

Don't get too caught up in the calculations. the important thing is to understand the meaning of a likelihood ratio. They have unique properties that make them particularly relevant to clinicians:

- **The LR+ corresponds to the clinical concept of 'ruling-in disease'**
- **The LR– corresponds to the clinical concept of 'ruling-out disease'**
- The LR+ and LR– don't change as the underlying probability of disease changes (predictive values do change, as you just learned)
- LR's using multiple 'levels' of positive (i.e. not just a simple yes/no or positive/negative result) provide much richer, more useful information to you as a clinician.

Interpreting likelihood ratios: general guidelines

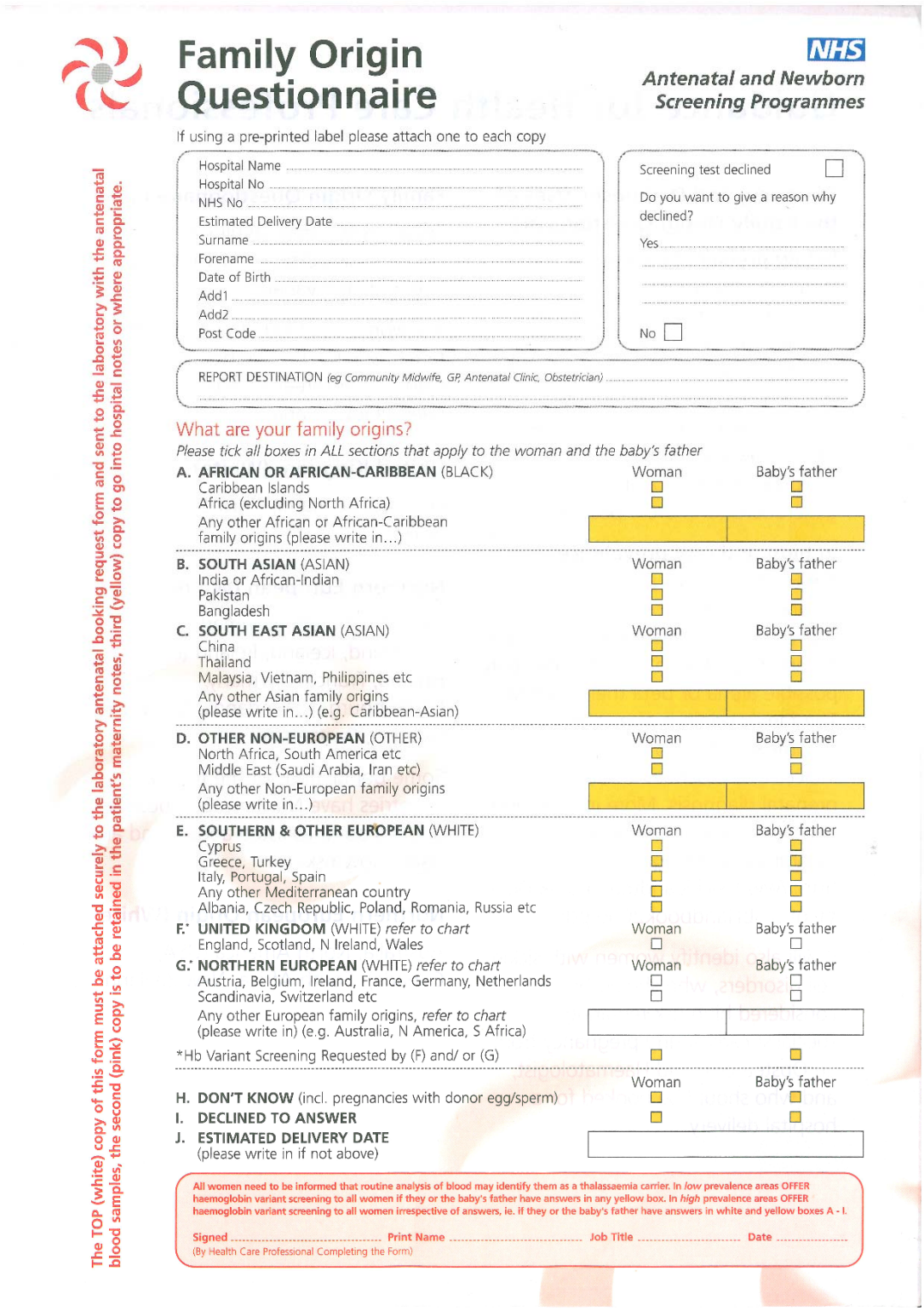
The first thing to realise about LR's is that an LR > 1 indicates an increased probability that the target disorder is present, and an LR < 1 indicates a decreased probability that the target disorder is present. The following are general guidelines, which must be correlated with the clinical scenario:

LR	Interpretation
> 10	Large and often conclusive increase in the likelihood of disease
5–10	Moderate increase in the likelihood of disease
2–5	Small increase in the likelihood of disease
1–2	Minimal increase in the likelihood of disease
1	No change in the likelihood of disease
0.5–1.0	Minimal decrease in the likelihood of disease
0.2–0.5	Small decrease in the likelihood of disease
0.1–0.2	Moderate decrease in the likelihood of disease
< 0.1	Large and often conclusive decrease in the likelihood of disease

The decision to order a test is also based on our initial assessment of the likelihood of the target disorder, and how important it is to rule-in or rule-out disease. For example, a chest x-ray might have a good likelihood ratio for pneumonia. But if you believe a patient has a simple cold, this test, no matter how good the LR, probably shouldn't be ordered. It is sometimes helpful to be able to calculate the exact probability of disease given a positive or negative test. We saw that this is next to impossible using sensitivity and specificity at the bedside (unless you can do Bayes' Theorem in your head!).

Appendix F

Family origin questionnaire



Family Origin Questionnaire

NHS
Antenatal and Newborn Screening Programmes

If using a pre-printed label please attach one to each copy

Hospital Name .....
Hospital No .....
NHS No .....
Estimated Delivery Date .....
Surname .....
Forename .....
Date of Birth .....
Add1 .....
Add2 .....
Post Code .....

Screening test declined ☐

Do you want to give a reason why declined?

Yes .....

No ☐

REPORT DESTINATION *(eg Community Midwife, GP, Antenatal Clinic, Obstetrician)* .....

The TOP (white) copy of this form must be attached securely to the laboratory antenatal booking request form and sent to the laboratory with the antenatal blood samples, the second (pink) copy is to be retained in the patient's maternity notes, third (yellow) copy to go into hospital notes or where appropriate.

What are your family origins?

Please tick all boxes in ALL sections that apply to the woman and the baby's father

	Woman	Baby's father
A. AFRICAN OR AFRICAN-CARIBBEAN (BLACK)		
Caribbean Islands	☐	☐
Africa (excluding North Africa)	☐	☐
Any other African or African-Caribbean family origins (please write in…)		
B. SOUTH ASIAN (ASIAN)	Woman	Baby's father
India or African-Indian	☐	☐
Pakistan	☐	☐
Bangladesh	☐	☐
C. SOUTH EAST ASIAN (ASIAN)	Woman	Baby's father
China	☐	☐
Thailand	☐	☐
Malaysia, Vietnam, Philippines etc	☐	☐
Any other Asian family origins (please write in…) (e.g. Caribbean-Asian)		
D. OTHER NON-EUROPEAN (OTHER)	Woman	Baby's father
North Africa, South America etc	☐	☐
Middle East (Saudi Arabia, Iran etc)	☐	☐
Any other Non-European family origins (please write in…)		
E. SOUTHERN & OTHER EUROPEAN (WHITE)	Woman	Baby's father
Cyprus	☐	☐
Greece, Turkey	☐	☐
Italy, Portugal, Spain	☐	☐
Any other Mediterranean country	☐	☐
Albania, Czech Republic, Poland, Romania, Russia etc	☐	☐
F.* UNITED KINGDOM (WHITE) *refer to chart*	Woman	Baby's father
England, Scotland, N Ireland, Wales	☐	☐
G.* NORTHERN EUROPEAN (WHITE) *refer to chart*	Woman	Baby's father
Austria, Belgium, Ireland, France, Germany, Netherlands	☐	☐
Scandinavia, Switzerland etc	☐	☐
Any other European family origins, *refer to chart* (please write in) (e.g. Australia, N America, S Africa)		
*Hb Variant Screening Requested by (F) and/ or (G)	☐	☐
	Woman	Baby's father
H. DON'T KNOW (incl. pregnancies with donor egg/sperm)	☐	☐
I. DECLINED TO ANSWER	☐	☐
J. ESTIMATED DELIVERY DATE (please write in if not above)		

All women need to be informed that routine analysis of blood may identify them as a thalassaemia carrier. In *low* prevalence areas OFFER haemoglobin variant screening to all women if they or the baby's father have answers in any yellow box. In *high* prevalence areas OFFER haemoglobin variant screening to all women irrespective of answers, ie. if they or the baby's father have answers in white and yellow boxes A - I.

Signed ..... Print Name ..... Job Title ..... Date .....
(By Health Care Professional Completing the Form)

Appendix G

Deleted material from the 2003 version

2.1 Summary of recommendations

Chapter 3 Woman-centred care and informed decision making

3.2 Antenatal education

Pregnant women should be offered opportunities to attend antenatal classes and have written information about antenatal care. [A]

Pregnant women should be offered evidence-based information and support to enable them to make informed decisions regarding their care. Information should include details of where they will be seen and who will undertake their care. Addressing women's choices should be recognised as being integral to the decision-making process. [C]

At the first contact, pregnant women should be offered information about the pregnancy care services and options available, lifestyle considerations, including dietary information, and screening tests. [C]

Pregnant women should be informed about the purpose of any screening test before it is performed. The right of a woman to accept or decline a test should be made clear. [D]

At each antenatal appointment, midwives and doctors should offer consistent information and clear explanations and should provide pregnant women with an opportunity to discuss issues and ask questions. [D]

Communication and information should be provided in a form that is accessible to pregnant women who have additional needs, such as those with physical, cognitive or sensory disabilities and those who do not speak or read English. [Good practice point]

4.6 Gestational age assessment: LMP and ultrasound

Pregnant women should be offered an early ultrasound scan to determine gestational age (in lieu of last menstrual period (LMP) for all cases) and to detect multiple pregnancies. This will ensure consistency of gestational age assessments, improve the performance of mid-trimester serum screening for Down's syndrome and reduce the need for induction of labour after 41 weeks. [A]

Ideally, scans should be performed between 10 and 13 weeks and use crown–rump length measurement to determine gestational age. Pregnant women who present at or beyond 14 weeks of gestation should be offered an ultrasound scan to estimate gestational age using head circumference or biparietal diameter. [Good practice point]

Chapter 5 Lifestyle considerations

5.5 Nutritional supplements

There is insufficient evidence to evaluate the effectiveness of vitamin D in pregnancy. In the absence of evidence of benefit, vitamin D supplementation should not be offered routinely to all pregnant women. [A]

5.12 Alcohol and smoking in pregnancy

Excess alcohol has an adverse effect on the fetus. Therefore it is suggested that women limit alcohol consumption to no more than one standard unit per day. Each of the following constitutes one 'unit' of alcohol: a single measure of spirits, one small glass of wine, and a half pint of ordinary strength beer, lager or cider. [C]

Chapter 9 Screening for fetal anomalies

9.1 Screening for structural anomalies

Pregnant women should be offered an ultrasound scan to screen for structural anomalies, ideally between 18 and 20 weeks of gestation, by an appropriately trained sonographer and with equipment of an appropriate standard as outlined by the National Screening Committee. [A]

9.2 Screening for Down's syndrome

Pregnant women should be offered screening for Down's syndrome with a test that provides the current standard of a detection rate above 60% and a false positive rate of less than 5%. The following tests meet this standard:

- From 11 to 14 weeks:
  - nuchal translucency (NT)
  - the combined test (NT, hCG and PAPP-A)
  - From 14 to 20 weeks:
  - the triple test (hCG, AFP and uE_3)
  - the quadruple test (hCG, AFP, uE_3, inhibin A)
- From 11 to 14 weeks AND 14 to 20 weeks:
  - the integrated test (NT, PAPP-A + hCG, AFP, uE_3, inhibin A)
  - the serum integrated test (PAPP-A + hCG, AFP, uE_3, inhibin A). [B]

By April 2007, pregnant women should be offered screening for Down's syndrome with a test which provides a detection rate above 75% and a false positive rate of less than 3%. These performance measures should be age standardised and based on a cutoff of 1/250 at term. The following tests currently meet this standard:

- From 11 to 14 weeks:
  - the combined test (NT, hCG and PAPP-A)
- From 14 to 20 weeks:
  - the quadruple test (hCG, AFP, uE_3, inhibin A)
- From 11 to 14 weeks AND 14 to 20 weeks:
  - the integrated test (NT, PAPP-A + hCG, AFP, uE_3, inhibin A)
  - the serum integrated test (PAPP-A + hCG, AFP, uE_3, inhibin A). [B]

Pregnant women should be given information about the detection rates and false positive rates of any Down's syndrome screening test being offered and about further diagnostic tests that may be offered. The woman's right to accept or decline the test should be made clear. [D]

10.3 Chlamydia trachomatis

Pregnant women should not be offered routine screening for asymptomatic chlamydia because there is insufficient evidence on its effectiveness and cost effectiveness. However, this policy is likely to change with the implementation of the national opportunistic chlamydia screening programme. [C]

Chapter 11 Screening for clinical conditions

11.1 Gestational diabetes mellitus

The evidence does not support routine screening for gestational diabetes mellitus (GDM) and therefore it should not be offered. [B]

11.2 Pre-eclampsia

At first contact a woman's level of risk for pre-eclampsia should be evaluated so that a plan for her subsequent schedule of antenatal appointments can be formulated. The likelihood of developing pre-eclampsia during a pregnancy is increased in women who:

- are nulliparous
- are age 40 or older
- have a family history of pre-eclampsia (e.g., pre-eclampsia in a mother or sister)
- have a prior history of pre-eclampsia
- have a body mass index (BMI) at or above 35 at first contact
- have a multiple pregnancy or pre-existing vascular disease (for example, hypertension or diabetes). [C]

Whenever blood pressure is measured in pregnancy, a urine sample should be tested at the same time for proteinuria. [C]

Standardised equipment, techniques and conditions for blood-pressure measurement should be used by all personnel whenever blood pressure is measured in the antenatal period so that valid comparisons can be made. [C]

Pregnant women should be informed of the symptoms of advanced pre-eclampsia because these may be associated with poorer pregnancy outcomes for the mother or baby. Symptoms include headache, problems with vision, such as blurring or flashing before the eyes, bad pain just below the ribs, vomiting and sudden swelling of face, hands or feet. [D]

11.3 Preterm birth

Routine vaginal examination to assess the cervix is not an effective method of predicting preterm birth and should not be offered. [A]

Although cervical shortening identified by transvaginal ultrasound examination and increased levels of fetal fibronectin are associated with an increased risk for preterm birth, the evidence does not indicate that this information improves outcomes; therefore, neither routine antenatal cervical assessment by transvaginal ultrasound nor the measurement of fetal fibronectin should be used to predict preterm birth in healthy pregnant women. [B]

Chapter 12 Fetal growth and wellbeing

12.1 Abdominal palpation for fetal presentation

Fetal presentation should be assessed by abdominal palpation at 36 weeks or later, when presentation is likely to influence the plans for the birth. Routine assessment of presentation by abdominal palpation should not be offered before 36 weeks because it is not always accurate and may be uncomfortable. [C]

Suspected fetal malpresentation should be confirmed by an ultrasound assessment. [Good practice point]

12.2 Measurement of symphysis–fundal distance

Pregnant women should be offered estimation of fetal size at each antenatal appointment to detect small- or large-for-gestational-age infants. [A]

Symphysis–fundal height should be measured and plotted at each antenatal appointment. [Good practice point]

12.3 Routine monitoring of fetal movements

Routine formal fetal-movement counting should not be offered. [A]

12.4 Auscultation of fetal heart

Auscultation of the fetal heart may confirm that the fetus is alive but is unlikely to have any predictive value and routine listening is therefore not recommended. However, when requested by the mother, auscultation of the fetal heart may provide reassurance. [D]

12.5 Cardiotocography

The evidence does not support the routine use of antenatal electronic fetal heart rate monitoring (cardiotocography) for fetal assessment in women with an uncomplicated pregnancy and therefore it should not be offered. [A]

12.6 Ultrasound assessment in the third trimester

The evidence does not support the routine use of ultrasound scanning after 24 weeks of gestation and therefore it should not be offered. [A]

12.7 Umbilical and uterine artery Doppler ultrasound

The use of umbilical artery Doppler ultrasound for the prediction of fetal growth restriction should not be offered routinely. [A]

The use of uterine artery Doppler ultrasound for the prediction of pre-eclampsia should not be offered routinely. [B]

3.1 Provision of information

Informed decision making has been described as 'a reasoned choice made by a reasonable individual using relevant information about the advantages and disadvantages of all the possible courses of action, in accord with the individual's beliefs'.[8]

In 1993, the Expert Maternity Group from the Department of Health released the *Changing Childbirth* report, which made explicit the right of women to be involved in decisions regarding all aspects of their antenatal care.[9] One of the priorities of antenatal care is to enable women to be able to make informed decisions about their care, such as where they will be seen, who will undertake their care, which screening tests they will undertake and where they plan to give birth. To do so, women require access to evidence-based information to take part in discussions with caregivers about these decisions. In practice however, it is reported that women feel that they have less say over some aspects of care than others and a substantial number of women would like to have more information about their options for care and services.[10] [Evidence level 3]

In a survey of maternity services in the NHS, just over 30% of recent mothers reported that they felt they had the option to choose where they received their pregnancy care. With screening tests, however, 60% of mothers reported feeling that they had been offered a choice. Women's assessment of information and communication in antenatal care indicated that 32–40% felt that they had not received enough spoken or written information about the risks and benefits of having different screening tests during pregnancy.[10] [Evidence level 3] Before making a decision about whether or not to have a test a woman needs to have information about what the test is looking for, what the test involves and any risks of the test itself to herself and her pregnancy, the type of result that will be reported (such as a probability or risk, the false positive and false negative rate) and the decisions she might face as a result of the test. However, it is not clear how this information should be given and how much information is optimal, as this is likely to vary among individual women.

In one survey, 1188 pregnant women's point of view on information needs were explored by means of self-completed postal questionnaires.[3] Half of the women reported that they would have liked additional information to be provided at their first antenatal appointment, with first time mothers most likely to believe that they had been provided with too little information. Written sources of information were also highly valued. [Evidence level 3]

In order to meet individual women's needs, it is likely that a variety of ways of giving information will be required. Written information varies widely in quality. A study of 81 leaflets used in antenatal screening programmes in England and Wales found that only 11 (14%) included comprehensive information on all aspects of screening.[11] [Evidence level 3]

An RCT that compared three methods of giving information about antenatal screening tests randomised pregnant women into three groups. In the first group, extra information was delivered to women on an individual basis. In the second group, women received extra information in classes and the third group (the control group), received routine antenatal clinic information. The study reported no differences between the groups in the uptake of screening for Down's syndrome and other fetal anomalies, haemoglobinopathies or cystic fibrosis. Anxiety, however, was reported to be higher by 20 weeks of gestation among women who were not offered extra information compared with women who received individual information.[12] [Evidence level 1b]

Another RCT assessed the impact of evidence-based leaflets to promote informed decision making among pregnant women compared with no leaflets.[13] The leaflets were designed to be used in a conscious and controlled way (i.e., not left in a rack at an antenatal clinic or GP office) and the information provided in them was the result of systematic review of the best available evidence and they were peer reviewed. No differences were detected in the proportion of women who reported that they had exercised informed choice or among those who reported an 'active' decision making role during antenatal care between the groups. Satisfaction with the amount of information between the two groups, however, was higher in the group that received the leaflets. [Evidence level 1b] Qualitative assessment within the trial of the use of the leaflets found that their potential as decision aids was greatly reduced due to competing demands within the clinical environment.[14] Time pressures limited discussion and hierarchical power structures resulted in defined norms, which dictated which 'choices' were available. This meant that women complied with their carers' choice rather than making an informed decision. [Evidence level 3]

Much of the responsibility for providing information, which should be unbiased and evidence-based, falls upon the healthcare provider. Although users of antenatal care services report that they place high value on quality information that will allow them to make an informed decision about antenatal screening tests,[15,16] [Evidence level 3] a study that recorded consultations in the USA and UK found that the information provided on antenatal screening tests was insufficient for informed decision making and occasionally misleading or inaccurate.[17] This may be explained by a lack of knowledge on the part of the carer,[18] [Evidence level 3] a lack of training on how to present information in an understandable way[19] or a lack of time and resources to present the information.[20] A comparison of those who completed and those who did not complete training to improve information providing skills in an RCT[19] found that those who dropped out were the ones who had poorer communication skills at baseline, suggesting that those most likely to need training in effective communication are the ones least likely to avail themselves of it.[21] [Evidence level 3]

Beyond the issue of poor understanding of tests undergone or declined, additional issues reported to be associated with antenatal screening programmes include anxiety following false positive results and false negative reassurance in those receiving negative test results.[22] This highlights the importance of the need for information on the outcomes of testing in order to make informed decisions. Although more is known about antenatal screening than other aspects of antenatal care, more research is needed to help ascertain how best to help parents make informed decisions about choices around antenatal testing. In addition, although the provision of information is perhaps a necessary condition for informed decision making, it is not sufficient. Other factors are necessary to achieve informed decision making and this may be difficult in the context of health care as, historically, pregnant women are not expected to make decisions themselves.

Available information

All first time pregnant women in England and Wales should be offered *The pregnancy book* (published by health departments in England and Wales)[23] by their carer. This book provides information on many aspects of pregnancy including: how the fetus develops; deciding where to have a baby; feelings and relationships during pregnancy; antenatal care and classes; a section for expectant fathers; problems in pregnancy; when pregnancy goes wrong; rights and benefits information and a list of useful organisations.

The Cochrane Database of Systematic Reviews (www.update-software.com/clibng/cliblogon.htm) provides the best available evidence on safe and effective antenatal care.

The MIDIRS Informed Choice initiative has produced 15 leaflets to assist women in making informed objective decisions during pregnancy. Each leaflet has a corresponding leaflet for professionals, aiming to help them guide pregnant women through decisions. Access to this resource is available online at www.nelh.nhs.uk/maternity.

A leaflet entitled *Tests for you and your baby during pregnancy* provides information to assist women in making informed decisions about the screening tests that are offered in pregnancy. It is published by Bro Taf Health Authority and may be tailored for specific health authorities.[24]

3.2 Antenatal education

There are many different ways of providing antenatal classes and antenatal education. There is variation in the underlying aims of antenatal education, in the number of classes offered, whether classes are offered individually or in groups, when during the course of pregnancy the classes are offered and the content of the classes. These factors may impact on the effectiveness of antenatal education programmes.

Antenatal classes are often used to give information regarding a woman's pregnancy, childbirth and parenting to expectant parents. However, antenatal education can encompass a broader concept of educational and supportive measures that help parents and prospective parents to understand and explore their own social, emotional, psychological and physical needs during pregnancy, labour and parenthood and enable them to be confident in their abilities to give birth and to parent successfully. In a study of three groups of childbirth teachers working in different organisations in the UK who were asked to identify the aims of antenatal education, the need to build women's confidence in their ability to give birth and care for their babies was reported as the most important aim.[25]

The scope of this guideline covers antenatal education relating to pregnancy, and does not cover important aspects of antenatal education that relate to childbirth or parenthood, although it is recognised that antenatal education is often considered the first step in the pathway of becoming a parent. Although women who experience fear of childbirth are not necessarily more likely to have interventions during labour such as emergency caesarean section, it is possible that building up a woman's confidence during pregnancy in her ability to give birth has the potential to influence her choices for the birth of her baby and the interventions she receives during birth.[26]

A systematic review based on six RCTs involving 1443 women assessed the effects of antenatal education on knowledge acquisition, anxiety, sense of control, pain, support, breastfeeding, infant care abilities, and psychological and social adjustment. The largest study (n = 1275) examined an educational intervention to increase vaginal birth after caesarean section only. The remaining five trials (combined n = 168, range n = 10–67) included more general educational interventions; however, the methodological quality of these trials is uncertain, as they do not report randomisation procedures, allocation concealment or accrual and loss of participants. None of the trials included labour and birth outcomes, anxiety, breastfeeding success or general social support. The effects on knowledge acquisition and infant care competencies were measured but interpretation is difficult because of the size and methodological quality of the trials.[27] [Evidence level 1b] The findings of observational studies are also inconsistent.[28–30] [Evidence level 3] One survey found acquisition of knowledge was increased among all women who attended antenatal education classes compared with women who did not attend, although antenatal classes appear to have stronger effects on women from higher socio-economic classes.[28] [Evidence level 3] Women who attended antenatal classes were also less anxious than women who did not attend antenatal classes. The inconsistency across the observational studies maybe explained by confounding factors for which it is not possible to control in an analysis.

A survey of what women would like to learn in antenatal classes found that information on physical and psychological changes during pregnancy, fetal development, what will happen during labour and childbirth, their options during labour and childbirth and how to care for themselves during this time, possible complications and how to care for the baby after birth were the main issues.[31] [Evidence level 3] Evidence for the best method to deliver antenatal education is lacking. Ideally, the aims of antenatal education might include facilitating pregnant women to make informed decisions and to communicate more effectively with their carers, thus enabling them to contribute to the design of future antenatal education, to convey the issues they feel are most important to learn about and to feel empowered by their pregnancy and birth experience.

RECOMMENDATIONS

Pregnant women should be offered opportunities to attend antenatal classes and have written information about antenatal care. [A]

Pregnant women should be offered evidence-based information and support to enable them to make informed decisions regarding their care. Information should include details of where they will be seen and who will undertake their care. Addressing women's choices should be recognised as being integral to the decision-making process. [C]

At the first contact, pregnant women should be offered information about the pregnancy care services and options available, lifestyle considerations, including dietary information, and screening tests. [C]

Pregnant women should be informed about the purpose of any screening test before it is performed. The right of a woman to accept or decline a test should be made clear. [D]

At each antenatal appointment, midwives and doctors should offer consistent information and clear explanations and should provide pregnant women with an opportunity to discuss issues and ask questions. [D]

Communication and information should be provided in a form that is accessible to pregnant women who have additional needs, such as those with physical, cognitive or sensory disabilities and those who do not speak or read English. [Good practice point]

Future research

Effective ways of helping health professionals to support pregnant women in making informed decisions should be investigated.

4.6 Gestational age assessment: LMP and ultrasound

Estimates of gestational duration based on the timing of the last normal menstrual period (LMP) are dependent upon a woman's ability to recall the dates accurately, the regularity or irregularity of her menstrual cycles and variations in the interval between bleeding and anovulation. Between 11% and 42% of gestational age estimates from LMP are reported as inaccurate.[52] However, there is thought to be little variation in fetal growth rate up to mid-pregnancy and therefore, estimates of fetal size by ultrasound scan provides estimates of gestational age which are not subject to the same human error as LMP.

Ultrasound assessment of gestational age at 10–13 weeks is usually calculated by measurement of the crown–rump length. For pregnant women who present in the second trimester, gestational age can be assessed with ultrasound measurement of biparietal diameter or head circumference. Ultrasound measurement of biparietal diameter is reported to provide a better estimate of date of delivery for term births than first day of the LMP.[53–55] [Evidence level 2a] Gestational age assessment with ultrasound occurs routinely prior to 24 weeks and where discrepancies between ultrasound and LMP exist, choosing to use the ultrasound dating reduces the number of births considered to be post-term.[53–56] [Evidence level 2a]

Routine ultrasound before 24 weeks is also associated with a reduction in rates of intervention for post-term pregnancies. One systematic review of nine RCTs found ultrasound scanning before 24 weeks to be associated with a reduction in the rate of induced labour for post-term pregnancy when compared to selective use of ultrasound (Peto OR 0.61, 95% CI 0.52 to 0.72). This may have consequences when pregnancies are misclassified as pre- or post-term and inappropriate action is taken. Earlier detection of multiple pregnancy was also reported, although this did not have a significant affect on perinatal mortality (twins undiagnosed at 26 weeks: Peto OR 0.08, 95% CI 0.04 to 0.16). No adverse influence on school performance or neurobehavioural function as a consequence of antenatal exposure to ultrasound was observed.[57] [Evidence level 1a]

Accurate assessment of gestational age also permits optimal timing of antenatal screening for Down's syndrome and fetal structural anomalies. Reliable dating is important when interpreting Down's syndrome serum results as it may reduce the number of false positives for a given detection rate. An RCT evaluating ultrasound assessment at the first antenatal appointment at less than 17 weeks of gestation compared with no ultrasound found that fewer women needed adjustment of the date of delivery in mid-gestation (9% versus 18%; RR 0.52, 95% CI 0.34 to 0.79) and that women who had an ultrasound at their first appointment reported more positive feelings about their pregnancy.[52] [Evidence level 1b]

Recommendations

Pregnant women should be offered an early ultrasound scan to determine gestational age (in lieu of LMP for all cases) and to detect multiple pregnancies. This will ensure consistency of gestational age assessments, improve the performance of mid-trimester serum screening for Down's syndrome and reduce the need for induction of labour after 41 weeks. [A]

Ideally, scans should be performed between 10 and 13 weeks and use crown–rump length measurement to determine gestational age. Pregnant women who present at or beyond 14 weeks of gestation should be offered an ultrasound scan to estimate gestational age using head circumference or biparietal diameter. [Good practice point]

5.5 Nutritional supplements

Vitamin D

Vitamin D requirements are thought to increase during pregnancy to aid calcium absorption. The main sources of vitamin D are sunlight and oily fish. Daily exposure to sunlight should avoid vitamin D deficiency. Maternal deficiency in Vitamin D is purported to be associated with neonatal rickets although this is a theoretical risk as we were unable to find evidence to quantify it.

Women from the Indian subcontinent living in England and Wales are thought to be particularly vulnerable to vitamin D deficiency. Those women who remain indoors, whose clothing leaves little exposed skin, who live in a sunless climate and who are vegetarian are also thought to be at higher risk of vitamin D deficiency.

One systematic review assessed the effects of vitamin D supplementation on pregnancy outcome.[82] Only two small RCTs were included (n = 232). Neonatal hypocalcaemia was less common in the supplemented group (OR 0.13, 95% CI 0.02 to 0.65). However, there were no other significant findings and there was not enough evidence to evaluate the effects of vitamin D supplementation during pregnancy. [Evidence level 1a]

Although the Food Standards Agency recommends vitamin D supplementation during pregnancy, there is no indication of what evidence this recommendation is based on.

RECOMMENDATION

There is insufficient evidence to evaluate the effectiveness of vitamin D in pregnancy. In the absence of evidence of benefit, vitamin D supplementation should not be offered routinely to pregnant women. [A]

5.12 Alcohol and smoking in pregnancy

Alcohol consumption in pregnancy

Alcohol passes freely across the placenta to the fetus and, while there is general agreement that women should not drink excessively during pregnancy, it remains unclear what level of drinking is harmful to a pregnant woman and her fetus. Investigating the effects of maternal drinking on fetal development is difficult, due to confounding factors such as socio-economic status and smoking.

Research evidence is consistent in finding no evidence of fetal harm among women who drink one or two units of alcohol per week.[106] There is also little or no evidence of harm in women who drink up to ten units per week. However, binge drinking or otherwise heavy consumption of alcohol is associated with adverse baby outcomes such as low birthweight[107,108] and behavioural and intellectual difficulties later in life.[109] [Evidence level 3] Binge drinking is also associated with fetal alcohol syndrome and the incidence in Europe is reported to be 0.4 cases/1000.[110]

As a safe low level of alcohol consumption has yet to be ascertained and associations with fetal alcohol syndrome exist only with binge or heavy drinking, guidance from professional bodies is slightly inconsistent. One guideline recommends that while there is no conclusive evidence that consumption levels below 15 units/week have an adverse effect on fetal growth or childhood IQ levels, pregnant women should be careful about the amount of alcohol they consume and limit it to no more than one standard unit of alcohol per day.[111] [Evidence level 4] Other guidance (e.g. MIDIRS Informed Choice and Foods Standards Agency) recommends one to two units once or twice a week. [Evidence level 4]

RECOMMENDATION

Excess alcohol has an adverse effect on the fetus. Therefore it is suggested that women limit alcohol consumption to no more than one standard unit per day. Each of the following constitutes one 'unit' of alcohol: a single measure of spirits, one small glass of wine, and a half pint of ordinary strength beer, lager or cider. [C]

8.2 Screening for sickle cell disorders and thalassaemia

Haemoglobin (Hb) disorders are autosomal recessive; however, it is possible to inherit more than one haemoglobin disorder. Sickle cell disorders include a variety of disorders, the most common of which are haemoglobins SS, Hb SC, Hb SD Punjab, HbS B thalassaemia and HbS O Arab. Hb SS causes anaemia, increased susceptibility to infection and infarction of various organs, including the brain. It is characterised by sickle-shaped red blood cells, resulting in their premature removal from the circulation. The prevalence of sickle cell trait in Northern European populations is 0.05% compared with 4% to 11% in black Caribbean populations, 20% (range 10% to 28%) in black African populations, 1% (range 0% to 1%) in Indians and 0.75% (range 0.5% to 10%) in Cypriot populations.[275] It is estimated 160 babies are born each year with sickle cell disorder in England. Implementation of the national universal screening of newborn babies for sickle cell disorders began in April 2003 in England and Wales.

Beta thalassaemia major causes severe anaemia from infancy, which is usually fatal within ten years if not treated. It is most common in people of Mediterranean origin and across the Middle and Far East. Prevalence estimates for thalassaemia trait are 0.9% among black Caribbean populations and black African populations, 3.5% (range 2.55 to 4.5%) among Indian populations, 4.5% (range 3.5% to 5.5%) among Pakistani populations, 3.0% among Bangladeshi populations (range 2.0% to 4.0%) and Chinese populations (range 1.0% to 4.0%) and 16% among Cypriot populations, compared with 0.1% among Northern Europeans.[275] Seventeen babies are born each year with thalassaemia, but there may be two to three times this number of pregnancies affected.[275] [Evidence level 3]

The aim of antenatal screening for sickle cell disorders and thalassaemia is to identify women at risk early in pregnancy, so that genetic counselling can be provided and women may make timely and informed reproductive choices. An audit of current practice in the UK indicated that about 50% of thalassaemia-affected pregnancies in England were not offered prenatal diagnosis, although a risk was recognised in 43–55% of pregnancies,[276] [Evidence level 3] while an audit of prenatal diagnosis found that only 50% and 13% of couples at risk for thalassaemia and sickle cell disorder, respectively, actually have a prenatal diagnosis.[277] [Evidence level 3]

Screening may be based on an ethnic question used to identify pregnant women at higher risk, who are then investigated for haemoglobin abnormalities, or on offering laboratory screening to all pregnant women. Irrespective of which method is used, information on ethnicity (ancestry) needs to be collected for interpretation of screening results.

In 1993, the UK Standing Medical Advisory Committee recommended screening using laboratory methods in districts where 15% or more of the antenatal population were from ethnic minorities.[278] [Evidence level 4] More recently, two Health Technology Assessment (HTA) reports have evaluated the effectiveness of screening in the antenatal, neonatal or preconceptual period and have addressed the question of screening using an ethnic question or using laboratory methods.[275,279]

Screening using an ethnic question is based on questions to identify ethnic origin of the pregnant woman. Ethnic origin is an important issue in screening, as sickle cell trait is found predominantly in people of African-Caribbean and sub-Saharan African origin, and thalassaemia trait is found predominantly in people of Arab, Mediterranean and Indian origin. The effectiveness and suitability of questions about ethnic origin is uncertain.[280] It is reported that data from the Department of Health showed that ethnic origin information was missing from 43% of records in London and 37% in England although the collection of this information is mandatory.[281] Substantial variability in practice and in the quality of data collected has also been reported, with up to 20% of high-risk ethnic origins being misclassified.[281] Further evaluation of using an ethnic question as the basis for screening is currently underway.

Screening antenatal women using laboratory methods involves both screening to detect haemoglobin variants and the interpretation of red cell indices with investigation of those identified as screen positive. If the pregnant woman has confirmed sickle cell or thalassaemia trait (or any other genetic mutation of haemoglobin), the father of the fetus should be offered testing. If both parents have the trait, counselling should be offered. Prenatal diagnosis usually involves chorionic villus sampling. Parents who would like to consider prenatal diagnosis of the fetus must be referred to a specialist centre.[282] More information on screening for thalassaemia and abnormal

haemoglobins is available from the NHS sickle cell and thalassaemia website (www.kcl-phs.org.uk/haemscreening/).

Issues around the psychological impact of screening for haemoglobinopathies also exist as ending the pregnancy may be considered if the fetus is affected. For this reason, women at risk should be identified as soon as possible. Among couples counselled in the first trimester, one study reported that 85–95% of couples at risk request prenatal diagnosis for thalassaemias and 50–80% request prenatal diagnosis for sickle cell disorders.[282,283] A UK audit reported that the uptake of prenatal diagnosis for thalassaemia trait is sensitive to gestational age and that when offered, uptake ranged from 70% to 95% in the first trimester, depending upon ethnic origin with 11 of 12 affected pregnancies being terminated among British Pakistani women.[276] [Evidence level 3] In a study of the response of Muslim communities in Pakistan to antenatal diagnosis and termination of pregnancies due to thalassaemia, 89% of woman carrying an affected fetus chose to terminate their pregnancy.[284] [Evidence level 3]

Economic considerations

The search for economic papers on this topic found 13 studies including two HTA reports. The first HTA examined the total costs of screening programmes in high and low prevalence areas of people of specific ethnic origins.[279] The report indicated that the relative cost effectiveness of the strategies were highly sensitive to:

- the uptake of screening
- the presumed fetal prevalence of sickle cell disease
- the ethnic composition
- the inter-ethnic union rates.

The second HTA report included a systematic review of published studies.[275] No studies reporting the full benefits of screening and no good-quality UK-based cost data were found. A cost study based on one hospital estimated that the cost of identification of an at-risk fetus was £2455 per woman, including follow-up costs. The cost of treatment was estimated to be around £5000 per annum. The question of whether a universal or selective programme should be adopted was not directly addressed but it was suggested that a screening programme would be cost effective in areas with haemoglobinopathy traits at or above 2.5%.

It was first envisaged that a model could be constructed for this guideline, using census data to assess which areas of the UK might benefit from a more selective approach to screening. However, despite efforts to obtain these data, it was not possible in the end to construct the model due to the inadequacy of the data that could be obtained.

The parameters that they suggest may be important in deciding whether to adopt a selective screening strategy are the ethnic composition of geographical area and the number of inter-ethnic unions resulting in a pregnancy. Since these rates may change quickly in any given population, this policy may not be effective or equitable to implement in practice.

Future research

The effectiveness and costs of an ethnic question for antenatal screening for sickle cell and thalassaemia is needed.

The effectiveness and costs of laboratory methods for antenatal screening for sickle cell and thalassaemia is needed.

9 Screening for fetal anomalies

Screening tests that aim to detect structural and chromosomal anomalies include ultrasound scan assessment and maternal serum screening (for open neural tube defects and Down's syndrome) early in pregnancy. The objectives of fetal anomaly screening include the identification of:[293]

- anomalies that are not compatible with life
- anomalies associated with high morbidity and long-term disability
- fetal conditions with the potential for intrauterine therapy
- fetal conditions that will require postnatal investigation or treatment.

The scope of any screening test for fetal anomalies should be made clear to women when the screening is offered. Although results from RCTs have not yet demonstrated whether informed decision making in screening affects uptake,[294] the UK National Screening Committee has adopted the principle that screening programmes should offer choice to individuals and that each person should make an informed decision about screening based upon appreciation of the risks and benefits.[295] Although the amount of information needed to make choices about antenatal screening varies from person to person, a report from the RCOG outlines the topics that should be discussed with a woman before screening.[296] Written information should be provided on details of the nature and purpose of the screening (i.e. for ultrasound scans, explanation of the structures examined), the screening procedure, details of detection rates for defined common conditions, the meaning of a positive and negative screening result, and actions to be taken if a test is reported as 'normal' or 'abnormal'.

9.1 Screening for structural anomalies

The aim of screening for fetal anomalies is to identify specific structural malformations. This allows the parents to plan appropriate care during pregnancy and childbirth or for the parents to be offered other reproductive choices. The detection of fetal anomalies varies, depending upon the anatomical system being examined, the gestational age at assessment, the skill of the operator and the quality of the equipment.

Ultrasound scanning for structural anomalies

A systematic review, based on 11 studies (one RCT, six retrospective cohorts and four prospective cohorts) was undertaken to examine the use of routine ultrasound to detect fetal anomalies.[297] The studies, which included 96,633 babies, were performed in Europe, the USA and Korea between 1988 and 1996. The overall prevalence of fetal anomaly was 2.09%, ranging from 0.76% to 2.45% in individual studies and including major and minor anomalies. [Evidence level IIa]

None of the studies conducted screening for anomalies at less than 15 weeks of gestation. Detection rates at less than 24 weeks was 41.3%, and 18.6% at greater than 24 weeks. Overall, detection of fetal anomaly was 44.7%, with a range of 15.0% to 85.3%, as different anomalies are more or less likely to be correctly identified. For example, anomaly scanning at 14 to 22 weeks for anencephaly can detect nearly 100% of cases.[298] [Evidence level 3]

Detection rates of ultrasound in the studies from the review may be inflated, as some studies reported the number of anomalies detected rather than the number of babies with structural anomalies. However, the authors also only included studies that reported adequate methods of postnatal ascertainment of anomalies to verify their presence and allow a more accurate calculation of test performance. Variation in detection rate occurs with:

- the type of anomaly being screened (see Table 9.1)

- the gestational age at scanning
- the skill of the operator
- the quality of the equipment being used•
- the time allocated for the scan.

Table 9.1 Percentage of fetal anomalies detected by routine ultrasound screening in the second trimester according to anatomical system.[297] [Evidence level IIa]

Anatomical systems	Percentage detected (%)
Central nervous system	76
Urinary tract	67
Pulmonary	50
Gastrointestinal	42
Skeletal	24
Cardiac	17

The use of ultrasound to detect fetal anomalies reduces perinatal mortality only if the parents choose to end the pregnancy following the detection of those anomalies.[297] [Evidence level 1b & 2a]

Another RCT that was not included in the above review compared routine ultrasound scanning with selective ultrasound.[299] [Evidence level 1b] A better detection rate for major malformations was reported for routine ultrasound than for selective ultrasound (40% versus 28%). A significantly lower perinatal mortality rate in the routine ultrasound group was also reported and was mainly attributed to differences in termination of pregnancy after detection. There was more than a two-fold difference in the detection rates between the two hospitals that participated in this trial (75% versus 35%), which reinforces the need to ensure a high skill level among those performing the scan.

As detection rates vary, those providing ultrasound scanning need to monitor the quality of their service. This requires the collection of follow-up information on all babies scanned during pregnancy. As detection rates are influenced both by the skill of the operator and the quality of the ultrasound scanning equipment, the RCOG working party report outlined standards for training and equipment (Appendix 3).

The detection rate of fetal structural anomalies also varies with gestational age at the time of ultrasound. An observational study on the detection of major structural anomalies with a scan at 12 to 13 weeks reported an 84% detection rate for anencephaly.[300] [Evidence level 3] The potential benefit of scanning for structural anomalies in the first trimester is that gestational age assessment (see Section 4.6) and Down's syndrome screening (i.e. nuchal translucency) could be performed concurrently.

In Wales, 100% of maternity units currently offer a routine 18- to 20-week anomaly scan.[301] A UK recommended minimum standard for the 20-week anomaly scan is provided by the RCOG (Box 9.1). The standards for an 'optimal scan' include additional features to improve the detection of cardiac anomalies and facial cleft defects.[302] [Evidence level 4] Although many maternity units may not currently be able to afford the additional scanning time or scans required, these have been included as a standard that maternity units may aspire to achieve.

Box 9.1 Minimum standards for the 20-week anomaly scan, derived from the RCOG[302]

Fetal normality:

- Head shape and size and internal structures (cavum pellucidum, cerebellum, ventricular size at atrium < 10 mm)
- Spine: longitudinal and transverse
- Abdominal shape and content at level of stomach
- Abdominal shape and content at level of kidneys and umbilicus
- Renal pelvis < 5 mm anterior–posterior measurement
- Longitudinal axis abdominal–thoracic appearance (diaphragm and bladder)
- Thorax at level of a four-chamber cardiac view
- Arms: three bones and hand (not counting fingers)

- Legs: three bones and foot (not counting toes)

Optimal standard for a 20-week anomaly scan:

- Cardiac outflow tracts
- Face and lips

When a screening result for structural anomalies suggests a malformation, all women should be offered a more detailed ultrasound scan, if necessary at a regional centre, for a definitive diagnosis.

RECOMMENDATION

Pregnant women should be offered an ultrasound scan to screen for structural anomalies, ideally between 18 to 20 weeks of gestation, by an appropriately trained sonographer and with equipment of an appropriate standard as outlined by the National Screening Committee. [A]

9.2 Screening for Down's syndrome

Down's syndrome, also termed Trisomy 21, is a congenital syndrome that arises when the affected baby has an extra copy of chromosome 21. The birth incidence of Down's syndrome in England and Wales was 6.2/10,000 live and still births in 1998.[303] [Evidence level 3] The main clinical feature of this disorder is intellectual impairment, although it is also associated with excess mortality due to congenital malformations (of which cardiac anomalies are the most common), leukaemia and increased incidence of thyroid disorders, epilepsy and Alzheimer's disease. An estimated 80% of children affected with Down's syndrome will have profound or severe intellectual disability and 20% will have mild or no intellectual disability. About 46% of children with Down's syndrome are born with a congenital heart defect that may require surgery.[304]

Principles of screening for Down's syndrome

The first step of any screening for congenital anomalies should include the provision of unbiased, evidence-based information so that the pregnant woman will be able to make autonomous informed decisions. This should include information on Down's syndrome, the characteristics of the screening test the woman is being offered and the implications of the test results.[305] The results of a cross-sectional study have shown, however, that although many women understand practical aspects of the test (e.g. that serum screening occurs at 16 to 18 weeks of gestation and that blood would be needed for the test), they lack knowledge about the likelihood and implications of possible results.[306] Women were surveyed after consultation with a midwife or obstetrician during which serum screening for Down's syndrome was offered and only 36% of women answered correctly the question, 'Negative results do not guarantee that everything is all right with the baby'. [Evidence level 3] Women should be made aware that they could opt out of the screening process at any time. However, knowing about a problem that the baby may have will allow for reproductive choice and also the opportunity for doctors and midwives to provide optimal care during pregnancy and childbirth.

Antenatal screening for Down's syndrome can take place during the first or second trimester of pregnancy and a variety of screening tests can be used. In the first trimester, nuchal translucency (NT), which is the measurement of the normal subcutaneous space between the skin and the cervical spine in the fetus early in pregnancy, can be used to identify women at increased risk of carrying a Down's syndrome baby at around 10 to 14 weeks. Nuchal translucency may be used with or without two first-trimester maternal serum markers, human chorionic gonadotrophin (hCG) and pregnancy-associated plasma protein A (PAPP-A): i.e., the combined test, or as part of the integrated test. In the early second trimester, screening techniques include biochemical marker screening at around 15 to 16 weeks.

Once a screening test is performed, the risk of Down's syndrome is calculated, taking into account maternal age, gestational age and the levels of biochemical markers. Results are 'positive' or classified as 'high risk' if the risk is equal to or greater than a locally agreed cutoff level. This is often expressed numerically to indicate the likelihood that a woman has a baby with Down's syndrome when a positive screening result is returned; e.g., a 1/250 chance that a pregnant woman is carrying an affected baby. When a high-risk screening result is returned, a woman will usually be

offered a diagnostic test, such as amniocentesis, which has an excess fetal loss rate of 1%.[307] [Evidence level 1b]

It should be made clear to the woman that the nature of screening tests is such that a number of 'false positives' and 'false negatives' will result from a screening programme. The effectiveness of Down's syndrome screening tests are often reported with a 'false positive rate', which indicates the proportion of positive screening tests that indicate there may be a problem when there is not.

Differences in the performance of screening tests between studies may occur for a number of reasons:

- variation in statistical models of both prior age-related maternal risk and risk calculation from biochemical markers
- variation in biochemical assays used
- variation in the test thresholds, i.e. cutoff levels
- methodological quality of studies leading to both under- or over-ascertainment of cases in cohort studies or the use of case–control designs leading to biased estimates of test performance.308,309
- chance variation.

An associated increase in miscarriage throughout pregnancy has been reported among pregnant women known to have a fetus affected by Down's syndrome compared with pregnant women with unaffected fetuses.310 [Evidence level 3] Therefore the prevalence of Down's syndrome is likely to be higher early in pregnancy than at birth. Down's syndrome screening tests performed early in pregnancy will identify fetuses that may be lost spontaneously later in pregnancy. This affects the accuracy of cutoff rates in the determination of women who are 'high risk' or will be offered a diagnostic test and becomes relevant when the 'detection rate' of an earlier screening test is compared with that of a later screening test. A later screening test may not identify as high a proportion of Down's syndrome fetuses as an earlier test. However, it should not necessarily be interpreted that the later test is less efficient than the earlier test. Adjustment for the loss of Down's syndrome fetuses that have been terminated or spontaneously aborted needs to be made in order to provide accurate estimates of risk and screening performance.

Methods of screening for Down's syndrome

The risk of Down's syndrome increases with maternal age. The odds of having a baby affected by Down's syndrome at age 20 years are approximately 1:1,440 rising to 1:338 at 35 years and 1:32 at 45 years.[311] [Evidence level 3] Therefore, before the development of biochemical and ultrasound screening methods, screening for Down's syndrome was based on maternal age only and all women over the age of 35 to 37 years were offered amniocentesis as a screening test. In 2000, in England and Wales, 16.5% of mothers were older than 35 years at the birth of their baby[312] and would have been offered invasive diagnostic testing, based on a policy of screening by maternal age alone.

Invasive diagnostic testing and karyotyping is the gold standard test for confirming the diagnosis but it is associated with an excess risk for fetal loss of 1% compared with women with no invasive diagnostic testing.[307] In 1998, a survey found that 8% of UK health authorities screened on the basis of maternal age alone.[313] One study estimated that screening by maternal age alone detected 53% of Down's syndrome cases antenatally over a three-year period, though this was thought to be an overestimate, as the total number of liveborn Down's syndrome babies was not obtainable.[314]

In the 1980s, a number of biochemical markers were found to be associated with Down's syndrome and this marked the advent of screening being offered to women younger than 35 years. This was important because, although the risk of Down's syndrome increases with age, younger women have the majority of pregnancies and therefore give birth to the majority of children with Down's syndrome. First-trimester biochemical markers now include hCG (total and free beta) and PAPP-A. hCG may also be measured in the second trimester. Other second-trimester biochemical markers include alphafetoprotein (AFP), unconjugated oestriol (uE_3) and dimeric inhibin A.

The associations between specific ultrasonographic markers and Down's syndrome have also been identified. One meta-analysis assessed which second-trimester ultrasound markers were effective for the detection of fetuses with Down's syndrome. The findings suggested that a thickened nuchal fold was the most accurate ultrasound marker in the second trimester. The six other markers that

were assessed were reported to be of little value in screening for Down's syndrome, as they would result in more fetal losses than cases of Down's syndrome detected.[315] [Evidence level 2a & 3] However, the review concluded that the sensitivity of a thickened nuchal fold in the second trimester was not high enough to be used as a practical screening test for Down's syndrome on its own. NT measurement for Down's syndrome screening commonly occurs between 11 and 14 weeks of gestation and detection rates for this are reported below. The presence or absence of fetal nasal bone, another possible ultrasound marker, is currently being researched.

Current screening for Down's syndrome

There is an extensive body of literature on Down's syndrome screening that investigates the numerous combinations of individual and multimarker screening in the first or second trimester, ultrasound screening and the integrated approach, which includes screening tests in the both the first and second trimester. If PAPP-A, hCG and NT are used as a first-trimester screening test (at 10 to 12 weeks), this is commonly referred to as the 'combined test'. When hCG and AFP are used between 14 to 20 weeks as a screening test, this is often called the 'double test'. If uE_3 is added to the double test combination, it becomes known as the 'triple test'. The addition of inhibin A to the triple test comprises the 'quadruple test'. The 'integrated test' uses NT and PAPP-A at 10 to 12 weeks of gestation with hCG, AFP, uE_3 and inhibin A at 14 to 20 weeks of gestation, requiring women to be managed through the first and second trimester for screening. Although the efficacy of this test is known, the acceptability of this approach to testing to pregnant women is not known. The 'serum integrated test' is the same as the integrated test without NT.

A 2001 survey of all maternity centres and primary care trusts in England indicated that the majority of units offered some form of screening for Down's syndrome. However, a variety of screening tests are used including: first-trimester NT screening with or without biochemical markers or biochemical marker screening in the second trimester (personal communication, Helen Janecek, 2003). In addition, an HTA monograph presented results for the integrated test.[316] The detection rates for each of these screening test combinations are presented in Table 9.2.

Table 9.2 Detection and false positive rates for various combinations of markers used for Down's syndrome screening

Measurements (cutoff)	False positive rate (%)	Detection rate (%)
Nuchal translucency at 9 to 14 weeks* (13 cohort studies, n = 170,343)[317]	4.7	77
Combined test : NT plus serum screening (10 studies, range reported)[318]	5	85–89
Double test (6 cohort studies, n = 110,254)[319]	Not reported**	66
Triple test (20 cohort studies, n = 194, 326, medians and ranges reported)[320]		
For a risk cutoff 1:190–200	4 (range 3–7)	67 (range 48–91)
For a risk cutoff 1:250–295	6 (range 4–7)	71 (range 48–80)
For a risk cutoff 1:350–380	8 (range 7–13)	73 (range 70–80)
Quadruple test (1 cohort study, n=46,193)[321]	5	75 (95% CI 66–84)
Serum integrated test (1 nested case–control study, n = 28,434)[316]	2.7	85
Integrated test (1 nested case–control study, n = 28,434)[316]	1.3	85

* These data are from published cohort studies; data from the SURUSS report[316] have not been included as this was a nested case–control study and higher level evidence was available

** Due to variation in practice between screening programmes being compared

Considerable discrepancy between reported detection and false positive rates between studies often exist, due to differences in study design, varying cutoff rates, skill of the ultrasound operator, and the times at which the screening was conducted. All these factors should be taken into account when planning which screening method will be used for a pregnant population. In addition, other factors, such as the practicality of managing women through two trimesters for screening or the introduction of NT for Down's syndrome screening in the context of extra time required for

ultrasound (assuming that a unit already offers first trimester dating scans) should also be considered.

Diagnosis after a positive screening result

Diagnostic tests are offered to women identified as at high risk of having an affected pregnancy. Antenatal diagnosis of Down's syndrome is currently done by culture of fetal cells and fetal cells can currently only be acquired by invasive methods: amniocentesis, chorionic villus sampling (CVS) or fetal blood sampling. All of these methods carry a risk of miscarriage. The excess risk of miscarriage following amniocentesis is approximately 1%.[307] [Evidence level 1b] Among women who were screened in the first trimester and had a positive result, the reported rate of uptake for invasive testing for prenatal diagnosis was 77%.[322] [Evidence level 2a] Among women who were screened in the second trimester and had a positive result, reported uptake of invasive testing ranged from 43% to 74%, depending upon the magnitude of the risk.[321]

CVS is commonly performed between 11 and 13 weeks of gestation and amniocentesis after 15 weeks of gestation. However, first-trimester CVS is associated with a higher sampling failure rate (Peto OR 2.86, 95% CI 1.93 to 4.24) and also a higher pregnancy loss rate (Peto OR 1.33, 95% CI 1.17 to 1.52) than second-trimester amniocentesis.[323] [Evidence level 1a] Amniocentesis should not be carried out in the first trimester. When compared with CVS, early amniocentesis was associated with a higher failure rate (0.4% versus 2%, RR 0.23, 95% CI 0.08 to 0.65) though there was no significant difference in pregnancy loss between the two procedures (6.2% versus 5%, RR 1.24, 95% CI 0.85 to 1.81)[324] [Evidence level 1a] When early amniocentesis (before 14 weeks) was compared with amniocentesis at 15 weeks or later, however, a significantly higher rate of fetal loss (7.6% versus 5.9%, p = 0.012), fetal talipes (1.3% versus 0.1%, p = 0.0001) and sampling difficulty has been reported.[307] [Evidence level 1b] Therefore, associated risks are lowest for amniocentesis performed after fifteen weeks and highest for CVS at all times during pregnancy.

When a pregnant woman is offered a diagnostic test after a positive screening result, she should be informed of the risks associated with invasive testing and that other chromosomal anomalies, not just Down's syndrome, may be identified and that in some cases the prognosis for the fetus may not be clear. Although considerable anxiety is reported to be associated with diagnostic testing for Down's syndrome,[325,326] uptake of diagnostic testing after a high-risk screening result (1:250–300) in UK populations has been reported to range from 43% to 77%.[321,322]

A recent study examining the effect of prenatal diagnosis on infant mortality reported a decline in infant deaths due to congenital anomalies.[327] The authors suggested that the increased availability of reproductive choice upon diagnosis of congenital anomaly was related to the observed decrease in overall infant mortality. [Evidence level 3]

The future of Down's syndrome screening

The recommendations stated below accord with the current recommendations of the Antenatal Subcommittee of the UK National Screening Committee (NSC). However, as some screening tests for Down's syndrome are performed early in pregnancy, consideration should be given to ensuring that pregnant women who present late for antenatal care can also be offered screening for Down's syndrome.

Research surrounding the issue of screening for Down's syndrome is moving quickly and, while the NSC hopes that all units will achieve the standard of a 60% detection rate with a 5% false positive rate by April 2004, they also propose that a 75% detection rate with a less than 3% false positive rate should be achieved by April 2007 (www.nelh.nhs.uk/screening/dssp/home.htm). These performance meaures should be age standardised and based on a cutoff of 1/250 at term. A pilot programme in preparation for the introduction of inhibin A for Down's syndrome screening to address concerns about its reliability is currently under way. The feasibility and acceptability of the integrated and serum-integrated approach are also being explored.

RECOMMENDATIONS

Pregnant women should be offered screening for Down's syndrome with a test that provides the current standard of a detection rate above 60% and a false positive rate of less than 5%. The following tests meet this standard:

- From 11 to 14 weeks:

- nuchal translucency (NT)
- the combined test (NT, hCG and PAPP-A)

- From 14 to 20 weeks:
  - the triple test (hCG, AFP and uE3)
  - the quadruple test (hCG, AFP, uE3, inhibin A)

- From 11 to 14 weeks AND 14 to 20 weeks:
  - the integrated test (NT, PAPP-A + hCG, AFP, uE3, inhibin A)
  - the serum integrated test (PAPP-A + hCG, AFP, uE3, inhibin A). [B]

By April 2007, pregnant women should be offered screening for Down's syndrome with a test which provides a detection rate above 75% and a false positive rate of less than 3%. These performance measures should be age standardised and based on a cutoff of 1/250 at term. The following tests currently meet this standard:

- From 11 to 14 weeks:
  - the combined test (NT, hCG and PAPP-A)

- From 14 to 20 weeks:
  - the quadruple test (hCG, AFP, uE3, inhibin A)

- From 11 to 14 weeks AND 14 to 20 weeks:
  - the integrated test (NT, PAPP-A + hCG, AFP, uE3, inhibin A)
  - the serum integrated test (PAPP-A + hCG, AFP, uE3, inhibin A). [B]

Pregnant women should be given information about the detection rates and false positive rates of any Down's syndrome screening test being offered and about further diagnostic tests that may be offered. The woman's right to accept or decline the test should be made clear. [D]

10.3 Chlamydia trachomatis

Chlamydia trachomatis is a common sexually transmitted infection in European countries.[364] Chlamydia prevalence during pregnancy has been estimated at 6% in one English study.[365] [Evidence level 3] It is more frequent in women who are younger, black, single and those attending genitourinary medicine clinics.[365,366] [Evidence level 3]

Chlamydia infection during pregnancy is associated with higher rates of preterm birth (OR 1.6, 90%CI 1.01 to 2.5) and intrauterine growth restriction (OR 2.5, 90%CI 1.32 to 4.18). 367 [Evidence level 2a] Left untreated, it has also been associated with increased low birthweight and infant mortality.[368] [Evidence level 2b] In a review of randomised control trials, the number of women with positive cultures for chlamydia was reduced by 90% when treated with antibiotics compared with placebo (OR 0.06, 95% CI 0.03 to 0.12).[369] [Evidence level 1a] However this did not alter the incidence of birth before 37 weeks.

In studies of infants born to mothers who have cultured positive to *C. trachomatis*, approximately 25% of the infants have subsequently cultured positive to *C. trachomatis*.[370,371] [Evidence level 3] These infants are also reported to have higher rates of neonatal conjunctivitis, lower respiratory tract infections and pneumonia.[370,371] [Evidence level 3]

Currently, no simple inexpensive laboratory tests for diagnosing *C. trachomatis* exist and different screening tests require samples to be taken from different anatomical sites. Tissue culture is expensive and, although it has good specificity, its sensitivity ranges from 75% to 85% because of inadequate sampling techniques (e.g., not rotating the swab firmly against the tissue for 15 to 30 seconds, removal from os must be without touching vaginal mucosa, use of lubricating jelly decreases chance of detection) and because the bacteria do not always survive transportation to the laboratory.[372] [Evidence level 4] Rapid tests include direct fluorescent antibody staining (50% to 90% sensitive), enzyme-linked immunoassays (sensitivity 75% to 80% and specificity 85% to 100%) and RNA-DNA hybridisation (sensitivity 70% to 85%).[364,372] [Evidence level 4] Direct fluorescent antibody staining, however, is labour intensive and therefore unsuitable for large numbers of samples.[364] [Evidence level 4] Serology is not useful in the diagnosis of acute chlamydial infection.[364,372] [Evidence level 4]

Nucleic acid amplification has sensitivity of 70% to 95% and specificity of 97% to 99%, with the advantage of being able to test invasive as well as noninvasive samples (e.g. urine) and it is suitable for large numbers of samples. However, it is an expensive test and inhibitors may be a problem in urine samples in pregnancy.[364,372] [Evidence level 4]

Due to the high rates of chlamydial infection observed among 16- to 24-year-olds in England, Wales and Northern Ireland, the UK Department of Health (DoH) has initiated a national opportunistic screening programme for all men and women under the age of 25 years. The first phase to roll out this programme has commenced in ten areas in England and the second phase is expected to commence by 2004. One of the healthcare settings for opportunistic screening is antenatal clinics. Therefore, when the roll out is complete, all pregnant women under the age of 25 years attending antenatal clinics will be offered screening for chlamydia.

Further information on screening for chlamydia in pregnant women can be found in the Scottish Intercollegiate Guidelines Network (SIGN) guideline, *Management of genital Chlamydia trachomatis infection*.[373]

Recommendation

Pregnant women should not be offered routine screening for asymptomatic chlamydia because there is insufficient evidence on its effectiveness and cost effectiveness. However, this policy is likely to change with the implementation of the national opportunistic chlamydia screening programme. [C]

Future research

Further investigation into the benefits of screening for chlamydia in pregnancy is needed.

11.1 Gestational diabetes mellitus

There is no consensus on the definition, management or treatment of gestational diabetes mellitus (GDM).[480] According to WHO, GDM is defined as 'carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during the pregnancy'.[481] This definition, however, encompasses women diagnosed with diabetes mellitus or impaired glucose tolerance (IGT) during pregnancy, using the same cut-off levels as for non-pregnant women.[482] In pregnancy, glucose levels are usually raised above the level considered 'normal' in non-pregnant women. Therefore, GDM, by the WHO definition, includes all IGT pregnancies and is based on non-pregnant standards that do not take into account the physiological increase in glucose levels during pregnancy. This results in a large range of women who will have gestational 'diabetes' and who may not be at increased risk for adverse pregnancy outcomes.

In a review commissioned by the NHS, it was concluded that there remains considerable debate regarding the definition of gestational diabetes. There is no evidence-based threshold for diagnosis and no standardisation for the use of the terms GDM and IGT in pregnancy.[483]

The incidence of GDM varies according to how it is defined but is reported to range from 3% to 10% in developed countries[484] and to be around 2% in the UK.[483] Women who develop GDM are more likely to develop type-2 diabetes later in life.[485] [Evidence level 2a] However, it is unclear whether the detection of GDM delays or prevents the subsequent development of diabetes mellitus and there are potentially increased adverse outcomes associated with screening, such as increased obstetric intervention.[486] [Evidence level 3] Therefore, without specific advantages for the mother, pregnancy is not an ideal time to conduct population screening for diabetes mellitus.

Observational studies indicate an association between GDM and an increase in mortality rates in babies.[487] [Evidence level 3] Because mortality is rare, measuring more common adverse events as a composite measure of perinatal morbidity has also been used. Morbidity measures include factors such as neonatal encephalopathy, neonatal seizures and birth trauma. GDM has been shown to be associated with fetal macrosomia;[486] [Evidence level 3] fetal macrosomia may be associated with birth trauma as a result of shoulder dystocia. However, while macrosomia may be associated with some poor outcomes (as a marker) there is not a direct causal relationship between macrosomia, shoulder dystocia and birth trauma. Factors such as maternal size and post-maturity are also closely associated with macrosomia.[488] The use of macrosomia as a surrogate outcome is further complicated by the variation in definitions used.[483]

To be effective, a screening programme should identify women at risk and there should be an effective intervention that improves the pregnancy outcome. The rationale for screening for gestational diabetes is to reduce poor perinatal outcome. There is global variation in screening patterns, which reflects the lack of evidence about the value of screening.[489] There are several methods used for GDM screening, which may be used independently or in combination.

Risk-factor screening

The use of risk-factor screening has led to high numbers of diagnostic tests being performed but high proportions of women with GDM being missed. In one US study, 42% of pregnant women had risk factors for GDM, but the same proportion of women with GDM was found among women with risk factors as women without risk factors (3.2% versus 2.4%, $p = 0.57$).[490] [Evidence level 2b] There was also no association found between the number of risk factors and risk of GDM.[490] [Evidence level 2b] In an older US study, similar results were reported with 44% of pregnant women without GDM having at least one risk factor.[491] [Evidence level 2a] Risk factor screening on its own is 50% sensitive and 58% specific.[490] [Evidence level 2b]

Universal screening

In Canada, a comparison was made with an area of universal screening and an area that did not implement screening for GDM. From 1990 to 1996, the incidence of GDM increased in the area of universal screening but not in the area of no screening (1.6% to 2.2% versus 1.4% to 1.0%, respectively). Rates of pre-eclampsia, fetal macrosomia, caesarean delivery, polyhydramnios and amniotic infections, however, remained the same in both regions.[492] [Evidence level 3]

Urinanalysis

Urine testing has low sensitivity and is a poor screening test for GDM. Reported sensitivities for urine testing for the presence of glucose range from 7% to 46%, but with high specificities ranging from 84% to 99% when compared with the 50-g glucose challenge test (GCT).[493] [Evidence level 2b] [494,495] [Evidence level 3] Glucosuria is also common in pregnant women unaffected by GDM (i.e., a high number of false positives).[493] [Evidence level 2b]

Blood tests

Blood tests include the measurement of glucose in the blood or plasma, with or without prior intake of oral glucose, and the measurement of fructosamine and glycosylated haemoglobin levels (HbA1c). There exists debate regarding cutoff levels for diagnosis, the amount of oral glucose that should be administered and whether glucose testing should be preceded by fasting.

Random plasma glucose (RPG), which measures non-fasting glucose levels, is measured without administration of a glucose load and at no particular fixed time after meals. Analysis can be on plasma or whole blood. Wide variations in the sensitivity of this test have been reported, depending upon the time of day the test is administered and the threshold that is used. One study reported a sensitivity of 46% and specificity of 86% (at a threshold of 6.1 mmol/l) with the RPG in pregnant women who had eaten in the last two hours.[496] [Evidence level 2b] Another study reported a range of sensitivities and specificities, depending upon what time the test was taken. For a threshold of 5.6 mmol/l, sensitivity was 29% to 80% and specificity was 74% to 80%. For a threshold of 6.1 mmol/l, sensitivity ranged from 41% to 58% and specificity ranged from 74% to 96%. The highest sensitivity for both thresholds was found at 3 p.m.[497] [Evidence level 3]

Fasting plasma glucose is meant to be measured after a period of fasting, usually overnight. The following studies that reported sensitivities and specificities did not report the period of fasting used. In Brazil, examining a range of thresholds, maximum sensitivity (88%) and specificity (78%) was found at 4.9 mmol/l.[498] [Evidence level 2a] In Switzerland, maximum sensitivity and specificity (81% and 76%, respectively) was found at a threshold of 4.8 mmol/l.[499] [Evidence level 2a]

The 1-hour, 50-g GCT measures the blood glucose 1 hour after taking 50 g glucose (plus 150 ml fluid) orally; usually performed between 24 and 28 weeks of gestation. The sensitivity and specificity of this test is reported to be 79% and 87%, respectively.[491] [Evidence level 2a] Although glucose testing is usually performed with no regard to fasting status, studies have suggested that time since the last meal affects glucose levels. A test evaluation study compared glucose levels in women with and without GDM after three 50-g GCT tests: one after fasting, 1 hour after a meal and one 2 hours after a meal. In the control group, the fasting GCT was significantly higher than 1 or 2 hours after a meal ($p < 0.01$), leading to a false positive rate of 58% in the fasting state. Among the women with GDM, glucose levels 2 hours after the GCT were significantly lower than in the fasting state or 1 hour after the test ($p < 0.03$).[500] [Evidence level 3]

The optimal time for screening in pregnancy has been evaluated in several studies. Screening in the third trimester is reported to be the optimal time for the GCT. However, studies have also shown success with repeat testing during the three trimesters. In studies that only confirmed GDM (with 3-hour, 100-g glucose tolerance test, GTT) in women who screened positive with the 1-hour, 50-g GCT, women were screened three times during pregnancy. In one study, an estimated 11% of the GDM population would have been missed if screening had not continued past 28 weeks.[501] [Evidence level 3] In another study, 33% of the GDM population would have been missed had screening not continued past 31 weeks of gestation.[502] [Evidence level 3]

The GTT is regarded as the gold standard for the diagnosis of GDM after a positive screening result. However, the quantity of glucose load and threshold for diagnosis lack consistency. Commonly used criteria are summarised in Table 11.1.

Table 11.1 Examples of diagnostic criteria employed for gestational diabetes mellitus

	75-g glucose load (mmol/l)		
	American Diabetic Association[503]	SIGN[480]	WHO[481]
Fasting	5.3	5.5	7.0
1-hour	10.0	–	–

2-hour	8.6	9.0	11.1
Minimum required criteria (n)	2	1	1

The first line of intervention for all pregnant women diagnosed with gestational diabetes is diet. However, a systematic review of RCTs found no difference between women treated with diet compared with women who received no dietary advice in frequencies of birthweight greater than 4000 g or 4500 g, caesarean section rates, preterm birth, birth trauma or maternal hypertensive disorders.[504] [Evidence level 1a] Although most pregnant women are treated with diet alone, 15% to 20% are thought to need insulin.[483]

In a trial that randomised women to diet alone or to diet plus insulin, no difference in outcomes was found. However, 14% of the diet-alone group received insulin owing to poor control and this may explain the lack of difference observed between the two groups.[505] [Evidence level 1b] Another study found that, while detection and treatment of GDM normalised birthweights, rates of caesarean delivery were still higher among pregnant women with GDM compared with pregnant women without GDM (34% versus 20%, RR 1.96, 95% CI 1.40 to 2.74).[506] [Evidence level 2a]

In an RCT of exercise as an intervention for GDM, in which only 29 out 144 subjects were successfully recruited and the method of randomisation was not clear, no differences in outcomes were seen.[507] [Evidence level 1b]

Intensive glucose monitoring has been reported to reduce incidence of macrosomia from 24% to 9% ($p < 0.05$) through the detection of women with high glucose levels who were then treated with insulin.[508] [Evidence level 3]

At present, screening for gestational diabetes appears to be hampered by the lack of a clear definition, agreed diagnostic criteria and evidence to show that intervention and treatment for this condition leads to improved outcomes for the mother and fetus. Although fasting plasma glucose and GCT have the highest reported sensitivities and specificities in the literature, there also exists considerable debate about which screening test should be used if there is to be screening. A continuum of risk for GDM should be researched and risk of adverse pregnancy outcomes clarified on such a continuum. This would help to form the basis for diagnosis. The most appropriate strategies for screening, diagnosing and managing asymptomatic GDM remain controversial.

The results of two ongoing studies are expected to resolve some of the issues surrounding the question of whether women should be routinely screened for gestational diabetes. The ACHOIS (Australian Carbohydrate Intolerance in Pregnancy Study) trial is assessing two forms of care for treating women with glucose intolerance of pregnancy detected through screening and includes 1000 women in Australia. The results of this study are expected to be available in 2004. The second trial, the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study, aims to define uniform standards for the detection and diagnosis of diabetes occurring in pregnancy to reduce adverse effects on mother and baby. It is an international study of 25,000 pregnant women and results are also expected to be available in 2004.

Recommendation

The evidence does not support routine screening for gestational diabetes mellitus and therefore it should not be offered. [B]

11.2 Pre-eclampsia

Pre-eclampsia is a multisystem disorder associated with increased maternal and neonatal morbidity and mortality. The incidence of pre-eclampsia ranges from 2% to 10%, depending upon the population studied and the criteria used to diagnose the disorder. Maternal symptoms of advanced pre-eclampsia may include (www.apec.org.uk/index.htm):

- bad headache
- problems with vision, such as blurring or flashing before the eyes
- bad pain just below the ribs
- vomiting
- sudden swelling of face, hands or feet.

Definitions

Pre-eclampsia	Hypertension new to pregnancy manifesting after 20 weeks of gestation that is associated with a new onset of proteinuria, which resolves after delivery.
Pregnancy-induced hypertension	Hypertension new to pregnancy that resolves after delivery but is not associated with proteinuria.
Chronic hypertension	Hypertension that predates a pregnancy or appears prior to 20 weeks of gestation.

This categorisation is helpful as it relates to the prognostic outcome of the pregnancy. Most women with hypertension in pregnancy have no clinical symptoms. Hypertension is frequently the only early sign that predates serious disease. Blood pressure measurement is routinely performed in antenatal care to allow the diagnosis and classification of hypertension in pregnancy.

Pre-eclampsia is thought to be caused by widespread endothelial cell damage secondary to an ischaemic placenta.[509] Hypertension and proteinuria are two easily measured signs associated with pre-eclampsia, although they are surrogate markers indicating end-organ damage.

Eclampsia is rare. It occurs in nearly 1/2000 pregnancies in the UK.[510] It is associated with high maternal morbidity and it accounts for over 50% of the maternal deaths associated with hypertensive disorders in pregnancy. Blood pressure may be of limited importance in identifying women who are going to develop eclampsia as about one-third of first fits occur in women with normal or a mild increase in blood pressure.[510]

Oedema was originally part of the triad of signs describing pre-eclampsia but it occurs in too many pregnant women (up to 80%) to be discriminatory and has been abandoned as a marker in classification schemes.[511a]

Physiological changes to blood pressure during pregnancy

In normal pregnancies, blood pressure usually falls during the first part of pregnancy before rising again towards term to a level similar to the value in the non-pregnant population.[512] Women with chronic hypertension may become normotensive by 10 to 13 weeks of gestation when antenatal care is usually initiated.

Defining hypertension during pregnancy

Blood pressure is a continuous variable and a cutoff point is employed to define 'normal' from 'abnormal' values. In defining an abnormal value, we should aim to identify those women who are at greater risk of an adverse outcome than those who are 'normal'. The conventional definition of hypertension in pregnancy is two readings of 140/90 mmHg taken at least 4 hours apart. Perinatal mortality is increased above this level.[513] However, about 20% of pregnant women in the UK have this reading at least once after 20 weeks of gestation. This will lead to intervention in 10% of all pregnant women but pre-eclampsia will develop only in 2% to 4% of pregnant women.[514] In a case series of 748 women who developed hypertension in pregnancy between 24 and 35 weeks (defined as greater than or equal to 140 mmHg systolic or greater than or equal to 90 mmHg diastolic), 46% later developed proteinuria greater than or equal to 1+ by dipstick on at least two occasions and 9.6% progressed to 'severe pre-eclampsia' (defined as hypertension greater than 160/110 mmHg with proteinuria, greater than 3+ of protein or thrombocytopenia).[515] The rate of progression to proteinuria was greater in those who enrolled in the study before 30 weeks. Pre-eclampsia was associated with a higher stillbirth and perinatal death rate. [Evidence level 3]

A large cohort study (n = 14,833) found that women with mean arterial pressure in the second trimester above 85 mmHg experienced a continuum of increased perinatal death, postnatal morbidity and small-for-gestational-age infants.[516a] In the third trimester, a similar continuum of increasing fetal deaths and morbidity was observed with mean arterial pressure above 95 mmHg.[516b] With or without proteinuria, an increased mean arterial pressure, at or above 90 mmHg, of extended duration in the second trimester, was associated with a higher stillbirth rate, pre-eclampsia and small-for-gestational-age infants. [Evidence level 2a]

The figure of 90 mmHg for the diastolic value corresponds approximately to 3 SD above the mean in early and mid pregnancy, 2 SD above the mean between 34 and 38 weeks of gestation and to 1.5 SD above the mean at term.[517] The finding of such a reading may therefore be more significant at 28 weeks of gestation than at term.

The diagnostic criteria of a 90 mmHg threshold with a 25 mmHg incremental rise is a definition based on evidence,[518–520] rather than the previously recommended diagnostic criteria by the American College of Obstetricians and Gynecologists (ACOG) (a rise in systolic blood pressure of 30 mmHg or of 15 mmHg in the diastolic pressure compared with booking or early pregnancy values),[511b] which included women who were not likely to suffer increased adverse outcomes. Subsequent guidelines from the US National Institutes of Health have advocated the abandonment of the ACOG diagnostic criteria.[511a]

Measuring blood pressure

The diagnosis of hypertension is dependent upon the accurate measurement of blood pressure. This accuracy depends largely on minimising measurement error. Failure to standardise technique will increase error and variability in measurement. A survey of midwives and obstetricians in one UK district general hospital reported in 1991 showed that compliance with recommendations on blood pressure measurement technique in pregnancy was poor.[521] The recommendations below relate to the American Heart Association guidelines produced in 1987,[522] which echoed previous expert opinion,[523] and concur with Shennan and Halligan's recommendations.[524]

- Use accurate equipment (mercury sphygmomanometer or validated alternative method).
- Use sitting or semi-reclining position so that the arm to be used is at the level of the heart. The practice of taking the blood pressure in the upper arm with the woman on her side will give falsely lower readings.
- Use appropriate size of cuff: at least 33 x 15 cm. There is less error introduced by using too large a cuff than by too small a cuff.
- Deflate slowly with a rate of 2 mmHg to 3 mmHg per second, taking at least 30 seconds to complete the whole deflation.
- Measure to nearest 2 mmHg to avoid digit preference.
- Obtain an estimated systolic pressure by palpation, to avoid auscultatory gap.
- Use Korotkoff V (disappearance of heart sounds) for measurement of diastolic pressure, as this is subject to less intra-observer and inter-observer variation than Korotkoff IV (muffling of heart sounds) and seems to correlate best with intra-arterial pressure in pregnancy. In the 15% of pregnant women whose diastolic pressure falls to zero before the last sound is heard, then both phase IV and phase V readings should be recorded (e.g. 148/84/0 mmHg).
- If two readings are necessary, use the average of the readings and not just the lowest reading, in order to minimise threshold avoidance.

As mercury will soon be eliminated from health settings (EU directive, EN 1060-2), a meta-analysis of validation studies of automated devices for blood pressure monitoring in pregnancy was conducted.[525] The findings indicated that, while the automated devices were accurate in pregnancy, they under-read by clinically significant amounts in women with pre-eclampsia. [Evidence level 3] This makes it important for automated devices to be assessed for accuracy before use, by a recognised protocol such as that recommended by the British Hypertension Society, and for readings from automated devices to be interpreted with caution.

A 15-cm cuff size may not be appropriate to use in the case of very thin arms, as blood pressure may be underestimated in those with arm circumferences less than 33 cm. For women with an arm circumference greater than 33 cm but less than 41 cm, a larger cuff should be used. In the case of very obese women, (arm circumference greater than 41 cm) thigh cuffs should be used.[526]

Regarding the use of which sound to use when recording diastolic blood pressure, an RCT of pregnancies managed by Korotkoff phase IV or phase V found that, although more episodes of severe hypertension were recorded with the use of the fourth Korotkoff sound, no differences in requirements for antihypertensive treatment, birthweight, fetal growth restriction or perinatal mortality were reported.[527] [Evidence level 1b] The fifth Korotkoff sound is also closer to the actual intra-arterial pressure and more reliably detected than the fourth Korotkoff sound.[528]

Assessment of risk factors for pre-eclampsia

Risk factors for pre-eclampsia are thought to include older age,[529] nulliparity,[530] long pregnancy interval,[531] a prior history of pre-eclampsia,[530] presence of a multiple pregnancy,[532] genetic susceptibility,[533] high BMI at first contact, and the presence of microvascular medical conditions such as diabetes or hypertension.[534] In the context of frequency of antenatal appointments, the

assessment of a pregnant woman's overall level of risk for pre-eclampsia should be assessed at her first antenatal appointment so that a tailored plan of antenatal care can be formulated. Women with any of the following risk factors should be considered for an increased schedule of blood pressure screening [Evidence levels 2b and 3]:[512]

- nulliparity (OR 2.71, 95% CI 1.16 to 6.34)
- age of 40 years and above (nulliparous OR 2.17, 95% CI 1.36 to 3.47; parous OR 2.05, 95% CI 1.47 to 2.87)
- family history of pre-eclampsia (e.g., pre-eclampsia in a mother or a sister, OR 5.27, 95% CI 1.57 to 17.64)
- history of previous pre-eclampsia (in first pregnancy, OR 8.23, 95% CI 6.49 to 10.45)
- BMI at or above 35 at first contact (OR 2.29, 95% CI 1.61 to 3.24)
- presence of multiple pregnancy (OR 2.76, 95% CI 1.99 to 3.82)
- pre-existing vascular disease (e.g., hypertension or diabetes).

Frequency of blood pressure monitoring

No evidence was found on when and how often blood pressure measurements should be taken. However, in a systematic review of RCTs comparing a reduced number of antenatal appointments with the standard number of antenatal appointments, no difference in the rates of pre-eclampsia were reported (pooled OR 0.37, 95% CI: 0.22 to 1.64).32 [Evidence level 1a]

Urinalysis

The diagnosis of pre-eclampsia depends on the presence of significant proteinuria as well as raised blood pressure. Reagent strips or 'dipsticks' are commonly used to detect proteinuria. The incidence of false positive results in random urine specimens may be up to 25% in trace reactions and 6% with 1+ reactions.[535] Therefore, dipsticks can only be a screening test and will not have much utility when not used in combination with blood pressure measurements.[536] Due to considerable observer errors involved in dipstick urinanalysis, an RCOG Study Group recommended that automated dipstick readers be employed.[537] This can significantly improve false positive and false negative rates. An initial sample of 1+ or greater should be confirmed by a 24-hour urinary protein measurement or protein/creatinine ratio determination.[538] Although a finding of 300 mg/24 hours or more or a protein/creatinine ratio of 30 mg/mmol of creatinine is customarily regarded as significant,[539,540] a proteinuria threshold of 500 mg/24 hours has been suggested to be more predictive in relation to the likelihood of adverse outcome.[537]

Recommendation

At first contact, a woman's level of risk for pre-eclampsia should be evaluated so that a plan for her subsequent schedule of antenatal appointments can be formulated. The likelihood of developing pre-eclampsia during a pregnancy is increased in women who:

- are nulliparous
- are age 40 years or older
- have a family history of pre-eclampsia (e.g., pre-eclampsia in a mother or sister)
- have a prior history of pre-eclampsia
- have a BMI at or above 35 at first contact
- have a multiple pregnancy or pre-existing vascular disease (for example, hypertension or diabetes). [C]

Whenever blood pressure is measured in pregnancy, a urine sample should be tested at the same time for proteinuria. [C]

Standardised equipment, techniques and conditions for blood-pressure measurement should be used by all personnel whenever blood pressure is measured in the antenatal period, so that valid comparisons can be made. [C]

Pregnant women should be informed of the symptoms of advanced pre-eclampsia because these may be associated with poorer pregnancy outcomes for the mother or baby. Symptoms include headache, problems with vision, such as blurring or flashing before the eyes, bad pain just below the ribs, vomiting, and sudden swelling of face, hands or feet. [D]

Future research

Research is needed to determine the optimal frequency and timing of blood pressure measurement and on the role of screening for proteinuria.

11.3 Preterm birth

Preterm birth, or the birth of a baby before 37 weeks of gestation (less than 259 days) is one of the largest contributors to neonatal morbidity and mortality in industrialised countries. It is estimated to occur in 6% of babies in the UK, although this is difficult to assess since the UK does not collect gestational-age data at a national level.[541] Trials for the antenatal detection of preterm birth through routine cervical assessment or risk factor assessment have proved largely unsuccessful.

Vaginal examination assesses the maturation of the cervix, its dilatation at the internal os, length, consistency and position. Criteria for an abnormal 'test' result vary. A European multicentre RCT of 5440 women compared routine cervical examination at each antenatal appointment with a policy of avoiding cervical examination unless medically indicated.[542] Preterm birth occurred in 5.7% and 6.4% of the women assigned to the two groups (RR 0.88, 95% CI 0.72 to 1.09). The results of this study do not suggest a benefit from routine cervical examination. [Evidence level 1b]

A prospective multicentre study of vaginal ultrasonography assessed the association between cervical length and risk of preterm delivery.[543] A total of 2915 women were assessed at 24 weeks and 2531 of these women were assessed again at 28 weeks. The risk of preterm delivery was found to increase as the length of the cervix decreased. Women with shorter cervices were compared with women whose cervical lengths were above the 75th percentile. The relative risks are shown in Table 11.2. The sensitivity of this method as a screening test, however, was low at 54% and 70% for women with cervical lengths at or below 30 mm for 24 weeks and 28 weeks, respectively. [Evidence level 2a] Although transvaginal ultrasound screening appears to be able to predict increase risk of preterm birth, there is no evidence that this information can be used to improve outcomes.

Table 11.2 Relative risk of preterm delivery at 24 and 28 weeks of gestation by cervical length

Cervical length		24 weeks		28 weeks	
Percentile	(mm)	RR	95% CI	RR	95% CI
≤ 75th	40	1.98	1.2 to 3.27	2.8	1.41 to 5.56
≤ 50th	35	2.35	1.42 to 3.89	3.52	1.79 to 6.92
≤ 25th	30	3.79	2.32 to 6.19	5.39	2.82 to 10.28
≤ 10th	26	6.19	3.84 to 9.97	9.57	5.24 to 17.48
≤ 5th	22	9.49	5.95 to 15.15	13.88	7.68 to 25.10
≤ 1st	13	13.99	7.89 to 24.78	24.94	13.81 to 45.04

The same multicentre study also assessed the use of fetal fibronectin to predict preterm birth.[544] Measurements of fetal fibronectin in 10,456 women at 8 to 22 weeks were taken and high values after 13 weeks of gestation (with the exception of those from weeks 17 to 18) were found to be associated with a two- to three-fold increased risk of preterm birth (defined as less than 35 weeks of gestation). [Evidence level 2a] A slightly older multicentre cohort study reported that the presence of fetal fibronectin in the cervix and vagina from 22 to 24 weeks of gestation had a sensitivity of 63% for the prediction of preterm birth at less than 28 weeks.[545] [Evidence level 2a]

Using clinical risk assessment at 23 to 24 weeks of gestation, 2929 women were evaluated to assess the ability of this method to predict preterm birth.[546] Demographic factors, socioeconomic status, home and work environment, drug and alcohol use, and clinical history as well as current pregnancy factors were evaluated. Although specific risk factors were highly associated with preterm birth, this risk factor assessment failed to identify most women who subsequently had a preterm delivery. [Evidence level 2a]

RECOMMENDATION

Routine vaginal examination to assess the cervix is not an effective method of predicting preterm birth and should not be offered. [A]

Although cervical shortening identified by transvaginal ultrasound examination and increased levels of fetal fibronectin are associated with an increased risk for preterm birth, the evidence does not indicate that this information improves outcomes; therefore neither routine antenatal cervical assessment by transvaginal ultrasound nor the measurement of fetal fibronectin should be used to predict preterm birth in healthy pregnant women. [B]

12.1 Abdominal palpation for fetal presentation

A study of clinicians using Leopold manoeuvres to assess presentation and engagement if the presenting part found that 53% of all malpresentations were detected and that there was a definite correlation with years of clinical experience and better results.[562] [Evidence level 3] This finding was supported by another study which looked specifically detection of breech presentation.[563] [Evidence level 3] The sensitivity and specificity of Leopold manoeuvres is reported to be about 28% and 94%, respectively.[564] [Evidence level 3]

One descriptive study reported that women do not enjoy being palpated, finding it uncomfortable and not reassuring or informative.[565] [Evidence level 3]

RECOMMENDATIONS

Fetal presentation should be assessed by abdominal palpation at 36 weeks or later, when presentation is likely to influence the plans for the birth. Routine assessment of presentation by abdominal palpation should not be offered before 36 weeks because it is not always accurate and may be uncomfortable. [C]

Suspected fetal malpresentation should be confirmed by an ultrasound assessment. [Good practice point]

12.2 Measurement of symphysis–fundal distance

Use of measurement of symphysis–fundal height (in centimetres) may assist in recording an objective measure of uterine size. Interpretation of fetal growth from changes in fundal height measurement or palpation should bear in mind the errors intrinsic in the use of this technique in predicting placental insufficiency. Sequential measurements of symphysis–fundal height offer the potential to observe changes in fetal growth rate. The common causes of a size-for-dates discrepancy are:

small-for-gestational-age
hydramnios
multifetal pregnancies
molar pregnancy
errors in estimating gestational age.

A systematic review of controlled trials compared symphysis–fundal height measurement with assessment by abdominal palpation alone.[566] Only one trial was included and no differences were detected in any of the outcomes measured, i.e. perinatal mortality, Apgar score less than 4 at 1 minute and 5 minutes, umbilical artery pH less than 7.15, admission to neonatal unit, antenatal hospitalisation for small-for-gestational-age, labour induction for small-for-gestational-age, caesarean section for small-for-gestational-age, birthweight less than tenth centile.

There is not enough evidence to evaluate the use of symphysis–fundal height measurement during antenatal care and it would seem unwise to abandon its use unless a much larger trial shows that it is unhelpful. Symphysis–fundal height measurement is among the least expensive tools in antenatal care, requiring minimal equipment, training and time.

The use of customised fundal height charts as a screening method to detect fetal growth anomalies was assessed in a non-randomised controlled trial.[567] Customised fundal height charts display curves for fetal weight and fundal height while adjusting for maternal height, weight, parity and ethnic group. In this study, fundal height measurements were taken and plotted by community midwives in the intervention area at each antenatal appointment. In the control area, women received usual management, including fundal height assessment by abdominal palpation and standard recording. A significantly higher antenatal detection rate of small- and large-for-gestational-age babies was observed in the group from the study area compared with the women from the control area (OR 2.2, 95% CI 1.1 to 4.5 for small-for-gestational-age; OR 2.6, 95% CI 1.3 to 5.5 for large babies) with no increase in number of scans, but a reduction in the number of referrals for further investigation. No differences in perinatal outcome were reported. [Evidence level 2a] While this study showed that the use of customised growth charts might reduce false positive rates, the

benefits of detecting small- or large-for-gestational-age infants without effective interventions remain unclear.

RECOMMENDATION

Pregnant women should be offered estimation of fetal size at each antenatal appointment to detect small- or large-for-gestational-age infants. [A]

Symphysis–fundal height should be measured and plotted at each antenatal appointment. [Good practice point]

Future research

Further research on more effective ways to detect and manage small- and large-for-gestational age fetuses is needed.

12.3 Routine monitoring of fetal movements

There is often no obvious cause of late fetal death of normally formed singleton births. Many of these deaths are unpredictable and occur in women who are healthy and who have had otherwise uncomplicated pregnancies.

Maternal recognition of decreased fetal movement has long been used during antenatal care in an attempt to identify the jeopardised fetus and intervene to prevent death. Given the low prevalence of fetal compromise and an estimated specificity of 90% to 95%, the positive predictive value of the maternal perception of reduced fetal movements for fetal compromise is low, 2% to 7%.[568]

One RCT was found that assessed the ability of the 'count to ten' method to reduce the prevalence of antenatal fetal death.[569] [Evidence level 1b] The method records on a chart the time interval each day required to feel ten fetal movements. This cluster RCT randomised 68,000 women to either routine formal fetal-movement counting or to standard care. It found that there was no decrease in perinatal mortality in the test group and this policy would have to be used by about 1250 women to prevent one unexplained death.

Following a reduction in fetal movements women should be advised to contact their midwife or hospital for further assessment.

The evidence does not support the routine use of formal fetal movement counting to prevent late fetal death.

RECOMMENDATION

Routine formal fetal-movement counting should not be offered. [A]

12.4 Auscultation of fetal heart

Auscultation of the fetal heart is a component of the abdominal examination and forms an integral part of a standard antenatal examination. Although hearing the fetal heart confirms that the fetus is alive there appears to be no other clinical or predictive value.[570,571] [Evidence level 3] This is because it is unlikely that detailed information on the fetal heart such as decelerations or variability can be heard on auscultation.

There is a perception among doctors and midwives that fetal heart rate auscultation is enjoyable and reassuring for pregnant women and therefore worthwhile. This is not based on published evidence and may not be a correct assumption. Research done on attitudes of women towards auscultation compared with electronic fetal monitoring in labour revealed that many women found the abdominal pressure from auscultation uncomfortable,[572] [Evidence level 3] so perhaps their attitudes to antenatal auscultation cannot be presumed.

RECOMMENDATION

Auscultation of the fetal heart may confirm that the fetus is alive but is unlikely to have any predictive value and routine listening is therefore not recommended. However, when requested by the mother, auscultation of the fetal heart may provide reassurance. [D]

12.5 Cardiotocography

There is no evidence to evaluate the use of antenatal cardiotocography (CTG) for routine fetal assessment in normal pregnancies. RCTs which included women who were healthy and who had uncomplicated pregnancies were not found.

A systematic review of RCTs assessed the effects of antenatal CTG monitoring on perinatal morbidity and mortality and maternal morbidity.[573] [Evidence level 1a] Four trials were included randomising 1588 woman who satisfied the inclusion criteria. In these trials, carried out on high- or intermediate-risk women, antenatal CTG appeared to have no significant effect on perinatal morbidity or mortality. There was no increase in the incidence of interventions such as elective caesarean section or induction of labour.

RECOMMENDATION

The evidence does not support the routine use of antenatal electronic fetal heart rate monitoring (cardiotocography) for fetal assessment in women with an uncomplicated pregnancy and therefore it should not be offered. [A]

12.6 Ultrasound assessment in the third trimester

One systematic review of seven RCTs examined the use of routine ultrasound after 24 weeks in an unselected and designated low-risk population. There was a wide variation in the provision of ultrasound within the studies. The main comparison group of six studies compared routine ultrasound after 24 weeks with no, selective or concealed ultrasound after 24 weeks.[574] [Evidence level 1a]

There were no differences between preterm delivery, birth weight or perinatal mortality. The screened group was less likely to deliver post-term (over 42 weeks), although this may be a result of more accurate dating prior to 24 weeks, as outlined above. Similarly, there were no differences in other outcomes of antenatal, obstetric or neonatal interventions.[574]

RECOMMENDATION

The evidence does not support the routine use of ultrasound scanning after 24 weeks of gestation and therefore it should not be offered. [A]

12.7 Umbilical and uterine artery Doppler ultrasound

One systematic review of five RCTs concluded that routine use of umbilical Doppler ultrasound had no effect on obstetric or neonatal outcomes, including perinatal mortality. The routine use of umbilical Doppler ultrasound increased the likelihood of needing further diagnostic interventions.[575] [Evidence level 1a]

A second systematic review of 27 primary observational studies examined the use of uterine Doppler ultrasound for the prediction of pre-eclampsia, fetal growth restriction and perinatal death in low- and high-risk populations. The predictive value was poor in women who were healthy and who had uncomplicated pregnancies (i.e. low-risk populations).[576] [Evidence level 2a]

RECOMMENDATIONS

The use of umbilical artery Doppler ultrasound for the prediction of fetal growth restriction should not be offered routinely. [A]

The use of uterine artery Doppler ultrasound for the prediction of pre-eclampsia should not be offered routinely. [B]

Appendix 1

Routine antenatal care for healthy pregnant women. Understanding NICE guidance: information for pregnant women, their families and the public

About this information

This information describes the guidance that the National Institute for Clinical Excellence (called NICE for short) has issued to the NHS on antenatal care. It is based on *Antenatal care: routine antenatal care for healthy pregnant women*, which is a clinical guideline produced by NICE for doctors, midwives and others working in the NHS in England and Wales. Although this information has been written chiefly for women who are pregnant or thinking of becoming pregnant, it may also be useful for family members and anyone with an interest in pregnancy or in healthcare in general.

Clinical guidelines

Clinical guidelines are recommendations for good practice. The recommendations in NICE guidelines are prepared by groups of health professionals, lay representatives with experience or knowledge of the condition being discussed, and scientists. The groups look at the evidence available on the best way of treating or managing a condition and make recommendations based on this evidence.

There is more about NICE and the way that the NICE guidelines are developed on the NICE website (www.nice.org.uk). You can download the booklet *The guideline development process – information for the public and the NHS* from the website, or you can order a copy by phoning 0870 1555 455.

What the recommendations cover

NICE clinical guidelines can look at different areas of diagnosis, treatment, care, self-help or a combination of these. The areas that a guideline covers depend on the topic. They are laid out at the start of the development of the guideline in a document called the scope.

The recommendations in *Antenatal care: routine antenatal care for healthy pregnant women*, which are also described here, cover:

- the care you can expect to receive from your midwife and doctors during your pregnancy, whether you plan to give birth at home or in hospital
- the information you can expect to receive
- what you can expect from antenatal appointments
- aspects of your lifestyle that you may want to consider (such as diet, exercise, alcohol and drug intake, sexual activity and smoking)
- routine screening tests for specific conditions
- occupational risk factors in pregnancy
- what will happen if your pregnancy goes beyond 41 weeks
- what will happen if your baby is bottom first (known as the breech position) for the birth.

They do not cover:

- information on birth or parenthood and on preparing for them
- extra care you may need if you are expecting more than one baby
- extra care you may need if you develop additional problems (such as pre-eclampsia) or if your unborn baby has any abnormalities.

The information that follows tells you about the NICE guideline on antenatal care. It doesn't attempt to explain pregnancy or describe any extra care you may need for specific problems. If you want to find out more about pregnancy and antenatal care, or if you have questions about the specific treatments and options mentioned in this booklet, talk to your local midwife or doctor.

How guidelines are used in the NHS

In general, health professionals working in the NHS are expected to follow NICE's clinical guidelines. But there will be times when the recommendations won't be suitable for someone because of a specific medical condition, general health, their wishes or a combination of these. If you think that the treatment or care you receive does not match the treatment or care described in the pages that follow, you should discuss your concerns with your midwife or doctor.

If you want to read the other versions of this guideline

There are three versions of this guideline:

- this one
- the 'NICE guideline' *Antenatal care: routine antenatal care for healthy pregnant women*, which has been issued to people working in the NHS
- the full guideline, which contains all the details of the guideline recommendations, how they were developed and information about the evidence on which they are based.

All versions of the guideline are available from the NICE website (www.nice.org.uk/). This version and the NICE guideline are also available from the NHS Response Line – phone 0870 1555 455 and give the reference number(s) of the booklet(s) you want (N0310 for this version, N0311 for this version in English and Welsh, and N0309 for the NICE guideline).

Guideline recommendations

The guideline recommendations cover the routine care that all healthy pregnant women can expect to receive during their pregnancy.

You will receive extra care, in addition to what we describe here, if you are pregnant with more than one baby, if you already have certain medical conditions or if you develop a health problem during your pregnancy.

The guideline does not cover the care that women receive during or after a birth.

About antenatal care

Antenatal care is the care that you receive from health professionals during your pregnancy. It includes information on services that are available and support to help you make choices. You should be able to access antenatal care services that are readily and easily available and sensitive to your needs.

During your pregnancy you should be offered a series of antenatal appointments to check on your health and the health of your baby. During these appointments you should be given information about your care.

Your midwife or doctor should give you information in writing or in some other form that you can easily access and understand. If you have a physical, cognitive or sensory disability, for example, or if you do not speak or read English, they should provide you with information in an appropriate format.

A record should be kept of the care you receive. You should be asked to keep your maternity notes at home with you and to bring them along to all your antenatal appointments.

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You have a right to take part in making decisions about your care. To be able to do this you will need to feel confident that you:

- understand what is involved
- feel comfortable about asking questions
- can discuss your choices with your antenatal care team.

Your care team should support you in this by making sure you have access to antenatal classes and information that is based on the best research evidence available.

While you are pregnant you should normally see a small number of health practitioners, led by your midwife and/or doctor (GP), on a regular basis. They should be people with whom you feel comfortable.

Antenatal appointments

The exact number of antenatal appointments and how often you have them will depend on your individual situation. If you are expecting your first child, you are likely to have up to ten appointments. If you have had children before, you should have around seven appointments. Some of them may take place at your home if this suits you. Your antenatal appointments should take place in a setting where you feel able to discuss sensitive issues that may affect you (such as domestic violence, sexual abuse, mental illness or drug use).

Early in your pregnancy your midwife or doctor should give you appropriate written or other information about the likely number, timing and purpose of your appointments, according to the options that are available to you. You should have a chance to discuss the schedule with them.

The table on page xx [20] gives a brief guide to what usually happens at each antenatal appointment.

What should happen at the appointments

The aim of antenatal appointments is to check on you and your baby's progress and to provide you with clear information and explanations, in discussions with you, about your care. At each appointment you should have the chance to ask questions and discuss any concerns you have with your midwife or doctor.

Each appointment should have a specific purpose. You will need longer appointments early in your pregnancy to allow plenty of time for your midwife or doctor to assess you and discuss your care. Wherever possible the appointments should include any routine tests you need, to cut down on any inconvenience to you.

Appointments in early pregnancy

Your first appointment should be fairly early in your pregnancy (before 12 weeks). Your midwife or doctor should use it to identify your needs (such as whether you need additional care) and should ask you about your health and any previous physical or mental illness you have had, so that you can be referred for further assessment or care, if necessary.

They should also give you an opportunity to let them know, if you wish, if you are in a vulnerable situation or if you have experienced anything which means you might need extra support, such as domestic violence, sexual abuse or female genital mutilation (such as female circumcision).

Your midwife or doctor should give you information on pregnancy care services and the options available, maternity benefits, diet, other aspects of your life which may affect your health or the health of your baby, and on routine screening tests. They should explain to you that decisions on whether to have these tests rest with you, and they should make sure that you understand what those decisions will mean for you and your baby.

During one of these early appointments your midwife or doctor should check your blood pressure and test your urine for the presence of protein. They should also weigh you and measure your height. If you are significantly overweight or underweight you may need extra care. You should not usually be weighed again.

Appointments in later pregnancy

The rest of your antenatal appointments should be tailored according to your individual health needs. They should include some routine tests (see page 120) which are used to check for certain conditions or infections. Most women are not affected by these conditions, but the tests are offered so that the small number of women who are affected can be identified and offered treatment.

Your midwife or doctor should explain to you in advance the reason for offering you a particular test. When discussing the test with you, they should make it clear that you can choose whether or not to have the test, as you wish.

During your appointments your midwife or doctor should give you the results of any tests you have had. You should be able to discuss your options with them and what you want to do.

Checking on your baby's development

At each antenatal appointment your midwife or doctor should check on your baby's growth. To do this, they should measure the distance from the top of your womb to your pubic bone. The measurement should be recorded in your notes.

The rest of this information tells you more about what you can expect from your midwife and/or doctor during your pregnancy and about the tests that you should be offered. It also tells you what you can expect if your pregnancy continues a week or more beyond your due date or if your baby is in the breech position (that is, bottom first) prior to birth.

Advice on money matters and work

Your midwife or doctor should give you information about your maternity and benefits rights. You can also get information from the Department of Trade and Industry – phone the helpline on 08457 47 47 47, call 08701 502 500 for information leaflets or visit the website at www.dti.gov.uk/er/workingparents.htm. The Government's interactive guidance website (www.tiger.gov.uk) also has information. Up-to-date information on maternity benefits can also be found on the Department for Work and Pensions website (www.dwp.gov.uk).

Your midwife or doctor should ask you about the work that you do, and should tell you about any possible risks to your pregnancy. For most women it is safe to continue working while you are pregnant, but there are hazards in some jobs that could put you at risk. More information about risks at work is available from the Health and Safety Executive; the website address is www.hse.gov.uk/mothers/index.htm or you can phone 08701 545 500 for information.

Lifestyle advice

There are a number of things you can do to help yourself stay healthy while you are pregnant. Your midwife or doctor can tell you more about them.

Exercise

You can continue or start moderate exercise before or during your pregnancy. Some vigorous activities, however, such as contact sports or vigorous racquet games, may carry extra risks, such as falling or putting too much strain on your joints. You should avoid scuba diving while you are pregnant as this can cause problems in the developing baby.

Alcohol

Excess alcohol can harm your unborn baby. If you do drink while you are pregnant, it is better to limit yourself to one standard unit of alcohol a day (roughly the equivalent of 125 ml – a small glass – of wine, half a pint of beer, cider or lager, or a single measure of spirits).

Smoking

Smoking increases the risks of your baby being underweight or being born too early – in both instances, your baby's health may be affected. You will reduce these risks if you can give up smoking, or at least smoke less, while you are pregnant. You and your baby will benefit if you can give up, no matter how late in your pregnancy.

If you need it, your midwife or doctor should offer you help to give up or cut down on smoking

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or to stay off it if you have recently given up. The NHS pregnancy smoking helpline can also provide advice and support – the phone number is 0800 169 9 169.

Cannabis

If you use cannabis, and especially if you smoke it, it may be harmful to your baby.

Sexual activity

There is no evidence that sexual activity is harmful while you are pregnant.

Travel

When you travel by car you should always wear a three-point seatbelt above and below your bump (not over it).

If you are planning to travel abroad you should talk to your midwife or doctor, who should tell you more about flying, vaccinations and travel insurance.

The risk of deep vein thrombosis from travelling by air may be higher when you are pregnant. Your midwife or doctor can tell you more about how you may be able to reduce the risk by wearing correctly fitted compression stockings.

Prescription and over-the-counter medicines

Only a few prescription and over-the-counter medicines have been shown to be safe for pregnant women by good-quality studies. While you are pregnant, your doctor should only prescribe medicines where the benefits are greater than the risks. You should use as few over-the counter-medicines as possible.

Complementary therapies

Few complementary therapies are known to be safe and effective during pregnancy. You should check with your midwife, doctor or pharmacist before using them.

Diet and food

Folic acid

Your midwife or doctor should give you information about taking folic acid (400 micrograms a day). If you do this when you are trying to get pregnant and for the first 12 weeks of your pregnancy it reduces the risk of having a baby with conditions which are known as neural tube defects, such as spina bifida (a condition where parts of the backbone do not form properly, leaving a gap or split which causes damage to the baby's central nervous system).

Vitamin A

Excess levels of vitamin A can cause abnormalities in unborn babies. You should avoid taking vitamin A supplements (with more than 700 micrograms of vitamin A) while you are pregnant. You should also avoid eating liver (which may contain high levels of vitamin A), or anything made from liver.

Other food supplements

You do not need to take iron supplements as a matter of routine while you are pregnant. They do not improve your health and you may experience unpleasant side effects, such as constipation.

You should not be offered vitamin D supplements as a matter of routine while you are pregnant. There is not enough evidence to tell whether they are of any benefit to pregnant women.

Food hygiene

Your midwife or doctor should give you information on bacterial infections such as listeriosis and salmonella that can be picked up from food and can harm your unborn baby. In order to avoid them while you are pregnant it is best:

- if you drink milk, to keep to pasteurised or UHT milk
- avoid eating mould-ripened soft cheese such as Camembert or Brie and blue-veined cheese (there is no risk with hard cheese such as Cheddar, or with cottage cheese or processed cheese)

- avoid eating paté (even vegetable paté)
- avoid eating uncooked or undercooked ready?prepared meals
- avoid eating raw or partially cooked eggs or food that may contain them (such as mayonnaise)
- avoid raw or partially cooked meat, especially poultry.

Toxoplasmosis is an infection that does not usually cause symptoms in healthy women. Very occasionally it can cause problems for the unborn baby of an infected mother. You can pick it up from undercooked or uncooked meat (such as salami, which is cured) and from the faeces of infected cats or contaminated soil or water. To help avoid this infection while you are pregnant it is best to:

- wash your hands before you handle food
- wash all fruit and vegetables, including ready?prepared salads, before you eat them
- make sure you thoroughly cook raw meats and ready?prepared chilled meats
- wear gloves and wash your hands thoroughly after gardening or handling soil
- avoid contact with cat faeces (in cat litter or in soil).

Screening tests

Early in your pregnancy you should be offered a number of tests. The purpose of these tests is to check whether you have any conditions or infections that could affect you or your baby's health.

Your doctor or midwife should tell you more about the purpose of any test you are offered. You do not have to have a particular test if you do not want it. However, the information they can provide may help your antenatal care team to provide the best care possible during your pregnancy and the birth. The test results may also help you to make choices during pregnancy.

Ultrasound scans

Early in your pregnancy (usually around 10 to 13 weeks) you should be offered an ultrasound scan to estimate when your baby is due and to check whether you are expecting more than one baby. If you see your midwife or doctor for the first time when you are more than 13 weeks pregnant, they should offer you a scan then.

Between 18 and 20 weeks you should be offered another scan to check for physical abnormalities in your baby. You should not have any further routine scans, as they have not been shown to be useful.

Blood tests

Anaemia

You should be offered two tests for anaemia: one at your first antenatal appointment and another between your 28th and 30th week. Anaemia is often caused by a lack of iron. If you develop anaemia while you are pregnant it is usually because you do not have enough iron to meet your baby's need for it in addition to your own; you may be offered further blood tests. You should be offered an iron supplement if appropriate.

Blood group and rhesus D status

Early in your pregnancy you should be offered tests to find out your blood group and your Rhesus D (RhD) status. Your midwife or doctor should tell you more about them and what they are for. If you are RhD negative you should be offered an anti-D injection to prevent future babies developing problems. Your partner may also be offered tests to confirm whether you need an anti-D injection. You can find more information about this in Guidance on the routine use of anti-D prophylaxis for RhD negative women: information for patients, published by NICE in 2002 and available at www.nice.org.uk/pdf/Anti_d_patient_leaflet.pdf.

Early in your pregnancy, and again between your 28th and 36th week, you should be offered tests to check for red cell antibodies. If the levels of these antibodies are significant, you should be offered a referral to a specialist centre for more investigation and advice on managing the rest of your pregnancy.

Screening for infections

Your midwife or doctor should offer you a number of tests, as a matter of routine, to check for certain infections. These infections are not common, but they can cause problems if they are not detected and treated.

Asymptomatic bacteriuria

Asymptomatic bacteriuria is a bladder infection that has no symptoms. Identifying and treating it can reduce the risk of giving birth too early. It can be detected by testing a urine sample.

Hepatitis B virus

Hepatitis B virus is a potentially serious infection that can affect the liver. Many people have no symptoms, however. It can be passed from a mother to her baby (through blood or body fluids), but may be prevented if the baby is vaccinated at birth. The infection can be detected in the mother's blood.

HIV

HIV usually causes no symptoms at first but can lead to AIDS. HIV can be passed from a mother to her baby, but this risk can be greatly reduced if the mother is diagnosed before the birth. The infection can be detected through a blood test. If you are pregnant and are diagnosed with HIV you should receive specialist care.

German measles (rubella)

Screening for German measles (rubella) is offered so that if you are not immune you can choose to be vaccinated after you have given birth. This should usually protect you and future pregnancies. Testing you for rubella in pregnancy does not aim to identify it in the baby you are carrying.

Syphilis

Syphilis is rare in the UK. It is a sexually transmitted infection that can also be passed from a mother to her baby. Mothers and babies can be successfully treated if it is detected and treated early. A person with syphilis may show no symptoms for many years. A positive test result does not always mean you have syphilis, but your healthcare providers should have clear procedures for managing your care if you test positive.

Screening tests for Down's syndrome

Down's syndrome is a condition caused by the presence of an extra chromosome in a baby's cells. It occurs by chance at conception and is irreversible.

In the first part of your pregnancy you should be offered screening tests to check whether your baby is likely to have Down's syndrome. Your midwife or doctor should tell you more about Down's syndrome, the tests you are being offered and what the results may mean for you. You have the right to choose whether to have all, some or none of these tests. You can opt out of the screening process at any time if you wish.

Screening tests will only indicate that a baby may have Down's syndrome. If the test results are positive, you should be offered further tests to confirm whether your baby does, in fact, have Down's syndrome. The time at which you are tested will depend on what kinds of tests are used.

Screening tests for Down's syndrome are not always right. They can sometimes wrongly show as positive, suggesting the baby does have Down's syndrome when in fact it does not. This type of result is known as a 'false positive'. The number of occasions on which this happens with a particular test is called its 'false-positive rate'.

At present you should be offered screening tests with a false-positive rate of less than 5 out of 100 and which detect at least 60 out of 100 cases of Down's syndrome. The tests which meet this standard are:

- from 11 to 14 weeks:
  - nuchal translucency (an ultrasound scan)
  - combined test (an ultrasound scan and blood test)

- from 14 to 20 weeks:
  - triple test (a blood test)
  - quadruple test (a blood test)
- from 11 to 14 weeks and 14 to 20 weeks:
  - integrated test (an ultrasound scan and blood test)
  - serum integrated test (a blood test).

By April 2007 all pregnant women should be offered screening tests for Down's syndrome with a false-positive rate of less than 3 out of 100 and which detect more than 75 out of 100 cases. The tests which meet this standard are:

- from 11 to 14 weeks
  - combined test
- from 14 to 20 weeks
  - uadruple test
- from 11 to 14 weeks and 14 to 20 weeks
  - integrated test
  - serum integrated test.

Pre-eclampsia

Pre-eclampsia is an illness that happens in the second half of pregnancy. Although it is usually mild, it can cause serious problems for you and your baby if it is not detected and treated.

Your midwife or doctor should tell you more about the symptoms of advanced pre-eclampsia, which include:

- headache
- problems with vision, such as blurred vision or lights flashing before the eyes
- bad pain just below the ribs
- vomiting
- sudden swelling of the face, hands or feet.

They should assess your risk of pre-eclampsia at your first antenatal appointment in order to plan for the rest of your appointments.

You are more likely to develop pre-eclampsia when you are pregnant if you:

- have had it before
- have not been pregnant before
- are 40 years old or more
- have a mother or sister who has had pre-eclampsia
- are overweight at the time of your first antenatal appointment
- are expecting more than one baby or you already have high blood pressure or diabetes.

Whenever your blood pressure is measured during your pregnancy, a urine sample should be tested at the same time for protein (as this can be another sign of pre-eclampsia).

Whenever a member of your healthcare team measures your blood pressure they should use the same type of equipment, method and conditions so that the results at different times of your pregnancy can be compared.

Placenta praevia

Placenta praevia is when the placenta is low lying in the womb and covers all or part of the entrance (the cervix). In most women, the placenta usually goes back into a normal position before the birth and does not cause a problem. If it does not, you may need a Caesarean section.

If the 20th week ultrasound scan shows that your placenta extends over the cervix you should be offered another abdominal scan at 36 weeks. If this second abdominal scan is unclear, you should be offered a vaginal scan.

Tests not offered as a matter of routine

There are a number of screening tests which have sometimes been offered to women in the past or have been suggested for routine antenatal care. The following tests should not be offered to you as a matter of routine because they have not been shown to improve outcomes for mothers or babies:

- cardiotocography (a record of the trace of a baby's heartbeat, which is monitored through electronic sensors placed on the mother's abdomen, sometimes called a trace or CTG)
- Doppler ultrasound (an ultrasound scan which measures the blood flow between the baby and the mother)
- vaginal examinations to predict whether a baby may be born too early
- routine breast and pelvic examinations
- screening for gestational diabetes mellitus (a form of diabetes triggered by pregnancy)
- daily counting and recording of the baby's movements
- routine screening for infection with:
  - group B streptococcus (GBS); this is a bacterial infection that can affect the baby (if you have previously had a baby with neonatal GBS, you should be offered treatment around the time of your labour)
  - toxoplasmosis (see page 120)
  - asymptomatic bacterial vaginosis (a vaginal infection which produces no symptoms)
  - cytomegalovirus; infection with this virus can affect the baby
  - chlamydia trachomatis (a vaginal infection) where there are no symptoms (a national screening programme for chlamydia is due to start soon, so arrangements for this will probably change).

There is not enough evidence about the effectiveness or cost effectiveness of routine screening for hepatitis C virus to justify it.

Managing common problems

Pregnancy brings a variety of physical and emotional changes. Many of these changes are normal, and pose no danger to you or your baby, even though some of them may cause you discomfort. If you want to discuss these things, your midwife or doctor is there to give you information and support.

Nausea and sickness

You may feel sick or experience vomiting in the early part of your pregnancy. This does not indicate that anything is wrong. It usually stops around your 16th to 20th week. Your midwife or doctor should give you information about this. You may find that using wrist acupressure or taking ginger tablets or syrup helps to relieve these symptoms. If you have severe problems your doctor may give you further help or prescribe antihistamine tablets for sickness.

Heartburn

Your midwife or doctor should give you information about what to do if you suffer from heartburn during your pregnancy. If it persists they should offer you antacids to relieve the symptoms.

Constipation

If you suffer from constipation while you are pregnant your midwife or doctor should tell you ways in which you can change your diet (such as eating more bran or wheat fibre) to help relieve the problem.

Haemorrhoids

There is no research evidence on how well treatments for haemorrhoids work. If you suffer from haemorrhoids, however, your midwife or doctor should give you information on what you can do to change your diet. If your symptoms continue to be troublesome they may offer you a cream to help relieve the problem.

Backache

Backache is common in pregnant women. You may find that massage therapy, exercising in water or going to group or individual back care classes may help you to relieve the pain.

Varicose veins

Varicose veins are also common. They are not harmful during pregnancy. Compression stockings may relieve the symptoms (such as swelling of your legs), although they will not stop the veins from appearing.

Vaginal discharge

You may get more vaginal discharge than usual while you are pregnant. This is usually nothing to worry about. However, if the discharge becomes itchy or sore, or smells unpleasant, or you have pain on passing urine, tell your midwife or doctor, as you may have an infection.

Thrush

If you have thrush (a yeast infection – also known as Candida or vaginal candidiasis) your doctor may prescribe cream and/or pessaries for you to apply to the area for 1 week.

While you are pregnant it is best to avoid taking any medicine for thrush that needs to be swallowed. There is no evidence about how safe or effective these are for pregnant women.

If you are pregnant beyond 41 weeks

If your pregnancy goes beyond 41 weeks there is a greater risk of certain problems for your baby. You should be offered a 'membrane sweep', which involves having a vaginal examination; this stimulates the neck of your womb (known as the cervix) to produce hormones which may trigger spontaneous labour. If you choose not to have a membrane sweep, or it does not cause you to go into labour, you should be offered a date to have your labour induced (started off).

If you decide against having labour induced and your pregnancy continues to 42 weeks or beyond, you should be offered ultrasound scans and may have your baby's heartbeat monitored regularly, depending on your individual care plan.

You can find more information about what induction of labour means from the guideline, which you can find on the NICE website at: www.nice.org.uk/pdf/inductionoflabourinfoforwomen.pdf.

If your baby is positioned bottom first

At around 36 weeks your midwife or doctor will check your baby's position by examining your abdomen. If they think the baby is not in a 'head down' position, which is best for the birth, you should be offered an ultrasound scan to check.

If your baby is bottom first (known as the breech position) your midwife or doctor should offer you a procedure called external cephalic version (ECV). ECV means they will gently push the baby from outside, to move it round to 'head first'. It does not always work.

Your midwife or doctor should give you more information about what ECV involves.

You should not be offered ECV if you:

- are in labour
- have a scar or abnormality in your womb
- have vaginal bleeding
- have a medical condition

or if:

- your waters have broken
- your baby's health seems fragile.

If you choose to have ECV and it cannot be done at 37 weeks, it should be done at 36 weeks.

Where you can find more information

If this is your first pregnancy, your midwife or doctor should give you a copy of *The pregnancy book* (published by Health Departments in England and Wales). It tells you about many aspects of pregnancy including: how the baby develops; deciding where to have a baby; feelings and relationships during pregnancy; antenatal care and classes; information for expectant fathers; problems in pregnancy; when pregnancy goes wrong; and rights and benefits information. It also contains a list of useful organisations.

If you need further information about any aspects of antenatal care or the care that you are receiving, please ask your midwife, doctor or a relevant member of your health team. You can discuss this guideline with them if you wish, especially if you aren't sure about anything in this booklet. They will be able to explain things to you.

For further information about the National Institute for Clinical Excellence (NICE), the Clinical Guidelines Programme or other versions of this guideline (including the sources of evidence used to inform the recommendations for care), you can visit the NICE website at www.nice.org.uk. At the NICE website you can also find information for the public about other maternity-related guidance on:

- pregnancy and childbirth: electronic fetal monitoring (guideline C)
- pregnancy and childbirth: induction of labour (guideline D)
- pregnancy – routine anti-D prophylaxis for rhesus negative women (technology appraisal no. 41).

You can get information on common problems during pregnancy from NHS Direct (telephone 0845 46 47; website www.nhsdirect.nhs.uk).

SUMMARY OF YOUR ROUTINE APPOINTMENTS DURING PREGNANCY

At each appointment, you should be given information with an opportunity to discuss issues and ask questions.
You should usually be asked to keep your own case notes at home with you and bring them to appointments.
Your midwife or doctor should tell you the results of all tests and have a system in place to do this.
As well as face-to-face information you should have access to antenatal classes and written information that is based on the best research evidence available.

Wherever possible you should be cared for by a small group of people with whom you feel comfortable. They should assess your particular needs as an individual and give you continuity of care.

Have you had a baby before?

- **Yes** → You should discuss this with your midwife or carer. You may need additional care.
- **No** → **Were the pregnancy and birth uncomplicated?**
  - **No** → You should discuss this with your midwife or carer. You may need additional care.
  - **Yes**

Appointment schedule

- ✓ Have had a baby before
- ✓ For first baby

STAGE OF YOUR PREGNANCY

	Have had a baby before	For first baby
Before 12 weeks (may be 2 appointments)	Give information on diet and lifestyle considerations, pregnancy care services, maternity benefits, and screening tests. Your midwife or doctor should: • Find out if you need additional care. • Tell you how taking folic acid (400 micrograms per day for up to 12 weeks) can reduce certain health risks for your baby. • Offer you screening tests and make sure you understand what is involved before you decide to have any of them. • Offer you an ultrasound scan to estimate when baby is due. • Measure your blood pressure, height and weight. • Test your urine for the presence of protein. • Offer you help to stop smoking if you want it. • Offer you an ultrasound scan at 18–20 weeks to check the physical development of the baby.	✓	✓
At 16 weeks	Your midwife or doctor should review, discuss and record results of any screening tests, measure your blood pressure and test your urine.	✓	✓
25	Check the size of your abdomen. Measure your blood pressure and test your urine.		✓
28	Checks on the size of your abdomen, your blood pressure and urine. More screening tests for anaemia and red cell antibodies if you wish them. If you are rhesus negative, first anti-D treatment if you wish it.	✓	✓
31	Checks on the size of your abdomen, your blood pressure and urine.		✓
34	Checks on the size of your abdomen, your blood pressure and urine. If you are rhesus negative, second anti-D treatment if you wish.	✓	✓
36	Checks on the size of your abdomen, your blood pressure and urine. Check to see if the baby is head first — discuss options to turn the baby if it is feet first (breech position).	✓	✓
38	Checks on the size of your abdomen, your blood pressure and urine.	✓	✓
40	Checks on the size of your abdomen, your blood pressure and urine.		✓
41	Checks on the size of your abdomen, your blood pressure and urine. Discuss option of membrane sweep. Discuss whether you want your labour to be induced after 41 weeks.		

7 : total appointments if you've had a baby before

Total appointments if this is your first baby: **10**

1

Evidence tables

(2008 update)

What, how and when information should be offered during the antenatal period to inform women's decisions about care during pregnancy, labour, birth and the postnatal period?

Effectiveness of information provision

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
Dyson et al, 2005	637	7 RCTS involving 1388 women	To examine the interventions that aim to encourage women to breastfeed, to evaluate their effectiveness	The number of women who initiate breastfeeding and any other effects of such interventions.	5 trials involving 582 women showed that breastfeeding education had a significant effect on increasing initiation rates compared to routine care RR 1.53 [95% CI 1.25-1.88].	Cochrane review. The 7 studies suffered from a high overall risk of bias due to unclear or inadequate allocation concealment. 3 of 7 studies reported breastfeeding initiation for all participants, the remaining 4 studies had up to 25% losses to follow up between recruitment and breastfeeding initiation.	Systematic review of RCTs	1+
Fairbank et al,	638	59 studies of	Evaluation of evidence to identify which	The number of women	There is limited impact on initiation rates of	Health	Extensive	1+

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
2000		which 14 were RCTs, 16 non-RCTs and 29 before-after studies. Intervention were grouped into categories: health education; health sector initiatives (HSI) – general; HSI Baby Friendly Hospital Initiative (BFHI); HSI-training of health professionals; HSI – US Department of Agriculture's Special Supplemental Nutrition Program for Women, Infants, and Children (WIC); HSI – social support from health professionals; peer support; media campaigns; and multifaceted interventions.	promotion programmes are effective at improving breastfeeding rates.	who start to breastfeed, duration and exclusivity of breastfeeding.	breastfeeding by giving breastfeeding literature alone, or combined with a more formal, non-interactive method of health education. Small, informal, group health education classes, delivered in the antenatal period, can be an effective intervention to increase initiation rates, and in some cases the duration of breastfeeding, among women from different income or ethnic groups. Amedia campaign as a stand-alone intervention, and particularly television commercials, may improve attitudes towards, and increase initiation rates of breastfeeding. Multifaceted interventions comprising a media campaign and/or a peer support programme combined with structural changes to the health sector (HSI) or, in fewer cases, combined with health education activities are effective in increasing initiation rates (and duration and exclusivity of breastfeeding).	Technology Assessment	literature review	
Lavender et al, 2005	639	Women who expressed a desire to breast-feed at the start of their pregnancy booked at an inner-city teaching hospital. Sample n=1249	To evaluate the effect of an antenatal breastfeeding intervention on breastfeeding duration (delivered as an extra antenatal class session). Comparison group: usual antenatal classes	Main outcome: proportion of women who fulfilled their expectation of breastfeeding.	No difference between the groups in the proportion of women who attained their expected duration of breastfeeding (OR 1.2; 95% CI 0.89-1.6). There were no differences between the groups in the uptake of breastfeeding on discharge (OR = 1.2; 95% CI 0.8-1.7) or exclusively at four months (OR = 1.1; 95% CI 0.6-1.8).	UK	Cluster RCT	1-
Mattar et al, 2007	640	'Low risk' women booked at a tertiary referral centre May 2002 to December 2004.	To evaluate the impact of breastfeeding educational material and breastfeeding coaching on breastfeeding practice.	Duration of exclusive and predominant breastfeeding.	Women who received simple antenatal instruction with a short, single, individual counselling session combined with educational material were practiced exclusive and predominant breastfeeding more often than women receiving routine care alone at 3	Singapore Note: There was contamination between the groups and	RCT	1-

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		Sample n=401			months (odds ratio [OR] 2.6, 95% confidence interval [CI] 1.2-5.4) and 6 months (OR 2.4, 95% CI 1.0-5.7) postpartum. More women practiced exclusive and predominant breastfeeding at 6 months among women receiving individual counselling compared with women exposed to educational material alone (OR 2.5, 95% CI 1.0-6.3).	women in the control group came to know about the interventions offered to the other groups simply by speaking to women in those groups. The study was underpowered.		
Noel-Weiss et al, 2006	641	Nulliparous women with an uncomplicated pregnancy. Sample n=110	To evaluate the effects of a breastfeeding workshop on breastfeeding self-efficacy and duration.	Maternal breastfeeding self-efficacy (measured with a revised breastfeeding self-efficacy scale) and breastfeeding duration (measured at 4 weeks and 8 weeks postpartum).	Maternal breastfeeding scores increased in both groups. Self-efficacy scores (mean (std. dev.)): At registration: Intervention 42.73 (9.2) vs control 42.02 (9.7); t= -0.345 [95% CI -4.76 to 3.35]; p=0.731. At 4 weeks postpartum: Intervention 57.98 (8.6) vs control 53.38 (9.1); t= -2.32 [95% CI -8.53 to -0.65]; p=0.023. At 8 weeks postpartum: Intervention 61.70 (5.8) vs control 58.91 (9.1); t= -1.60 [95% CI -6.28 to -0.70]; p=0.115. Exclusive breastfeeding at 8 weeks: Intervention 33/47 vs. control 26/45; χ^2=8.41, p=0.135.	Canada	RCT	1-
Reifsnider and Eckhart, 1996	642	Women who expressed a wish to breastfeed and who qualified for the US WIC programme living in rural areas of Oklahoma. Intervention group n=14 Comparison group n=17	To investigate the effects of antenatal breastfeeding education on breastfeeding incidence and duration.	Breastfeeding incidence and duration.	A significantly higher percentage of women still breastfeeding at 3 and 4 months postpartum in the experimental group versus the control group. The control group breastfed for 29.5 +/- 43.6 days, while the experimental group breastfed for 76 days +/- 104.3 (p =0.05).	USA	Non-randomised trail	1-
Wiles, 1984	643	Nulliparous	Evaluation of antenatal breastfeeding	Woman's own perception	At 1-2 days:	USA	Prospective	2

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		women expressing a wish to breastfeed. Sample n=40	education programme.	of breastfeeding 'success'. Woman's perceptions of her baby (measured using the Neonatal Perception Inventory (NPI)) Outcomes measured 1-2 days postpartum and 1 month postpartum.	Intervention group had lower NPI scores than comparison group (U=125.5, p=0.05) At 1 month: Intervention group had significantly higher NRI scores than comparison group (U=94, p=0.01) 18/20 women in intervention group fully breastfeeding vs. 6/20 in the comparison group.		cohort study	
Pugin et al, 1996	644	Women attending university hospital for antenatal care. Intervention (antenatal skills-based session) n=59 Comparison 1 (5 other breastfeeding interventions) n=363 Comparison 2 (no interventions) n=313	Evaluation of the effectiveness of an antenatal skill-based education session for breastfeeding.	Number of women fully breastfeeding at 6 months	Fully breastfeeding at 6 months: Intervention group: 47/59 (80%) Comaparison group 1: 235/363 (65%) Comparison group 2: 99/313 (32%) Chi-square analysis showed these differences to be statistically significant.	Chile	Prospective cohort study	2
Sheehan et al, 2003	645	Purposive sample of 29 women interviewed antenatally.	To describe women's decision-making regarding infant feeding.	What woman's decision is regarding feeding her baby. Influences on the decision to breastfeed. How the woman feels about breastfeeding Woman's expectations of what breastfeeding will feel like.	Thematic analysis revealed the following key themes: 1. Assuming I'll breastfeed 2. Definitely going to breastfeed 3. Playing it by ear 4. Definitely going to bottle feed	Australia	Qualitative interview-based study	3
Gulick, 1982	646	Nulliparous women attending antenatal classes associated with 12 medical centres in both urban and rural areas. Sample n=251	To investigate whether women with more breastfeeding knowledge antenatally breastfeed for longer than those with less antenatal knowledge.	Breastfeeding for longer than 4 weeks.	Women with more antenatal knowledge were more likely to breastfeed for longer than 4 weeks compared with those with less knowledge (t=2.72, p=0.004. Degrees of freedom not reported).	USA	Prospective descriptive study	3
Kramer, 1996	65	4 RCTs including	To assess the effects of advising	Main outcomes:	Advice to increase energy and protein intakes	Cochrane	Systematic	1+

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		1108 women	pregnant women to increase their energy and protein intakes.	Dietary intake, gestational weight gain and pregnancy outcomes	seems to be successful in achieving those goals, but the increases are lower than those reported in trials of actual protein/energy supplementation. The evidence regarding the effects on pregnancy outcome are not truly representative as available only from one trial with very narrow confidence intervals. None of the trials reported any potential adverse effects that might accompany increased fetal size, such as an increased risk of prolonged labour or caesarean section.	systematic review	review	
Campbell et al, 2004	647	Sample n=307 (response rate 74.8%). 96% participants were females, 20% were pregnant, and 50% were minorities (African American and other).	Evaluation of effectiveness of interactive CD-ROM consisting of targeted video soap opera, dietary assessment and individualised dietary feedback and strategies to help change.	Total fat and fruit and vegetable intake; knowledge of low-fat; infant feeding knowledge; self-efficacy. Outcomes measured at baseline and then 1-2 months post-intervention.	Low-fat knowledge (mean (SD)): Intervention group: baseline 1.94 (1.2) vs follow-up 2.76 (0.46); p<0.05. Control group: baseline 1.86 (1.2) vs. follow-up 2.63 (0.55); NS Infant feeding knowledge: Intervention group: baseline 2.29 (0.82) vs follow-up 2.62 (0.62); p<0.01. Control group: baseline 2.25 (0.86) vs. follow-up 2.40 (0.75); NS	USA	RCT	1+
Olsen et al, 2004	648	Healthy pregnant women with normal or overweight body mass index. Intervention group n=179 Comparison group (historical) n=381	To evaluate the efficacy of an educational intervention aimed at keeping pregnancy weight gain within Institute of Medicine (IOM) recommended limits.	Proportion of women exceeding upper limit of the IOM recommended weight gain range for pregnancy.	Sub-group analysis performed for low-income and high-income groups: Gaining above IOM range: Low income group: OR 0.41 [95% CI 0.20 to 0.81] High income group: OR 1.15 [95% CI 0.69 to 1.93]	USA	Prospective cohort study	2+
Szwajcer et al, 2005	649	5 groups of 12 women including women who wanted a child (but not yet pregnant), women in the first,	Exploration of the nutrition-related information sources and information seeking behaviours of women during pregnancy.	Sources of information used by women and information seeking behaviours.	Women in the first trimester mainly sought nutrition information in the media, such as the internet, books, magazines, 9-month calendars and brochures. In the second trimester, nutrition information was sought from the 9-month calendar (fun and tips) and	Netherlands	Qualitative group interview –based study	3

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		second and third trimester of their first pregnancy and women in the first trimester of their second pregnancy.			friends (experienced). Women in the third trimester sought information from friends (information on breastfeeding). Second-time pregnant women relied on their experience, the midwife and books for specific questions.			
Orstead et al, 1985	650	Women attending antenatal clinic at inner-city hospital 1975-1981. Intervention group: n=114 (1975-1977) Control group n=86 (1979-1981)	Evaluation of an intensive nutritional education group programme comprising 15 minute film ('Inside my Mom'), basic dietary advice given by dietician with explanation for increasing intake of particular foods during pregnancy. Leaflets also given out and women invited to meet with dietician at each subsequent antenatal visit for further counselling and follow-up.	Main outcomes: Maternal weight ain during pregnancy Birthweight Gestational age at birth	Maternal weight gain: Control group 9.5 kg (=/- 0.5) vs intervention group 7.0 (+/- 0.6); p<0.001. Birthweight: Control group 3130g (=/- 50) vs intervention group 3231g (=/- 47) Birthweight < 2500g: Control group n=11 vs intervention group n=5, NS	USA Poor quality study design	Retrospective cross-sectional study	2-

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Lumley et al, 2004	651	Systematic review of 51 RCTs with 20, 931 pregnant women and 6 cluster RCTs with 7,500 pregnant women	Smoking cessation programmes implemented during pregnancy	Continuation of smoking in late pregnancy Birth weight Incidence of low birthweight Incidence of very low birthweight Preterm birth Stillbirths Perinatal mortality	Continuation of smoking in late pregnancy: RR 0.94 [95% CI 0.92 to 0.96] (n=47 trials) but heterogeneity I^2=59.7% Mean birth weight: RR 33.03 [95% CI 11.32 to 54.74] (n=16 trials) Heterogeneity I^2=19.8% Incidence of low birthweight (under 2500g): RR 0.82 [95% CI 0.70 to 0.95] (n=13 trials) Heterogeneity I^2=0.0% Incidence of very low birthweight (under 1500g): RR 1.26 [95% CI 0.69 to 2.32] (n=3 trials) Heterogeneity I^2=0.0% Preterm birth (under 37 or under 36 weeks): RR 0.84 [95% CI 0.72 to 0.98] (n=11 trials) Heterogeneity I^2=0.0% Stillbirths: RR 1.16 [95% CI 0.71 to 1.88] (n=5 trials) NS Perinatal mortality:	Cochrane review	Systematic review	1++

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					RR 1.13 [95% CI 0.72 to 1.77] (n=3 trials) NS			
Acharya et al, 2002	652	Pregnant women booked at 2 inner-city hospitals who reported smoking during current pregnancy. Sample n=63	Leaflets and direct counselling given during first trimester booking visit	Average no. cigarettes smoked per day Smoking behaviour of partner Changes in smoking behaviour following booking anti-smoking intervention Whether or not had read the anti-smoking advice leaflet Receipt of smoking counselling	Av. no. cigarettes smoked per day: 14 [95% CI 12 to 15] Smoking behaviour of partner: 53 women had partners who were also smokers. Changes in smoking behaviour following booking anti-smoking intervention: 53 women (84.1%) made no change 7 (11.1%) reduced smoking by 3-5 cigarettes per day 3 (4%) gave up smoking altogether Whether or not had read the anti-smoking advice leaflet: All women had seen the leaflet Receipt of smoking counselling: 39 active smokers (62%) reported receiving anti-smoking advice	UK	Prospective study	2+
Rigotti et al, 2006	653	Pregnant smokers 18+ years old , and at or below 26 weeks of pregnancy. Intervention n=209 Control n=212	Pregnancy-tailored telephone smoking counselling using motivational counselling compared with a brief counselling session. Phone calls made throughout pregnancy and for 2 months postpartum (mean no. calls=5, mean total contact=68 minutes).	Smoking cessation outcomes Tobacco abstinence (7 days) – cotinine validated and self-report Significant reduction (50% or more)	Cotinine-validated: End of pregnancy OR 1.37 [95% CI 0.69 to 2.70]; p=0.39 3 months postpartum OR 0.93 [95% CI 0.44 to 1.99]; p=1.00 Sustained abstinence OR 1.46 [95% CI 0.54 to 3.90]; p=0.47 Self-report: End of pregnancy OR 1.48 [95% CI 0.88 to 2.48]; p=0.15 3 months postpartum OR 1.11 [95% CI 0.60 to2.05]; p=0.75 Sustained abstinence OR 1.70 [95% CI 0.78 to 3.70]; p=0.18 Significant reduction: End of pregnancy OR 1.49 [95% CI 0.96 to 2.31]; p=0.09 3 months postpartum OR 1.11 [95% CI 0.67 to 1.86]; p=0.69	USA	RCT	1+
Byrd et al, 1993	654	Pregnant smokers	Smoking cessation booklet, videotape	Smoking cessation	1 month follow-up:	USA	RCT	1+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		selected from 2 community-based clinics Sample n=57 Mean age 23 years (range 17-40) 79% women black, 17% white. 70% single 77% unemployed	and nurse counselling	outcomes (self-report): Quit Quit attempts Daily mean cigarette consumption Measured at 1 month follow-up, ninth month of pregnancy, 1 month postpartum.	Quit: 7 (14%) Quit attempt: 31 (54%) Mean cigarette consumption: 6.2 per day Ninth month of pregnancy: Quit: 10 (18%) Quit attempt: 23 (40%) Mean cigarette consumption: 5.7 per day 1 month postpartum: Quit: 5(9%) Quit attempt: 21 (37%) Mean cigarette consumption: 8.2 per day			
McLeod et al, 2004	655	Pregnant women who smoked at the time of conception. Sample n=283 Control group n=57 Breast-feeding education n=57 Smoking cessation education n=68 Combined group n=101	3 interventions: - Programme of education and support for smoking cessation and reduction provided by midwives - Programme of education and support fro breastfeeding provided by midwives - Both programmes	Smoking cessation Smoking reduction Rates of breastfeeding Measured at 28 weeks and 36 weeks of pregnancy, at midwife discharge, 6 weeks and 4 months postpartum	Maintenance of smoking change – Breastfeeding education group (n=57) 28 weeks pregnancy: Adjusted OR 1.52 [95% CI 0.61 to 3.81] 36 weeks of pregnancy: Adjusted OR 1.98 [95% CI 0.80 to 4.86] Midwife discharge: Adjusted OR 0.76 [95% CI 0.32 to 1.79] 6 weeks postnatal: 0.76 [95% CI 0.27 to 2.16] 4 months postnatal: 1.54 [95% CI 0.53 to 4.40] Smoking education group (n=68) 28 weeks pregnancy: Adjusted OR 2.61 [95% CI 1.13 to 6.04] 36 weeks of pregnancy: Adjusted OR 2.71 [95% CI 1.17 to 6.28] Midwife discharge: Adjusted OR 1.32 [95% CI 0.60 to 2.93] 6 weeks postnatal:1.81 [95% CI 0.72 to 4.51], 4 months postnatal: 1.95 [95% CI 0.72 to 5.28] Combined group (n=101) 28 weeks pregnancy: Adjusted OR 1.65 [95% CI 0.74 to 3.67] 36 weeks of pregnancy: Adjusted OR 2.39 [95% CI 1.08 to 5.31] Midwife discharge: Adjusted OR 0.92 [95% CI 0.43 to 1.95] 6 weeks postnatal:1.48 [95% CI 0.62 to 3.52], 4 months postnatal: 1.48 [95% CI 0.57 to 3.86]	New Zealand	Cluster RCT	1+
Goodson et al, 1985	656	Couples attending antenatal classes	Half hour lecture during antenatal classes including a discussion of car safety,	Use of care seats and car restraints as tested using	'How does your child usually ride?': Intervention group: 99% reported use of a	USA	Prospective cohort study	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		at 2 hospitals. Sample n=136 Intervention group n=76 Comparison group n=60	demonstration of use of care restraints and car seats for infants, a film showing outcomes of car impact on unrestrained infants using reconstructions and follow up brochure to take home.	a telephone-based questionnaire 4-6 months after birth. Primary questions: 'When riding in a car, how does your child usually ride?' 'The last time you and your baby were in a car, how did your baby ride?'	child car safety seat. Comparison group: 90% reported use of a child car safety seat. 'The last time you and your baby were in a car, how did your baby ride?': Intervention group: Used a crash-tested car seat: 96.1% (n=73) Comparison group: Used a crash-tested car seat: 78.3% (n=47)			
Greenberg and Coleman, 1982	657	Postnatal women on day of discharge from one hospital. Sample n=75 couples (completing 1 questionnaire)	Demonstration of car safety using a mannequin and approved car restraint in usual antenatal class plus 5 minute lecture on child mortality and morbidity associated with car accidents. For latter phase of study parents also received a postnatal car safety programme including short film and pamphlet to read and take home. Nurses on postnatal ward also encouraged to promote car safety.	Use of car safety restraints for baby's journey home from hospital.	Of 75 couples: 27 reported receiving only antenatal information re car safety 30 reported receiving both antenatal and postnatal information 11 reported receiving only postnatal information 7 did not recall receiving any information about car safety. 35/75 couples reported using car restraint on baby's first journey home. Nurses' reported observation of couple leaving hospital verified this for 78% of cases.	USA	Prospective cohort study	2-
Waterson and Murray-Lyon, 1990	658	Women attending antenatal clinic at an inner city hospital between May 1982 and January 1983. Study 1 Sample at 28 weeks of pregnancy n=611 (response rate 59%) Postpartum sample n=766 (response rate 74%) Study 2 Sample at 28 weeks of pregnancy n=532 (response rate 50%)	Study 1: Written information (leaflet) regarding alcohol consumption during pregnancy including advice on recommended safe levels compared with written information plus verbal advice from doctor during antenatal consultation. Study 2: Written information (leaflet) regarding alcohol consumption during pregnancy including advice on recommended safe levels compared with written information plus verbal advice from doctor during antenatal consultation plus 4 minute video.	Self-reported alcohol consumption at 28 weeks of pregnancy and week before giving birth, measured using questionnaire.	No significant difference between groups. Study 1: Written information only: 63% women reported drinking < 7 units of alcohol per week at both stages of pregnancy. 6% women reported an increase in pregnancy from pre-pregnancy levels. Written+verbal information: 68% women reported drinking < 7 units of alcohol per week at both stages of pregnancy. 8% women reported an increase in pregnancy from pre-pregnancy levels. Study 2: Written information only: 69% women reported drinking < 7 units of alcohol per week at both stages of pregnancy. 5% women reported an increase in pregnancy from pre-pregnancy levels. Written+verbal+video information: 66% women reported drinking < 7 units of alcohol per week at both stages of pregnancy. 8% women reported an increase in pregnancy from pre-	UK	Prospective cohort study	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		Postpartum sample n=361 (response rate 34%)			pregnancy levels.			
Smits et al, 1995	659	Pregnant women with gestational diabetes attending one inner city hospital for antenatal care. Intervention group sample n=82 Comparison group sample n=80	An outpatient education programme (known as the nursing intervention) compared with usual care for women with gestational diabetes provided by obstetricians only. Both models include dietary counselling, training and support for self-monitoring of blood glucose and surveillance of fetal development.	'Healthy woman' – defined as: no pregnancy complications, no prematurity or postmaturity, normal birth, postnatal stay of 1-4 days. Abnormal pregnancy outcome - defined as: Polyhydramnios, pre-eclampsia, premature contractions, vaginal bleeding due to placenta praevia, birth at < 37 weeks or > 42 weeks, labour and birth complications such as induction of labour, caesarean section, forceps or vacuum birth, postnatal stay of 5 days or longer. 'Healthy baby' – defined as: APGAR 8-10 at 1 and 4 minutes, birthweight 10th – 90th centile, postnatal stay 1-4 days, no diagnosed complications. Abnormal outcomes for baby - defined as: APGAR 7 or less at 1 and 5 minutes, birthweight < 10th centile or > 90th centile, postnatal stay of 5 days or longer, hypoglycaemia (blood glucose < 37 mg/dL), respiratory distress	A logistic regression procedure was used to control for confounding variables such as proportion of nulliparous women and women requiring medication for gestational diabetes since these were found to be significantly different between the 2 study groups. After controlling for confounding factors no significant differences were found between the 2 study groups regarding incidence of abnormal pregnancy or abnormal outcomes for the baby (figures not reported). Confounding variables were found to have a significant impact on outcomes: Nulliparous women had a 3.31 times greater risk of an abnormal pregnancy outcome. Women taking medication for gestational diabetes had a 2.69 times greater risk of an abnormal pregnancy outcome than women with gestational diabetes who were not taking medication. Women with gestational diabetes who experienced complications during pregnancy were found to have a 4.2 times greater risk of having a baby with one or more abnormal outcomes.	USA	Retrospective descriptive study	2-

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
				syndrome (requiring oxygen), polycythemia (haematocrit > 65%), birth trauma including shoulder dystocia.				

How information is provided antenatally

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
Thornton et al, 1995	12	Women booking before 15 weeks' gestation. Sample n=1691 n=567 in control group n=563 in individual group n=561 in class group	To compare routine information given in antenatal clinics at booking visit by the doctor or midwife (control group), extra information given individually before 16 weeks or at an extra hospital visit by a research midwife (individual group), and extra information given to a group of 4 to12 women separate from the routine antenatal clinics (class group)	Attendance at extra information sessions; uptake rates of prenatal tests; levels of anxiety; understanding; satisfaction with decisions taken.	Attendance at the extra sessions was low (overall 52%) and was lower at classes than at individual appointments (adj. OR 0.45; 95%CI 0.35 to 0.58). Uptake of ultrasound at 18 weeks was almost universal (99%) and not affected by either intervention. Low uptake of Down's syndrome screening in the control group improved slightly after the intervention in the individual group (OR 1.45; 95% CI 1.04-2.02) but was not affected by extra information given in classes. High uptake of cystic fibrosis screening at the baseline was lowered both in the individual group (OR 0.44; 95%CI 0.20-0.97) and the class group (OR 0.39; 95%CI 0.18-0.86). Women in the individual group were found to have significantly reduced levels of anxiety at 20 weeks (p=0.02) compared to the control group, and thereafter anxiety was reduced but not significantly	UK	RCT	1+
Graham et al, 2000	660	Low and high risk pregnant women booking appointment for antenatal care Initial sample n=875 Only 64% women returned all 3 questionnaires giving final samples of Control group n=358 Intervention group n=376	To compare touch screen information provision and information leaflet with leaflet only.	Primary outcome measured was women's informed decision making on prenatal testing as measured by their uptake and understanding of the purpose of 5 screening tests (ultrasound scan at booking, serum screening, detailed anomaly scan, amniocentesis and chorionic villus sampling). Secondary outcomes included woman's satisfaction with the information and their anxiety levels.	More women in the intervention group underwent detailed anomaly scan compared to the control group (94% versus 87%, p=0.01), but for rest of the screening tests uptake rates were similar. All women in the trial had good baseline knowledge of the screening tests and this increased significantly in both the groups after the intervention, but no apparent greater gain in knowledge was seen among women in the intervention arm compared to the control arm. Levels of anxiety declined significantly among the nulliparous women in the intervention group (p<0.001). Both groups reported high level of satisfaction with the information leaflets (>95%), and a similar proportion of women in the intervention group reported that they would recommend the touch screen to other women. T	UK	RCT	1+
O'Cathain et al, 2002	13	12 maternity units each having more	To assess the effect of 10 evidence-based leaflets on promoting informed	Primary outcome measured was the	Proportion of women who reported exercising informed choice increased slightly after the	UK	Cluster RCT	1-

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		than 1000 deliveries annually were grouped into 10 clusters	choice in pregnant women.	change in proportion of women who reported exercising informed choice, while secondary outcomes were women's levels of knowledge, satisfaction with information, and possible consequences of informed choice. Outcomes were assessed using a postal questionnaire	intervention in both the units, but there was no significant difference in the change between the two groups for either the antenatal or the postnatal sample. A small increase in satisfaction with information was observed in the antenatal sample of the population in the intervention units compared to the control units (OR 1.40; 95%CI 1.05 to 1.88). However due to operational difficulties, just 75% of the women in the intervention units reported receiving at least one of the information leaflets.			
Glazier, 1997	661	Women with singleton pregnancies less than 18 weeks gestational age, recruited from 6 different sites in both urban and rural areas.	To evaluate use of a pamphlet on triple-marker screening in the intervention group, or similar appearing pamphlet on daily activities during pregnancy in the control group.	The primary outcome was woman's knowledge as tested using the Maternal Serum Screening Knowledge Questionnaire (a validated 14-item scale).	Mean overall knowledge score was significantly higher in the intervention group (0.89 versus 0.52 on a scale from -2 to +2, p<0.001) compared to the control group. Also women receiving pamphlet on triple screening had higher scores for the domains of test characteristics, ancillary tests, and target conditions (p<0.001) but not for the domains of indication and timing of tests	Canada	RCT	1+
Bekker et al, 2004	662	Pregnant women receiving a screen positive maternal serum screening (MSS) test for Down's syndrome (risk $\geq$ 1 in 250) Intervention n=133 Control n=64	Comparison of a decision analysis consultation using three prompts was employed - a decision tree representing test options and consequences, a utility elicitation question prompting women to choose between the burden of having a child with Down's syndrome and that of pregnancy termination, and a threshold graph identifying the alternatives with usual consultation.	Main outcomes measured were risk perception, test decision, subjective expected utilities, knowledge, informed decision making, conflict in decision making, anxiety, and perceived usefulness of consultation.	Similar proportion of women chose to have a diagnostic test – 47/58 (81%) in the control group versus 48/59 (81%) in the intervention group. Choice of test did not differ by group allocation, but decision analysis women evaluated more information during their consultation both positively and negatively than those in the control group (positive evaluation - mean score 3.18 versus 2.55, F=6.30, p=0.01; negative evaluation - mean score 3.00 versus 2.37, F=5.98, p=0.02). These women also perceived the risk more realistic (p=0.05) and had a lower decisional conflict over time. Decision analysis consultations lasted about 6 minutes longer but women did not perceive consultations to be any more or less directive, useful or anxiety provoking than the routine ones	UK	RCT	1+
Leung et al, 2004	663	All Chinese women attending a prenatal clinic in a tertiary hospital before 20 weeks of gestation. Intervention n=100	Comparison of information leaflet, 30-minute video and then browsing IMDA (intervention group) or information leaflet and watching 30-minute video only (control group).	Primary outcome evaluated was uptake of the screening test, and secondary outcomes measured were women's initial decision, understanding, and satisfaction with the	There were no significant differences in the initial decision for and the final uptake of the screening test between the intervention and the control group (p value for all the tests > 0.05). After watching the video 54.1% women in the control group and 55.1% in the intervention group reported that they had no more questions. After browsing the IMDA the	Hong Kong, China	RCT	1+

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		Control n=101		information that they received.	proportion of women having no more questions increased to 77.0% (p<0.001), and 86.6% women agreed that IMDA was user-friendly and 78.9% that it was acceptable. A higher proportion of younger women (age < 35 years) accepted IMDA compared to those over 35 years of age (p=0.03), but the difference was not significant after adjusting for confounding variables.			
Hewison et al, 2001	664	Consecutive pregnant women referred for antenatal care. n=993 women in video group n=1007 in control group	Comparison of video sent to women at home before the hospital booking visit (intervention group) with the control group who received usual care.	Outcomes evaluated were test uptake (using record linkage), knowledge (multiple-choice questionnaire with 12 items), worries (multiple-choice questionnaire with 16 items), and anxiety (Hospital Anxiety and Depression scale).	No statistically significant difference was observed in the screening uptake rate between the two groups (64.2% versus 64.7%). Questionnaires were sent at 17-19 weeks only to the first 1200 women randomized in the two groups, and after exclusions the sample size was 499 (video group) and 552 (control group). Rate of questionnaire completion was similar between the two groups. Knowledge about screening was increased in the video group with a mean score of 7.3 compared with 6.7 in the controls (p=0.0005), but there was no difference between the two groups in specific worries about abnormalities in the baby, and general anxiety.	UK	Quasi RCT	1-
Andersen, 1989	665	All women beginning antenatal care by 36 weeks and not at high risk for preterm delivery were enrolled for the study and offered a class. n=487	Class about recognizing the signs and symptoms of preterm labour - 15-minute videotape presentation followed by a 15-minute discussion led by a registered nurse staff member where several printed educational materials were also given.	Outcome evaluated were the rates of preterm delivery and low birth weight.	There were no significant differences between the class attendees and non-attendees for the baseline demographic and obstetric variables. Women attending classes had babies with a higher mean birth weight (p=0.03) and gestational age (p=0.12), but improvement in gestational age did not reach statistical significance. The preterm birth rate was reduced by 17% and low birth weight rate by 27% among women attending the classes compared to the non-attendees, but these differences were statistically not significant	USA	Cohort study	2-
Simpson et al, 1998	666	All pregnant women booked in a tertiary hospital in UK were invited to participate in the trial. Sample n=3024	Four different combinations of providing information using a leaflet sent with booking information package ('all blood tests information' or 'HIV specific test information') and discussion with a midwife ('Minimal' or 'Comprehensive') were compared.	Main outcomes were uptake of testing and women's knowledge of HIV, satisfaction with consultation, and anxiety.	Uptake rates were 6% for the control group and each of the methods of directly offering the test resulted in a higher uptake than in the control group (chi-square test, df = 4, p<0.0001). However there was no significant difference between the four groups where the test was offered directly (chi-square test, df = 3, p=0.37). The best independent predictor of uptake was being directly offered the test. General knowledge of HIV was good and did not differ significantly by the method of offering	UK	RCT	1+

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
					testing, but specific knowledge about HIV and benefits of testing increased with the amount of information given (chi-square test of linear trend, df = 4, p<0.001). No significant difference was found regarding anxiety and satisfaction			
Hunt et al, 2005	667	Sample n=50 clinicians n=40 pregnant women Observation of 101 genetic counselling sessions	To examine how clinicians assure informed consent prior to antenatal genetic testing and communicate information regarding genetics/inheritance and risk calculation.	Information provided during consultation.	Clinicians discussed all the essential elements of information giving in only 59% of the consultations. Elements most consistently covered were that the test is optional, risks of procedure, and risks for the anomaly, while the least covered elements were the nature of anomaly and alternatives to amniocentesis. Patients overall knowledge score averaged about 53% and the elements for which they showed most complete knowledge included reasons for doing amniocentesis, test is optional, nature of the invasive procedure, and what information can this test give. The elements least completely discussed included risk of anomaly, alternatives to amniocentesis, and nature of the anomaly. But there was no statistical correlation between the completeness of information included in consultant's consultations and the level of knowledge exhibited by the patients during the interviews (Pearson correlation=0.204, p=0.289).	USA	Qualitative descriptive study	3
Williams et al, 2002	668	Health practitioners whose work was related directly or indirectly to perinatal care Sample n=56	To explore the information given to pregnant women and their partners about Down's syndrome from the perspective of health care practitioners	Perceptions of health care providers of information given.	Practitioners felt that more time was spent explaining the complexities of the actual screening process rather than the condition being screened. Though many practitioners felt that their way of providing information influenced decision-making by pregnant women, they seldom made any positive and realistic statement about the condition. Most practitioners themselves had little time and practical experience of dealing with DS cases. They relied on medical textbooks, leaflets and articles for knowledge and these sources usually focussed on the potential problems of the syndrome and its management strategies.	UK	Qualitative descriptive study	3

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
Stapleton et al, 2002	14	A total of 886 episodes of consultations with pregnant women were observed - 653 held by midwives, 167 by obstetricians and 66 by the obstetric ultrasonographers. 383 face-to-face interviews were conducted (173 childbearing women, 177 midwives, 28 obstetricians, 12 obstetric ultrasonographers, and 3 obstetric anaesthetists).	To examine the use of evidence-based information leaflets and to understand the social context in which the leaflets were used.	How the leaflets were used and how informed choice and decision making occurred in practice	Though the health professionals were positive about the leaflet and their potential in helping women make informed choices, they were seldom used to maximum effect in clinical practice. The various reasons observed were the time constraint, unavailability of choice in regular practice, disagreement of staff with its content or an option given in it, and their distribution usually in a concealed manner or 'wrapped' up with other advertising material. Health professionals were also observed to influence decision making in pregnant women towards technological intervention by conveying information which either minimized the risk of the intervention or emphasized the potential for harm without the intervention. They reinforced notions of 'right' and 'wrong' choices instead of 'informed choices' and this was promoted by their fear of litigation. A strong hierarchy was observed within the maternity services with the obstetricians at the top, midwives and health professionals other than doctors in the middle, and pregnant women at the bottom.	UK	Qualitative descriptive study	3
Jaques et al, 2004	669	Pregnant women from eighteen hospitals in Australia at approximately 24 weeks gestational age and over 37 years of age at the estimated date of delivery. n=539 women undergoing prenatal testing (tested group) n=185 not going for prenatal testing (untested group).	To examine whom women perceived as influencing their decisions about antenatal testing for fetal anomalies, with whom they would have liked to have talked more and what sources of information they preferred.	Women's reports of who influenced their decision-making, who they would have liked to talk with more and preferred sources of information.	More than 90% women in both the groups reported that they themselves had a strong influence on their decision to be tested or not, and 70% reported their partner as strongly influencing their decision. Statistically no significant difference was observed between the two groups for the above parameters, but significantly higher proportion of women in the tested group were influenced by their doctor or genetic counsellor ($p<0.001$ for both) and a friend or a nurse ($p<0.01$ for both). 35.7% of women in the tested group were more likely to talk to other women who have had the tests as compared to 21% women in the untested group ($p<0.001$). Higher proportion of tested women would have preferred to talk to a genetic counsellor (9.5% versus 8.6%, $p=0.002$), while women in the untested group were more likely to talk to a pastoral carer (2.5% versus 10.6%, $p<0.001$). There were no significant differences between the groups with respect to a specialist, general practitioner, friend, nurse/midwife or other pregnant women. In both the tested and the untested	Australia	Retrospective cohort study	2+

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
					groups, the preferred source of getting information was face-to-face discussion or counselling (69.1% tested group, 47.4% untested group), and the difference between the two groups was statistically significant ($p<0.001$). The second preferred choice was pamphlet (48.7% tested group, 42.8% untested group, $p=0.18$) followed by video (35.2% tested group, 24.9% untested group, $p=0.01$).			

Women's views of general and specific antenatal information provision

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
Bennett et al, 2006	674	African-American women receiving Medicaid who had given birth in the previous 48 hours Sample n=237	To explore effects of low literacy level on uptake and perceptions of antenatal care.	Uptake of antenatal care. Women's views and experiences of antenatal care. To determine literacy level women undertook a literacy (reading) assessment as part of the interview (Rapid Estimate of Adult Literacy in Medicine).	Cultural consensus analysis of findings (n=9 women with low literacy level; n=31 women with higher literacy) (from most to least salient): Finding out if everything is okay; long wait; questions (communication with carer); needles (blood tests); woman's weight and hearing the baby's heartbeat. Cultural consensus factor analysis returned a single factor (eigenvalue 0.881, SD 0.058) showing a high degree of shared knowledge among participants of lower and higher literacy level. Findings from the focus groups confirmed these salient factors across both sub-groups. Items associated with communication between women and their carers were identified as central when women were discussing obstacles to care.	USA	Qualitative study - concurrent mixed methods (including individual face-to-face interviews and focus groups).	3
Vonderheid et al, 2003	675	African-American and Mexican-American women living on a low income and booked to a 'low-risk' antenatal clinic. Sample n=159 n=112 African-American women n= 47 Mexican-American women. 72% younger than 24 years. 65% multiparous. 39% less than 12 years education 45% household incomes of less than $1000 per month.	To compare issues women to discuss during antenatal consultations with issues actually discussed.	Items identified by women as something they wanted or needed information about and whether or not the topic was discussed (identified from a list of 27 health promotion topics).	Note: Statistical analysis performed using the Sign test for paired data. Although p values are given values for the Sign statistic are not reported. Significantly more women wanted or needed information but did not discuss using seatbelts safely, dealing with stress and conflict, family planning, and caring for the new baby. Women did not want or feel they needed information but discussed taking vitamin/mineral supplements, eating specific food groups, drinking adequate amounts of water, stopping specific substance use. More differences were reported between information wanted or needed and information discussed for African-American women compared with Mexican-American women (adjusted regression analysis R^2=0.39, p<0.001).	USA	Cross-sectional interview-based descriptive study.	3
Benn et al, 1999	676	Volunteer sample	Investigation of women's information	Identified information	Information sources: Midwife (37%)	New Zealand	Cross-sectional	3

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		of women planning a pregnancy (n=7); pregnant women (n=30 and women in first 3 months postnatally.	needs about pregnancy issues.	needs Sources of information Usefulness of information received	Friends (23%) GP (13%). The theme of reassurance was prominent amongst women's responses. Topics that pregnant women wanted information about included: Knowing what is normal How to prepare for birth Coping with labour and birth How to look after the baby What to expect after birth. Multiparous women identified some different information needs including: Coping with morning sickness Self care during pregnancy Birth after caesarean section Financial needs and options.		questionnaire survey	
Ussher et al, 2006	677	Pregnant smokers and pregnant recent ex-smokers. Sample n=443	To identify perceived barriers to and benefits of a smoking cessation course.	Responses to a 20-item decisional-balance measure	Most frequently endorsed barriers to attending a smoking cessation course: 'I am afraid I would disappoint myself' (54.2%), 'I do not tend to seek help for this sort of thing' (40.6%), 'I do not have access to such a course' (40.5%) 'I do not have time to attend the appointments' (39.8%). The 2 statements with the least agreement were: 'People that are close to me would not support me attending such a course' (9.8%) and 'Stopping smoking is not particularly important to me' (7.6%). The most frequently endorsed benefits of attending a smoking cessation course were: 'Advice about managing my cigarette cravings would be useful' (74.2%); 'Praise and encouragement with stopping smoking would be helpful' (70.7%); 'Advice about safe medications to help me stop smoking would be useful' (69.2%) and 'Someone my checking my progress would be helpful' (64.5%). Respondents who agreed with the benefits of attending a smoking cessation course were significantly more likely to express an interest in receiving help of this kind (ANOVA, all at $p<0.01$).	International (mainly UK and USA)	Web-based cross-sectional survey	3
Cates et al, 2004	678	Pregnant women	Evaluation of women's responses to health education messages regarding	Knowledge regarding: Listeriosis infection	Few women reported receiving information about food safety from health care	USA	Descriptive study – focus	3

Study	Ref.	Population	Aim of study	Outcomes	Results	Comments	Study type	EL
		Sample n=63 64% multiparous 87% caucasian	listeriosis.	Food safety Sources of information	professionals contacted during pregnancy, and none remembered receiving information specifically about listeriosis. Commonly cited sources of information about food safety included books and magazines on antenatal care. Women suggested that written information on listeriosis be provided as part of the antenatal booking information package. Participants also felt that knowledge of listeriosis should be improved amongst the general population and suggested using the media to deliver public health food safety messages.		groups	
Orr and Simmons, 1979	[679]	Women between 34 and 38 weeks of pregnancy. Sample n=92	Investigation of women's perceptions of dietary information and advice provided during pregnancy.	Women's perceptions of need for dietary advice – generally and personally. Women's satisfaction with dietary advice received.	75% women felt pregnant women in general needed dietary advice. 50% women felt they personally needed such advice. The most common reasons for this response was that advice was remembered from a previous pregnancy (39%) or that the woman already had a good knowledge of dietary requirements (35%). Only 11% women reported that they had acquired dietary information from other sources (eg. books/leaflets). One third of respondents reported that complying with dietary advice worried them 'a lot', with the most common concern being excessive weight gain during pregnancy. A similar proportion of women reported difficulty complying with dietary advice, especially that relating to dietary restrictions. When asked about their satisfaction with dietary information only 3 women reported any shortfall. Only 36 women (39%) were able to recall specific dietary information.	USA	Cross-sectional descriptive interview-based study.	3

The effectiveness of antenatal education/classes

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Gagnon, 2001	27	5 RCTs including 168 women	Any structured educational programme relating to preparation for childbirth, caring for a baby or parenthood.	Knowledge acquisition Anxiety Sense of control Participation in decision-making Pain and pain relief Obstetric interventions during labour Breastfeeding Psychological adjustment following childbirth	The only outcomes reported were knowledge acquisition and competencies relating to care of baby. Satisfaction with preparation for motherhood improved following maternal role preparation vs no preparation: WMD 21.59 points [CI 11.23 to 31.95] (1 study, n=16, response rate 73%). Maternal attachment behaviour more frequent when maternal attachment preparation included in classes: WMD 52.60 points [CI 21.82 to 83.38] (1 study, n=10. Knowledge acquisition: Fathers' preparation classes vs. no classes WMD 9.55 [CI 1.25 to 17.85] (1 study, n=28) Expanded childbirth education classes vs traditional classes: WMD 1.62 [CI 0.49 to 2.75] (1 study, n=48)	Meta-analysis not possible due to heterogeneity of studies.	Systematic review of randomised controlled trials	1+
Spiby et al, 2003	680	Women who had given birth to their first baby in the preceding 72 hours Sample n=121	3 coping strategies taught during antenatal classes during labour, and reasons for discontinuing where appropriate.	Women's reports of using and discontinuing the following coping strategies: Breathing technique Postural change Relaxation techniques	88% women (n=106) used 'sighing out slowly' breathing, 51% (n=61) used change of position and 40% (n=48) used a relaxation technique. Relaxation techniques were reported by 33% of the women who used it as being effective in providing relaxation. Only 12% women who used this technique reported that it provided a distraction. Change of position was reported by 14% women as providing a distraction, whilst only 6% found it relaxing. Change in position was the most effective in terms of pain relief with 22% of women reporting that it provided some pain relief. 19% of women who used 'sighing out slowly' breathing and 12% of those who used relaxation techniques reported that they provided some pain relief.	UK	Retrospective descriptive interview-based survey	3
Maestas L, 2003	681	Women attending 10 sets of antenatal classes Sample n=57 pre-test questionnaire Sample n=42	Antenatal classes.	Women's beliefs and perceptions of childbirth: Fear of childbirth; childbearing locus of control; passive compliance vs. active participation in childbirth; personal values about childbearing and child rearing	Women's mean scores for fear of childbirth and passive compliance vs. active participation decreased significantly after participation in the antenatal classes: Fear (n=37) 9.68 vs. 8.32, $p<0.05$; Compliance vs. active participation (n=38) 3.84 vs. 2.89, $p<0.02$). No significant change in scores for locus of control (n=41;	USA	Descriptive before and after study	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		post-test questionnaire.			x=1.98 vs. 1.49) and personal values about childbearing (n=39; x=4.03 vs. 3.97).			
Hart M, 1994	682	Couples enrolled in antenatal classes at a tertiary hospital. Sample n=119 couples	Antenatal classes.	Self-care agency as measured using the Appraisal of Self-Care Agency scale (Evers, 1986)	Self-care agency was very high in women and men both before and after attendance at a series of antenatal classes. Women: no significant difference between scores obtained before and after antenatal classes (mean score pre-class 97.1; post class 97.5). Men: significant increase following class attendance (mean scores 91.3 and 94.7).	USA	Descriptive before and after study	3
Rolls and Cutts, 2001	683	Couples enrolled in antenatal classes in a public hospital Sept. – Oct. 1998. Sample n=70 couples n=34 participant-led classes (intervention) n=34 traditional classes (comparison)	Participant-led antenatal classes compared with traditional classes	Knowledge of pregnancy issues eg. smoking, alcohol intake, diet; Information for labour eg. birth positions, pain relief, role of the midwife; Postnatal issues eg. body changes after birth, relationships with partner; Infant care eg. bathing, dressing, holding and settling a baby.	Women who attended participant-led antenatal classes reported significantly higher levels of increased knowledge relating to childbirth, baby care and becoming a parent than women attending traditional classes ($F(1, 59)=11.89$, $p<0.01$). This difference was not evident for men attending the classes ($F(1, 57)=2.59$, NS). Women in the intervention group also reported higher level of preparedness for the experience of pregnancy ($t=3.05$, $p<0.01$) and for self-care following birth ($t=3.12$, $p<0.01$). No differences were found for preparedness for labour, birth, mood and lifestyle changes following birth, or caring for the baby.	Australia	Prospective longitudinal before and after study	3
Redman et al, 1991	684	Phase 1: All nulliparous women giving birth in a large teaching hospital in a 4 month period. Sample n=325 women (response rate 91%) Phase 2 : Women and their partners attending classes over a 3 month period. Sample n=117 women (response rate 82%) Sample n= 82 men (response rate (58%).	Antenatal education programme	Phase 1: Characteristics of attenders Phase 2: Changes in knowledge (eg. what to do when you think you are in labour; care during labour and what to expect during labour; what to expect after the birth) Satisfaction of participants	Phase 1: 82% nulliparous women attended antenatal classes. Women who chose to attend classes were older, of a higher educational level, more likely to be married or living as married, and more likely to have private health insurance than women who chose not to attend. Phase 2: Women's and men's knowledge of issues relating to pregnancy and childbirth increased significantly following attendance at antenatal classes across all topic areas measured. Most of the course components were rated as either 'very' or 'quite' useful by the majority of respondents. Of the 24 items included, 17 were rated as very or quite useful by at least 70% of participants. Items relating to labour were rated as very or quite useful by over 90% of participants. Items with fewer ratings of very or quite useful were: family planning; baby health centres; and nutrition and weight gain.	Australia	Phase 1: Cross-sectional survey Phase 2: Before and after longitudinal questionnaire-based study	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Schmied et al, 2002	685	First-time parents participating in hospital's antenatal programme Sample n= 59 (21 couples plus 2 single women) Response rate = 64% for the intervention group and 47% for the comparison group.	Expanded course of antenatal classes aimed at preparing couples for parenting and early lifestyle changes following childbirth compared with traditional classes.	Satisfaction with care eg. 'Labour managed as I liked' 'Pain managed as I liked'. Psychological outcomes following birth eg. 'Evaluation of parenting experience'; 'Life change''	Significantly more women in the intervention group stated that their labour had been 'managed as [they] liked' (84% vs. 43%; χ^2=5.4, p<0.05). No significant differences were found between the 2 groups regarding women's experience of pain or views of pain relief used during labour (again figures not given). Women in the intervention group were also more likely to rate their parenting experience more highly than women in the control group (mean score on parenting rating scale x=89.4 vs. x=83.6; t(31)=2.06, p<0.05). No significant difference was seen between the 2 groups regarding adjustment to life change following birth (mean score x=38.0 vs. 37.0; t(31)=0.36, NS).	Australia	Descriptive cross-sectional study	3

Women's experiences and views of antenatal classes

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
??	686	Pregnant women attending antenatal classes Sample n=13 Most women well educated (12/13 had a degree or diploma) 11 were in full-time employment. 12 of the women were Caucasian and 1 was Australian-Chinese. All were booked for a hospital birth.	Antenatal classes	Women's experience of classes, what they considered to be important and usefulness of information provided.	Most women were satisfied with the amount of information provided about labour and pain relief. For some women the emphasis some antenatal teachers placed on labouring without drugs was a concern. Women were less pleased with the amount of information provided concerning breastfeeding and care of the new baby, and they contrasted this lack of information with the large amount of information given about labour and birth. Women's responses indicated that more practical advice, including practical advice on breastfeeding and what to expect when feeding, would have been welcome. The women felt classes had not prepared them for labour. The preference for more practical information and advice about infant feeding (not just breastfeeding), how to handle and communicate with your baby and general baby care (eg. bathing, playing with your baby) was also commonly expressed. Lack of information about discomfort following birth was also noted.	Australian	Longitudinal qualitative study – grounded theory approach	3
//	687	All women giving birth at the 2 study hospitals in a 1 month period in 1997. 143 completed questionnaires were returned, a response rate of 62% (56%of the target population). Of the respondents, 50 had attended antenatal classes (35%). Sample n= 33 women who had attended all essions.	Antenatal classes	Women's reasons for attending classes, expectations of classes and whether expectations were being met.	All women stated that they attended classes in order to gain information. Other important reasons for attending classes were: 'to reduce anxiety or increase confidence' (94%), 'to have partner present and involved' (85%); and 'to have a more positive emotional experience' (76%). Expectations had been met for the majority of women. Most women reported that they felt the amount of information was right regarding normal labour (97%), pain relief in labour (91%), choices in decision-making during childbirth (88%), and complications/interventions during labour and birth (91%). There were 3 areas where a fair proportion of women reported that the amount of information proved was too little: relaxation and breathing for labour (33%), nutrition/diet (27%), and infant care (21%).	Australia	Retrospective cross-sectional questionnaire survey	3
//	688	All women	Antenatal classes	Women's reasons for not attending	3 most common reasons women gave for not attending	Canada	Cross-sectional	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		attending antenatal classes in the study area during one specified week in 1990. At the time the survey was undertaken 46% of the classes were in the early pregnancy section of the course. Sample n=437, a response rate of 98.9%.	including community-based and hospital-based classes, some of which charged a registration fee. All courses included early pregnancy classes which focussed on pregnancy and healthy lifestyle issues, although women could choose when to join the course.	early (first trimester) antenatal classes and women's interest in attending early classes	early pregnancy classes were: insufficient knowledge about the classes (69%); early classes were not considered useful (29%); and early classes not convenient (18%) (women were invited to give multiple responses if appropriate). An open-ended question asking for ideas on how to encourage women to attend early classes elicited the following responses: encourage doctors to promote early classes and using a public awareness programme to advertise the content and availability of the classes. Women reported that they would like information in early classes on how the baby develops, signs and symptoms of miscarriage, nutrition and exercise.		questionnaire survey	

Clinical Question: What is the diagnostic value and effectiveness of screening methods in determining gestational age?

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Alexander, 1995	690	A sample size of 150,898 cases that contained both CE and LMP-based values with a range of 20 to 45 weeks were selected.	Examined the comparability of the LMP-based and the clinical examination of gestational age as collected on one state (South Carolina's) vital records. They also investigated the concordance between these measures and explored whether sociodemographic or delivery hospital characteristics influenced their agreement.		LMP-based measure produced higher percentages of pre-term and post-term births. More than 60 percent of the last menstrual period-based preterm births were classified as preterm by the clinical estimate. The sensitivity of the clinical estimate was 27 percent for post-term births. The overall concordance (the percentage of cases with the same value for both measures) was 47 percent, but it varied considerably by gestational age. Between 30 and 35 weeks, the clinical estimate exceeded the last menstrual period-based value by 2 weeks or more for more than 40 percent of the cases. Concordance also varied by race of mother, hospital delivery size, trimester prenatal care began, and birth weight.		Retrospective study	II
Olesen, 2006	691	657 spontaneous deliveries were used for analysis, *n* = 339 and 318 in the certain and uncertain LMP groups, respectively. Healthy women who were enrolled at the first visit during their pregnancy underwent ultrasound examinations in the first and second trimesters.	compared the predicted date of delivery LMP, CRL and BPD with the actual date of delivery in a population of pregnant women divided into those with certain and those with uncertain LMP		median prediction errors (predicted - actual date of delivery) estimated by ultrasonography in the first and second trimesters and by corrected LMP according to cycle length were 2.32, 0.16, and 3.00 days, respectively, in women with certain LMP, and 1.71, 0.00, and 3.00 days, respectively, in women with uncertain LMP. The median gestational age at delivery estimated by ultrasonography in the first and second trimesters and by corrected		Prospective study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					LMP according to cycle length was 282, 280, and 283 days, respectively, in both groups.			
Taipale, 2001	692	17,221 non-selected singleton pregnancies at 8–16 completed weeks were scanned by ultrasound. The last menstrual period (LMP) was considered certain in 13,541 and uncertain in 3680 cases.	Compared different ultrasound measurements CRL, BPD, and FL, for predicting the day of delivery at 8–16 weeks' gestation. Also compared them to prediction by certain and uncertain LMP		at all gestational ages, ultrasound was superior to certain LMP in predicting the day of delivery to at least 1.7 days. CRL of 15–60 mm was superior to BPD, but at a later gestation BPD (at least 21 mm) was more precise. Regression models using a combination of any two or three ultrasonic variables did not improve accuracy of prediction. When ultrasound was used instead of certain LMP, the number of post-term pregnancies decreased from 10.3% to 2.7% ($P < .001$).		Prospective study	II
Savitz, 2002	53	The women were enrolled at 24 to 29 weeks of gestation. 3147 women had both LMP and early ultrasound scan and were recruited and interviewed in the comparisons of pregnancy dating.	4 algorithms were compared: LMP only, ultrasound scans only, use of LMP except when there was a disparity of ≥7 days in the estimated date of confinement in which case ultrasound scanning was used and the use of LMP except when there was a disparity of ≥ 14 days in the estimated date of confinement in which case ultrasound scanning was used.	Accuracy of algorithms for the assignment of gestational age with the use of the last menstrual period and early ultrasound information. There was an evaluation of digit preference in the last menstrual period dates and a comparison of mean gestational age, preterm and post-term categories with the use of kappa statistics, difference between actual and expected delivery date, and birth weight among subgroups with discrepant assignments.	last menstrual period reports showed digit preference, assign gestation 2.8 days longer on average than ultrasound scanning, yield substantially more post-term births (12.1% vs 3.4%), and predict delivery among term births less accurately. Misclassification of births as post-term was more common in younger women, those of non-optimal pre-pregnancy body weight, cigarette smokers, and women who reported last menstrual period using preferred dates of the month.		Prospective cohort study	II
Neufeld, 2006	693	Gestational age at birth was determined by an early second trimester measure of BPD, LMP, the Capurro neonatal examination and symphysio-fundal height (SFH) for 171 women-infant pairs	Regression modelling was used to determine which method provided the best estimate of gestational age using ultrasound as the reference.	Best method for gestational age estimation	Gestational age estimated by LMP was within +/-14 days of the ultrasound estimate for 94% of the sample. LMP-estimated gestational age explained 46% of the variance in gestational age estimated by ultrasound whereas the neonatal examination	When trained field personnel assist women to recall their date of LMP, this date provides the best estimate of gestational age. SFH measured during the second trimester may provide a reasonable alternative when LMP is unavailable.	Longitudinal study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					explained only 20%.			
Mustafa, 2001	694	476,034 computerized birth records from 20-44 weeks of gestation	Concordance between gestational age data obtained by clinical estimate with data calculated from the date of the last menstrual period (LMP) as recorded on birth certificates		The overall exact concordance of 46% between the two measurements. For +1 week it was 78%, and for +2 weeks it was 87%. The incidence of prematurity with menstrual gestational age was 16%, while it was 12% with the clinical estimate. About 47% of the LMP-based preterm births were classified as term by clinical estimate. 83% of clinically estimated preterm births were also preterm by LMP-based gestation.	Agreement between menstrual and clinical estimates of gestational age occurs most often close to term, with significant disagreement in preterm and post-term births.	Retrospective study	II
Johnsen, 2006	695	4179 consecutive women attending the second trimester routine ultrasound examination at 17–20 weeks of gestation were included	The difference between the time of delivery and the predicted date of delivery calculated with HC and BPD (based on pregnancy duration of 282 days) was noted.	Whether the HC predicts the day of confinement better than BPD	for the group of spontaneous onset of labour (n=3336), 5.6% were post-term (≥296 days) according to HC and 5.7% according to BPD. Premature births (< 37 weeks) were 3.9% with HC measurement and 3.6% with BPD method. For the entire group, the median differences between actual and predicted delivery with HC and BPD were 0.9 and 1.2 days, respectively. In the spontaneous onset of labour group the corresponding differences were 0.9 and 1.4 days. The difference between the HC and BPD methods was significant (P<0.0001).		Prospective study	II
Nguyen, 1999	696	14,805 spontaneous deliveries with a reliable LMP were included and their predicted dates of delivery were calculated using two assumptions: average length of pregnancy of 280 and of 282 days.	Compared the error in the predicted date of delivery using BPD with the error using the LMP		The average discrepancy between predicted date of delivery from BPD and LMP and date of spontaneous delivery was 7.96 and 8.63 days, respectively (p< 0.0001). Adding 282 instead of 280 days to the first day of the LMP reduced the error of the LMP method from 8.63 to 8.41 days, reduced the percentage	It was found that none of the models of combined use of LMP and BPD were superior to the use of BPD alone.	Retrospective study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					of classified post-term deliveries from 7.9 to 5.2% and increased the preterm births from 3.96 to 4.48%.			
Rowlands, 1993	697	106 women	The two methods compared were: a calculation based on LMP or a prediction based on the measurement by ultrasound scan	Determine the most accurate predictor of the date of delivery for pregnant women in a community-based population	At an error of ±5 days, the scan prediction is accurate in 52% of cases and last menstrual period in 37%, a difference of 15% (95% confidence interval 4% to 23%).	The scan accuracy is significantly better than LMP accuracy.	Prospective study	II
Okonofua, 1989	698	84 Nigerian women who had no complications of pregnancy and delivered infants whose birth weights were appropriate for 40 weeks were assessed		Accuracy of gestational age using the locally produced normogram and compared with predictors based on menstrual dates	ultrasound dating was more accurate than menstrual dating as evident from the number of women who delivered on and within 1 or 2 weeks of predicted delivery dates. 12/84 (14.3%) women delivered on the days predicted by ultrasound whereas only 3/84 (3.6%) delivered on days estimated by LMP. 69/84 (82.1%) ultrasound predictions were correct to within 1 week of predicted dates as compared to 42/84 (50%) predictions based on LMP. The difference reached statistical significance $p < 0.05$.		Prospective study	II
Campbell, 1985	699	4257 consecutive pregnancies were scanned in 4246 patients as part of a routine antenatal two-tier ultrasonic screening program.	The first-tier scans were performed before 20th week of gestation, whereas the second-tier scans were performed between 26 weeks and term. The estimated date of confinement based on ultrasound measurements was compared with menstrual history in its ability to predict the actual onset of spontaneous labor.	Determine if a single ultrasonic measurement performed in a technician oriented routine screening program was more accurately predictive of gestational age than menstrual history. In addition they determined whether a single BPD or CRL measurement was more predictive of gestational age and how the predictive accuracy of these measurements changed throughout pregnancy.	84.7% patients with optimal menstrual history delivered within ±2 weeks of the predicted date. Only 69.7% delivered within ±2 weeks of the estimate date of confinement based on suspect menstrual history. CRL measurements were as predictive (84.6%) as optimal menstrual history. BPD measurements done between 12 and 18 weeks' gestation were significantly more accurate in gestational		Population study	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					predictions (89.4%) than those based on menstrual history (P< .001).			
Kopta, 1983	700	27 women	The actual delivery date was compared with the estimated date of confinement predicted by the CRL and the BPD.	Compared the relative accuracy of estimated dates of confinement predicted by first trimester CRL versus second trimester BPD measurements	A statistically insignificant (p>0.9) difference of mean error between predicting the actual date of delivery by CRL (7.73 days) and BPD (7.65 days). In both methods there was a greater tendency to overestimate the actual date of delivery.		Prospective study	II
Selbing, 1983	701	53 women with regular, 28-day interval menstrual cycles were extracted consecutively from the register of the ultrasound laboratory.		Evaluation of the fetal CRL screening program	25% of pregnant women had a difference between menstrual age and gestational age estimated on the basis of CRL, exceeding 7 days. Regular menstrual cycles and reliable menstrual history reduced this to 19%. Post-mature deliveries > 294 days were reduced from 1 in 15 to 1 in 300 by using CRL.		Prospective study	II
Bennett KA, 2004	702	Low-risk population	Routine first trimester ultrasound screening	Induction of labour	5/104 women in the first trimester screening group and 12/92 women in the second trimester screening group had labour induced for post term pregnancy (P= 0.04, RR 0.37, 95% CI 0.14-0.96).		Randomised controlled trial	1+
Crowther, 1999	52	648 women attending for their first antenatal visit at less than 17 weeks of gestation with no previous ultrasound scan in the pregnancy, who were expected to give birth at the hospital, and for whom there was no indication for an ultrasound at their first visit.	Eligible consenting women were enrolled by telephone randomisation into either the ultrasound at first visit group, who had an ultrasound at the time of their first antenatal visit, or the control group in whom no ultrasound assessment was done at their first antenatal visit.	efficacy of an ultrasound scan at the first antenatal visit	9% of women in the ultrasound at first visit group needed adjustment of their expected date of delivery as a result of the 18 to 20 week ultrasound, compared with 18% of women in the control group (RR 0.52, 95% CI 0.34-0.79; P = 0.002). Fewer women in the ultrasound at first visit group reported feeling worried about their pregnancy (RR 0.80, 95% CI 0.65-0.99; P = 0.04) or not		Randomised clinical trial	1+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					feeling relaxed about their pregnancy (RR 0.73, 95% CI 0.56-0.96; P = 0.02), compared with women in the control group.			
Waldenstrom, 1988	[703]	4997 women were randomized into a screening group where women had an ultrasound scan at about 15 weeks and a control/non-screening group where women did not have a scan before 19 weeks	All women in the screening group had gestational age and expected date of delivery estimation from BPD with charts derived from a Swedish population. For the control group, last menstrual period with specialty calibrated calendars was used.	effectiveness of one-stage screening in the second trimester in pregnant women with no clear indication for elective scanning	that labour was less often induced among screened women both for all reasons 5.9% *vs.* 9.1%, p< 0.0001 and for suspected post-term pregnancy 1.7% *vs.* 3.7%, p< 0.0001. Among babies born to screened women, fewer had a birth weight < 2500g (59 *vs.* 95, p=0.005) and mean birth weight was 42g higher (p=0.008).		Randomized controlled trial	1+
Eik-Nes, 2000	[704]	825 women were allocated to an ultrasound scan between 18-32 weeks of gestation in addition to receiving routine antenatal care.	Standard antenatal care, but could only be referred for ultrasound examination on clinical indication.	Benefits of the routine use of ultrasound screening in pregnancy	incidence of induced labor due to apparent post-term pregnancies was 70% lower in the ultrasound-screened group. Inductions from all causes were also less frequent among ultrasound-screened women. There were six perinatal deaths among the screened and seven among the controls after excluding three lethal malformations among the controls. The proportion of infants with Apgar score less than 8 after 5 min was lower among the screened group (P = 0.04). The need for positive pressure ventilation for more than 1 min was lower among the screened group (P = 0.02).		Randomized controlled trial	1+
Morin, 2005	[705]	46,514 women with both menstrual and early ultrasound-based gestational age estimates.		Association between maternal and fetal characteristics, discrepancy between last normal menstrual period and early (<20 weeks) ultrasound-based gestational age and the association between discrepancies and pregnancy outcomes	positive discrepancies between LMP and early ultrasound scan were more likely in multiparous mothers and those with diabetes, small stature or high pre-pregnancy body mass index. The proportion of women with		Cohort study	2++

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					discrepancies ≥+7 days was significantly higher among chromosomally malformed and female fetuses. With increasingly positive differences between LMP and ultrasound scan, the mean birthweight declined and the risk of low birthweight increased. Associations with fetal growth measures were more plausible with early ultrasound estimates.			
Neilson, 1999	57	Nine good quality trials were included		Assessed whether routine early pregnancy ultrasound influences the diagnosis of fetal malformations and of multiple pregnancies, the rate of clinical interventions, and the incidence of adverse fetal outcome compared with its selective use.	Routine ultrasound examination significantly reduced the rates of induction of labour for post-term pregnancy (OR 0.61, 95% CI 0.52-0.72).		Systematic review	1+

Clinical Question: What is the minimum level of alcohol intake associated with fetal alcohol syndrome and other baby outcomes?

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Gray, 2006	[707]	10 outcomes with low-to-moderate consumption of alcohol. A total of 11 separate studies examined the effect of binge drinking on the 10 outcomes above.	Determine whether an intake of up to six drinks a week was associated with more risk than total abstention and whether binge drinking by low-to-moderate drinkers is associated with harm. They also aimed to evaluate a 'safe level'. Two definitions were used in the review:	Fetal effects of low-to-moderate prenatal alcohol exposure and binge drinking	Spontaneous abortion: A total of 8 studies looked at the effects of low-to-moderate alcohol consumption on spontaneous abortion. 5 of these reported a significant effect: 2 had significant limitations, one had significant results among heavy smokers and the remaining 2 were of borderline statistical significance. The highest reported risk was a relative risk of 3.79 (95% CI 1.18 to 12.17) associated with consuming up to 10 units (equivalent to 6.7 drinks). Stillbirth: 5 studies examined stillbirth as the outcome and only one study reported significantly increased rates of stillbirth in babies of women who drank up to 25-60g per week in pregnancy. Three studies reported higher rates of stillbirth in women who abstained but these were not statistically significant differences and were unadjusted for potential confounders. APH: One study included antepartum haemorrhage (APH) as an outcome and found no increase in risk of APH with low-to-moderate level of alcohol consumption. IUGR: 7 studies examined intrauterine growth restriction as an outcome and only one study found a significant association but it was unadjusted for potential confounders. Three studies found low-to-moderate alcohol consumption to be mildly protective but, although of borderline statistical significance, two may have been subject to recall bias. Birthweight: 20 studies included birth weight as an outcome but only one reported a significant increase in the risk of low birth weight with consumption of <0.1 oz alcohol per day (adjusted RR 3.20, 95% CI 1.87 to 5.46). However, at 0.1 - 0.25 oz per day, the RR was lower at 1.36 (95% CI 0.48 to 3.88). This result was inconsistent as higher levels were not associated with increased risk. It appeared that small amounts of alcohol exerted a mildly protective effect. Preterm birth: One out of a total of 16 studies that examined preterm birth as an outcome reported a significantly increased risk of preterm birth (RR of 2.11 and 2.15 in women consuming <0.1 oz and 0.1-0.25 oz respectively of absolute alcohol per day at 7 months gestation). This study suffered from residual confounding as it was unadjusted for socioeconomic status. Malformation: None of the 6 studies that examined malformations as the outcome reported a significant association with low-to-moderate alcohol consumption although a trend in that direction was apparent in some studies. HC and birth length: A total of 5 studies looked at head circumference and birth length as the outcome and only one found a higher proportion of low birth weight babies among those whose mothers drank low-to-moderate amounts in pregnancy. However, this study suffered from lack of		Systematic review	2++

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					adjustment for potential confounders. None of the other studies reported any differences at these levels of consumption. Postnatal growth: 2 studies that examined the association between alcohol exposure and postnatal growth differed in their results. One of these studies, which followed children up to age 14, found that children of women who drank small amounts in pregnancy were consistently lighter. However, the other study found that children of abstainers tended to be lighter. Neither of the results was significant. Neurodevelopmental outcome: 7 studies looked at neurodevelopmental outcomes; one was conducted at birth as compared to others that were later in childhood. 1 study found a statistically insignificant poorer result in children of low-to-moderate drinkers and this analysis was unadjusted for potential confounders. Out of these 4 studies looked at neurodevelopmental outcomes and showed consistently poorer results in children exposed to binge drinking in pregnancy. The effects although quite small, included an increase in 'disinhibited behaviour', a reduction in verbal IQ and increase in delinquent behaviour, and more learning problems and poorer performance. The studies suffered from a possible overlap between binge drinkers who otherwise drink little and binge drinkers who generally drink substantial amounts. These studies represent the most consistent evidence suggesting that binge drinking in pregnancy may be associated with poor neurodevelopmental outcomes.			
Mariscal, 2006	[708]	Cases (n=552) were mothers delivering a single newborn weighing < 2500g and controls (n=1451) were selected randomly from all delivering women.	Influence of alcohol drinking during pregnancy. Personal interviews, clinical charts, and prenatal care records were used for obtaining information.	low birth weight	Alcohol consumption of less than 6 g/day decreased the risk for low birth weight (adjusted OR = 0.64; 95% CI, 0.46-0.88). A similar result was obtained for moderate drinkers (<12 g/day) on weekends only. The opposite relationship was observed between alcohol consumption on weekdays of 12 g/day or greater (adjusted OR = 2.67; 95% CI, 1.39-5.12), not observed in those drinking on weekends only.	Alcohol consumption of 12 g/day or greater increased the risk for low birth weight, whereas lower consumption during weekends showed the opposite effect (mainly in nonsmokers).	case control study	2+
Weatherhead, 2007	[709]	555 cases, women (mean age 31 years, range 16-43) who delivered SGA babies and 1966 controls, women (mean age 31 years, range 14-43) who gave birth at term (> or =37 weeks of gestation) to healthy infants of normal weight at the hospitals where cases had been identified were included in the study.		Effect of alcohol intake on the risk of SGA birth, preterm or at term, and the potential interaction between alcohol consumption and risk factors for SGA birth	No increase in the risk of SGA birth observed in women drinking one or two drinks/day in pregnancy. The Odds ratios of 3 or more drink per day were 3.2 (1.7-6.2) for ≥ 3 drinks during the first trimester, 2.7 (1.4-5.3) during the second and 2.9 (1.5-5.7) during the third.	an increased risk of SGA births in mothers who drink ≥3 units/day of alcohol in pregnancy	case control study	2+

What is the diagnostic value and effectiveness of the following screening methods in identifying clinically significant thalassaemia and thalassaemia carrier status (trait): history; ethnic background; full blood count; electrophoresis; ferritin; mean cell volume.

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Rogers et al, 1995	714	Pregnant women Sample n=857	Comparison of mean corpuscular volume (MCV) <85 fl vs. mean corpuscular haemoglobin <27 pg as cut off points for thalassaemia screening.	β thalassaemia status	Of 857 women, 606 had both an MCV < 85 fl and an MCH < 27 pg. 56 of these women (6.5%) were β thalassaemia carriers. At a cut off of MCH < 27pg would have identified all cases of β thalassaemia carrier status (trait).	UK study	Diagnostic case-control study	III
Bain, 1988	715	Pregnant women Sample n=696	Comparison of mean corpuscular volume <83 fl vs. mean corpuscular haemoglobin (MCH) <27.1 pg as cut off points for thalassaemia screening.	β thalassaemia status	Of 696 women with an MCV at booking of less than 83 fl. 96 (13.8%) were found to have abnormal haemoglobin. In the other 600 women a HbA_2 estimation indicated a further 56 women with β thalassaemia carrier status (trait) (8% of total group screened). All MCH values for women with β thalassaemia carrier status (trait) fell below the cut-off point of 27.1pg.	UK study	Case series	III
Sirichotiyakul, 2005	716	Pregnant women Sample n=439	Diagnostic accuracy of mean corpuscular volume < 80 fl as cut off point for thalassaemia screening.	α thalassaemia-1 and β thalassaemia status	Sensitivity 92.9% (39/42) [95% CI 83.7 to 96.4%]. Specificity 83.9% (333/397) [95% CI 80.8 to 87.6%]. Positive predictive value 37.9% (39/103) [95% CI 33.8 to 42.7%] . Negative predictive value 99.1% (333/336) [95% CI 98.2 to 99.9%].	Thailand	Diagnostic accuracy	III
Ghosh et al, 1985	717	Pregnant women at gestation < 24 weeks. Sample n=299	Diagnostic value of mean corpuscular volume followed by HbA_2 estimation compared with that of mean corpuscular volume plus ferritin and haemoglobin level followed by HbA_2 estimation. HbA_2 > 4.5% was taken to be diagnostic of β thalassaemia carrier status (trait). 8ng/ml was taken as the lower limit for a normal ferritin level. Mean corpuscular volume cut-off point was 80 fl.	α thalassaemia-1 and β thalassaemia status	18 women (6%) had HbA_2 levels > 4.5% and were diagnosed to be carrying β thalassaemia. All of these 18 women had an MCV < 75fl (in 15 the MCV was < 70fl). 49 women had an MCV < 80fl, of these women 18 had low ferritin levels (< 8ng/ml). 2 of these women had HbA2 levels over 4.5% and were diagnosed to be carrying β thalassaemia with iron deficiency. 37 women were found to have Hb levels < 10g/dl. They included 9 β thalassaemia carriers, 19 women with iron deficiency and 9 presumed α thalassaemia carriers. At a cut-off level MCV < 80fl all β thalassaemia carriers were detected; false positive rate 63%. At a cut-off level of MCV 75fl the detection rate remained 100%; false positive rate 47%.	Hong Kong	Diagnostic case-control study	III

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					At a cut-off of 70fl the specificity of the test increased to 97% with a sensitivity of 83% and false negative rate of 16%. The study was repeated with a larger sample (n=1166), with similar findings. 61 β thalassaemia carriers were identified (5.2%), all with an MCV < 75fl.			
Name	718	Pregnant women at booking Sample n=5834	Diagnostic value of mean corpuscular volume <= 75 fl as cut off point for thalassaemia screening.	Thalassaemia status	At a cut-off of MCV < 75fl 1859 thalassaemia carriers were identified, plus 57 women carrying other haemoglobin variants (86% of those identified by screening test). The number of false positives was 313/2229 (14%).	Hong Kong	Descriptive study (large case-series)	III
Name	719	Pregnant women at booking Sample n=3696	Diagnostic value of mean corpuscular volume <= 80 fl as cut off point for thalassaemia screening.	Thalassaemia status	A cut off of MCV < 80fl identified 494/3696 (13.4%) women. Of these women, 56 (11.3%) and 23 (4.7%) were confirmed to be carrying thalassaemia and HbE respectively, giving a false positive rate of 84%.	Singapore	Descriptive study (large case-series)	III
Modell et al, 2001	720	Women pregnant with a baby affected by β thalassaemia major Sample n=136 records	Women's care regarding screening for β thalassaemia assessed against a minimum standard.	(a) Risk identification and offer of prenatal diagnosis before 23 weeks of a first pregnancy. (b) Offer of prenatal diagnosis in the first trimester in subsequent pregnancies.	50% of at-risk couples were identified and informed of their risk in time for an offer of pre-natal diagnosis in the first pregnancy. Risk was identified too late in 11% of pregnancies and not at all in 38% pregnancies. 28% of couples discovered their risk through diagnosis of an affected child.	UK	Retrospective audit	3Ahmed et al, 2005
Ahmed et al, 2006	721	Pregnant Pakistani women Sample n=43	Exploration of Pakistani women's views.	Pakistani women's views towards antenatal diagnosis for thalassaemia and termination of pregnancy for β thalassaemia major.	Most women would opt for diagnosis because they would want 'to know', not because they would consider termination of pregnancy. Women's attitudes towards termination of pregnancy for an affected baby did not seem to relate to the woman's carrier status and were influenced by, but not solely dependant upon, their religious viewpoint (all women were Muslim). Women's responses suggested that the more severe the perception of thalassaemia major, the more likely the woman was to be in favour of antenatal diagnosis and termination of pregnancy. Some women also expressed the view that termination of pregnancy was only acceptable early in pregnancy.	UK	Qualitative interview study	3
Ahmed et al, 2005	722	Pregnant Pakistani women	Exploration of Pakistani women's attitudes to issues surrounding antenatal	Pakistani women's attitudes towards	113/146 women (77.4%) had not been told about thalassaemia carrier testing, and 97 of	UK	Qualitative study – questionnaires	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		Sample n=146: 110 women who were not carriers for thalassaemia plus 36 women identified as carriers.	thalassaemia carrier status testing.	informed consent for carrier status testing and perceived pre-test information needs.	these (85.8%) said they would have wanted to have been told before the screening was carried out. Some women mentioned the increased anxiety associated with receiving information prior to screening, most saw this as inevitable part of being pregnant. Women who went on to discover they were thalassaemia carriers felt that prior information would have helped them prepare for this news. Women expressed a desire to know about the condition itself, when the results would be available, the meaning of positive and negative results and possible action following a positive result. This was not universal however, and carrier status affected women's responses with non-carriers being less likely to say they wanted detailed pre-screening information		and interviews.	

Women's views and experiences of thalassaemia screening in pregnancy

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Modell et al, 2001	720	Women pregnant with a baby affected by β thalassaemia major Sample n=136 records	Women's care regarding screening for β thalassaemia assessed against a minimum standard.	(a) Risk identification and offer of prenatal diagnosis before 23 weeks of a first pregnancy. (b) Offer of prenatal diagnosis in the first trimester in subsequent pregnancies.	50% of at-risk couples were identified and informed of their risk in time for an offer of pre-natal diagnosis in the first pregnancy. Risk was identified too late in 11% of pregnancies and not at all in 38% pregnancies. 28% of couples discovered their risk through diagnosis of an affected child.	UK	Retrospective audit	3Ahmed et al, 2005
Ahmed et al, 2006	721	Pregnant Pakistani women Sample n=43	Exploration of Pakistani women's views.	Pakistani women's views towards antenatal diagnosis for thalassaemia and termination of pregnancy for β thalassaemia major.	Most women would opt for diagnosis because they would want 'to know', not because they would consider termination of pregnancy. Women's attitudes towards termination of pregnancy for an affected baby did not seem to relate to the woman's carrier status and were influenced by, but not solely dependant upon, their religious viewpoint (all women were Muslim). Women's responses suggested that the more severe the perception of thalassaemia major, the more likely the woman was to be in favour of antenatal diagnosis and termination of pregnancy. Some women also expressed the view that termination of pregnancy was only acceptable early in pregnancy.	UK	Qualitative interview study	3
Ahmed et al, 2005	722	Pregnant Pakistani women Sample n=146: 110 women who were not carriers for thalassaemia plus 36 women identified as carriers.	Exploration of Pakistani women's attitudes to issues surrounding antenatal thalassaemia carrier status testing.	Pakistani women's attitudes towards informed consent for carrier status testing and perceived pre-test information needs.	113/146 women (77.4%) had not been told about thalassaemia carrier testing, and 97 of these (85.8%) said they would have wanted to have been told before the screening was carried out. Some women mentioned the increased anxiety associated with receiving information prior to screening, most saw this as inevitable part of being pregnant. Women who went on to discover they were thalassaemia carriers felt that prior information would have helped them prepare for this news. Women expressed a desire to know about the condition itself, when the results would be available, the meaning of positive and negative results and possible action following a positive result. This was not universal however, and carrier status affected women's responses with non-carriers being less likely to say they wanted detailed pre-screening information	UK	Qualitative study – questionnaires and interviews.	3

What is the diagnostic value and effectiveness of the following screening methods in identifying clinically important genotypes of sickle cell disease and sickle cell carrier status (trait) including: history taking; ethnic background; full blood count: haemoglobin electrophoresis; blood film; sickledex?

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Chasen et al, 1999	711	Pregnant women Sample n=631	Diagnostic accuracy of haemoglobin electrophoresis with selective use of haemoglobin electrophoresis following sickle cell solubility testing and investigation of red blood cell indices.	Sickle cell disease	Sensitivity 88.9% (32/36) and specificity 79.4% (473/595) for the selective screening model. Positive predictive value = 20.8% Negative predictive value = 99.2%.	USA	Diagnostic accuracy	III

Women's views and experiences of antenatal screening for sickle cell disease/trait

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Durosinmi et al, 1997	723	Well-educated, city-dwelling Nigerians, aged 15-50 years. Sample n=433 (n=204 males)	Investigation of views of antenatal diagnosis.	Acceptability of antenatal diagnosis of sickle cell disease.	78% of respondents felt antenatal sickle cell diagnosis should be available. 45% reported that they would decide to terminate a baby affected with sickle cell disease. Cross-tabulations showed that neither religion nor educational level significantly affected a person's decision whether or not to terminate an affected pregnancy.	Nigeria	Interview-based descriptive study.	3

Joint screening for sickle cell disease and thalassaemia

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Dyson et al, 2006	724	Pregnant women at booking Sample n=4559	Comparison of 2 family origins screening questions: Question A: classification question plus a 'tick all that apply' subsidiary section to record mixed heritage. Question B: 2 parts. Part One: binary question to identify women with ancestors outside the British Isles. Part Two: 5 free text boxes for addition of information regarding ancestry.	Test-retest reliability and proportion of carriers missed.	Question A: 3.2% cases were missing or uninterpretable. Question B: 4.7% cases were missing or uninterpretable. Test-retest error rate for reliability: Question A 4.3% vs. Question B 9.5% (CI -8.5% to -1.8%; p=0.003). Carriers of clinically relevant haemoglobinopathies missed: Question A 7/122 (5.74%). Question B 10/103 (9.7%) (p=0.026 using a chi-square test (chi-square value not reported)).	UK	RCT	1+
Greengross et al, 1999	725	All women found to be positive for haemoglobinopathy carrier state or disease at universal testing in one tertiary hospital from 1986 to 1995. Sample n=1444 women referred in 1688 pregnancies	Comparison of unselected laboratory-based antenatal screening for sickle cell trait with antenatal unselected laboratory-based screening for thalassaemia trait.	Gestation at booking Attendance for counselling Partner attendance at counselling Take-up of antenatal diagnosis Take-up of partner testing	Women found to be carrying sickle cell disease booked 2.7 weeks [95% CI 0.14 to 5.1] later in pregnancy than women who were carrying thalassaemia. Women carrying sickle cell disease less likely to choose to receive counselling (83% vs. 93%, RR 0.89 [95% CI 0.85 to 0.94]); their partners were less likely to be tested (77% vs. 95%, RR 0.81 [95% CI 0.77 to 0.83]); and they were less likely to choose prenatal diagnosis (22% vs. 90%, RR 0.37 [95% CI 0.24 to 0.57]) compared with women carrying thalassaemia. Of the tertiary referrals over 99% women attended counselling and had their partners tested. There was no difference in acceptance of prenatal diagnosis between those at risk of sickle cell disease and those at risk of thalassaemia.	UK	Retrospective descriptive study	3
Thomas et al, 2005	726	Pregnant women at first screening for haemoglobinopathy Sample total n=648: n=241 women from 6 general practices n=276 from 2 hospital antenatal booking clinics n=131 women from community midwife clinics	Evaluation of screening for sickle cell and thalassaemia in early pregnancy in UK general practice	Gestation at screening Stakeholder views of screening system and its implementation	General practices that already had a screening system in place were able to screen a high proportion of women (63% - 86%). However, 3 practices without an existing system only managed to screen between 3% and 26% of women. Women who were screened in general practices were screened at an earlier gestation than those screened at their first hospital booking visit (4.05 weeks [95% CI 3.41 to 4.68], p<0.001) or at midwifery clinics (2.9 weeks [95% CI 2.1 to 3.7], p<0.001).	UK	Participatory action research	3

Screening for structural anomalies

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Chitty 1991	297	1988-1989 UK (Luton), District general hospital Unselected n=8785 (Multiple pregnancies not mentioned)	US done by Radiographers Number of scans not mentioned Scanned at 18-20 weeks Soft markers: yes	Diagnostic test characteristics at < 24 weeks	Prevalence of anomalous fetuses: 1.50% (130 fetuses) but anomalies not reported. Sensitivity: 71.5% Specificity: 99.98% LR+ 3095.83 LR- 0.44		Retrospective	
Shirley 1991	297	1989-1990 UK (Hillingdon), District general hospital Unselected n=6412 (73 multiple pregnancies)	By Radiographers Number of scans not mentioned Scanned at 19 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks	Prevalence of Anomalous fetuses: 1.40% (89 fetuses), but anomalies not reported False-positive: 1 Sensitivity: 57.3% Specificity: 99.97%		Retrospective	
Levi 1991	297	1984-1989 Belgium (Brussels) 5 hospitals Unselected n=15654 (? 240 multiple pregnancies)	By obstetricians, technicians and sonographers Scanned at 1st trimester, 16-20 weeks and 3rd trimester Soft markers: no	Diagnostic test characteristics at < 24 weeks and > 24 weeks taking only those defects exposed to scan at 12-24 weeks	Prevalence of Anomalous fetuses: 2.30% (381 fetuses) and Anomalies: 2.66% (417 anomalies) At < 24 weeks Sensitivity: 21.0% Specificity: 100.00% At > 24 weeks Sensitivity: (37.2%) Specificity: ? Overall detection False-positive: 8 Sensitivity: 40.4% Specificity: 99.94%		Prospective	
Luck 1992	297	1988-1991 UK (Ascot), District general hospital Unselected N=8844	By radiographers Scanned at 12-14 weeks and 19 wks Soft markers: yes	Diagnostic test characteristics at < 24 weeks with results based on number of anomalies	Prevalence of Anomalous fetuses: Not reported Anomalies: 1.90% (164 anomalies) False-positive: 3 Sensitivity: 85.3% Specificity: 99.90%		Prospective	
Crane 1994	297	1987-1991 USA (RADIUS)	By technicians, physicians, sonologists	Diagnostic test characteristics at < 24	Prevalence of Anomalous fetuses: 2.30% (187 fetuses) and Anomalies:		RCT	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		Low risk primary plus 28 laboratories N=7575 (Multiple pregnancies not mentioned)	and radiologists Scanned at 15-22 weeks and 31-35 weeks Soft markers: no	weeks and > 24 weeks	(232 anomalies) At < 24 weeks Sensitivity: 16.6% Specificity: 99.90% At > 24 weeks Sensitivity: 18.2% Specificity: ? Overall detection False-positive: 7 Sensitivity: 34.8% Specificity: 99.90%			
Levi 1995	297	1990-1992 Belgium (Brussels) 5 hospitals Unselected n=9601 (? 209 multiple pregnancies)	By obstetricians, technicians, sonographers Scanned at 1st trimester, 16-20 weeks, and 3rd trimester Soft markers: no	Diagnostic test characteristics at < 24 weeks and > 24 weeks, with results based on number of anomalies given in brackets	Prevalence of Anomalous fetuses: 2.45% (235 fetuses) and Anomalies: 2.81% (270 anomalies) At < 24 weeks Sensitivity: (25.6%) Specificity: Not reported At > 24 weeks Sensitivity: (40.4%) Specificity: Not reported Overall detection False-positive: 9 Sensitivity: 51.0% (65.9%) Specificity: 99.90%		Prospective	
Skupski 1996	297	1990-1994 USA (Texas) Tertiary hospital, single centre Low risk N=860 (6 twins)	By experienced sonographers Scanned at 18-20 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks	Prevalence of Anomalous fetuses: 1.16% (20 fetuses) but Anomalies not reported False-positive: 1 Sensitivity: 15.0% Specificity: 99.80%		Retrospective	
Magriples 1998	297	? 18months USA (Connecticut) Tertiary centre, single centre Low risk N=911 (10 twins)	By sonographers Scanned at 16-19 weeks and 3rd trimester Soft markers: yes	Diagnostic test characteristics at < 24 weeks	Prevalence of Anomalous fetuses: 3.07% (28 fetuses), and Anomalies: 40 anomalies False-positive: 5 Sensitivity: 71.4% Specificity: 99.40%		Retrospective	
Lee 1998	297	1990-1994 Korea Tertiary hospital, single	By trained obstetric fellow Scanned at 18-20	Diagnostic test characteristics at < 24 weeks and > 24 weeks	Prevalence of Anomalous fetuses: 0.76% (23 fetuses) and Anomalies: (37 anomalies)		Retrospective	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		centre Low risk N=3004 (twins excluded)	weeks and 32-34 weeks Soft markers: no	with results based on number of anomalies given in brackets	<u>At < 24 weeks</u> Sensitivity: 13.5% (13.5%) Specificity: 100.00% <u>At > 24 weeks</u> Sensitivity: 21.7% (16.2%) Specificity: 100.00% <u>Overall detection</u> False-positive: 0 Sensitivity: 34.8% (29.7%) Specificity: 100.00%			
Van Dorsten 1998	297	1993-1996 USA (S.Carolina) Mixed population from two sites Unselected N=1611 (Twins excluded)	By registered diagnostic medical sonographers Scanned at 15-22 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks	Prevalence of Anomalous fetuses: 1.30% (21 fetuses), and Anomalies: (29 anomalies) False-positive: 1 Sensitivity: 47.6% Specificity: 99.90%		Prospective	
Boyd 1998	297	1991-1996 UK (Oxford) Tertiary single centre Unselected N=33376 (Twins not specified)	Sonographers not mentioned Scanned at 18-22 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks	Prevalence of Anomalous fetuses: 2.17% (725 fetuses) but Anomalies not reported False-positive: 15 Sensitivity: 41.1% Specificity: 99.90%		Retrospective	
Whitelow 1999	300,[743]	Not known UK (London) Single university hospital Unselected N=6443 (77 twins; 4 triplets)	Sonographers: 6 different clinicians Scanned at 11-14weeks either trasnabdominally or transvaginally Soft markers: yes	Diagnostic test characteristics at < 15 weeks and < 24 weeks	Prevalence of Anomalous fetuses: 1.4% (92 fetuses), but Anomalies: not reported <u>At < 15 weeks</u> Sensitivity: 58.7% Specificity: 99.90% <u>At < 24 weeks</u> Sensitivity: 81.0% Specificity: no data		Prospective	
Eurenius 1999	[727]	1990-1992 Sweden (Uppsala) Tertiary hospital, single centre	By trained midwife Scanned at 15-22 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks	Anomalous fetuses: 0.74% (145 fetuses) Anomalies: not reported		Prospective	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		Unselected N=8324 (111 twins, 3 triplets)			False-positive: 20 Sensitivity: 22.1% Specificity: 99.80%			
Stefos 1999	728	1990-1996 Greece (Ioannina) Tertiary, single centre Unselected N=7326 (86 twins)	By experienced obstetricians Scanned at 18-22 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks	Anomalous fetuses: 2.24% (162 fetuses) Anomalies: not reported False-positive: 8 Sensitivity: 80.25% Specificity: 99.88%		Prospective	
Taipale 2004	729	1994-1996 Finland (Helsinki) Tertiary hospital, single centre Low risk N=4855 (multiples excluded)	By obstetrician and trained midwives Scanned at 13-14 weeks transvaginally and 18-22 weeks transabdominally	Diagnostic test characteristics at < 24 weeks	Anomalous fetuses: 0.7% (33 fetuses) Anomalies: not reported False-positive: 2 Sensitivity: 48.5% Specificity: 99.96%		Prospective	
Nakling 2005	730	1989-1999 Norway (Oppland), District general hospitals Unselected N=18181 (? Multiples)	By trained midwives and obstetricians Scanned at 13-24 weeks Soft markers: no	Diagnostic test characteristics at < 24 weeks	Anomalous fetuses: 1.47% (267 fetuses), but Anomalies: not reported False-positive: 11 Sensitivity: 39.0% Specificity: 99.94%		Prospective	
Souka 2006	731	2002 Greece (Athens) Unselected Tertiary, single hospital N=1148 (? Multiples)	By obstetricians Scanned at 11-14 weeks on Nuchal translucency measurement and at 22-24 weeks Soft markers: yes	Diagnostic test characteristics at < 24 weeks and overall detection rate	Anomalous fetuses: 1.21% (14 fetuses), but Anomalies: Not reported <u>At < 24 weeks</u> Sensitivity: 85.7% <u>Overall detection</u> False-positive: 3 Sensitivity: 92.9% Specificity: 99.74%		Prospective	
Nikkila 2006	732	1984-1999 Denmark (Malmohus) 5 hospitals Unselected n=141240	Sonographers not mentioned Scanned at 18 weeks, some had scan at 33 weeks, as well	Diagnostic test characteristics at < 24 weeks and overall detection rate	Anomalous fetuses: 2.56% (3614 fetuses) Anomalies: not reported <u>At < 24 weeks</u>		Retrospective	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			Soft markers: yes		Sensitivity: 38.9% Specificity: Not obtained Overall False-positive: 265 Sensitivity: 28.4% Specificity: 99.81%			
Rustico 1995	[749]	Italy Tertiary referral centre Low risk women N=7024 Prevalence of congenital heart disease: 9.3 per 1000	20-22 weeks Four-chamber view plus outflow tracts 5/3.5 MHz Results confirmed by neonatal and paediatric examination, autopsy postnatally (neonatal echo and ECG, 24month follow up)	Diagnostic accuracy results for cardiac defects – major, minor, and all defects. Results for non-structural defects or arrhythmias not reported	Sensitivity Major defects: 84.6% [95%CI 54.6 to 98.1] Minor defects 23.1% [95%CI 12.5 to 36.8] All defects 35.4% [95%CI 23.9 to 48.2] Specificity Major defects: 99.9% [95%CI 99.9 to 100] Minor defects 99.9% [95%CI 99.9 to 100] All defects 99.9% [95%CI 99.8 to 99.9]		Prospective	
Anandakumar 2002	[749]	Singapore Tertiary referral centre Unselected women N=39808 Prevalence of congenital heart disease: 7.6 per 1000	21-22 weeks Four-chamber view plus outflow tracts, and Doppler colour-flow mapping if suspected 5/3.5MHz Results confirmed by neonatal examination (6months follow up)	Diagnostic accuracy results for cardiac defects – major, minor, non-structural / arrhythmias and all defects.	Sensitivity Major defects: 94.0% [95%CI 84.4 to 98.5] Minor defects 82.1% [95%CI 76.5 to 86.9] Non-structural defects/ arrhythmias 95.2% [95%CI 76.2 to 99.9] All defects 85.4% [95%CI 80.9 to 89.2] Specificity Major defects: 100.0% [95%CI 99.9 to 100] Minor defects 99.9% [95%CI 99.9 to 99.9] Non-structural defects/ arrhythmias 99.9% [95%CI 99.9 to 99.9] All defects 99.9% [95%CI 99.9 to 99.9]		Retrospective	
Hafner 1998	[749]	Austria District general hospital	22 and 34 weeks Four-chamber view plus		Sensitivity Major defects:		Prospective	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		Low risk women N=6541 Prevalence of congenital heart disease: 13.6 per 1000	outflow tracts, and Doppler colour-flow mapping if suspected Results confirmed by neonatal examination (neonatal echo)		87.5% [95%CI 65.1 to 97.9] Minor defects 32.4% [95%CI 21.5 to 44.8] Non-structural defects/ arrhythmias 83.3% [95%CI 17.7 to 19.9] All defects 46.1% [95%CI 35.4 to 57.0] <u>Specificity</u> Major defects: 99.9% [95%CI 99.9 to 100] Minor defects 99.9% [95%CI 99.9 to 100] Non-structural defects/ arrhythmias 99.9% [95%CI 99.9 to 100] All defects 99.6% [95%CI 99.5 to 99.8]			
Achiron 1992	[749]	Israel Tertiary referral centre Low risk women N=5347 Prevalence of congenital heart disease: 4.3 per 1000	18-24 weeks Four-chamber view plus outflow tracts, and Doppler colour-flow mapping if suspected 5/3.5MHz Results confirmed by neonatal examination and autopsy (Neonatal echo)	Diagnostic accuracy results for cardiac defects – major, minor, non-structural / arrhythmias and all defects	<u>Sensitivity</u> Major defects: 83.3% [95%CI 55.6 to 97.1] Minor defects 50.0% [95%CI 11.8 to 88.2] Non-structural defects/ arrhythmias 87.5% [95%CI 28.4 to 99.9] All defects 78.3% [95%CI 56.3 to 92.5] <u>Specificity</u> Major defects: 99.9% [95%CI 99.9 to 100] Minor defects 99.9% [95%CI 99.9 to 100] Non-structural defects/ arrhythmias 99.9% [95%CI 99.9 to 100] All defects 99.9% [95%CI 99.9 to 100]		Prospective	
Stumpflen 1996	[749]	Austria Tertiary referral centre Low risk women N=2181 Prevalence of congenital heart disease: 7.8 per 1000	18-28 weeks Four-chamber view plus outflow tracts and Doppler colour-flow mapping 3.5MHz Results confirmed by neonatal examination and autopsy (diagnostic investigations)	Diagnostic accuracy results for cardiac defects – major, minor, non-structural / arrhythmias and all defects Results for major, minor, and non-structural / arrhythmias not reported	<u>For All defects only</u> Sensitivity: 86.1% [95%CI 61.9 to 97.6] Specificity: 99.9% [95%CI 99.8 to 100]		Prospective	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Buskens 1996	750	Netherlands Tertiary referral centre Low risk women N=5319 Prevalence of congenital heart disease: 8.3 per 1000	16-24 weeks Four-chamber view plus outflow tracts 3.5Mhz Results confirmed by neonatal examination and autopsy (Neonatal echo)	Diagnostic accuracy results for all cardiac defects only. Diagnostic accuracy results reported for major and all cardiac defects only.	Major defects Sensitivity: 16.7% [95%CI 2.1 to 48.4] Specificity: Not reported All defects Sensitivity: 4.5% [95%CI 0.6 to 15.0] Specificity: 99.9% [95%CI 99.8 to 100]		Prospective	
Tegnander 2006	751	Norway Tertiary referral centre Unselected women N=29460 Prevalence of congenital heart disease: 14.6 per 1000	16-22 weeks Four-chamber view plus outflow tracts for first 5 years, then four-chamber view plus outflow tract plus venous return for next 5 years 5/3.5Mhz Results confirmed by neonatal examination and autopsy (Neonatal echo)	Results reported for Sensitivities for major, minor and all cardiac defects only.	Sensitivity Major defects: 56.7% [95%CI 46.9 to 66.5] Minor defects 3.6% [95%CI 3.4 to 3.8] All defects 15.6% [95%CI 12.1 to 19.0]		Prospective	
Bilardo 1998	754	N=1590 Excluded chromosomal abnormalities=50	US done at 10-14 weeks	Diagnostic accuracy results for NT threshold of 3.0mm or greater	Sensitivity: 50% Specificity: 97.2%		Prospective	
Hafner 1998	754	N=4214 Excluded chromosomal abnormalities=19	US done at 10-13 weeks	Diagnostic accuracy results for NT threshold of 2.5mm or greater	Sensitivity: 28.6% Specificity: 98.6%		Prospective	
Josefsson 1998	754	N=1460 Excluded chromosomal abnormalities=0	US done at gestational age of CRL 31-84 mm	Diagnostic accuracy results for NT threshold of 2.5mm or greater, and 3.5 mm or greater	NT > 2.5 mm Sensitivity: 38.5% Specificity: 91.1% NT > 3.5 mm Sensitivity: 0% Specificity: 99.6%		Prospective	
Hyett 1999	754;763	N=29154 Excluded chromosomal abnormalities=323	US done at 10-14 weeks	Diagnostic accuracy results for two thresholds – NT greater than 95th	NT > 95th centile Sensitivity: 56.0% Specificity: 93.8%		Prospective	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
				centile or greater than 3.5 mm	NT > 3.5 mm Sensitivity: 40.0% Specificity: 99.0%			
Schwarzler 1999	754;764	N=4474 Excluded chromosomal abnormalities=23	US done at 10-14 weeks	Diagnostic accuracy results for NT threshold of 2.5mm or greater	Sensitivity: 11.1% Specificity: 97.3%		Prospective	
Michailidis 2001	754;765	N=6606 Excluded chromosomal abnormalities=44	US done at 12-13 weeks	Diagnostic accuracy results for two thresholds – NT greater than 95th centile or greater than 99th centile	NT > 95th centile Sensitivity: 36.4% Specificity: 96.5% NT > 99th centile Sensitivity: 27.3% Specificity: 98.9%		Retrospective	
Marides 2001	754;766	N=7339 Excluded chromosomal abnormalities, not defined	US done at 10-14 weeks	Diagnostic accuracy results for NT threshold of 2.5mm or greater, and 3.5 mm or greater	NT > 2.5 mm Sensitivity: 15.4% Specificity: 96.5% NT > 3.5mm Sensitivity: 11.5% Specificity: 99.2%		Prospective	
Orvos 2002	754	N=3655 Excluded chromosomal abnormalities=15	US done at 10-13 weeks	Diagnostic accuracy results for NT threshold of 3.0mm or greater	Sensitivity: 51.4% Specificity: 97.7%		Retrospective	
Atzei 2005	756	N=6921 Chromosomal abnormalities excluded (no number obtained)	US done at 11-13 weeks	Diagnostic accuracy results for four thresholds – NT greater than 95th centile, 3.5mm or greater, 4.5mm or greater, and 5.5mm or greater.	NT > 95th centile Sensitivity: 79.5% Specificity: 50.9% NT > 3.5mm Sensitivity: 48.5.0% Specificity: 85.1% NT > 4.5mm Sensitivity: 31.1% Specificity: 94.4% NT > 5.5mm Sensitivity: 21.2%		Prospective	

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Specificity: 97.2%			
Bahado-Singh 2005	[755]	N=8167 Excluded chromosomal abnormalities=101	US done at 10-13 weeks	Diagnostic accuracy results for three thresholds – NT equal to or greater than 2.0mm, 2.5mm, and 3.5mm	NT > 2.0mm Sensitivity: 38.1% Specificity: 82.8% NT > 2.5mm Sensitivity: 14.3% Specificity: 95.4% NT > 3.5mm Sensitivity: 4.8% Specificity: 99.5%		Retrospective	
Westin 2006	[757]	N=16383 Excluded chromosomal abnormalities=80	US done at 12-14 weeks	Diagnostic accuracy results for three thresholds – NT greater than 95th centile, 3.0mm or greater, and 3.5mm or greater	NT > 2.0 MoM Sensitivity: 15.4% Specificity: 98.4% NT > 2.5 MoM Sensitivity: 13.5% Specificity: 99.4% NT > 3.0 MoM Sensitivity: 9.6% Specificity: 99.7%		Retrospective	
Simpson 2007	[758]	N=34,266 Excluded chromosomal abnormalities=104	US done at 10 3/7 to 13 6/7 weeks	Diagnostic accuracy results for three thresholds – NT value 2.0 MoM (98.3RD centile) or greater, 2.5 MoM (99.4TH centile) or greater, and 3.0 MoM (99.7TH centile) or greater	NT > 2.0 MoM Sensitivity: 15.4% Specificity: 98.4% NT > 2.5 MoM Sensitivity: 13.5% Specificity: 99.4% NT > 3.0 MoM Sensitivity: 9.6% Specificity: 99.7%		Retrospective	

Down's syndrome

Diagnostic accuracy studies

Table I A. First trimester screening for Down's syndrome and other chromosomal anomalies

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Nicolaides et al., 2005	768	1998 – 2003 6 hospitals, 1 fetal medicine unit UK Sample size 75,821 (96.7% of study population) Unselected (booked for maternity care) Maternal age: Median – 31 (Range 13 to 49) Exclusions: adequately described	Combined (NT + β-HCG + PAPP-A) Validated reference standard: Yes (prenatal karyotype, pregnancy records) Risk cut off ≥ 1 in 300 for all	Diagnostic test characteristics	Number of cases (prevalence in %) DS 325 (0.43) T 18/13 122 (0.16) Others 97 (0.13) Estimated Detection Rate for FPR 5.2% DS 92.6 T 18/13 88.5 Others 85.6		Cohort study	Ib
Wapner et al., 2003	769	Unspecified period. 12 prenatal diagnostic centres USA Sample size 8216 (93.2% of study population) Selected (12 diagnostic centres)(small sample) Maternal age: Mean – 34.5 (SD 4.6) Exclusions: adequately described	Combined Validated reference standard: Yes (karyotype – pre/postnatal, pregnancy records) Risk cut off 1:270 for DS, 1:150 for T 18	Diagnostic test characteristics	Number of cases (prevalence in %) DS 61 (0.74) T18 11 (0.13) Observed Detection Rate & FPR (with 95% CI) DS 85.2 (73.8 to 93.0) with FPR 9.4% (8.8 to 10.1) T18 90.9 (58.7 to 99.8) with FPR 2% (1.7 to 2.3)		Cohort study	II
Stenhouse et al., 2004	770	3 years ANC clinic of 1 hospital UK Sample size 5000 (98.3 %of study population) Selected (75% screening uptake, 27% ≥ 35 years) Maternal age: Median 31.5 (Range 14 to 45) Exclusions: adequately described	Combined Validated reference: Yes (prenatal karyotype, pregnancy records) Risk cut off ≥ 1:250 for all	Diagnostic test characteristics	Number of cases (prevalence in %) DS 15 (0.3) All 26 (0.52) Observed Detection Rate DS 93 at FPR 5.9% All 96 at FPR 6.3%		Cohort study	II
Malone et al., 2005	771	8 months 15 specialist centres USA Sample size 6228 (98.5%of study population) Selected (small sample) Maternal age: Mean 30.1 SD 5.7 Range 16 to 47	Fetal nasal bone (NB) Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) DS 11 (0.18) T18 2 (0.03) All 13 (0.21)		Cohort study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		Exclusions: adequately described			Observed detection rate & FPR (with 95% CI) DS 0 (no case detected) All 7.7 (0.2 to 36) with FPR 0.3 (0.2 to 0.5)			
Cicero et al., 2006	772	2001 to 2004 1 fetal medicine unit UK 20,418 (96.9% of study population) Selected (Single Centre) Maternal age: 35 Range 18 to 50 Exclusions: adequately described	Combined ± NB Validated reference: Yes (karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) DS 140 (0.68) T18 40 (0.13) Others 73 (0.36) Estimated detection rate FOR DS CASES ONLY Combined 90 with 5% FPR Combined + NB 93.6 with 5% FPR		Cohort study	II
Prefumo et al., 2006	773	2001 to 2003 1 fetal medicine unit UK 7626 (100% of study population) Selected 6.7% Unselected 93.3% (Routine ANC & referrals) Maternal age: Median 31.6 Range 14.5 to 50.2 Exclusions: adequately described	Fetal Nasal Bone (NB) Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) DS 35 (0.5) *Selected* 23 (4.5) *Unselected* 12 (0.2) All 64 (0.8) Observed performance (with 95% CI) FOR DS CASES ONLY *Selected* Sensit. 47.6 (25.7 - 70.2) Specif. 95.3 (92.9 - 97.1) PPV 33.3 (17.3 – 52.8) NPV 97.4 (95.3 – 98.7) *Unselected* Sensit. 16.7 (2.1 – 48.4) Specif. 97.3 (96.9 - 97.7) PPV 1.1 (0.1 – 4.1) NPV 99.8 (99.7 – 99.9)		Cohort study	II
Weingertner et al., 2006	779	2002 to 2004 1 reference centre France 2044 (91.5% of study population) Selected – 33% Unselected 67% (Single reference centre) Maternal age: Median 32 Range 16 to 47 Exclusions: adequately described	NT ± NB Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (Prevalence in %) DS 30 (1.47) T18 14 (0.68) Others 35 (1.71) i) Observed performance for DS Risk 1:250 (NT), ≤ 0.60 MoM (NB) NT NT + NB ST 88 (86-90) 100		Cohort study	III

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					FPR 23 (21-26) 5 (3-6) ii) Performance of only NB ST 32 FPR 10 +LR 4.4 (2.0 – 9.4)			
Ramos-Corpas et al., 2006	774	2003 to 2004 1 fetal medicine unit Spain 1800 (45% of population) Selected (Single centre, only 45% participated) Maternal age: Mean 30.09, SD 5.37 Range 15 to 46 Exclusions: Not described	Fetal nasal bone (NB) Validated reference: Yes (karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) DS 7 (0.39) Others 3 (0.17) Observed performance of NB for DS ST 33.3 (4.3 – 77.7) FPR 1.13 SP 98.9 (98.5 – 99.4) PPV 9.5 (1.2 – 30.4) NPV 99.7 (99.4 – 99.9)		Cohort study	III
Orlandi et al., 2005	780	Unspecified period. 1 fetal medicine unit Italy 2411 (unspecified % of population) Selected (details not specified) Maternal age: 30.5 SD 4.115 Exclusions: Not described	Combined + NB Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) DS 15 (0.62) i) Observed performance of NB for DS ST 53.3 (26.6 – 78.7) SP 99.5 (99.3 – 99.8) PPV 47.1 (23.3 – 70.8) +LR 142 (63 – 318) -LR 0.47 (0.27 – 0.80) ii) Estimated performance (Risk 1:250) *Comb.* *Comb. + NB* DR 87 90 FPR 4.3 2.5		Cohort study	III
Kozlowski et al., 2006	965	2002 to 2004 1 prenatal centre Germany 2973 (92.4 % of study population) Selected (single centre, 46% > 35 yrs) Maternal age: 34 Range 14 to 46 Exclusions: adequately described	Combined + NB Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) DS 18 (0.60) Others 22 (0.74) Estimated performance for DS Risk cutoff 1:300 *Comb.* *Comb.* + NB DR 94.4 77.8 FPR 5.5 2.8		Cohort study	III
Zoppi et al., 2003	776	2001 to 2002 1 prenatal diagnosis unit Italy	Fetal nasal bone (NB) Validated reference standard: Incomplete info. For 35% of	Diagnostic test characteristics	Number of cases (prevalence in %)		Cohort study	III

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		3503 (64.6% of study population) Selected (single study centre) Maternal age: Median 32 Range 15 to 48 Exclusions: adequately described	study population		DS 27 (0.77) Others 13 (0.37) Observed performance of NB for DS DR 70 FPR ??			
Viora et al., 2003	[777]	2001 to 2002 1 prenatal diagnosis unit Italy 1906 (unspecified % of study population) Selected (referred women) Maternal age: 32.2 Range 18 to 47 Exclusions: adequately described	Fetal Nasal Bone (NB) Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) DS 10 (0.57) Others 9 (0.51) Observed performance of NB for DS DR 60 FPR 1.4		Cohort study	III

Table I B. First trimester screening for Down's syndrome only

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Rozenberg et al., 2006	[778]	2001 to 2002 10 perinatal units France 14,380 (96.3% of study population) Unselected (in a health authority) Materrnal age: Median 30.7 25th to 75th centile – 28 to 33.9 Exclusions: adequately described	Combined Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of DS cases (prevalence in %) 51 (0.34) Observed results (95% CI) Detection rate (%) 79.6 FPR (%) 2.7 Risk cut-off 1:250		Cohort study	Ib
Avgidou et al., 2005	[781]	1999 – 2001 1 hospital, 1 fetal medicine unit UK 30,564 (95.8% of study population) Selected (48.5% ≥ 35 years) Maternal age: Median 34 Range 15 to 49 Exclusions: adequately described	Combined Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of DS cases (prevalence in %) 196 (0.64) Estimated results: Detection rate (%) 90.3 FPR (%) 5 (fixed) Risk cut-off 1:250		Cohort study	II
Crossley et al., 2002	[767]	2 years 15 maternity units UK 17,229 (100% of study population) Unselected (for routine ANC care) Maternal age: Median 29.9 Range 15 to 49 Exclusions: not applicable (100% follow up)	Combined Validated reference: Yes (prenatal karyotype, pregnancy records	Diagnostic test characteristics	Number of DS cases (prevalence in %) 45 (0.57) Observed results: Detection rate (%) 82 (65 – 93) with 34 cases FPR (%) 5 Risk cut-off 1:250		Cohort study	II

Table II A. Second trimester screening for Down's syndrome and other chromosomal anomalies

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Jaques, 2006	[782]	1998 – 2000 3 databases Australia 19,143 (99.2% of study population) Sample size for analysis of Down's and T18 – 16,607 (86.7%) Sample size for analysis of Neural tube defects – 17,288 (90.3%) Maternal age: Mean 30.3 (range 14-51) 20.1% > 35 years	Quadruple test	Diagnostic test characteristics	Number of cases (prevalence in %) DS 27 (0.16) T18 8 (0.05) NTD 14 (0.08) Observed results: *For DS* Quadruple test (Risk ≥ 1:250) DR 85 (72 – 99) FPR 6.8 PPV 2 Quadruple test (FPR fixed at 5%) DR 78 FPR 5.0 PPV 2.5 *For T18* Quadruple test (Risk ≥ 1:200) DR 44 (12 – 77) FPR 0.5 PPV 4.7 *For NTD (AFP ≥ 2.5 MoM)* All NTD DR 73 FPR 1.1 PPV 5.6 Spina bifida DR 50 FPR 1.1 PPV 2.1 Anencephaly DR 100 FPR 1.1 PPV 3.1		Cohort study	II

Table II B. Second trimester screening for Down's only

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Smith-Bindman, 2001	315	56 english language studies taken from MEDLINE 1980 - 1999 132,295 Exclusion criteria well defined	Ultrasound (US) Validated reference Yes (karyotyping in 53 of the 56 studies)	Diagnostic test characteristics	Number of DS cases (prevalence in %) 1930 (1.5) Results: Summary measures (with 95% CI) for US markers when seen individually Thickened Nuchal fold ST 0.04 (0.02 – 0.01) SP 0.99 (0.99 – 0.99) +LR 17 (8 – 38) -LR 0.97 (0.94 – 1.00) Fetal loss per case 0.6 Choroid plexus cyst ST 0.01 (0 – 0.03) SP 0.99 (0.97 – 1.00) +LR 1.00 (0.12 – 9.4) -LR 1.00 (0.97 – 1.00) Fetal loss per case 4.3 Femur length ST 0.16 (0.05 – 0.40) SP 0.96 (0.94 – 0.98) +LR 2.7 (1.2 – 6.0) -LR 0.87 (0.67 – 1.1) Fetal loss per case 1.2 Humerus length ST 0.09 (0 – 0.60) SP 0.97 (0.91 – 0.99) +LR 7.5 (4.7 – 12) -LR 0.87 (0.67 – 1.1) Fetal loss per case 1.9 Echogenic bowel ST 0.04 (0.01 – 0.24) SP 0.99 (0.97 – 1.00) +LR 6.1 (3.0 – 12.6) -LR 1.00 (0.98 – 1.00) Fetal loss per case 1.0 Echogenic intracardiac focus ST 0.11 (0.06 – 0.18) SP 0.96 (0.94 – 0.97) +LR 2.8 (1.5 – 5.5)		Meta-analysis	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					-LR 0.95 (0.89 – 1.00) Fetal loss per case 2.0 Renal pyelectasis ST 0.02 (0.01 – 0.06) SP 0.99 (0.98 – 1.00) +LR 1.9 (0.7 – 5.1) -LR 1.00 (1.00 – 1.00) Fetal loss per case 2.6			
Conde-Agudelo, 1998	320	20 cohort studies taken from MEDLINE search from 1966 – November 1996 (English, French or German language) 194,326 Maternal age: Mean varied between 24.5 and 33.5 Inclusion and exclusion criteria well defined	Triple marker screen for DS Validated reference: - 4 studies obtained fetal karyotypes. In other studies CVS or amniocentesis was offered to screen-positive women. Proportion of women accepting prenatal diagnostic testing ranged from 67 to 92. Follow-up information on pregnancy outcome incomplete in 8 studies	Diagnostic test characteristics	Results Cut-offs 1:190 – 200 Maternal age (MA) $\geq$ 35 years ST (Range) 89 (78 – 100) FPR (Range) 25 (20 – 29) All ages ST 67 (48 – 91) FPR 4 (3 – 7) Cut-offs 1:250 – 295 MA $\geq$ 35 ST 80 (75 - 100) FPR 21 (20 – 21) MA < 35 ST 57 (53 – 58) FPR 4 (3 – 6) All ages ST 71 (48 – 80) FPR 6 (4 – 7) Cut-offs 1:350 - 380 All ages ST 73 (70 – 80) FPR 8 (7 – 13)		Meta-analysis	III
Sotiriadis, 2003	[783]	11 studies taken from MEDLINE and EMBASE between 1985 to August 2002 (English, French and German language) 51,831 Maternal age: Mean ranged between 29 – 35 years	Intracardiac echogenic foci	Diagnostic test characteristics	Data included 51,831 fetuses with 333 Down's syndrome cases ('combined'- 27,360 with 321 Down's syndrome cases, 'isolated' – 39,360 with 130 Down's syndrome cases). Results: Random effects model (REM) 'Combined Setting' ST 0.26 (0.19 – 0.35) SP 0.963 (0.937 – 0.979) 'Isolated setting ST 0.22 (0.14 – 0.33)		Meta-analysis	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					SP 0.959 (0.910 – 0.982) All ST 0.26 (0.19 – 0.34) SP 0.958 (0.922 – 0.978) Fixed effects model (FEM) 'Combined setting' ST 0.30 (0.25 – 0.36) SP 0.927 (0.924 – 0.931) 'Isolated setting' ST 0.22 (0.15 – 0.30) SP 0.964 (0.961 – 0.966) All ST 0.30 (0.25 – 0.36) SP 0.940 (0.937 – 0.942) Further it was estimated that the probability of DS (assuming + LR of 6.2) after an intracardiac echogenic foci has been detected would be 0.44% in a population with prevalence of 1:1400, 0.62% with prevalence of 1:1000, and 1.03% with prevalence of 1:600			
Coco, 2005	[784]	1998 – 2002 single medical centre Italy 12,672 (77.8% of study population) Maternal age: Mean 27.2 ± 5.5years	US detection of Fetal pyelectasis as a screening test. Validated reference: Yes (karyotyping, postnatal records, information from mother)	Diagnostic tests characteristics	Number of cases (prevalence in %) DS 11 (0.09) Pyelectasis 367 (2.9%) Only one case of Down's syndrome identified with pyelectasis. Results: Isolated pyelectasis ST 9.1 (1.62 – 37.4) SP 97.6 (97.32 – 97.85) PPV 0.33 NPV 99.9 +LR 3.8 (0.58 – 24.61) -LR 0.9 (0.77 – 11.2) Pylectasis + other markers ST 9.1 SP 99.5 PPV 1.6 NPV 99.9 +LR 19.2		Cohort study	II

Table III. First and second trimester screening for Down's syndrome only

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Malone et al., 2005	[785]	1999 – 2002 15 medical centres USA 33547 (82% of study population) with complete data from both trimesters Unselected Maternal age: Mean 30.1 SD 5.8 Exclusions: adequately described	All serum tests with NT (Combined, Quad, Integrated & Serum Integrated) Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) 92 (0.27) Results: Detection rate at fixed FPR 5% (95% CI) Combined (11 weeks) – 87 (82 – 92) Quadruple (15-17 weeks) – 81 (70 - 86) Serum integrated – 88 (81 – 92) Fully integrated – 96 (92 – 97)		Cohort study	Ib
Wald et al., 2003	316	1996 – 2001 25 maternity centres UK & Austria 43,712 (92% of study population). 98 cases, 490 controls for screening performance. 600 controls added for statistical power Unselected Unspecified maternal age	All serum and urine biochemical markers with NT Validated reference: yes (karyotype – pre/postnatal pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) 101 (0.23) Results: Estimated Detection Rate at fixed FPR 5% 1st trimester (10 – 13 wk) PAPP-A + NT 76 Combined 84 Combined + Inhibin A 87 2nd trimester (15 – 20) Double 71 Triple 77 Quad 83 Integrated screening (both 1st and 2nd trimester) NT (10wks) + Quad 90 Serum integrated 90 Integrated 93		Nested Case-control (within a cohort)	II
Knight et al., 2005	[786]	2001 – 2003 229/260 prenatal care practitioners USA 8773 (78.6% of study population) Selected (61% enrolled for study) Maternal age: Mean – 27.8 SD 5.5	Integrated serum screening Validated reference: Yes (prenatal karyotype, pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) 16 (0.18) Results: Observed screening performance with 95% CI Triple Risk 1:270 DR 67 (43 – 84) FPR 6.4 (5.9 – 6.9)		Cohort study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Quad Risk 1:150 DR 56 (33 – 76) FPR 3.3 (2.9 – 3.7) Serum integrated Risk 1:100 DR 79 (55 – 92) FPR 3.2 (2.8 – 3.6)			
Platt et al., 2004	[787]	Unspecified period 122 prenatal diagnostic centres USA 4325 *1st trimester screen positive* 180 (52.7% of study population) *1st trimester screen-negative* 4145 Selected (low uptake of 2nd trimester screening) (small sample) Maternal age: Mean 34.5 SD – 4.6	Sequential screening using Triple marker after 1st trimester Combined test Validated reference: Yes (karyotype – prenatal pregnancy records)	Diagnostic test characteristics	Number of cases (prevalence in %) 13 (0.30) Results: Observed screening performance with 95% CI among 1st trimester screen-negative women Risk 1:270 DR 85.7 (42.1 -99.6) FPR 8.9 (8.0 – 9.8)		Cohort study	II

Table IV. Modelling studies for comparing different Down's syndrome screening tests

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Wright, 2006	[789]		'Contingent screening', the protocol involves measuring free β-HCG and PAPP-A in all pregnant women at 10 weeks in the first stage. Those with low risk were screened negative at this stage, the remainder underwent NT measurement in the second stage and the risk reassessed (for combined test). After the second stage, those with low risk were screened negative and those with very high risk were offered diagnostic tests. In the third stage, women with	Potential value of three-stage sequential screening for Down's syndrome	With full adherence to a three stage policy, an overall detection rate of nearly 90% and a false-positive rate of below 2% can be achieved. About two-thirds of the women can be screened on the basis of first trimester biochemistry alone and about 80% by the combined test. The DR for first trimester screening is about 60%. This protocol allows most of the Down's syndrome pregnancies to be detected in the first trimester.		Modelling	III

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			intermediate risk received second trimester quad test. Risk was reassessed according to the integrated test and high risk women were offered diagnosis.					
Wald, 2006	[790]		compared the Integrated test in three policies for screening – i) Integrated screening for all women ii) Sequential screening (based on first trimester tests, high risk pregnancies to be diagnosed and remaining to undergo integrated test) iii) Contingent screening. Detection and false-positive rates were estimated based on the data from a large cohort (nested case-control study) done in UK.		integrated screening had the best screening performance. As the first trimester test FPR was decreased, the performance of other two policies approached that of the integrated screen. Setting the first trimester risk cut-off to $\geq$ 1 in 300 with a fixed DR of 90%, sequential and contingent screening gave overall FPR's of 2.3% and 2.4% respectively, and 66% of affected pregnancies were detected by the first trimester tests. The integrated test on all women gave a FPR of 2.2%.	If pregnancies with a first trimester risk of $\leq$ 1 in 2000 are classified screen negative and receive no further testing, then 99.5% of women with sequential screening or 30% with contingent screening would proceed to integrated screening.	Modelling	III

Effectiveness studies

Table V. Effectiveness of different Down's syndrome screening tests

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Saltvedt, 2005	[791]	8 Swedish Hospitals 39,572 (19,796 in 12 weeks, 19,776 in 18 weeks)	Comparison of routine ultrasound scan at 12-14 weeks by nuchal translucency *versus* routine ultrasound at 15-20 weeks by maternal age. Validated reference: yes (karyotyping, pregnancy outcome)	Screening test effectiveness	Number of DS cases (prevalence in %) 98 (0.25) Results: Outcome 12-week group 18-week group p-value Prevalence rate 55/19,796 (0.28) 43/19,776 (0.22) 0.18 Rate of liveborn DS babies (at > 22 weeks) 10/19,796 (0.05) 16/19,776 (0.08) 0.25 Antenatal detection rate (< 22 weeks in living fetus) 42/55 (76) 25/41* (61) 0.12 Antenatal detection rate (if karyotyping performed only for defined policy) 39/55 (71) 21/41* (51) 0.06 Detection rate (other chromosomal anomalies) 20/35 (57) 25/35 (71) 0.32 Terminations done for DS 39/19,796 (0.20) 24/19,776 (0.12) 0.08		RCT	1+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Fetal loss rate in DS fetuses (terminations and miscarriages) 45/19,796 (0.23) 27/19,776 (0.14) 0.04 Rate of invasive tests (for karyotyping) 1593/19,796 (8) 2118/19,776 (0.14) < 0.001 Spontaneous fetal loss rate after invasive tests in normal fetuses 14/1507 (0.9) 15/2041 (0.7) 0.58 No. of invasive tests per one case of DS detected (<22 weeks)(if karyotyping performed only for defined policy) 16 89 * of the 43 cases of DS, diagnosis was made in one case by amniocentesis at < 22 weeks but pregnancy continued, and in other diagnosis made at 35 weeks – leaving 41 cases for calculating DR			
Wald, 2003	316	See Table III	Safety in terms of number of unaffected fetal losses per 100,000 women screened and number of DS pregnancies detected for each procedure related unaffected fetal loss	Screening test effectiveness	Results: FPR (5%) Combined 6.1 Double 13.1 Triple 9.3 Quadruple 6.2 Serum integrated 2.7 Integrated 1.2 Unaffected fetal losses per 100,000 women Combined 44 Double 94 Triple 67 Quadruple 45 Serum integrated 19 Integrated 9 DS cases detected for each procedure related fetal loss Combined 3.9		Nested case control	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Double 1.8 Triple 2.6 Quadruple 3.8 Serum integrated 9.1 Integrated 19.2			
Biggio, 2004	[792]	Hypothetical cohort of 1,000,000 women < 35 years	Comparison of 5 screening strategies (1) first trimester combined screen (2) second trimester quad screen (3) second trimester triple screen (4) integrated screen (5) sequential screen.	Screening test effectiveness	Prevalence of Down's syndrome at 10 weeks gestation was estimated as 1 in 595 pregnancies, and baseline live birth rate 1 of 1030 Results: No screening Cost of programme (million US$) 662 DS cases detected (n) 0 DS live births averted (n) 0 Euploid loss due to procedure 0 Triple screen, no sonogram Cost of programme (million US$) 497 DS cases detected (n) 529 DS live births averted (n) 366 Euploid loss due to procedure 311 Triple screen, with sonogram Cost of programme (million US$) 566 DS cases detected (n) 365 DS live births averted (n) 253 Euploid loss due to procedure 25 Quad screen, no sonogram Cost of programme (million US$) 472 DS cases detected (n) 618 DS live births averted (n) 427 Euploid loss due to procedure 311 Quad screen, with sonogram Cost of programme (million US$) 554 DS cases detected (n) 426 DS live births averted (n) 295 Euploid loss due to procedure 25 Combined screen Cost of programme (million US$) 486 DS cases detected (n) 941 DS live births averted (n) 490 Euploid loss due to procedure 559 Integrated screen		Decision analysis model	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Cost of programme (million US$) 521 DS cases detected (n) 750 DS live births averted (n) 520 Euploid loss due to procedure 62 Sequential screen Cost of programme (million US$) 455 DS cases detected (n) 1213 DS live births averted (n) 678 Euploid loss due to procedure 859			
Smith-Bindman, 2001	315	For details see Table II B	See table II B	Screening test effectiveness	See table II B	See table II B	See table II B	See table II B
Comstock CH, 2006	[793]	Analysis of multi-centre prospective trial in USA (FASTER trial) 36,120 Maternal age: ≥ 16 Exclusions: well defined	Determine whether there is a NT measurement above which immediate invasive testing should be offered without waiting for serum testing and computerized aneuploidy risk assessment	Screening test effectiveness	Results (in %) ≥2mm 10 weeks 2.0 11 weeks 1.5 12 weeks 2.5 13 weeks 5.1 Total 3.0 ≥3mm 10 weeks 0.4 11 weeks 0.5 12 weeks 0.3 13 weeks 0.4 Total 0.4 ≥4mm 10 weeks 0.16 11 weeks 0.1 12 weeks 0.1 13 weeks 0.05 Total 0.09 ≥5mm 10 weeks 0 11 weeks 0.04 12 weeks 0.09 13 weeks 0 Total 0.05 On comparison of outcome of pregnancies based on the various nuchal translucencies cut-offs, the following results were observed:			2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					≥2mm Number (%) 1081 (3.0) Aneuploidy 51 T21 39 T18 5 ≥3mm Number (%) 128 (0.4) Aneuploidy 22 T21 17 T18 4 ≥4mm Number (%) 32 (0.09) Aneuploidy 10 T21 6 T18 4			

Women's Views

Table VI

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Green, 2004	[794]	Any genetic screening programme aimed at pregnant women or newborn babies was included. Both comparative and descriptive studies which reported data collected directly from pregnant women or parents were included. There were no geographical or methodological limits except that studies asking hypothetical questions, case reviews and those where US was done to detect structural anomalies only (and not include chromosomal anomalies) were excluded.	5 broad questions concerned with i) knowledge ii) anxiety iii) other emotional aspects iv) factors associated with participation in the programmes and v) long-term sequelae of the results.	Psychosocial aspects of genetic screening of pregnant women and newborns	Knowledge and understanding of screening for DS – 30 studies were selected: 7 used pre-test measures only, 6 employed both before and after test measures (ideal for comparing), and 17 employed after test measures only. Eight areas of information as specified in RCOG 1993 professional guidelines were used as a 'validated/gold standard questionnaire' for evaluating knowledge in the selected studies. 30 studies related to knowledge were reviewed, but owing to disparate research aims, poorly operationalised measures for evaluation, and variation in timing of assessment, it was concluded that none of the study evaluated all the 8 areas and hence knowledge was inadequately assessed by all of them. Influence on anxiety in prenatal screening for DS – Of the 24 studies measuring anxiety, 13 used a validated scale (mainly State-Trait Anxiety Inventory). Most studies were carried out in UK. As knowledge influences anxiety and attitudes, the findings from studies represents the feelings and views of many		Systematic review	2++

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					people who are in fact not well informed about the topic under discussion. Understanding decision making about screening – Of the 52 studies included, 34 were concerned with DS screening and 11 of them compared differences in those screened with those not screened. Most studies employed questionnaire or interview survey methods.			
Rowe HJ, 2006	[795]	4 antenatal clinics in Australia. pregnant women between 8 and 14 weeks attending at their first prenatal visit	A validated measure, and to compare anxiety levels in women who are well informed versus poorly informed. Written and oral information was provided to all participants as per the existing hospital policy. Informed choice was measured by Multidimensional Measure of Informed Choice (MMIC), a validated measure of informed choice which assesses knowledge and attitude dimensions and also confirms whether woman's participation in screening test matches her attitude. The Hospital Anxiety and Depression Scale (HADS) were used to measure anxiety and this scale specifically distinguishes between anxiety and depression. Both the scales were administered at the booking visit and HADS was repeated at 20 weeks (after participation in the test) and at 30 weeks using postal questionnaires	Assess informed choice in pregnant women to participate in second trimester serum screening	134 recruited women completing the first assessment in the second study, 63.9% returned the second questionnaire and 57.8% the third. The mean age of the sample was 29.1 ± 4.7 years and 89.6% were married. Using MMIC, 48.1% women were classified as having 'good knowledge' and 87.2% having a 'positive attitude' to screening. Overall only 37.3% of decisions to participate in screening were informed; those who participated in screening were more than twice as likely to have made an informed choice than those who did not participate (47% versus 20%, p=0.01). Informed decisions were not significantly associated with participant's age, gravidity, country of birth, or whether pregnancy was unwelcome or unexpected. No significant association was found between the knowledge levels and attitude to the test (p=0.27). Some important misconceptions were revealed about further testing; 31% did not know that miscarriage was a possible consequence of diagnostic testing subsequent to an increased risk screening result, and only 62% correctly identified that termination of pregnancy would be offered if Down syndrome was diagnosed. Regarding anxiety, no significant difference was found between the informed and not informed group in psychological outcomes at any of the three assessments, even after adjusting for repeated measures on individual participants.		Prospective cohort	2+
Georgsson, 2004	[796]		The 12-week group was the intervention group and 18-week group acted as the control. The State-Trait Anxiety Inventory (validated tool for evaluating general anxiety) and Edinburgh Postnatal Depression Scale (validated for evaluating anxiety in	Women's worries about the 'possibility of something being wrong with the baby' was measured by the Swedish version of Cambridge Worry Scale questionnaire including 16 items of common concerns	82.7% (854/1030) women in 12-week group, and 84.1% (837/996) in the 18-week group respectively who responded to all 3 questionnaires. The demographic characteristics of the two groups were similar. Emotional well-being at baseline in early pregnancy was also similar. In the early pregnancy 39.1% women in 12-week group and 36.0% in 18-week group were worried about something being wrong with the baby, but the difference was not statistically significant.		Qualitative	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			antenatal/postnatal period) were also used. Information was collected at 3 different timings – first questionnaire was filled at the antenatal clinic, second was sent at 24 weeks gestation (mid-pregnancy), and the last was posted 2 months after delivery. Same instruments were used for all the three questionnaires.	during pregnancy.	The prevalence decreased to 29.2% versus 27.8% during mid-pregnancy, and finally to 5.2% versus 6.6% at 2 months after delivery in the 2 groups. No statistically significant difference was found between the 2 groups during these periods also. Within both trial groups, there was statistically significant decrease in the levels of major worry about baby's health from early to mid-pregnancy ($p<0.001$), and from mid-pregnancy to 2 months after delivery ($p<0.001$).			
Lawson, 2006	[797]	Participants included high risk pregnant women (maternal age > 35 years) who opted for MSS or amniocentesis or did not opt for any testing.	Investigate the relationship between maternal serum screening (MSS) use and maternal attachment to pregnancy following the receipt of favourable results (i.e lowered risk ratio). Informational posters were placed at various places (physician offices, laboratories, maternity stores), and interested women who met the eligibility criteria were enrolled. The instrument used to collect information was a self-administered questionnaire by mail, and prenatal attachment was measured by 21-item Prenatal Attachment Inventory (construct validity and reliability of this scale were established). The three groups were compared using ANOVA and ANCOVA for statistical analysis.		One-way ANOVA indicated that attachment levels for MSS group (mean 51.7, SD 9.4) were significantly lower than those reported by amniocentesis group (mean 58.5, SD 10.7) and no test group (mean 57.0, SD 8.3) [$t(68) = 0.68$, $p = 0.02$]. Moreover amniocentesis group did not differ in bonding levels compared to the no testing group [$t(67) = 0.66$, $p = 0.51$], thereby proving both the hypothesis. This difference persisted even after removing the influence of maternal age and attitude towards abortion. There was no significant interaction between testing status of the 3 groups and timing of conducting survey (second or third trimester) when they were used as independent variables with PAI as the dependant variable.		Cross-sectional survey	3
Rowe, 2004	[798]		Studies were assessed in terms of a) utilization - number of women screened as a proportion of those eligible b) offer - number of women offered screening as a proportion of those eligible, and c) uptake – number of women	non participation rate and whether the distinction between utilization, offer and uptake was	these suggested that compared to White women, utilization of testing was lower in Asian women, two others indicated that both utilization and uptake was lower, and fourth study found both acceptance and uptake of amniocentesis lower in women from Asia. In the remaining 5 studies, no statistically significant association was found between socio-demographic factors and test utilization. Four studies reported on the offer of screening or diagnosis for DS. Two of these suggested that Asian		Systematic review	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			screened as a proportion of those offered screening		women were less likely to be offered amniocentesis, while in the third study fewer Bangladeshi than White women were offered screening, although this result was not statistically significant. The fourth study did not analyze the results according to the social class or ethnic group.			
Dormandy, 2005	[799]	two UK district hospitals	Attitudes towards undergoing the test were assessed by women's responses to a structured question with 4 items. Knowledge about the test was assessed using an 8 item questionnaire deemed important in professional guidelines for informed consent in screening. Choices were classified as 'informed' depending on the consistency between test uptake, women's attitude towards the test, and their knowledge about it.	Reasons for lower uptake of screening tests in women from minority ethnic groups and socio-economically (SE) disadvantaged sections of society. Screening uptake was evaluated from hospital records	a) Screening uptake – overall uptake was 49% (95% CI 47-52). Uptake was higher in white and SE advantaged women. b) Knowledge – Overall the mean knowledge score was above the mid-point of the scale. Knowledge was higher for white, SE advantaged and older women. c) Attitudes towards test: The mean overall score was above the scale mid-point, that is, overall women had positive attitude towards the test. No difference in attitudes was found related to ethnicity, SE status or parity; but older women had more positive attitude than younger ones. d) Uptake-attitude consistency – In women with positive attitudes, white and SE advantaged women were more likely to act in line with their attitudes (76% white women had test compared to 45% South Asian women, p<0.001) and (78% SE advantaged women had test compared with 63% SE disadvantaged women, p<0.001). In women with negative attitude, no difference was found between ethnic or social groups. e) Informed choice – rates of informed choice were higher for white women (56% vs 20% South Asian, p<0.001) and SE advantaged women (59% vs 14% for SE disadavantaged, p<0.001). After controlling for confounding variables (ethnicity, age, SE status, and hospital attended), it was found that both South Asian women and SE disadvantaged women with positive attitudes were less likely to act consistently with their attitudes compared to white and SE advantaged women (OR 0.22, 95%CI 0.10-0.45 for South Asian vs white) and (OR 0.62, 95%CI 0.41-0.93 for social groups).		Qualitative	3
Spencer, 2004	[800]	6 UK maternity units (3 in Scotland, 3 in England)	Pregnant women attending antenatal clinics were asked to put in order of preference four different approaches for screening (all with FPR of 5%) – (1) first trimester testing – 90% detection with results available in 1 hour (2) first trimester testing – 90%	To ascertain by means of a structured questionnaire women's preference for type of screening test	75% women selected first trimester screening (option 1 or option 2) as their first choice, with 68.2 % preferring results within 1 hour (option 1) and 6.8% preferring combined test. 24% opted for integrated test and just 1% opted for second trimester testing as their first choice.		Cross-sectional survey	3

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			detection with results within 2-3 days (combined test) (3) first trimester plus second trimester detection, 93% detection and results within 2-3 days of second test (integrated test) (4) second trimester testing, 75% detection and results available within 2-3 days.					

Chlamydia

Screening for chlamydia (diagnostic accuracy)

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Smith et al , 1987	805	Pregnant (n=231) and non-pregnant women (n=827) below the age of 35 years attending an obstetrics and gynecology clinic in USA. Prevalence 12.1% in pregnant women	Comparison of ELISA and DFA with culture (blind passage) of the endocervical swabs.	Diagnostic accuracy results for pregnant women only. Reference standard – positive by initial or repeat culture Threshold for positive EIA – optical density 0.100 greater than mean optical density of 3 negative controls Threshold for positive DFA – greater than 10 elementary bodies per slide	EIA (n=231) Sensitivity: 85.7% Specificity: 95.6% PPV: 72.7% NPV: 98.0% DFA (n=144) Sensitivity: 84.6% Specificity: 96.6% PPV: 84.6% NPV: 96.6% First culture with blind passage Sensitivity: 82.1% NPV: 98.8% First culture without blind passage Sensitivity: 60.7% NPV: 94.7%	Specimens collected randomly Blinding of technicians Test described adequately	CH	I b
Binns et al, 1988	966	Consecutive asymptomatic pregnant women opting for abortion and attending a counseling clinic in Canada (n=531). Prevalence 10.8%	Comparison of ELISA and DFA with culture of the endocervical swabs	Diagnostic accuracy results for two different reference standards– positive culture without blind passage or positive results for any two of the three tests	Positive culture as reference standard EIA (n=462) Sensitivity: 96% Specificity: 95% PPV: 69% NPV: 99.5% DFA (n=462) Sensitivity: 89% Specificity: 99% PPV: 78%	Blinding not specified Tests not described in details	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					NPV: 99% Any two positive tests as reference standard Culture (n=462) Sensitivity: 80% Specificity: 99.8% PPV: 98% NPV: 97% EIA (n=462) Sensitivity: 98% Specificity: 98% PPV: 87% NPV: 99.8% DFA (n=462) Sensitivity: 93% Specificity: 100% PPV: 100% NPV: 99%			
Baselski et al, 1987	806	Indigent pregnant women (n=255) at high risk of chlamydia and attending a regional medical centre in USA. Prevalence 21.2%	Comparison of ELISA and DFA of cervical swabs with culture.	Diagnostic accuracy Reference standard – positive cell culture Threshold for positive EIA – absorbance > mean value of negative controls plus 0.1 Threshold for positive DFA – presence of one or more typical inclusion bodies	EIA (n=250) Sensitivity: 96.3% Specificity: 92.9% PPV: 78.8% NPV: 98.9% DFA (n=247) Sensitivity: 98.1% Specificity: 95.4% PPV: 85.0% NPV: 99.5%	High risk population Blinding of technicians Test described adequately	CH	II
Stamm et al, 1984	807	A multi-centre study in USA recruited symptomatic men (n=576) and women (n=595) from sexually transmitted disease clinics, and	Comparison of DFA cervical swab with culture	Diagnostic accuracy Reference standard – positive cell culture on one occasion (done twice) Threshold for positive DFA – two or more elementary bodies.	DFA (n=225) Sensitivity: 86.2% Specificity: 99.0% PPV: 92.6% NPV: 98.0%	Blinding of technicians Test described adequately	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		asymptomatic pregnant women attending abortion clinic or prenatal clinic (n=225). Prevalence in asymptomatic women 13.0%						
Garland et al, 2000	808	Consecutive pregnant women going for legal termination of pregnancy at a tertiary hospital in Australia (n=1245) Prevalence 2.8%	Comparison of PCR (endocervical swab, urine, tampon), LCR (endocervical swab, urine, tampon), and cell culture (endocervical swab only)	Diagnostic accuracy Reference standard – positive culture and/or at least one other specimen positive by PCR and LCR	Sensitivity for endocervical swab Culture – 45.5% PCR – 81.8% LCR – 87.9% Culture endocervical swab vs PCR & LCR (n=1175) P < 0.0005 for both PCR vs LCR (n=1175) For urine P=0.25 For tampon P=0.5 For endocervical swab P=0.5	Representative population Blinding of technicians Test described adequately	CH	I b
Andrews et al, 1997	809	Unmarried, publicly funded pregnant women with many having risk factors for Chlamydia infection (n=478, mean age 22.9 ± 5.6 years) Prevalence 20.1%	Comparison of LCR (urine, endocervical swab) with culture endocervical swab	Diagnostic accuracy Reference standard – positive culture or negative culture with positive LCR confirmed by further testing with DFA or MOMP-LCR	Culture endocervix Sensitivity: 30.1% Specificity: 100% LCR endocervix Sensitivity: 90.3% Specificity: 100% LCR urine Sensitivity: 83.9% Specificity: 99.5%	High risk population Blinding not specified Test described adequately	CH	II
Thejls et al, 1994	810	Consecutive pregnant women seeking abortion at 3 hospitals in Sweden	Comparison of culture, DFA, EIA and PCR of	Diagnostic accuracy Reference standard – positive culture (first time or reculturing)	Culture (n=419) Sensitivity: 66.7% Specificity: 100%	Blinding not specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		during a six month period (n=419, 41.8 % women < 24 years) Prevalence 4.3%	endocervical specimens	or at least two positive non-culture tests. Threshold for positive DFA – ten or more elementary bodies per slide	PPV: 100% NPV: 98.5% DFA (n=419) Sensitivity: 61.1% Specificity: 99.8% PPV: 91.7% NPV: 98.3% EIA (n=419) Sensitivity: 64.7% Specificity: 100% PPV: 100% NPV: 98.5% PCR (n=381) Sensitivity: 71.4% Specificity: 100% PPV: 100% NPV: 98.9%			
MacMillan et al, 2003	811	Consecutive women less than 25 years of age attending abortion, family planning, and antenatal clinics in UK. Pregnant women 204/303 and prevalence in them 10.8%	Comparison of EIA endocervical swab, LCRs for first void urine sample, vaginal swab and endocervical swab	Diagnostic accuracy Positive EIA confirmed further by DFA, while positive LCR by MOMP-LCR Reference standard – one or more specimens positive by two independent tests	EIA Sensitivity: 82% Specificity: 100% LCR endocervix Sensitivity: 82% Specificity: 100% LCR vagina Sensitivity: 100% Specificity: 100% LCR urine Sensitivity: 91% Specificity: 100%	Single blinded Test adequately described	CH	II
Renton et al, 2006	812	Pregnant women presenting for termination of pregnancy at a family	Comparison of LCR and DFA of cervical swab, vaginal swab,	Diagnostic accuracy Reference standard – positive test result from any site or	Sensitivity with positive test result from any site as reference standard	Blinding not specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		planning clinic in UK (n=863) Prevalence 8.5%	and urine	positive LCR	LCR cervical swab 97.0% LCR vaginal swab 94.0% LCR urine 83.0% DFA cervical swab 93.0% DFA vaginal swab 92.0% DFA urine 78.0% Positive LCR as reference standard DFA cervical swab Sensitivity: 93.8% Specificity: 99.9% DFA vaginal swab Sensitivity: 92.1% Specificity: 99.5%			
Hosein et al, 1992	[813]	Consecutive low-income pregnant women attending a university medical centre in USA (n=322). Prevalence 13.4%	Comparison of DNA probe test with culture	Diagnostic accuracy Reference standard – positive culture Threshold for positive DNA probe test – one or more fluorescing inclusion bodies	DNA probe test (n=246) Sensitivity: 93.9% Specificity: 99.1% PPV: 93.9% NPV: 99.1%	Blinding of technicians Test described adequately Drop out rate > 20%	CH	II
Yang et al, 1991	[814]	Asymptomatic pregnant women attending for routine prenatal care (n=257), and women with symptoms of lower genital tract infection or history of STD (n=169) in USA Prevalence in pregnant women 8.6%	Comparison of DNA probe test with culture	Diagnostic accuracy In case of discrepant results, probe competition assays performed. Reference standard – positive culture or negative culture with positive two non-culture tests.	Culture (n=257) Sensitivity: 95.4% Specificity: 100% PPV: 100% NPV: 99.6% DNA probe test (n=257) Sensitivity: 86.4% Specificity: 100%	Blinding not specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					PPV: 100% NPV: 98.7% Diagnostic accuracy of DNA probe test with positive culture as reference standard Sensitivity: 85.7% Specificity: 99.6% PPV: 94.7% NPV: 98.7%			
Asbill et al, 2000	815	Pregnant women at their initial visit to an obstetric clinic or at 36 weeks gestation in USA (n=519, 63% women < 24 years of age) Prevalence 6.8%	Comparison of Gram stain (cervical mucous) with DNA probe test	Diagnostic accuracy Reference standard – positive DNA probe test Threshold for a positive gram stain – 10 or more polymorphonuclear leucocytes per high power field	Sensitivity: 91.0% Specificity: 18.0% PPV: 7.5% NPV: 96.7%	Blinding of technicians Test described adequately	CH	I b
Spence et al, 1986	816	Unselected pregnant women seeking first or second trimester termination of pregnancy at a tertiary hospital in USA (n=300, mean age 21.4 years) Prevalence 14.3%	Comparison of Pap smear with culture	Diagnostic accuracy Reference standard – positive culture Threshold of positive Pap smear findings – inflammation, consistent with Chlamydia infection, others or negative	Pap smear findings consistent with Chlamydia infection as threshold Sensitivity: 2.3% Specificity: 98.1% Pap smear findings consistent with Chlamydia infection plus inflammation as threshold Sensitivity: 60.5% Specificity: 56.4%	Blinding not specified Test described adequately	CH	II

Screening for chlamydia (effectiveness)

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Martin et al,	817	Pregnant women at 23-29	Treatment with	Pregnancy outcomes: mean	Mean birth weight ± SD (in	Adequate	RCT	1++

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
1997		weeks with Chlamydia isolated from endocervical specimens by culture and successfully completing a one week placebo run-in (n=414). Population selected from on-going multi-centre trial in USA looking at vaginal infections and premature births.	erythromycin base 333 gms TDS for 7 days (n=205) compared to placebo (n=209). Repeat cultures obtained 2-4 weeks after starting treatment, and outcomes stratified by study sites for placebo group into high clearance group (repeat culture negative) and low clearance group (repeat culture positive)	birth weight in gms, low birth weight (<2500 gms), preterm delivery (<37 weeks), PROM, still birth, neonatal death	grams) 3192 ± 524 vs. 3146 ± 552 P > 0.05 Low birth weight 17/201 (8%) vs. 22/199 (11%) P > 0.05 Preterm delivery 27/202 (13%) vs. 30/203 (15%) P > 0.05 PROM 21/196 (11%) vs. 25/193 (13%) P > 0.05 Stillbirth 2/202 (1%) vs. 1/203 (0.5%) P > 0.05 Neonatal death 1/202 (0.5%) vs. 0/203 P > 0.05 Low clearance groups Low birth weight 9/114 (8%) vs. 18/105 (17%) P = 0.04 Preterm delivery 15/115 (13%) vs. 18/105 (17%) P = 0.4 High clearance groups Low birth weight 8/87 (9%) vs. 4/94 (4%) P = 0.18 Preterm delivery 12/87 (14%) vs. 12/98 (12%) P = 0.75	randomization Concealment of allocation Groups compared Double blinded Intention-to-treat analysis		

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Ryan et al, 1990	818	Consecutive new obstetric patients (n=11,544) in a regional medical centre, USA. Population predominantly urban, black, lower socioeconomic status. Group 1 – untreated (n=1110), Group 2 – treated (n=1323) and Group 3 – culture negative (n=9111)	Initially no treatment given to culture positive group, but after 16 months of starting study, erythromycin 500/250 mg QID for 7 days, or sulfisoxazole 1 gm QID for 7 days given	PROM (rupture of membranes more than 1 hour before birth), low birth weight infants (< 2500 gms), newborn survival (those who left the hospital alive or alive after 28 days of hospitalization). Confounding variables controlled by logistic regression for PROM and newborn survival	<u>Group 1 vs Group 2</u> PROM 5.2% vs 2.9% p<0.001 low birth weight 19.6% vs 11.0% p<0.0001 newborn survival 97.6% vs 99.4% p<0.001 *After adjustment* PROM OR 0.56 (0.37-0.85) p<0.01 newborn survival OR 2.21 (0.89-5.49) p<0.08 <u>Group 1 vs Group 3</u> PROM 5.2% vs 2.7% p<0.001 low birth weight 19.6% vs 11.7% p<0.0001 newborn survival 97.6% vs 98.5% p<0.05 *After adjustment* PROM OR 2.12 (1.57-2.86) P<0.001 newborn survival p > 0.05 <u>Group 2 vs Group 3</u>	Confounders controlled Blinding not specified Population representative	CH	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					PROM 2.9% vs 2.7% p=0.556 low birth weight 11.0% vs 11.7% p=0.42 newborn survival 99.4% vs 98.5% p<0.01 *After adjustment* PROM p > 0.05 newborn survival p > 0.05			
Cohen et al, 1990	819	low income, indigent, and urban pregnant women considered at high risk for infection with Chlamydia trachomatis in USA (n=567) Group 1 – successfully treated (n=244), Group 2 – treated but remained chlamydia positive during pregnancy (n=79), and Group 3 – Chlamydia negative matched controls (n=244) Matching done for age, race, gravidity, parity, marital status, SE status and health habits	Treatment with erythromycin 500 mg QID for 7 days, and repeat culture after delivery.	PROM (rupture of membranes before onset of labour), Preterm delivery (labour < 37 weeks), Premature contractions, Small-for gestational age (SGA), Stillbirth, Antepartum hemorrhage (APH), Vaginal delivery, Caesarean section, Postpartum endometritis, mean fetal weight, mean gestational age	<u>Group 1 vs Group 2</u> Premature delivery 2.9% vs 13.9% p=0.00002 PROM 7.4% vs 20.2% p=0.02 Premature contractions 4.1% vs 24.0% p=0.00001 SGA 13.1% vs 25.3% p=0.001 Stillbirth 0.4% vs 0 p>0.05 APH 1.2% vs 2.5%	Groups comparable Blinding not specified Confounders partially controlled	Retrospectiv e	2-

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					p>0.05 Vaginal delivery 88.9% vs 82.3% p>0.05 Caesarean section 11.1% vs 17.7% p>0.05 Postpartum endometritis 2.9% vs 2.5% p>0.05 Gestational age (mean ± SD) 39.35 ± 2.25 vs 38.76 ± 2.97 p>0.05 Fetal weight (mean ± SD) 3202.6 ± 508.6 vs 3002.1 ± 626.5 p=0.004 <u>Group 1 vs Group 3</u> Premature delivery 2.9% vs 11.9% p=0.0001 PROM 7.4% vs 7.4% p>0.05 Premature contractions 4.1% vs 1.6% p>0.05 SGA 13.1% vs 11.9% p>0.05			

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Stillbirth 0.4% vs 0 p>0.05 APH 1.2% vs 0% p>0.05 Vaginal delivery 88.9% vs 84.4% p>0.05 Caesarean section 11.1% vs 15.6% p>0.05 Postpartum endometritis 2.9% vs 2.1% p>0.05 Gestational age (mean ± SD) 39.35 ± 2.25 vs 38.93 ± 2.42 p=0.05 Fetal weight (mean ± SD) 3202.6 ± 508.6 vs 3095.1 ± 577.1 p=0.03			
Black-Payne et al, 1990	820	Asymptomatic pregnant women with estimated gestational age 28-32 weeks attending a medical centre in USA (n=199) Chlamydiazyme-positive group (n=52), Chlamydiazyme-negative group (n=126)	To determine if rapid EIA test (Chlamydiazyme) can be used reliably for screening programme by comparing perinatal and neonatal outcomes between two groups. Test positive women treated with	Perinatal – ROM, preterm delivery (< 37 weeks), cesarean section rate, postpartum endometritis Neonatal – respiratory tract infections, conjunctivitis in first 6-8 weeks of life	Rupture of membranes < 6 hrs, 6-12 hrs, and > 12 hours 73% vs 69% 19% vs 27% 8% vs 4% p>0.05 for all Preterm birth 3% vs 6% p>0.05 Cesarean section 20% vs 15%	Groups compared Chance of bias	CH	2-

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			erythromycin 500 mg QID for 7 days		p>0.05 Postpartum endometritis 5% vs 12% p>0.05 Incidence of neonatal respiratory tract infections and conjunctivitis p>0.05 for both			
Rivlin et al, 1997	821	Pregnant women registering consecutively at university medical centre in USA (n=1350), but for this study, only women with positive Chlamydia culture taken. Treated group (n=23) Untreated group (n=58)	Women with positive DFA test treated with erythromycin 800 mg QID for 7 days, and those with negative test not treated.	Maternal complications – abortion, PROM, preterm delivery, chorioamnionitis, endomyometritis, mastitis. Neonatal complications – stillbirth, premature, RDS, tachypnoea, sepsis Infant complications – conjunctivitis, pneumonia, otitis, URI, bronchitis, diarrhea.	p>0.05 for all maternal, neonatal and infant complications between the two groups	Groups compared Clinicians blinded to culture results	Retrospective	2+
McMillan et al, 1985	822	Pregnant women with positive chlamydia culture at 32-36 weeks cared for in 3 obstetrical clinics in a university hospital in USA (n=85/1082). Infants of treated group (n=16) Infants of untreated group (n=21)	Women in treated group received erythromycin 500 mg BD for 10 days	Nasopharyngeal or conjunctival culture with episodes of conjunctivitis and pneumonia,	Positive nasopharyngeal or conjunctival culture and symptomatic for neonatal conjunctivitis and pneumonia 0% vs 23% p<0.04	Groups not compared Blinding not specified High risk of bias	CH	2-

Clinical Question: What is the diagnostic value and effectiveness of screening tests to identify women at risk of diabetes in pregnancy?

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Gribble, 1995	494	Pregnant women with at least 2 urinalysis tests during first 2 trimesters were included Women with preexisting DM, multiple gestation excluded Sample size 2965	All women were screened with 50 g GCT at 24-28 weeks. Positive screens (cut-off 140 mg/dl) started a 3-day CHO load, and fasting 100 g GTT. Categorised into 2 groups, negative or positive glycosuria groups Threshold 2 or more ≥ fasting 105; 1-h 190; 2-h 165 and 3-h 145 mg/dl Negative screens comparison of the 2 glycosuria groups in terms of outcomes	Prediction of gestational diabetes	Higher incidence of GDM in women with positive glycosuria in the first two trimesters (12.8% vs. 2.9% for negative screens). Sensitivity of glycosuria in first trimester as a predictor of GD was 7.1% Specificity 98.5% PPV 12.8% NPV 97.1%	Routine dipstick urinalysis for glucose can identify pregnant women at increased risk for GD and diagnose them earlier than 24-28 weeks.	Retrospective observational study	II
Watson, 1990	493	Pregnant women, Military dependants, unrestricted access to medical care without monetary cost Those with previous DM excluded Sample size 500	All women given random urinalysis for glucose at each antenatal visit (mean 10.8, SD 2.6). Diagnosis glycosuria if trace, 1+, 2+ or 3+ found on at least 2 visits. Severe glycosuria if ≥ 2+ on two visits At 28 weeks (no range given) 50-g GCT without regard to ingestion state. Threshold ≥ 140 mg/dl Diagnostic test fasting 100-g GTT, after 3 days high CHO diet Thresholds 2 or more values: fasting 105; 1-h 190; 2-h 165 and 3-h 145 mg/dl	Prediction of gestational diabetes	22 (4.4%) incidence of GD 85 (17%) showed glycosuria and 19 (3.8%) severe glycosuria 10 patients with glycosuria with GD (6 glycosuria, 4 severe glycosuria)	Routine random urine testing is a poor screening method but recommend that those classed as severe glycosuria before 24 weeks should have an earlier 50-g GCT	Non randomized population based study	II
Ostlund, 2004	837	All pregnant women without diabetes Sample size 3616	Random blood glucose (proposed every 4-6 weeks) and Risk factors (family history of diabetes, obesity, a prior LGA infant or prior GD) assessed. All were offered diagnostic test, 75g OGTT between 28-32 weeks of gestation	Diagnostic value	61/3616 or 1.7% had GD At a cut-off level of ≥ 8 mmol/l Sensitivity: 47.5% Specificity: 97%	Random blood glucose measurement has the same sensitivity for detecting GD as using traditional risk factors, but reduces the need to carry out the OGTT from 15.8% to 3.8% of the population Traditional risk factors have poor sensitivity for GD.	Prospective population based study	II
Nasrat, 1988	838	Healthy pregnant women Sample size 250	Random plasma glucose determined in 276 women and 250/276 women given a standard 75 g OGTT	Diagnostic value	3/250 or 1.2% had GD Using Lind and Anderson threshold (7.0 mmol/l < 2h 6.4 mmol/l > 2h) for random plasma glucose Sens: 16% Spec: 96% PPV: 47% Using 90th percentile of study group Sens: 29%	Random plasma glucose has limited predictive value	Prospective study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Spec: 89% PPV: 38%			
Seshiah, 2004	840	Consecutive pregnant women Sample size 1251	1h 50g GCT, 2 hr 75g OGTT, given to all during second and third trimesters	Diagnostic value	Positive screens 891 168/891 or 18.9% had GD Sens: 79.8%, Spec: 42.7%, PPV: 24.5%, NPV: 90.1%	Using 2h plasma glucose ≥ 140 mg/dl as once step procedure is simple and economical for countries more prone to GD	Prospective consecutive population based study	II
Perucchini, 1999	499	All pregnant women with singleton pregnancy giving birth after 28 weeks of gestation Exclusion criteria: pre-existing diabetes mellitus, lack of examination before 24 weeks of gestation. 772 eligible 558 consented 520 completed study	FPG, 50 g GCT, 3 hr 100g OGTT, given to all	Diagnostic value	52/520 or 10.2% had GD FPG at 4.8mmol/l, 50 g GCT 7.8 mmol/l Sens: FPG 81%, 50g GCT 59% Spec: FPG 76%, 50g GCT 91%	Sample representative of general population. Measuring FPG is easier than 50g GCT and allows 70% women to avoid the GCT.	Prospective population based observational study	
Cetin and Cetin, 1997	841	Pregnant women included if examined < 20 weeks' gestation Exclusion criteria: pre-existing diabetes mellitus, multiple pregnancy, preterm premature rupture of membranes, pre-eclampsia, birth ≤ 28 weeks, regular ingestion of any drug. 291/344 eligible, 274/291 completed study	1h 50g GCT, 100g OGTT, given to all between 24-28 weeks of gestation	Diagnostic value	17/274 or 6.2% had GD Sens: <2hr cut off 140 mg/dl 75%, cut off 148 mg/dl 63% 2-3hr cut off 140 mg/dl 60%, cut off 142 mg/dl 60% >3hr cut off 140 mg/dl 50%, cut off 150 mg/dl 50% Spec: <2hr cut off 140 mg/dl 86%, cut off 148 mg/dl 91% 2-3hr cut off 140 mg/dl 89% cut off 142 mg/dl 92% >3hr cut off 140 mg/dl 89%, cut off 150 mg/dl 92% PPV: <2hr cut off 140 mg/dl 27%, cut off 148 mg/dl 33% 2-3hr cut off 140 mg/dl 30% cut off 142 mg/dl 30% >3hr cut off 140 mg/dl 25%, cut off 150 mg/dl 33%	Sample too small. Standard cut off 140 mg/dl Sens 65% Spec 88% PPV 27% Suggested cut off Sens 59% spec 92% PPV 32%.	Prospective study	II
O'Sullivan, 1973	842	Prenatal women 752/ 986 (76%) eligible	1h 50g GCT, 3h OGTT given to all Weeks of gestation not reported	Diagnostic value	1hr 50g GCT ≥ 130mg/100ml cut off Sens: 78.9% Spec: 87.2% PPV: 13.8% NPV: 99.4%	Timing of testing in relation to stage of pregnancy not reported No quantity of glucose stated for GTT Sample collected between 1956 and 1957	Cohort study	III
Buhling,	843	Pregnant women	Comparison of 50g GCT with five portable meters	Diagnostic value of 5 portable meters	Sens:	The accuracy of Accu check,	Prospective	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
2003		Sample size 193			Accu check 84% Euro flash 100% Gluco touch 98% Hemo Cue 57% One touch 92% Precision 90% Spec: Accu check 98% Euro flash 79% Gluco touch 86% Hemo Cue 100% One touch 92% Precision 91%	Gluco touch, One touch and precision was acceptable for use in GD screening.	study	
Murphy, 1994	844	Pregnant women No other data given Sample size 124	3 groups, no control Tested at 24–28 weeks Non-fasting screening test: Group 1: 50 g glucose polymer Group 2: standard 50 g glucose solution Group 3: milk chocolate bar 50 g Blood test at 1 h Diagnostic test: 3-h 100-g GTT	Serum glucose response, side effects and women's subjective acceptance of the polymer or a candy bar (3 Musketeers, Mars) to the standard d-glucose solution	5/108 or 4.6% diagnosed with GD. Glucose ≥ 7.5 mmol/l Sens: overall 60% standard glucose 33.3% polymer 100% Spec: overall 84% standard glucose 73.6% polymer 92.8% PPV: overall 16% standard glucose 9% polymer 49%	The polymer is an inexpensive and well tolerated but the use of candy bar needs further research.	Randomised trial with no control	II
Court, 1985	845	Pregnant women Sample size: 100 women randomized to glucose screening test (48) and glucose polymer test (52) glucose polymer test given to additional 178 women so total 230 women received polymer test.	100g glucose screening test and 100g glucose polymer screening test, No cut-off value used, Diagnostic test: 3h 100g OGTT	Improvement of screening of GD with the use of glucose polymer rather than glucose	12/230 or 5.2% diagnosed with GD 8 mmol/l or 144 mg/dl, For glucose polymer Sens: 89% Spec: 81% PPV: 29%	The glucose polymer is preferable to glucose for CHO loading in pregnancy because of lower rates of nausea, better reproducibility of test results.	Randomised controlled trial	II
Reichelt, 1998	498	Inclusion criteria: women aged ≥ 20 years, with no diagnosis of DM and between 21 and 28 weeks on enrolment Sample size 5,579, 5,010 remaining in the study	FPG Diagnostic test given to all, 2 hr 75 g OGTT	Diagnostic value	379/5,010 or 7.6% diagnosed with GD At cut off value of 81 mg/dl or 4.5 mmol/l Sens: 94% Spec: 51% PPV: 0.6 NPV: 100 At cut off value of 85 mg/dl or	FPG is a useful screening test for GD, a threshold of 89mg/dl maximizes sensitivity and specificity.	Cohort study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					4.7 mmol/l Sens: 94% Spec: 66% PPV: 0.9 NPV: 100 At cut off value of 89 mg/dl or 4.9 mmol/l Sens: 88% Spec: 78% PPV: 1.3 NPV: 100			
Fadl, 2006	846	Pregnant women Sample size 3616	Fasting plasma glucose Diagnostic test given to all 2 hr 75g OGTT between 28-32 wks	Diagnostic value	55/3616 or 1.52% diagnosed with GD FPG Cutoff values between 4.0 and 5.0 mmol/l, Sensitivity 87% to 47% Specificity 51% and 96%. +LR and –LR best at ≥5.0 mmol/l.	Fasting plasma glucose was found to be an acceptable and useful screening test for gestational diabetes	Cross-sectional population based study	II
Lamar, 1999	847	Pregnant women Women with diabetes mellitus were excluded Sample size 160, 136 completed the study	Jelly beans vs. standard glucose (randomization done), Blood glucose ≥ 140 mg/dl 3h 100g fasting GTT used as diagnostic test	Diagnostic value using jelly beans	5/136 or 3.7% diagnosed with GD Using cut off140 mg/dl, standard glucose: Sens: 80% Spec: 82% PPV: 15% NPV: 99% Jelly beans: Sens: 40% Spec: 85% PPV: 9% NPV: 97%	There is no significant difference in screening performance for jelly beans and the standard glucose. Patients report fewer side effects after a jelly bean challenge than after a 50-g glucose beverage test. So jelly beans may be used an alternative to the 50g glucose beverage test.	Prospective study	II
Boyd, 1995	848	Pregnant women Exclusion criteria: Insulin dependent diabetics, women with a history of insulin usage for GD in a prior pregnancy and previously diagnosed gestational diabetics Sample size 157	Cola beverage vs. Jelly beans, Diagnostic test given to all participants 3h 100g GTT used as diagnostic test	Diagnostic value using jelly beans	13/157 or 8.3% diagnosed with GD Using cut off 140 mg/dl for cola beverage Sens: 46% Spec: 81% PPV: 18% Using cut off 120 mg/dl for jelly beans Sens: 54% Spec: 81% PPV: 20%	Patient tolerance was greater for jelly beans as compared with the 50 gm cola beverage. Jelly beans may serve as an alternative to a cola beverage containing 50 gm of glucose.	Prospective study	II
Griffin, 2000	832	Pregnant women Risk factor group has one or more risk factors for GD	The risk factor group had a 3h 100g OGTT at 32 weeks if any risk factor for GD was present. The universal group had a 50g GCT and if their plasma glucose at 1h was ≥ 7.8mmol/l, a formal 3h 100g OGTT was then performed.	Spontaneous vaginal delivery, macrosomia, caesarean section, prematurity, preeclampsia and admission to neonatal intensive care unit	Universal screening detected a GD prevalence of 2.7%, significantly 1.45% more than in the risk factor screened group.	Universal screening for GD was found to be superior to risk factor based screening as it detected more cases, facilitated early diagnosis and is associated with	Randomised controlled trial	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Universal screening group had higher rates of spontaneous vaginal delivery at term, lower rates of macrosomia, caesarean section, prematurity, preeclampsia and admission to neonatal intensive care unit.	improved pregnancy outcomes.		
Schytte, 2004	833	Pregnant women who accepted screening for GD Sample size 1392	Capillary fasting blood glucose measurements between 20 and 32 weeks of gestation If levels ≥4.1 mmol/l and < 6.7 mmol/l a 3 hr 75 g OGTT was offered	Clinical outcome of pregnant women in relation to separate components of the pre-screening procedure, presence of GD and the capillary blood glucose 120 min after glucose load ($CBG_{120\ min}$) concentration after a 75 g glucose load	Screening cFBG of 4.1 mmol/l unable to predict GD and adverse outcome Best predictor of complicated delivery was a high BMI. Best predictor of fetal adverse outcome was $CBG_{120\ min} \geq 9.0$ mmol/l after a 75 g glucose load Identical fraction complications were present in GD and non-GD.	Screening procedure for GD needs to be refined	Retrospective study	2-
Weijers, 2006	834	Pregnant women Sample size 2031	The following data were collected for all women: age and gestational age at entry into the study; prepregnancy body mass index (BMI); ethnicity; obstetric and clinical history, including the onset of early postpartum diabetes; pregnancy outcome; level of fasting C-peptide; and glycemic parameters of 50-g 1-h glucose challenge test and 100-g 3-h oral glucose tolerance test (diagnostic OGTT)	Diagnostic value of antepartum clinical characteristics	11/168 or 6.6% women developed early postpartum diabetes. Family history of diabetes showed association with early postpartum diabetes. ROC curve analysis identified all three glucose challenge-test parameters, including fasting glucose concentration, as poor diagnostic tests, with a PPV of 22%, whereas PPV associated with the area under the diagnostic OGTT curve increased progressively over monitoring time from 20.6% to 100%. Using a 3-h OGTT glucose area threshold of 35.7 mmol·h/L resulted in 100% sensitivity and 100% specificity, identifying the 11 women who developed early postpartum diabetes.	Early postpartum diabetes is rare in GD women (6.5%), and that the clinical usefulness of the total area under the diagnostic 3-h OGTT is superior to all other glycemic parameters for detecting early postpartum diabetes.	Cross sectional study	2-
Rajab, 1998	849	Pregnant women Sample size 3400	Screening test used was blood glucose 1h after 50g glucose load (GCT) given in fasting state between 28 and 32 weeks. If blood glucose was ≥ 7.7mmol/l then 3 h GTT was given	Pregnancy outcomes were compared for the following groups:	197/3400 or 5.8% women were considered to have abnormal GTT plus 199/3400 or 5.8% had impaired glucose tolerance. There was no	Study was on a small scale but it suggests that it is possible to raise the cut-off level requiring full GTT from 7.7 to 8.3 mmol/l without a serious adverse effect on	Prospective cohort study	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
				A. GCT > 7.7 and < 8.3 mmol/l (194 women) B. GCT ≥ 8.3 mmol/l (194 women) C. GCT < 7.7 mmol/l (194 women matched for age, parity and weight with group B)	significant difference in pregnancy induced hypertension between groups. Pre-term delivery was significantly more in group B. Birth weight > 4.5 kg was 4% in group C, 6% in group A and 9% in group B. The APGAR > 6 at 1 min found no significant differences between groups.	pregnancy outcome		
Yogev, 2005	[850]	Pregnant women Sample size 6854	A 50g GCT was performed at 24-28 weeks gestation and a screening value of ≥ 130 mg/dl was followed by a 100g OGTT	Women were categorized by prepregnancy BMI and by different GCT thresholds. Maternal outcome was defined by rate of preeclampsia, gestational age at delivery, cesarean section (CS) rate and the need for labor induction. Neonatal outcome was defined by fetal size (macrosomia/LGA), arterial cord pH, respiratory complications and neonatal intensive care unit (NICU) admission.	A positive GCT result (GCT ≥130 mg/dl) was identified in 2541/6854 or 37% women. 464/6854 or 6.8% of women were diagnosed with GD. In both groups of screening results (> 130 mg/dl and < 130 mg/dl), the obese women were significantly older, gained more weight during pregnancy and had a lower rate of nulliparity in comparison to the non obese women. The obese women had higher rates of macrosomia, LGA and induction of labor. No difference was found in mean birth weight, the total rate of cesarean section, preterm delivery, 5 minute Apgar score < or = 7, mean arterial cord pH, NICU admission and a need for respiratory support in comparison to non obese women in both groups of screening results. A gradual increase in the rate of macrosomia, LGA and cesarean section was identified in both obese and non-obese women in relation to increasing GCT severity categories.	Fetal size and cesarean section are associated with the degree of carbohydrate intolerance. Obesity remains the main contributor impacting fetal size.	Prospective cohort study	2+
Dietrich, 1987	[851]	Middle-class, healthy, Caucasian pregnant women Sample size 2000	Screening test involved a 50g GCT followed by a 3h OGTT if necessary	Compared the value of routine versus selective diabetes screening1. Those to undergo routine screening between 24 and 28 weeks gestation	Incidence of GD in the selectively screened group was twice (19/453, 4.2%) that in routinely screened group	This assessment has allowed clinical practice to safely eliminate the need for diabetes screening in more than half of their private	Prospective study	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
				2. Those to be tested selectively in the presence of standard risk factors.	(21/1000, 2.1%). Glucose intolerance without a risk factor was found in only one case (1/1000, 0.1%) in the routinely screened group.	patients, which reduces office time, patient inconvenience, and expense.		
Sun, 1995	852	Pregnant women, no history of diabetes mellitus before pregnancy Sample size 622	50g GCT and a 75g OGTT was performed if screening tests value was ≥ 7.78 mmol/l	Relationship between the 50g GCT and pregnancy outcomes	103/622 or 16.56% women underwent the diagnostic test, among whom, 32 were identified as having gestational impaired glucose tolerance (GIGT) and 12 as GD. The sensitivity of 50gGCT was 42.72% (44/103). The incidences of edema-proteinuria-hypertension syndrome (EPH-syndrome), premature rupture of membranes, fetal macrosomia, operative deliveries and perinatal morbidity were higher in women with GIGT/GD than in women without GIGT/GD.	50gGCT is an ideal method of screening for GD and should be performed on all pregnant women.	Prospective randomized study	2+
Rumbold, 2002	853	Total of 158 women participated in the study whereas 51 women participated after being screened	They tested the hypothesis that women with a positive result on the screen test will experience a reduction in quality of life, their health and that of their baby when compared with women with a normal screening result	Women's experiences of being screened for GD A Spielberger State-Trait Anxiety Inventory, Edinburgh Postnatal Depression Scale and Short Form 36 Item Health Survey were used to study the main outcome measures: anxiety, depression, health status, concerns about the health of the baby and perceived health	No differences in the levels of anxiety, depression or the women's concerns about the health of their babies. When positively screened women for GD were compared with negatively screened women, the positively screened group had significantly lower health perceptions, were significantly less likely to rate their health as 'much better than one year ago' and were significantly more likely to rate their health as 'fair' rather than 'very good' or 'excellent'.	There is a negative impact on the health perceptions in women screened positive for GD.	Prospective survey	2-
Kerbel, 1997	854	Women between 12 and 14 weeks' gestation with no previous history of diabetes mellitus or GD were included 809 women completed questionnaires at baseline, 32 weeks, and 36 weeks'	50g glucose challenge test	Whether false positive results of 50g glucose challenge test for GD are associated with adverse psychological effects.	At 32 weeks, 20% women with false positive GCT results significantly perceived their health as excellent as compared to 38% women with negative results or not tested. These results were sustained at 36 weeks. The study	False positive screening for GD is associated with a decreased perception of maternal health persisting at 36 weeks' gestation and this should be taken into account when setting a policy of screening all pregnant women for GD.	Prospective cohort study	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		gestation			showed no significant association between false positive test result and anxiety levels, depression or woman's concern for health of baby. These results were neither significant between baseline and 32 weeks nor at 36 weeks.			
Naylor, 1997	855	Pregnant women Sample size 3131	3131 women randomly divided into two groups- a derivation group and a validation group. The screening strategies were derived from the derivation group data which were then tested in the validation group by comparing the effectiveness and efficiency with those of usual care. The strategies used were; no screening for low-risk women, usual care for intermediate-risk women, and universal screening with lower thresholds -- plasma glucose values of 130 mg per deciliter (7.2 mmol per liter) or 128 mg per deciliter (7.1 mmol per liter) -- for high-risk women.	Using clinical characteristics for assessing women's risks of gestational diabetes could enhance the efficiency of screening	There was a 34.6% reduction (95% CI, 32.3 to 37.0) in the number of screening tests performed after using the new strategies. The detection rate of gestational diabetes with new strategies was 81.2 to 82.6 % compared with the 78.3% detected through usual care. There was a significant reduction in the percentage of false positive screening tests from 17.9 % with usual care to 16.0 % or 15.4 % (P<0.001) with the new strategies, depending on the threshold values for high-risk women.	The consideration of women's clinical characteristics allows efficient selective screening for gestational diabetes.	Prospective study	2+
Scott, 2002	483				Risk factors for gestational diabetes included obesity, advanced maternal age advanced maternal age, family history of diabetes, minority ethnic background, increased weight gain in early adulthood and current smoker.		Systematic review	2+
Dornhorst, 1992	829			frequency of gestational diabetes according age, BMI, parity and ethnic origin in women without known pre-existing diabetes mellitus and to analyse the influence of risk factors separately for each ethnic group	170/11205 (1.5%) women were diagnosed with gestational diabetes. Women with gestational diabetes were significantly older (32.3 versus 28.3 years; p<0.001) had higher BMI (27.7 versus 23.8; p<0.001) and more likely to be from an ethnic minority (55.4% versus 15.3%; p<0.0001). Rates of gestational diabetes by ethnicity were: white 0.4%		Retrospective study	2-

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					(26/6135), Black 1.5% (29/1977); South East Asian 3.5% (20/572); Indian 4.4% (54/1218). After adjusting for age, BMI and parity the RR (with white as the reference category) was as follows: Black 3.1 (95% CI 1.8 - 5.5); South East Asian 7.6 (95% CI 4.1 – 14.1); Indian 11.3 (95% CI 6.8-18.8).			
Moses, 1995	830			the proportion of women with gestational diabetes missed if testing was confined to risk factors	Women without GD were significantly younger (26.4:28.1, $p < 0.02$) and had a lower BMI (24.2:25.9, $p < 0.05$) than women with GD. 31 women (39.2%) with GD had no historical risk factors and would have been missed if only selective testing undertaken.		Observational study	3
Ostlund, 2003	835		Traditional risk factors used were family history of diabetes (first degree relative), obesity (≥90 kg), prior large for gestational age baby (≥ 4500g) or prior GD		Women who did not take the OGTT were more likely to be multiparous and of non-nordic origin but were less likely to have a family history of diabetes, prior macrosomic baby or prior gestational diabetes. 1.7% of women who were given OGTT were diagnosed with gestational diabetes. The risk factors with the strongest association were prior gestational diabetes (12/61, OR 23.6, 95% CI 11.6-48.0) and prior macrosomic baby (9/61, OR 5.59, 95% CI 2.68-11.7). Other risk factors were family history of diabetes (13/61, OR 2.74, CI 1.47-5.11) non-nordic origin (13/61, OR 2.19, 95% CI 1.18-4.08) weight (≥90kg: 8/61, OR 3.33, 95% CI 1.56-7.13) BMI (≥30: 11/61, OR 2.65, 95% CI 1.36-5.14) and age (≥ 25: 55/61,		Prospective population-based study	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					OR 3.37, 95% CI 1.45-7.85).			
Kim, 2007	836	13 studies were included		Recurrence rates and risk factors for gestational diabetes	The recurrence rate of glucose intolerance during subsequent pregnancies varied markedly across studies. The most consistent predictor of future recurrence appeared to be nonwhite race/ethnicity, although the racial breakdowns within a study were not always clearly described. The recurrence rates varied between 30 and 84% after the index pregnancy. The recurrence rates were higher in the minority populations (52–69%) as compared to lower rates found in non-Hispanic white populations (30–37%). No other risk factors were consistently associated with recurrence of GD across studies. Other risk factors, such as maternal age, parity, BMI, oral glucose tolerance test levels, and insulin use inconsistently predicted development of recurrent GD across studies.		Systematic review	2++

Clinical Question: What is the diagnostic value of different screening methods in identifying women at risk of developing pre-eclampsia?

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Yaron, 1999	857	Sample size 60040 Exclusion criteria: structural or chromosomal anomalies Age not reported 14-22 wks	Reference standard: SBP ≥140 mmHg or DBP ≥90 mmHg; presence of proteinuria Index cut off: Competitive RIA (Sanofi Diagnostics) 2.5 MoM	Diagnostic value of AFP screening test	Incidence of pre-eclampsia 3.2% Sens: 4.3% Spec: 97.4%	Multiple marker screening can be used for the detection of not only fetal anomalies and aneuploidy but also for detection of high-risk pregnancy	Prospective cohort study	II
Pouta, 1998	858	Sample size 637, Inclusion criteria: nulliparas Exclusion criteria: multiple pregnancies, foetal defects 27.7 ± 4.5 yrs 15-19 wks	Reference standard: BP ≥140/90 mmHg 6hrs apart or rise 30/15 mmHg; Prot. ≥300 mg/24 hrs Index cut off: time resolved FIA (Wallac) 2.0 MoM	Diagnostic value of AFP screening test	Incidence of pre-eclampsia 5.3% Sens: 3% Spec: 98%	AFP not helpful in predicting pre-eclampsia	Population-based cohort study	II
Cotter, 2004	859	Sample size 264 (88 cases and 176 controls) Inclusion criteria: Normotensive non-proteinuric women, male fetuses Exclusion criteria: aneuploid fetuses 26.1 ± 5.9 yrs, 15.7 ± 3.6 wks	Reference standard: BP ≥ 140/90 mmHg; Prot. ≥ 0.3 g/ 24 hrs or 1+/2+ dipstick Index cut off: fDNA Real-time PCR TaqMan SRY <10,000 copies/mL <50,000 >50,000	Diagnostic value of Foetal DNA screening test	SRY copies/mL <10,000 Sens: 94.32% Spec: 32.39% +LR: 1.39 <50,000 Sens: 81.82% Spec: 64.77% +LR: 2.32 >50,000 Sens: 38.64% Spec: 90.34% +LR: 4.00	Increased fetal DNA is present in the maternal circulation in early pregnancy in women who subsequently develop pre-eclampsia and there appears to be a graded response between the quantity of fetal DNA and the risk of developing pre-eclampsia.	Case control study (nested and matched)	II
Leung, 2001	860	Sample size: 51 (18 cases and 33 controls), Inclusion criteria: singleton pregnancies, male fetuses Age n.r. 11-22 wks	Reference standard: DBP ≥ 90 mmHg 2x ≥4 hrs apart or DBP ≥ 110 mmHg; Prot. ≥ 0.3 g/ 24 hrs or 2+ dipstick 2x ≥4 hrs apart,	Diagnostic value of Foetal DNA screening test	SRY ≥ 33.5 Geq/mL Sens: 67% Spec: 82%	Maternal plasma fetal DNA might be used as a marker for predicting pre-eclampsia.	Case control study (nested and matched)	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			Incidence n.r. Index cut off: fDNA Real-time PCR TaqMan SRY ≥ 33.5 Geq/mL		(cant calculate LRs)			
Yaron,1999	857	Sample size: 45565, Exclusion criteria: structural or chromosomal anomalies Age n.r. 14-22 wks	Reference standard: SBP ≥140 mmHg or DBP ≥90 mmHg; presence of proteinuria Index cut off: ß-hCG IRMA 2.5 MoM	Diagnostic value of β hCG screening test	Incidence of pre-eclampsia 3.0% Sens: 5.5% Spec: 96%	Multiple marker screening can be used for the detection of not only fetal anomalies and aneuploidy but also for detection of high-risk pregnancy	Prospective cohort study	II
Lambert-Messerlian , 2000	861	Sample size: 359 (60 cases, 299 controls) IN: singleton pregnancies EX: chronic hypertension, diabetes; 26.9 ± 7.3 yrs 15-21 wks	Reference standard: BP> 140/90 mmHg; Prot. >300mg/24 hrs or ≥2+ dipstick, Index cut off: Total hCG (Serono MAIO Clone) 2.3 MoM	Diagnostic value of β hCG screening test	Incidence of pre-eclampsia 16.7% With 95% specificity a modeled sensitivity of 15% (cant calculate LRs)	2nd trimester serum levels of hCG is a modest predictor of later onset preeclampsia.	Case control study	II
Ashour, 1997	862	Sample size: 6138, IN: singleton pregnancies EX: foetal/ chromosomal abnormalities, diabetes, chronic hypertension 28.1 ± 5.3 yrs 15-22 wks	Reference standard: SBP ≥140 mmHg or DBP ≥90 mmHg 2x 6 hrs apart; Prot. >300 mg/24 hrs or ≥1+ dipstick 2x 6 hrs apart Index cut off: ß-hCG (IMx Abbott) 2.0 MoM	Diagnostic value of β hCG screening test	Incidence of pre-eclampsia 3.2%	The utility of an elevated second-trimester β-hCG level as a screening test for preeclampsia is limited.	Prospective cohort study	II
Sanchez-Ramos, 1991	863	Sample size: 99, Inclusion criteria: Normotensive nulliparas Exclusion criteria: diabetes mellitus, renal disease, chronic hypertension, other chronic medical illnesses 18.7 ± 0.5 yrs, 10-24 wks	Reference standard: BP ≥ 140/90 mmHg twice ≥ 6 hrs apart or rise SBP ≥ 30 mmHg or DBP ≥ 15 mmHg Prot. ≥ 0.3 g/ 24 hrs or ≥ 1+ dipstick Index cut off: Colorimetric/ colorimetric autoanalyzer ≤ 195 mg/24 hrs	Diagnostic value of urinary calcium excretion screening test	Incidence of pre-eclampsia 8.1% Sens: 86% Spec: 84% PPV: 46% NPV: 98%	The study suggests a pathophysiologic role for altered urinary calcium excretion in women with preeclampsia that may contribute to early identification of patients at risk for the disease.	Prospective longitudinal study	II
Baker, 1994	864	Sample size: 500, Inclusion criteria: Normotensive nulliparas Exclusion criteria: renal disease, chronic hypertension Median 27 yrs (range 24-31), 18-19 wks	Reference standard: DBP ≥ 90 mmHg twice ≥ 4 hrs apart Prot. ≥ 0.3 g/ 24 hrs Index cut off: Perspective analyzer (colorimetric)/ Monarch centrifugal analyzer (kinetic) n.r.	Diagnostic value of urinary calcium excretion screening test	Incidence of pre-eclampsia: 2.6% Sens: 31% Spec: 72% (correctly predicted 71%)		Prospective, non-interventional study	II
Rogers, 1994	865	Sample size: 199, Inclusion criteria: normotensive primigravidas, singleton pregnancies Exclusion criteria: congenital malformations	Reference standard: BP ≥ 140/90 mmHg ≥ twice Prot. ≥ 0.3 g/L Index cut-off: Cresolphtalein method	Diagnostic value of calcium creatinine ratio screening test	Incidence of pre-eclampsia 4.0% Sens: 49% Spec: 90%		Cohort study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		27.1 ± 3.8 yrs, 18-26 wks	(American Monitor)/ Beckman Astra-8 analyzer 0.3					
Conde, 1994	866	Sample size: 387 women, Inclusion criteria: normotensive nulliparas, singleton pregnancies Exlcusion criteria: diabetes mellitus, renal disease, proteinuria, chronic hypertension, other chronic medical illnesses 23.8 ± 5.7 yrs, 20 wks	Reference standard: SBP ≥ 140 or DBP ≥ 90 mmHg twice ≥ 6 hrs apart Prot. ≥ 0.3 g/L Index cut off: Colorimetric (direct)/ picrato alcalino method 0.07	Diagnostic value of calcium creatinine ratio screening test	Incidence of pre-eclampsia 3.4% Sens: 33% Spec: 78% PPV: 5% NPV: 97%	Poor predictive values suggest that changes in the biochemical and hematologic tests occur only when preeclampsia has been established.	Prospective cohort study	II
Kazerooni, 2003	867	Sample size: 102, Inclusion criteria: nulliparas (18-35 years) Exclusion criteria: renal disease, diabetes mellitus, proteinuria, chronic hypertension, other chronic medical illnesses 22.8 ± 4.5 yrs, 20-24 wks	Reference standard: BP ≥ 140/90 mmHg or rise SBP ≥ 30 mmHg or DBP ≥ 15 mmHg twice ≥ 6 hrs apart Prot. ≥ 0.3 g/ 24 hrs or ≥ 1+ dipstick Index cut off: n.r. ≤ 0.229 (mg/dL:mg/dL)	Diagnostic value of calcium creatinine ratio screening test	Incidence of pre-eclampsia 7.8% Sens: 75% Spec: 77.7% PPV: 20.7% NPV: 97%	Single urine calcium to creatinine ratio may be an effective method for screening women at the greatest risk of pre-eclampsia.	Prospective cross sectional study	II
Baker, 1994	864	Sample size: 500, Inclusion criteria: Normotensive nulliparas Exclusion criteria: renal disease, chronic hypertension Median 27 yrs (range 24-31), 18-19 wks	Reference standard: DBP ≥ 90 mmHg twice ≥ 4 hrs apart Prot. ≥ 0.3 g/ 24 hrs Index cut off Perspective analyzer (colorimetric)/ Monarch centrifugal analyzer (kinetic) n.r.	Diagnostic value of calcium creatinine ratio screening test	Incidence of pre-eclampsia 2.6% Sens: 31% Spec: 55% (correctly predicted 71%)		Prospective, non-interventional study	II
Papageorghiou, 2001	868	Sample size: 7851, Inclusion criteria: singleton pregnancies, routine antenatal care. Exclusion criteria: foetal abnormalities 29.7 (16-47) yrs, 22-24 wks	Reference standard: DBP≥90 mmHg twice >4h apart, prot. ≥0.3 g/24h or ≥2+ dipstick twice if no 24h collection available Index cut off: CD+PW, transvaginal Acuson SP-10, Aloka 5000, Aloka 17000, ATL HDI 3000, ATL Hdi 3500, Hitachi, Toshiba, Siemens	Diagnostic value of bilateral notches screening test	Incidence of pre-eclampsia 1.4% Sens: 25.4% Spec: 90.9% PPV: 2.5% NPV: 99.3% +LR: 8.87 -LR: 0.62		Cohort study	II
Harrington, 1997	869	Sample size: 626, Inclusion criteria: Singleton pregnancies, unselected 15-49 yrs, 12-16 wks	Reference standard: SBP≥140 or DBP≥90 mmHg, prot >0.3g/24h Index cut off: CD+PW, transvaginal Acuson 128	Diagnostic value of bilateral notches screening test	Incidence of pre-eclampsia 4.8% Sens: 92.9% Spec: 85.1% PPV: 23.6% NPV: 99.5%		Cohort study	II
Marchesoni, 2003	870	895 (177 cases and 718 controls) Unselected women 31.7 ± 5.3 yrs, 20 wks,	Reference standard: BP> 140/90 mmHg, prot. >0.3g/24h Index cut off: CD Acuson Sequoia	Diagnostic value of bilateral notches screening test	Incidence of pre-eclampsia 2.9% Sens: 72% Spec: 94% PPV: 26%		Case control study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		24 wks			NPV: 99%			
Schwarze, 2005	871	Sample size: 346 women (19-22 wks- 215 women) (23-26 wks-131 women), Exclusion criteria: essential hypertension, DM, autoimmune disorders, history of PE, IUGR, IUD, placental abruption; multiple pregnancies, foetal abnormalities 31.4 (17-46) yrs, 19-22 wks, 23-26 wks	Reference standard: RR≥140/90 mmHg, prot. ≥0.3g/24h, no UTI Index cut off: CD Elegra (Siemens), Acuson 128 XP10	Diagnostic value of bilateral notches screening test	Incidence of pre-eclampsia 4.9% 19-22 wks vs 23-26 wks Sens: 40% vs 67% Spec: 82% vs 84% PPV: 10% vs 17% NPV: 97% vs 98%	The predictive value of uterine artery Doppler for adverse pregnancy outcome in a low-risk population is of limited diagnostic value. Performing uterine artery Doppler studies at 23-26 weeks' gestation increases the predictive value for adverse pregnancy outcomes.	Prospective study	II
Emine,2005	872	Sample size: 178, Exclusion criteria: multiple pregnancies, hypertension before 26 wks, diabetes or pregnancy with prenatal and postnatal diagnosis of a chromosomal/ structural abnormality, previous pregnancy complicated by pre-eclampsia, 28.8±5.1 30.6±4.3, 16-18 wks 24-26 wks	Reference standard: BP≥ 140/90 mmHg and first D_X after 20 wks, proteinuria ≥ 300mg/24hr Index cut off: Two site enzyme immunoassays, immunometric assays, two site chemiluminescent immunometric assay, ultrasound machines	Diagnostic value of integrated Doppler screening test	Incidence of pre-eclampsia 7.9% Bilateral notch Sens:85.7% Spec: 97.6% Bilateral notch + serum activin Sens: 78.6% Spec: 100% Bilateral notch+ serum inhibin Sens: 71.4% Spec: 100% Bilateral notch OR serum activin Sens: 100% Spec: 86%	Maternal serum inhibin A and activin A levels and uterine artery Doppler appear to be uselful screening tests during the second trimester for pre-eclampsia. However the addition of these hormonal markers to Doppler velocimetry only slightly improves the predictive efficacy.	Prospective study	II
Audibert, 2005	873	Sample size: 2615, EX: multiple pregnancies, without ultrasound between 10-14 wks, women refered for nuchal translucency, structural anomalies, chromosomal abnormalities, 30.9 ± 4.5 years, 14-18 wks 18-26 wks	Reference standard: SBP ≥140 mmHg or a DBP ≥90 mmHg twice, proteinuria > 0.3 g/24hr or at least 2+ protein on urine dipstick Index cut off: Amerlite kit	Diagnostic value of integrated Doppler screening test	Prevalence of PE 1.95% Bilateral notch Sens: 21.56% Spec: 95.94% History of pre-eclampsia or bilateral notch or hCG> 2.5 MoM Sens: 41.17% Spec: 91.61%	Combination of serum markers and abnormal uterine Doppler ultrasound improves the identification of women at risk for subsequent pregnancy complications. The care providers should be encouraged to perform a uterine Doppler ultrasound when serum markers are abnormal. However, the sensitivity of these tests is too low to provide an efficient generalized screening.	Cohort study	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Skjaerven et al., 2002	531	Sample size: 551,478 women who had 2 or more singleton deliveries and 209,423 women who had 3 or more singleton deliveries were studied	A large registry used in Norway to evaluate the effects on the risk of pre-eclampsia of both the interbirth interval and a change of partner	Time interval between pregnancies	Risk in a second or third pregnancy was directly related to the time elapsed since the previous delivery. The association between risk of pre-eclampsia and interval was more significant than the association between risk and change of partner. When the interval was 10 years or more the risk of pre-eclampsia was about the same as that in nulliparous women. After adjustment for the presence or absence of a change of partner, maternal age, and year of delivery, the probability of pre-eclampsia was increased by 1.12 for each year increase in the interval (odds ratio 1.12, 1.11 to 1.13).	The protective effect of previous pregnancy against pre-eclampsia is transient.	Prospective study	2+
Conde-Agudelo et al., 2000	874	456,889 parous women delivering singleton infants	Impact of interpregnancy interval	Maternal morbidity and mortality	women with more than 59 months between pregnancies had significantly increased risks of pre-eclampsia (relative risk 1.83, 1.72 to 1.94) compared with women with intervals of 18-23 months	interpregnancy intervals < 6 months and > 59 months are associated with an increased risk of adverse maternal outcomes.	Retrospective cross sectional study	3
Basso et al., 2001	875	Danish women with pre-eclampsia in the previous birth (8,401 women) all women with pre-eclampsia in second (but not first) birth together with a sample of women with two births (26,596 women)	Interpregnancy interval	Interpregnancy interval may confound or modify the paternal effect on pre-eclampsia	a long interval between pregnancies was associated with a significantly higher risk of pre-eclampsia in a second pregnancy when pre-eclampsia had not been present in the first pregnancy and paternity had not changed	The interval between births should be taken into consideration when studying the effect of changing partner on pre-eclampsia.	cohort study	2+
Reiss et al., 1987	876	30 patients met their criteria for preeclampsia and were matched for age, race, and parity with normotensive control subjects	Reviewed the outpatient charts of all patients with preeclampsia who received prenatal care at their clinics during the past 3 years	Blood pressure at booking	Both systolic and diastolic blood pressures were significantly higher ($p < 0.05$) in the first trimester for women with preeclampsia than for normal control subjects beginning in the first trimester.	This difference persisted throughout pregnancy and was also present at the 6-week postpartum visit ($p < 0.025$).	Retrospective study	2-
Sibai et al., 1995	877	2947 healthy women with a single fetus were prospectively followed up from randomization at 13 to 27 weeks' gestation to the end of pregnancy	Determine whether any maternal demographic or clinical characteristics are predictive of pre-eclampsia	Blood pressure at booking	Higher systolic and diastolic blood pressures at the first visit were associated with an increased incidence of pre-eclampsia (3.8% in women with diastolic blood pressure of < 55 mm Hg, 7.4% in those with diastolic blood pressure 70-84 mm Hg). However, their recruitment was limited to women with a first blood pressure reading of ≤ 135/85 mm Hg.	Risk factors should be of value to practitioners counseling women regarding pre-eclampsia.	Clinical trial	1+
Odegard et al.,	878	323 cases of pre-eclampsia and 650 healthy controls	Studied the associations between established	Clinical manifestations of	a systolic blood pressure ≥ 130 mm	Nulliparity and	Population based	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
2000		were selected	risk factors for pre eclampsia and different clinical manifestations of the disease	disease	Hg compared with < 110 mm Hg at the first visit before 18 weeks was significantly associated with the development of pre-eclampsia later in pregnancy (adjusted OR 3.6 [2.0 to 6.6]). The association with a diastolic pressure ≥ 80 mm Hg compared with < 60 mm Hg was similar but not significant (adjusted OR 1.8 [0.7 to 4.6]).	hypertension increased the risk for each subgroup of pre-eclampsia, but high maternal weight, previous pre-eclampsia and smoking were not consistently associated with each clinical subtype	nested case-control	
Stamilio et al., 2000	530	Cases with severe pre-eclampsia were compared with control subjects with respect to clinical data and multiple-marker screening test results. Patients were assigned a predictive score according to the presence or absence of predictive factors	To develop a clinical prediction rule for severe preeclampsia that was based on clinical risk factors and biochemical factors.		The only variables that remained significantly associated with severe preeclampsia were nulliparity (relative risk, 3.8; 95% confidence interval, 1.7-8.3), history of preeclampsia (relative risk, 5.0; 95% confidence interval, 1.7-17.2), elevated screening mean arterial pressure (relative risk, 3.5; 95% confidence interval, 1.7-7.2), and low unconjugated estriol concentration (relative risk, 1.7; 95% confidence interval, 0.9-3.4). This predictive model for severe preeclampsia, which included only these 4 variables, had a sensitivity of 76% and a specificity of 46%.	Even after incorporation of the strongest risk factors, the predictive model had only modest sensitivity and specificity for discrimination of patients at risk for development of severe preeclampsia.	Retrospective cohort study	2-
Stettler et al., 1992	879	65 pregnancies in 53 women with the following criteria: proteinuria exceeding 500 mg per day, no previously known renal disease, no reversible renal dysfunction, and no evidence for preeclampsia at discovery were studied.	Evaluated varying degrees of chronic proteinuria as a predictor of pregnancy outcome. Determined the significance of otherwise 'asymptomatic' proteinuria identified during pregnancy	Perinatal outcomes	58% of the women with proteinuria combined with renal insufficiency developed pre eclampsia. 100% of women with preteinuria combined with chronic hypertension developed preeclampsia whereas 77% of women with with all three together developed preeclampsia	'Asymptomatic' proteinuria is associated with a number of adverse pregnancy outcomes and serious long-term maternal morbidity.	Retrospective study	2-

Preterm labour (diagnostic accuracy)

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Goldenberg et al, 1998	880	Asymptomatic pregnant women with singleton pregnancies at 22-24 weeks in USA who already had a dating scan (n=2929). Mean age 23.7 ± 5.5 years, 63% Black, 42% nulliparaous	Predictive value, prevalence, and PAR. Reference standard – postnatal assessment of gestational age. Threshold of positive history – spontaneous previous birth at 20-37 weeks. Threshold for positive FFN test (single sample from posterior vaginal fornix at 24-26 weeks) – levels > 50 ng/ml. Threshold for short cervix on TVS at 24 and 28 weeks – length ≤ 25 mm	Spontaneous preterm delivery at < 32, < 35 and < 37 weeks	For SPTD < 37 wks H/O previous SPTB (n=1711) Sensitivity: 42% (35%, 49%) Specificity: 82% (80%, 83%) OR: 2.6 (1.9, 3.6) Positive FFN test (n=2929) Sensitivity: 19% (14%, 23%) Specificity: 95% (94%, 95%) OR nullipara: 2.9 (1.5, 5.5) OR multipara: 3.4 (2.1, 5.4) Short cervix (n=2929) Sensitivity: 24% (19%, 28%) Specificity: 93% (92%, 94%) OR nullipara: 4.6 (2.8, 7.5) OR multipara: 2.5 (1.6, 3.8)	Multi-centre study Representative population Blinding of outcome assessors Tests described in details	CH	I b
Iams et al, 1998	881	Asymptomatic parous women with singleton pregnancies at 22-24 weeks in USA who already had a dating scan, and with H/O previous SPTB (n=1282)	Estimation of risk of SPTD by H/O previous SPTB (from 18 to 37 weeks), positive FFN test (level > 50 ng/ml) and short cervical length (<25 mm on TVS)	Spontaneous preterm delivery at < 35 weeks	H/O previous SPTB at 18-26 wks RR (with short cervix): 0.25 (0.04, 0.72) RR (with short cervix + positive FFN): 0.64 (0.15, 0.95) H/O previous SPTB at 27-31 wks Sensitivity: 33% (23%, 44%) Specificity: 88% (86%, 89%) RR (with short cervix): 0.25 (0.04, 0.72) RR (with short cervix + positive FFN): 0.64 (0.14, 0.95) H/O previous SPTB at 32-36	Multi-centre study (retrospective analysis of data) Representative population Blinding of outcome assessors Tests described in details	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					wks Sensitivity: 67% (56%, 77%) Specificity: 73% (70%, 76%) RR (with short cervix): 0.25 (0.04, 0.70) RR (with short cervix + positive FFN): 0.63 (0.15, 0.94) H/O previous SPTB at > 37 wks RR (with short cervix): 0.06 (0.01, 0.25) RR (with short cervix + positive FFN): 0.25 (0.04, 0.71)			
Kristensen et al, 1995	[882]	All women with permanent address in Denmark who gave birth to their first singleton infant in 1982 and a second in 1982-87. (n=13965). Information obtained from National Medical Birth Register & National Register of Hospital Discharges	Relationship between preterm delivery in first pregnancy (both idiopathic and indicated) and complications in second pregnancy.	Preterm delivery at < 37 weeks (both idiopathic and indicated)	Diagnostic value for H/O idiopathic preterm delivery Sensitivity: 19% (14%, 23%) Specificity: 97% (96%, 97%) Relative risk for preterm delivery by conditions in first pregnancy SGA: 2.7 (2.0, 3.7) LGA: 1.2 (0.6, 2.3) Birthweight < 2500 gms: 4.7 (3.8, 5.6) Gest age < 32 wks: 6.0 (4.1, 8.8) Gest age 32-36 wks: 4.8 (3.9, 6.0)	Retrospective analysis of data Population representative Blinding not specified Test described in details	CH	II
Iams et al, 2002	[883]	Asymptomatic nulli and multiparous women with singleton pregnancies at 22-24 weeks in USA who already had a	To assess FFN levels (positive test if levels > 50 ng/ml), Bishop score (≥ 4 as threshold, digital examination done 4	Predictive value for spontaneous preterm delivery at < 35 weeks	Bishop score Sensitivity: 23.4% Specificity: 92.6% PPV: 9.1% NPV: 97.5%	Multi-centre study (retrospective analysis of data) Representative population	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		dating scan, and with no H/O previous SPTB (n=2107)	times before 35 wks) and short cervix (≤ 25 mm by TVS) as predictor of preterm delivery		RR: 3.6 (2.1, 6.3) Short cervix Sensitivity: 39.1% Specificity: 92.5% PPV: 14.0% NPV: 98.0% RR: 6.9 (4.3, 11.1) Positive FFN test Sensitivity: 23.4% Specificity: 97.0% PPV: 19.7% NPV: 98.0% RR: 8.2 (4.8, 13.9)	Blinding of outcome assessors Tests described in details		
Blondel et al, 1990	[884]	Women with single pregnancies attending two teaching hospitals in France (n=7641)	Clinical examination done at 25-28 and 29-31 wks for 5 signs – (1 cm internal os dilatation, short cervix ≤1 cms, mid position of cervix, soft or firm cervix, expansion of lower uterine segment). Two risk scores compared – Score 1 with maternal characteristics and symptoms, Score 2 with maternal characteristics, symptoms and vaginal examination.	Predictive value for spontaneous preterm delivery at < 35 weeks for clinical examination findings, and the two scores	At 25-28 weeks for nulliparaous 1) Cervical dilatation Sensitivity: 13% (8%, 19%) Specificity: 98% (98%, 99%) 2) Short cervix Sensitivity: 14% (9%, 20%) Specificity: 95% (94%, 96%) 3) Score 1 Sensitivity: 45.6% Specificity: 68.4% 3) Score 2 Sensitivity: 53.7% Specificity: 66.4% At 25-28 weeks for multiparaous 1) Cervical dilatation Sensitivity: 15% (9%, 23%) Specificity: 97% (96%, 98%) 2) Short cervix Sensitivity: 11% (6%, 17%) Specificity: 95% (94%, 96%) 3) Score 1 Sensitivity: 48.1% Specificity: 70.8%	Multi-centre study Blinding not specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					3) Score 2 Sensitivity: 57.5% Specificity: 68.5% At 29-31 weeks for nulliparaous 1) Score 1 Sensitivity: 55.0% Specificity: 66.0% 2) Score 2 Sensitivity: 63.3% Specificity: 62.7% At 29-31 weeks for multiparaous 1) Score 1 Sensitivity: 52.1% Specificity: 71.3% 2) Score 2 Sensitivity: 54.9% Specificity: 71.8%			
Chambers et al, 1990	885	Women with singleton pregnancies and with at least 2 visits to a hospital in France at < 28 weeks gestation (n=5758)	Clinical examination done once in two weeks. Threshold for short cervix – length ≤1 cms before 28 wks Threshold for cervical dilatation – length ≥1 cms before 37 wks.	Diagnostic accuracy results and risk for spontaneous preterm delivery < 37 weeks	Short cervix only Sensitivity: 21% (15%, 28%) Specificity: 89% (88%, 90%) RR: 2.15 Cervical dilatation Sensitivity: 37% (30%, 45%) Specificity: 83% (82%, 84%) RR: 2.73 Both together Sensitivity: 21.6% Specificity: 96.5% RR: 6.54	Population not representative Blinding not specified Test described adequately	CH	II
Parikh and Mehta, 1961	886	Singleton pregnancies attending antenatal clinic of a government hospital in India at 21	Vaginal examination done every 2 weeks from 21-36 weeks Threshold for open os –	Spontaneous preterm delivery < 37 weeks. Outcome of pregnancy also correlated with	Sensitivity: 49% (36%, 63%) Specificity: 57% (52%, 62%)	Population not representative. Blinding not specified Test described	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		weeks or more (n=655)	admit examining finger	parity, character of internal os, and duration of gestation		adequately		
Leveno et al, 1986	[887]	Low risk singleton pregnancies enrolled consecutively in a medical centre in USA (N=185)	Single vaginal examination done at 26-30 wks. Threshold for cervical dilatation – os >2cms dilated	Spontaneous preterm delivery < 34 weeks.	Sensitivity: 57% (18%, 90%) Specificity: 94% (89%, 98%)	Population not representative Blinding of outcome assessors Test described adequately	CH	II
Heath et al, 2000	[888]	Women with singleton pregnancies attending a fetal medicine unit in UK for routine second trimester anomaly scan (n=5146)	Risk ascertained for preterm delivery < 33 weeks for maternal characteristics (smoking, previous delivery at 24-33 weeks), FFN positivity (≥ 50 ng/ml) and cervical length (≤ 15 mm) by TVS. Two swabs taken from posterior vaginal fornix at 22-24 weeks.	Diagnostic value for predicting spontaneous preterm delivery < 34 weeks.	Positive FFN test Sensitivity: 32.6% Specificity: 96.9% PPV: 8.1% NPV: 99.4% Short cervical length Sensitivity: 27.9% Specificity: 99.5% PPV: 30.8% NPV: 99.4% Maternal smoking Sensitivity: 32.6% Specificity: 85.4% PPV: 1.9% NPV: 99.3% Previous delivery at 24-33 weeks Sensitivity: 9.3% Specificity: 98.6% PPV: 5.5% NPV: 99.2%	Representative population Blinding for FFN levels, not for cervical length Test described adequately	CH	I b
Chang et al, 1997	[889]	Asymptomatic women at 28 weeks with no risk factors for preterm labour attending an out-	To evaluate usefulness of FFN as a screening test. Single Dacron swab taken from	Spontaneous preterm delivery < 34 and < 37 weeks.	For delivery < 37 weeks Sensitivity: 16.7% Specificity: 99.1% PPV: 60.0%	Representative population Blinding of technicians Test described	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		patient clinic in Singapore (n=240)	posterior vaginal fornix at 22-25 weeks. Threshold ≥ 50 ng/ml for a positive test		NPV: 93.4% For delivery < 34 weeks Sensitivity: 50.0% Specificity: 99.1% PPV: 60.0% NPV: 98.7%	adequately.		
Faron et al, 1997	[890]	Consecutive pregnant women attending antenatal clinic of a hospital in Belgium for routine care with known gestational age (n=170)	To assess accuracy of single FFN test for predicting preterm delivery. Single swab taken from posterior vaginal fornix at 24-33 weeks. Threshold ≥ 50 ng/ml for a positive test	Spontaneous preterm delivery < 37 weeks	Positive FFN test Sensitivity: 26.7% Specificity: 95.7% PPV: 40.0% NPV: 92.4% History of prior preterm delivery (n=87) Sensitivity: 30% Specificity: 96% PPV: 50.0%	Population representative Blinding of technicians Test described adequately	CH	I b
Daskalakis et al, 2006	[891]	Singleton pregnancies having anomaly scan at 22-25 weeks in a fetal medicine unit in Greece (n=1287)	To evaluate incidence of bacterial vaginosis in a low risk population at 22-25 weeks. Dacron swabs taken from posterior vaginal fornix for FFN levels (level ≥ 50 ng/ml for a positive test), bacterial vaginosis (Gram stain score by Nugent' criterion), and culture for Group B streptococcus colonization. Cervical length was measured by TVS (≤ 20 mm as threshold). Threshold for funneling by TVS not defined.	Spontaneous preterm delivery < 37 weeks. Comparison of incidence of preterm delivery in women with and without the risk factors (in %), predictive accuracy, and risk association after controlling for confounding variables	FFN levels (n=718) 13.3% vs 6.1% (p=0.03) Sensitivity: 13% (5%, 23%) Specificity: 94% (92%, 96%) RR: 2.32 (1.00, 5.54) Bacterial vaginosis (n=1197) 15.4% vs 7.2% (p=0.003) Sensitivity: 15% (8%, 22%) Specificity: 93% (91%, 94%) RR: 2.19 (1.21, 3.98) GBS colonization on culture (n=1197) 5.8% vs 13.2% (p=0.03) RR: 0.43 (0.19, 1.00) Short cervix (n=1197) 4.8% vs 1.1% (p=0.01) Sensitivity: 5% (1%, 9%) Specificity: 99% (98%, 99%)	Population representative Blinding of technicians for bacterial vaginosis, GBS culture and TVS measurements, not for FFN levels. Test described adequately	CH	I b II (for FFN)

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					RR: 3.31 (1.04, 1.98) Funneling (n=1197) 8.6% vs 3.8% (p=0.07) Sensitivity: 9% (3%, 14%) Specificity: 96% (95%, 97%) RR: 2.07 (0.94, 4.54)			
Crane et al, 1999	892	Singleton pregnancies at 20-24 weeks recruited from the perinatal centre of a maternity hospital in USA (n=238)	To evaluate combination of vaginal and cervical FFN, and preterm birth risk score. Threshold of positive FFN test for both cervical and vaginal swabs – levels ≥ 50 ng/ml For Nova Scotia preterm birth risk score – presence of one major or two minor factors	Spontaneous preterm delivery < 37 weeks	Preterm birth risk score (n=140) Sensitivity: 77.8% Specificity: 80.2% PPV: 21.2% NPV: 98.1% Positive vaginal FFN levels (n=140) Sensitivity: 55.6% Specificity: 83.2% PPV: 18.5% NPV: 96.5% Preterm birth risk score & positive vaginal FFN levels Sensitivity: 44.4% Specificity: 97.7% PPV: 57.1% NPV: 96.2% Preterm birth risk score or positive vaginal FFN levels Sensitivity: 88.9% Specificity: 65.7% PPV: 15.1% NPV: 98.9%	Population not representative Blinding of technicians Test described adequately	CH	II
Lockwood et al, 1994	893	Women with singleton pregnancies attending a single obstetric clinic in USA (n=161). Study group (n=34) of	To determine if elevated IL-6 in vaginal & cervical secretions are associated with preterm delivery.	Spontaneous preterm delivery < 37 weeks ROC curve used to establish cutoff values for cervical and vaginal	Single value > 250 pg/ml as positive test Sensitivity: 50.0% Specificity: 85.0% PPV: 47.2%	Nested case-control study Population not representative Blinding of technicians	CC	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		women delivering spontaneously before 37 weeks, and control group (n=127) of consecutive women delivering at term.	Vaginal swabs were taken serially every 3-4 weeks between 24 and 36 weeks of gestation. Levels > 125 and 250 pg/ml used as threshold using the ROC curve	IL-6, and diagnostic values calculated. Characteristics of women with preterm deliveries and IL-6 > 250 pg/ml (n=17) compared with those having lower levels (n=17).	NPV: 86.4% Single value > 125 pg/ml as positive test Sensitivity: 45.5% Specificity: 86.6% Comparison of two groups Gestational age at delivery (weeks) 34.2 ± 3.2 vs 35.0 ± 2.5 (p=0.44) Time interval from sampling to delivery (weeks) 1.8 ± 1.3 vs 1.9 ± 0.9 (p=0.70) Birth weight (gms) 2341 ± 764 vs 2485 ± 576 (p=0.54)	Test described adequately		
Inglis et al, 1994	894	Singleton pregnancies between 15 to 40 years at < 37 wks and with intact membranes attending a medical centre in USA. Population included asymptomatic women (n=73), and those with threatened preterm labour (n=38).	To determine association of tumor necrosis factor, IL-6 and FFN identified in lower genital tract during pregnancy with preterm delivery. Vaginal swabs collected once at 20-36 wks (levels > 50 pg/ml for positive IL-6 test, levels > 50 microg/ml for positive FFN test)	Spontaneous preterm delivery < 37 weeks. Risk of preterm delivery was evaluated for these 3 factors (preterm vs term delivery)	Positive Tumor necrosis factor (n=73) 18.2% vs 16.1% RR: 1.13 (0.28, 4.46) Positive IL-6 factor (n=73) 9.1% vs 16.1% RR: 0.56 (0.08, 3.97) Positive FFN levels (n=73) 18.2% vs 17.7% RR: 1.02 (0.26, 4.01)	Population not representative Blinding of technicians Test described adequately	CH	II
Goepfert et al, 2001	895	Cohort of asymptomatic pregnant women (n=2929) with singleton pregnancies at 22-24	To evaluate association between cervical IL-6, FFN and preterm birth. Single vaginal swab	Spontaneous preterm delivery < 32 and < 35 weeks. Predictive accuracy	For delivery < 35 weeks IL-6 positive only Sensitivity: 20% Specificity: 90%	Case-control study nested within the multi-centre prospective cohort study (data	CC	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		weeks in USA and with a dating scan *Cases*: women with preterm delivery < 35 wks and cervical specimen available for IL-6 assay (n=125) *Controls*: women with term deliveries and matched for race, parity and centre (n=125)	taken at 22-24 wks. Levels > 305 pg/ml for positive IL-6 test, and > 50 ng/ml for positive FFN test.	calculated for < 29, < 32, and < 35 weeks.	FFN positive only Sensitivity: 23% Specificity: 97% Both IL-6 & FFN positive Sensitivity: 8% Specificity: 98% Either IL-6 or FFN positive Sensitivity: 35% Specificity: 90%	analyzed retrospectively) Population not representative Blinding of technicians Test described adequately		
Sakai et al, 2004	896	Singleton pregnancies who had perinatal care and delivery in 10 hospitals in Japan (n=13299)	Association between IL-8 and cervical length with preterm birth and preterm PROM. Swabs taken serially from cervical canal - once a month in 20-23 wks and then once biweekly in 24-28 wks. Levels > 360 ng/ml for a positive test for IL-8, and length < 25mm for short cervix on TVS	Spontaneous preterm delivery < 32, < 34 and < 37 weeks Comparison of risk of preterm delivery between women with positive IL-8 test (n=845) vs negative test (n=3358), and those with short cervix (85) vs not short cervix (n=4118).	<u>For IL-8 levels</u> < 32 weeks 0.9% vs 0.4% OR: 2.5 (1.0, 6.8) p=0.037 < 34 weeks 1.5% vs 0.5% OR: 3.2 (1.5, 6.9) p=0.0015 < 37 weeks 4.9% vs 3.3% OR: 1.5 (1.0, 2.2) p=0.02 <u>For short cervix</u> < 32 weeks 5.9% vs 0.3% OR: 18.6 (11.1, 31.3) p<0.0001 < 34 weeks 11.8% vs 0.4% OR: 28.5 (13.4, 60.4) p<0.0001 < 37 weeks 43.5% vs 2.5%	Population representative Blinding of technicians not specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					OR: 17.6 (12.9, 23.9) p<0.0001			
Sakai et al, 2004	[897]	Women with single pregnancy receiving prenatal care in outpatient clinic of a university hospital in Japan (n=501)	Relationship between vaginal pathogens and IL-8 in cervical mucus studied in relationship to preterm delivery. Single cervical specimen collected at 20-24 wks. Threshold of a positive IL-8 test 377 ng/ml, and culture done for bacterial pathogens	Spontaneous preterm delivery < 37 weeks. Comparison of pathogens between high IL-8 group (n=84) and normal IL-8 group (n=417). Also risk of premature births compared for IL-8 levels and Lactobacillus presence/absence	<u>Comparison of pathogens</u> Lactobacillus 56.0% vs 84.7% p<0.0001 Anaerobic 83.3% vs 43.9% p<0.0001 Aerobic 47.6% vs 52.3% p=0.43 Candida 17.9% vs 12.7% p=0.21 <u>Premature birth rates</u> For IL-8 levels 13.1% vs 3.6% OR: 4.0 (1.78, 14.0) p=0.0003 For Lactobacillus 11.9% vs 3.5% OR: 3.7 (1.66, 8.31) p=0.0007	Population representative Blinding not done/specified Test described adequately	CH	II
Simpson et al, 1995	[898]	Singleton pregnancies attending a regional medical centre in USA. Population mainly from lower socio-economic group, 80% black and 20% white. (n=753)	To evaluate if second and third trimester maternal serum AFP levels (taken at 15-20 and 24-36 weeks) predicts adverse pregnancy outcomes. Threshold for a positive test – AFP level <u>></u> 2.0 MoM.	Detection rates (DR), false positive rates (FPR), and odds ratios for four pregnancy complications – preterm birth (< 37 weeks), preterm PROM, IUGR (< 10th centile), and LBW (< 2500 gms)	AT 15-20 WEEKS (n=650) <u>Preterm birth</u> DR: 19% FPR: 6.3% OR: 3.5 (1.4, 8.7) <u>Preterm PROM</u> DR: 40% FPR: 6.0% OR: 10.4 (3.6, 29.4) <u>IUGR</u> DR: 16.7%	Population representative Blinding of clinicians Test described adequately	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					FPR: 6.8% OR: 2.7 (0.8, 10.6) LBW DR: 14.7% FPR: 6.2% OR: 2.6 (1.1, 5.8)			
Dugoff et al, 2005	899	Women ≥ 16 yrs age confirmed to have singleton pregnancies between 10-14 wks gestational age, and attending one of the 14 study centers (n=33145)	To estimate predictive relationship between second trimester levels (at 15-19 weeks) of AFP, HCG, unconjugated estriol (UE-3), and Inhibin-A, and obstetric complications. Threshold levels for AFP, HCG and Inhibin-A ≥ 2.0 MoM, and for UE-3 ≤ 0.5 MoM.	Comparison of incidence and association (OR after adjusting for confounding variables) of adverse complications – preterm delivery < 32 weeks, LBW < 10th centile, Fetal loss < 24 weeks, and Fetal demise > 24 weeks, between positive and negative serum levels	Preterm delivery AFP 3.4% vs 0.7% p < 0.001 OR: 1.76 (0.81, 3.84) HCG 1.5% vs 0.7% p < 0.001 OR: 0.83 (0.43, 1.58) UE-3 1.14% vs 0.8% p=0.4 OR: 1.68 (0.61, 4.64) Inhibin-A 3.1% vs 0.65% p < 0.001 OR: 2.38 (1.4, 3.95)	Retrospective analysis of data from FASTER trial Population representative Blinding not done/specified Test described adequately	CH	II
Morssink et al, 1995	900	Singleton pregnancies who underwent screening for Down's or neural tube defects in Netherlands (n=10305)	To examine association between second trimester AFP and HCG levels (at 15-20 weeks) and preterm delivery. Threshold for abnormal test – levels of AFP and HCG ≥ 2.5 MoM	Comparison of prevalence of outcomes (preterm delivery < 37 weeks, SGA < 10th centile) between elevated levels vs normal levels.	Preterm delivery (n=7992) AFP levels 14.3% vs 5.9% p < 0.01 RR: 2.4 HCG levels 8.6% vs 5.9% p > 0.05 Both AFP and HCG levels raised	Retrospective analysis of data Population representative Blinding not done/specified Test described adequately	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					15.4% vs 6.0% p > 0.05			
Ong et al, 2000	901	Singleton pregnancies without fetal & chromosomal anomalies attending antenatal clinics of two hospitals in UK (n=5548)	To evaluate first trimester (10-14 weeks) maternal HCG and PAPP-A as predictors pf pregnancy complications. Different thresholds - < 5th centile, < 10th centile, and < median values	Sensitivity of HCG and PAPP-A below 5th and 10th centile in the prediction of outcomes (spontaneous preterm delivery < 37 and < 34 weeks, birthweight < 10th centile, miscarriage).	Preterm delivery < 37 weeks (n=5297) HCG < 5th centile Sensitivity: 5.7% Specificity: 95% PAPP-A < 5th centile Sensitivity: 7.8% Preterm delivery < 34 weeks HCG < 5th centile Sensitivity: 8.5% PAPP-A < 5th centile Sensitivity: 14.9%	Population representative Blinding not done/specified Test described adequately	CH	II
Yaron et al, 2002	902	Consecutive singleton pregnancies undergoing first trimester screening for Down syndrome at prenatal diagnosis unit in Israel (n=1722)	To evaluate whether abnormal HCG in first trimester (10-13 weeks) is predictive of abnormal pregnancy outcomes. Different levels of HCG used as cut-off (< 1.00, 1.01-2.00, 2.01-3.00, 3.01-4.00, 4.01-5.00, > 5.01 MoM)	Complication rates for outcomes – spontaneous preterm delivery < 37 weeks, birth weight < 5th centile, spontaneous miscarriage	For preterm delivery (n=1622) HCG (threshold ≤ 2.0 MoM) Sensitivity: 73% (60%, 85%) Specificity: 21% (19%, 23%)	Population representative Blinding not done/specified Test described adequately	CH	II
Hvilsom et al, 2002	903	Pregnant women presenting for antenatal care at a university hospital in Denmark (n=2846). *Cases*: women with idiopathic spontaneous preterm delivery < 37 weeks (n=84)	To examine association between CRP levels and preterm delivery. Maternal CRP levels measured at 14-19 wks (median 16.3 wks). Threshold 7.6 ng/ml for a positive test.	Association (OR) between preterm delivery and CRP levels (cases vs controls) at various cut-off values.	CRP levels (5.6 mg/l) or cut-off 75th centile 7.35% vs 7.24% OR: 1.7 (1.0, 2.7) CRP levels (7.6 mg/l) or cut-off 85th centile 2.26% vs 8.14% OR: 2.0 (1.2, 3.5)	Nested case-control study Population representative Blinding not done/specified Test described adequately	CC	III

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		Controls: randomly selected women who had term delivery (n=400)			CRP levels (16.4 mg/l) or cut-off 95th centile 5.9% vs 1.5% OR: 1.9 (0.8, 4.4)			
Karinen et al, 2005	904	Women with a history of at least 1 delivery and data available on first pregnancy from the Northern Finland 1966 Birth Cohort (n=2309) *Cases*: women with idiopathic spontaneous preterm delivery < 37 weeks (n=104) *Controls*: randomly selected women who had term delivery matched on age and parity (n=402)	To evaluate association between Chlamydia trachomatis antibodies and CRP levels to preterm delivery. Serum samples collected at first trimester (mean age 10.4 weeks) obtained from serum bank. Threshold for positive CRP – levels > 4.3 ng/ml, and Chlamydia trachomatis IgG positive in 1:8 dilutions	Spontaneous preterm delivery < 37 weeks. Comparison of test results (OR) in cases vs controls for preterm delivery	Positive CRP only 20.2% vs 18.4% OR: 1.3 (0.7, 2.3) Positive Chlamydia trachomatis IgG levels only 14.4% vs 16.7% OR: 1.0 (0.5, 2.0) Both CRP and Chlamydia trachomatis IgG positive 14.4% vs 4.0% OR: 4.3 (2.0, 9.3)	Nested case-control study Population representative Blinding not done/specified Test described adequately	CC	III
Wren et al, 1969	905	All pregnant women booking at an antenatal clinic in Australia (n=3604)	To evaluate association between asymptomatic bacteriuria and pregnancy complications Mid-stream urine culture done at first visit, and repeated if positive. Threshold not specified	Comparison of cases of untreated bacilluria (n=90) and non-bacilluria controls (n=3009) for pregnancy complications (abortion, birthweight < 2500 gms, delivery < 37 weeks, stillbirths, neonatal death)	Abortion 6.7% vs 2.8% Birthweight < 2500 gms 15.5% vs 4.6% Delivery < 37 weeks 27.8% vs 6.8% Stillbirths 3.3% vs 0.4% Neonatal deaths 3.3% vs 1%	Population representative Blinding not done/specified Test described adequately	CH	II
Robertson et al, 1969	906	All pregnant women attending the booking antenatal clinic in UK	Investigation into the incidence and consequences of	Comparison of incidence of anemia (Hb < 10.gm%),	Anemia 18.0% vs 8.0%	Population representative Blinding not	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		(n=8275) Treatment was initiated later in the study for women with positive urine culture.	asymptomatic bacteriuria. Mid-stream urine sample obtained during the booking visit, and cultured if initial modified nitrite test was positive. Count > 100,000 for a positive culture	hypertension (BP > 140/90 mm Hg on two occasions), prematurity (gestational age < 36 weeks and birthweight < 2500 gms) between untreated bacteriuria positive (n=204) and control group (n=1980)	Hypertension 7.0% vs 12.0% Prematurity (gestational age < 36 weeks) 6.0% vs 3.0% Prematurity (birthweight < 2500 gms) 8.0% vs 6.0%	done/specified Test described adequately		
Uncu et al, 2001	907	All pregnant women up to 32 weeks seen at outpatient obstetrics clinic in Turkey (n=247)	To determine incidence of asymptomatic bacteriuria and its relation to pregnancy complications. Midstream sample of morning urine obtained for culture, and colony growth > 100,000 bacteria/ml considered positive.	Comparison of incidence of premature labour, PROM, IUGR, hypertension, anemia, and other complications between culture positive group (n=23) and culture negative group (n=163).	Premature labour 26.0% vs 9.8% PROM 4.3% vs 3.0% IUGR 0 vs 0.6% Hypertension 4.3% vs 4.2% Anemia 26.0% vs 21.4%	Population representative Blinding not done/specified Test described adequately	CH	II
Layton 1964	908	All pregnant women attending an antenatal clinic in UK before 32 weeks of gestation (n=1000)	To test the reliability of urine culture at first antenatal visit. Midstream urine sample collected & cultured at the booking visit and after 4 weeks of the first visit, and count over 100,000 regarded as significant.	Comparison between bacteriuric group (n=67) and control group (n=118) for outcomes – pre-eclamptic toxaemia (BP 140/90 + oedema), anaemia (Hb < 7.0 gm%), preterm delivery (<37 weeks) and LBW (< 5.5 pounds)	Pre-eclamptic toxaemia 14.9% vs 9.3% Anemia 31.3% vs 19.5% Preterm delivery 6.3% vs 8.0% LBW 16.9% vs 8.9%	Population representative Blinding not done/specified Test described adequately	CH	II
Klebanoff et al,	909	Pregnant women	To find association	Comparison of	At < 13 weeks	Population	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
2005		participating in a multi-center trial in USA at 8-22 weeks gestational age and with no major medical or obstetric complications, no symptoms of UTI, and not received any antibiotics within past 14 days (n=15864)	between timing of detection of BV and preterm delivery. Single vaginal swab taken at 8-22 weeks gestational age. Positive BV defined as vaginal Gram stain Nugent score ≥ 7 in conjunction with vaginal pH > 4.4.	incidence of spontaneous preterm delivery < 37 weeks between BV positive (n=4634) vs BV negative group (n=8303) at different gestational age	15.6% vs 14.0% At 13-14 weeks 15.3% vs 14.0% At 15-16 weeks 15.5% vs 11.7% At 17-18 weeks 13.3% vs 9.8% At 19-20 weeks 15.4% vs 10.0% At 21-22 weeks 13.2% vs 10.5%	representative Blinding of technicians and clinicians Test described adequately		
Hillier et al, 1995	910	Singleton pregnancies enrolled in one of seven medical centers in USA for routine prenatal care and at 23-26 gestational age wks (n=10397)	To find association between BV and preterm delivery after adjusting for other known risk factors. Single posterior fornix swab taken at 23-26 weeks. Threshold for a positive test – vaginal PH above 4.5 and Gram staining score > 7.	Comparison (OR) of adverse outcomes – preterm delivery (< 37 weeks), LBW (< 2500 gms), and PROM (rupture of membranes before regular uterine contractions) between women with positive BV vs those with negative BV	Mean birth weight (gms) 3204 ± 618 vs 3294 ± 576 Preterm delivery 6.3% vs 4.2% OR: 1.5 (1.2, 1.9) LBW 9.7% vs 6.6% OR: 1.5 (1.2, 1.9) PROM 3.1% vs 2.8% OR: 1.1 (0.8, 1.6)	Population representative Blinding of technicians and clinicians Test described adequately	CH	I b
Purwar et al, 2001	911	Randomly selected asymptomatic low risk pregnant women without vaginal discharge attending a government medical college in India (n=1006)	To find association of BV with adverse pregnancy outcomes. Single vaginal swab taken at 16-28 wks, and scored for BV according to Nugent's criterion.	Comparison of spontaneous preterm delivery (< 37 weeks), PROM (spontaneous rupture of membranes before onset of labour), preterm PROM (spontaneous rupture of membranes before	Preterm delivery 27.8% vs 4.9% RR: 5.7 (4.6, 8.3) p=0.001 PROM 22.6% vs 3.4% RR: 6.6 (5.0, 10.0) p=0.001	Population representative Blinding of technicians and clinicians Test described adequately	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
				onset of labour & before 37 weeks)	Preterm PROM 8.7% vs 0.7% RR: 11.9 (6.7, 32.4) p=0.001			
Gratacos et al, 1998	358	Women with singleton pregnancies at a hospital clinic in Spain at less than 35 wks gestational age (n=688)	To evaluate influence of BV on pregnancy complications Sampling done twice from the posterior fornix at < 24 and then < 35 weeks. BV diagnosed on the basis of Nugent criteria	Comparison of preterm delivery (< 37 weeks), PROM (rupture of membranes before 37 weeks or at least 6 hrs prior to onset of labour), premature labour (presence of regular contractions in woman with intact membranes)	Preterm delivery 15.2% vs 4.7% RR: 3.2 (1.8, 5.7) P < 0.0001 PROM 18.4% vs 5.4% RR: 3.3 (2.0, 5.6) P < 0.0001 Premature labour 16.0% vs 5.0% RR: 3.1 (1.8, 5.4) P < 0.0001	Population representative Blinding of technicians and clinicians Test described adequately	CH	I b
Taipale et al, 1998	912	Consecutive singleton pregnancies screened for routine anomalies by ultrasonography at 18-22 weeks in a hospital in Finland (n=4206)	To evaluate if TVS can predict preterm delivery. TVS done at 18-22 weeks by six different operators, but their prints checked by another operator. Different thresholds used but cervical length ≤ 29 mm was the best threshold identified using ROC curve	Spontaneous preterm delivery at < 35 and < 37 weeks. Diagnostic accuracy results and relative risk calculated for different thresholds.	Preterm delivery < 37 weeks (n=3694) Cx length ≤ 25 mm Sensitivity: 6% Specificity: 100% PPV: 39% RR: 17 (8, 35) Cx length ≤ 27 mm Sensitivity: 8% Specificity: 99% PPV: 23% RR: 10 (5, 20) Cx length ≤ 29 mm Sensitivity: 16% Specificity: 97% PPV: 13%	Population representative Blinding of technicians and clinicians Test described adequately	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					RR: 6 (4, 11) Cx length ≤ 35 mm Sensitivity: 35% Specificity: 73% PPV: 3% RR: 1.5 (1.0, 2.3)			
Leung et al, 2005	913	Ethnic Chinese women with singleton pregnancies with ultrasound measurement at 18-22 weeks in a tertiary obstetric unit in Hong Kong (n=2952)	To examine the predictive value of cervical length and funneling for spontaneous preterm delivery by mid-trimester TVS. Single TVS examination done at 18-22 weeks. Different thresholds used but cervical length ≤ 27 mm identified using ROC curve as the best threshold. Funneling defined as protrusion of amniotic membranes > 5 mm into cervical canal.	Diagnostic accuracy results for spontaneous preterm delivery at < 34 weeks. ROC curve used for prediction analysis for different percentiles/cut-offs for cervical length and funneling.	Cx length < 25 mm Sensitivity: 26.3% Specificity: 98.3% PPV: 9.4% NPV: 99.5% Cx length < 27 mm Sensitivity: 36.8% Specificity: 96.2% PPV: 6.1% NPV: 99.6% Cx length < 30 mm Sensitivity: 36.8% Specificity: 96.2% PPV: 6.1% NPV: 99.6% Funneling only Sensitivity: 31.6% Specificity: 93.9% PPV: 3.3% NPV: 99.5% Cx length < 27 mm + funneling Sensitivity: 26.3% Specificity: 99.0% PPV: 14.7% NPV: 99.5% Cx length < 27 mm or funneling Sensitivity: 42.1%	Population representative Blinding of technicians and clinicians Test described adequately	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Specificity: 91.1% PPV: 3.1% NPV: 99.6%			
Fukami et al, 2003	914	Women with singleton pregnancies scanned between 16-19 weeks at a medical school hospital in Japan (n=3367)	To compare shortened cervical length and absence of new parameter 'cervical gland area (CGA)' for predicting preterm delivery. Threshold for shortened cervix – length ≤ 30 mm, and CGA defined as sonographically hyper/hypoechoic zone surrounding the cervical canal.	Predictive accuracy calculated for spontaneous preterm delivery < 32 weeks and at 32-36 weeks	For 32-36 weeks (n=3030) Short cervix Sensitivity: 18.2% Specificity: 98.9% PPV: 33.3% NPV: 97.6% Absence of CGA Sensitivity: 2.3% Specificity: 99.7% PPV: 18.2% NPV: 97.2% Short cervix and absence of CGA Sensitivity: 2.3% Specificity: 99.7% PPV: 20.0% NPV: 97.2%	Population representative Blinding not done/ not specified Test described adequately	CH	II
To et al, 2001	915	Women with singleton pregnancies attending for routine ANC in a UK hospital, and undergoing 22-24 week cervical assessment using ultrasound scan. (n=6819)	To establish relationship of cervical length with preterm delivery. Single TVS was done at 22-24 weeks and threshold for funneling was dilatation of internal os ≥ 5 mm in width.	Regression analysis used to calculate relationship between cervical length and risk of spontaneous preterm delivery < 33 weeks.	Funneling group (n=231) vs no funneling group (n=6103) Preterm delivery 6.9% vs 0.7% p < 0.0001 Risk of preterm delivery Short cervix OR: 24.9 (p<0.0001) Funneling OR: 1.8 P=0.40	Population representative Blinding not done/ not specified Test described adequately	CH	II

Fetal growth (diagnostic accuracy)

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Bais et al, 2004	916	Retrospective analysis of database of a geographical cohort in Netherlands, and included all low risk singleton pregnancies at 20 weeks GA confirmed by US (n= 6725)	To evaluate performance of abdominal palpation as a screening test to detect IUGR, and US as diagnostic test for women referred with suspected IUGR. Abdominal palpation done by midwives after 20 weeks till referral or delivery (frequency not specified, and Threshold by clinical judgement). US done by consulted obstetricians	Predictive performance of abdominal palpation and US calculated for SGA (BW < 10th centile)and severe SGA (BW < 2.3rd centile)	Abdominal palpation (n=6318) For SGA Prevalence: 8.5% Sensitivity: 21.3% (17.8, 24.7) Specificity: 95.9% (95.4, 96.4) PPV: 32.6% (27.7, 37.5) NPV: 92.9% (92.3, 93.6) For severe SGA Prevalence: 1.5% Sensitivity: 27.9% (19.0, 37.0) Specificity: 94.8% (94.2, 95.4) PPV: 7.4% (4.7, 10.1) NPV: 98.9% (98.6, 99.1) Abdominal palpation + US (n=6318) For SGA Prevalence: 8.5% Sensitivity: 15.1% (12.1, 18.1) Specificity: 98.9% (98.6, 99.1) PPV: 55.1% (47.1, 63.1) NPV: 92.6% (92.0, 93.3) For severe SGA Prevalence: 1.5% Sensitivity: 24.7% (15.9, 33.5) Specificity: 98.0% (97.7, 98.4) PPV: 15.6% (9.8, 21.5) NPV: 98.9% (98.6, 99.1)	Retrospective analysis of database of a geographical cohort Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II
Secher et al, 1990	917	Randomly selected women with singleton pregnancies and confirmed GA by US at	To evaluate measurement of SFH alone and in combination with EFW	Predictive accuracy and risk calculated for SGA defined as BW < 85% of expected for GA (or <	Last EFW value < 10th centile Sensitivity: 45% Specificity: 91% PPV: 38%	Representative population Blinding not done/specified	CH	III

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		16-18 wks in a city in Denmark (n=199)	to detect SGA. SFH measured once a week from 33-36 weeks, EFW calculated and EFW curve generated using modeling. Sample for this study – women with > 3 measurements.	9.4th centile for GA).	NPV: 94% RR: 6.2 EFW curve < 10th centile Sensitivity: 38% Specificity: 92% PPV: 33% NPV: 93% RR: 4.8 Last SFH value < 10th centile Sensitivity: 33% Specificity: 93% PPV: 35% NPV: 93% RR: 4.8 Last SFH & EFW value < 10th centile Sensitivity: 12% Specificity: 100% PPV: 100% NPV: 91%	Test described adequately Reference test validated		
Persson et al, 1986	919	Consecutive singleton pregnancies with regular menstrual cycles and known LMP attending one of three hospitals in Sweden (n=3197)	To graphically illustrate progression of SFH in a sample of women, and use it to predict abnormal fetal size. SFH measured about 15 times during entire pregnancy and value < 2 SD of reference curve (generated from 1350 healthy pregnant women) used as threshold.	Predictive accuracy of SFH calculated for BW < 10th centile for GA (SGA), BW/length ratio below 2 SD, BW > 90th centile (LGA), and BW/length ratio above 2 SD.	BW < 10th centile Sensitivity: 26.6% Specificity: 88.0% PPV: 18.0% NPV: 92.4% BW > 90th centile Sensitivity: 37.5% Specificity: 87.9% PPV: 24.5% NPV: 93.1% BW/length ratio < 2 SD Sensitivity: 16.7% Specificity: 86.7% PPV: 1.8% NPV: 98.6% BW/length ratio > 2 SD	Multi-centre study Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Sensitivity: 31.8% Specificity: 85.7% PPV: 3.3% NPV: 98.8%			
Harding et al, 1995	920	Randomly selected group of pregnant women who had approx. 5 scans between 18-38 weeks in a hospital in Australia (n=1135). This cohort was selected from an ongoing RCT.	To find most appropriate cut-offs (using ROC curve) for detecting SGA at various gestational ages using SFH, AFI, and US measurement of FAC. SFH, AFI and US done 5 times at 18-20, 24, 28, 34, and 38 weeks. Threshold for SFH – single value < 10th centile or 28 cms (28 wks), 33.5 cms (34 wks) and 36 cms (38 wks). For AFI and FAC – single value < 10th centile	BW < 10th centile using charts constructed from Western Australian population.	<u>At 28 weeks (n=760)</u> For SFH Prevalence: 12.3% Sensitivity: 32% Specificity: 88% PPV: 28% NPV: 90% For AFI Prevalence: 12.6% Sensitivity: 21% Specificity: 93% PPV: 21% NPV: 93% <u>At 34 weeks (n=914)</u> For SFH Prevalence: 11.8% Sensitivity: 31% Specificity: 87% PPV: 24% NPV: 90% For AFI Prevalence: 11.7% Sensitivity: 11% Specificity: 89% PPV: 12% NPV: 88%	Representative population but loss to follow up Blinding of technicians Test described adequately Reference test validated	CH	I b
Rosenberg et al, 1982	918	All women having singleton pregnancies with confirmed GA (by careful history or US) of < 26 weeks attending an antenatal clinic in UK. (n=761)	To evaluate efficacy of SFH in identification of growth retardation. SFH measured from 20 weeks till delivery. *Threshold*: Two consecutive or three isolated SFH values <	Prediction of growth retardation (BW < 10th centile for GA) using different criterion for thresholds	<u>SFH (n=753)</u> Sensitivity: 56% (42%, 70%) Specificity: 85% (82%, 87%) <u>Threshold – 20% measurements < 10th centile</u> Sensitivity: 62% False positive rate: 21%	Retrospective cohort study Representative population Blinding not done/specified Test described adequately Reference test	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			10th centile of Reference curve (generated from 478 healthy pregnant women).		Threshold – 30% measurements < 10th centile Sensitivity: 52% False positive rate: 8%	validated		
Grover et al, 1991	921	Healthy singleton pregnancies with known GA and absence of obstetric complications attending a tertiary level hospital for antenatal care in India (n=400)	To analyze usefulness of SFH measurement for predicting altered fetal growth. SFH recorded fortnightly till 30 wks and then weekly till term. *Threshold*: SFH value < 1 SD of Reference curve generated from 200 healthy pregnant women.	Predictive accuracy calculated for Small-for-date (BW < 10th centile for GA) and LGA (BW > 90th centile for GA) babies	SFD (n=350) Sensitivity: 80.8% Specificity: 93.5% PPV: 84% False positive rate: 16% False negative rate: 8% LGA (n=350) Sensitivity: 79.2% Specificity: 95.2% PPV: 76% False positive rate: 24% False negative rate: 4%	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II
Rogers et al, 1985	922	Randomly selected pregnant women attending antenatal clinic of a hospital in UK (n=250).	To evaluate precision of SFH for predicting IUGR. SFH measured in the third trimester, and single value < 3 cms below mean of the sample or 3 consecutive static or declining values taken as the threshold.	Diagnostic accuracy for predicting IUGR (BW < 10th centile)	Sensitivity: 73.1% Specificity: 91.9% PPV: 51.3% NPV: 96.7%	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II
Warsof et al, 1986	923	Consecutive women with ultrasonographically confirmed singleton pregnancies before 24 weeks attending a tertiary level hospital in UK (n=4527)	US done once in the third trimester at 28, 30, 32, 34 or 36 weeks. Threshold for BPD, HC and AC – values < 25th centile or < 10th centile for GA	Diagnostic accuracy for predicting IUGR (BW < 10th centile)	For values < 10th centile as threshold Only BPD abnormal (n=7385) Sensitivity: 25% Specificity: 93% PPV: 39% NPV: 87% Only HC abnormal (n=3308) Sensitivity: 35%	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Specificity: 91% PPV: 49% NPV: 86% Only AC abnormal (n=4893) Sensitivity: 48% Specificity: 93% PPV: 61% NPV: 89% Both BPD & AC abnormal (n=4789) Sensitivity: 22% Specificity: 97% PPV: 64% NPV: 86% BPD or AC abnormal (n=4789) Sensitivity: 54% Specificity: 85% PPV: 43% NPV: 90%			
Skovron et al, 1991	[924]	Women with singleton gestation who had an US examination for fetal size determination in a medical centre in USA	US done once between 26 and 34 weeks, and then repeated in some cases. Threshold values for AC and EFW (Shepard's formula) at < 10th and < 25th centile for GA.	Predictive performance calculated for SGA babies (BW < 10th centile for GA) by ROC curve	<u>Single US examination & < 10th centile as threshold</u> AC Sensitivity: 72% Specificity: 69% PPV: 19% EFW Sensitivity: 25% Specificity: 97% PPV: 47% <u>Single US examination & < 25th centile as threshold</u> AC Sensitivity: 83% Specificity: 56% PPV: 16% EFW	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Sensitivity: 51% Specificity: 80% PPV: 20% Serial US and threshold < 10th centile for both AC measurement Sensitivity: 62% Specificity: 81% PPV: 31%			
Lin et al, 1990	927	Records of all women with singleton pregnancies who had undergone obstetric US at a tertiary hospital in USA (n=463)	To determine if oligohydramnios increases the accuracy of prenatal diagnosis of IUGR. US done (AC & AFI) twice in the third trimester at an interval of 2-4 weeks. Threshold for AC < 10th centile for GA, and vertical diameter < 2 cms for largest pocket for AFI.	IUGR defined as BW < 10th centile for GA.	For AC < 10th centile Sensitivity: 87.5% Specificity: 77.2% PPV: 38.1% NPV: 97.5% For AC < 5th centile Sensitivity: 50.0% Specificity: 90.0% PPV: 44.4% NPV: 91.8% For AC < 10th centile and oligo Sensitivity: 25.0% Specificity: 98.0% PPV: 66.7% NPV: 89.1%	Retrospective analysis of records Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II
Hedriana et al, 1994	926	Women with normal singleton pregnancy and known LMP confirmed by first trimester physical examination (n=302)	To determine if two or more US examination is superior to a single scan. Single scan (32-36 wks) and serial scans (two to five times between 28-42 weeks) *Threshold*: Slope ± SD calculated for AC and EFW (Shepard's formula) centile using regression analysis.	Diagnostic accuracy of parameters calculated for predicting SGA (BW < 10th centile) and LGA (BW >90th centile) babies	Single examination for SGA (n=249) EFW Sensitivity: 100% Specificity: 76% PPV: 25% NPV: 100% AC Sensitivity: 68% Specificity: 88% PPV: 33% NPV: 97%	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					Serial examinations for SGA (n=247) EFW Sensitivity: 100% Specificity: 75% PPV: 25% NPV: 100% AC Sensitivity: 100% Specificity: 88% PPV: 40% NPV: 100% Single examination for LGA (n=249) EFW Sensitivity: 48% Specificity: 94% PPV: 63% NPV: 89% AC Sensitivity: 54% Specificity: 89% PPV: 53% NPV: 90% Serial examinations for LGA (n=247) EFW Sensitivity: 62% Specificity: 100% PPV: 100% NPV: 92% AC Sensitivity: 84% Specificity: 100% PPV: 100% NPV: 97%			
Newnham et al,	925	Pregnant women with	To evaluate role for US	Diagnostic accuracy	IUGR at 28 weeks	Representative	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
1990		singleton gestation attending a public antenatal clinic of a tertiary hospital in Australia (n=615)	and Doppler US in predicting perinatal complications. Both US performed at 18, 24, 28 and 34 weeks. Threshold for abnormal AC < 5th centile for gestational age, and for abnormal Doppler – S/D ratio > 95th centile for GA	results for IUGR (BW < 10th centile for GA) and fetal hypoxia (operative delivery due to fetal hypoxia with umbilical artery ph < 7.20 or 5-min Apgar score < 7	Umb. artery S/D ratio (n=470) Prevalence: 9.1% Sensitivity: 18.6% Specificity: 95.6% PPV: 29.6% NPV: 92.1% Fetal AC (n=476) Prevalence: 9.2% Sensitivity: 27.3% Specificity: 96.1% PPV: 41.5% NPV: 92.8% <u>IUGR at 34 weeks</u> Umb. artery S/D ratio (n=445) Prevalence: 8.1% Sensitivity: 16.7% Specificity: 95.1% PPV: 23.1% NPV: 92.8% Fetal AC (n=451) Prevalence: 8.2% Sensitivity: 48.7% Specificity: 94.0% PPV: 41.9% NPV: 95.3%	population Blinding not done/specified Test described adequately Reference test validated		
Chauhan et al, 1999	928	*Cases*: Singleton pregnancies, AFI ≤ 5 cms, reliable GA and no known anomalies (n=162) *Controls*: Next pregnancy with same GA and AFI between 5.1 to 23.9 cms (n=162)	To assess predictive accuracy of oligohydramnios for detecting fetal growth restriction. Third trimester US done within 72 hours of delivery to evaluate for AFI (threshold ≤ 5 cms)	Diagnostic accuracy calculated for fetal growth restriction (BW < 10th centile for GA)	Sensitivity: 76% (56%, 89%) Specificity: 95% (90%, 98%) PPV: 78% (59%, 91%) NPV: 94% (89%, 98%)	Population not representative Blinding not done/specified Test described adequately Reference test validated	CH	III

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Beattie et al, 1989	929	Ultrasonically dated singleton pregnancies attending aa antenatal clinic in UK within 7 days of their 28th gestational week (n=2097)	To assess usefulness of Doppler US as a screening tool for detecting IUGR. Doppler US done at 28, 34 and 38 weeks and IUGR predicted using pulsatility index, systolic/diastolic ratio, and resistance parameter (threshold value > 90th centile for all)	IUGR taken as BW < 5th centile for GA	Pulsatility index at 28 weeks Sensitivity: 28% Specificity: 89% PPV: 11% NPV: 97% S/D ratio at 28 weeks Sensitivity: 31% Specificity: 90% PPV: 12% NPV: 97% Pulsatility index at 34 weeks Sensitivity: 32% Specificity: 89% PPV: 12% NPV: 97% S/D ratio at 34 weeks Sensitivity: 40% Specificity: 84% PPV: 11% NPV: 97%	Representative population Blinding of US operators Test described adequately Reference test validated	CH	I b
Todros et al, 1995	930	Singleton pregnancies with no obstetrical risk, pre-pegnancy pathological condition or anomaly attending out-patient clinics of six hospitals in Italy (n=962).	To assess efficacy of Doppler examination of umbilical and uterine arteries as a screening test for FGR or PIH. Doppler US done twice at 19-24 and 26-31 weeks. *Threshold*: S/D ratio of 4.5 (at 19-24 wks) and 3.5 (at 26-31 wks) derived from ROC curve.	Diagnostic accuracy of Doppler Umbilical arteries for SGA (BW < 10th centile for GA) and PIH (BP > 140/90 mm Hg at two measurements 4 hrs apart for the first time after 20 weeks GA)	n=916 for all SGA at 19-24 weeks Sensitivity: 46.1% Specificity: 74.1% PPV: 7.8% NPV: 96.7% SGA at 26-31 weeks Sensitivity: 43.2% Specificity: 80.5% PPV: 7.0% NPV: 96.8% PIH at 19-24 weeks Sensitivity: 37.9% Specificity: 73.9% PPV: 4.7% NPV: 97.2%	Multi-centre study Representative population Blinding of US operators Test described adequately Reference test validated	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					PIH at 26-31 weeks Sensitivity: 37.5% Specificity: 80.2% PPV: 7.0% NPV: 96.9%			
Sijmons et al, 1989	931	Randomly selected singleton pregnancies from a university hospital population in Netherlands (n=400).	To assess validity of umbilical artery Doppler as a screening tool at 28 and 34 weeks for predicting SGA infants. *Threshold*: Pulsatility index > 95th centile for GA in the study population.	Diagnostic accuracy of Doppler for predicting SGA (BW < 10th or 2.3rd centile) and low weight for length infants (ponderal index < 10th or 3rd centile)	SGA (BW < 10th centile) at 28 weeks (n=394) Prevalence: 22.6% Sensitivity: 16.9% Specificity: 95.1% PPV: 50.1% NPV: 79.6% Low weight for length (ponderal index < 10th centile) at 28 weeks (n=352) Prevalence: 10.2% Sensitivity: 19.4% Specificity: 94.9% PPV: 30.4% NPV: 91.2% SGA (BW < 10th centile) at 34 weeks (n=368) Prevalence: 22.2% Sensitivity: 22.0% Specificity: 94.4% PPV: 52.9% NPV: 80.8% Low weight for length (ponderal index < 10th centile) at 34 weeks (n=330) Prevalence: 8.8% Sensitivity: 24.1% Specificity: 92.7% PPV: 23.3% NPV: 92.7%	Representative population Blinding of US operators Test described adequately Reference test validated	CH	I b
Atkinson et al, 1994	932	Low risk nulliparaous women with singleton pregnancies enrolled in	To evaluate usefulness of umbilical artery Doppler for predicting	Diagnostic accuracy for predicting SGA (BW < 10th centile for GA) and	SGA at 20-26 weeks (n=490) Sensitivity: 18% Specificity: 91%	Representative population Blinding of US	CH	I b

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		a double-blind trial of low dose aspirin for pre-eclampsia prevention in USA (n=565)	FGR or preeclampsia at 20-26, 27-31, 32-36 and 37-42 weeks. *Threshold*: S/D ratio > 90th centile for GA in study population	preeclampsia	PPV: 13% NPV: 94% <u>SGA at 27-31 weeks (n=475)</u> Sensitivity: 20% Specificity: 91% PPV: 15% NPV: 93% <u>SGA at 32-36 weeks (n=439)</u> Sensitivity: 24% Specificity: 91% PPV: 17% NPV: 94%	operators Test described adequately Reference test validated		
Owens et al, 2003	933	Women with singleton pregnancies and confirmed GA < 85 days in a hospital in UK (n=330)	To compare two methods of predicting IUGR. Third trimester US done at 2 weekly intervals to calculate EFW (using BPD, abd. area, FL) and the last EFW prior to delivery used to obtain customized fetal weight centile. *Threshold:* Centile < 5th and < 10th for estimated values.	IUGR defined as Ponderal index < 25th centile. Other outcomes - skinfold thickness < 10th centile and mid-arm to occipito-frontal circumference ratio < 1SD.	<u>For customized EFW < 5th centile and Ponderal index < 25th centile (n=258)</u> Sensitivity: 19% Specificity: 97% PPV: 54% NPV: 87% <u>For customized EFW < 10th centile and Ponderal index < 25th centile (n=258)</u> Sensitivity: 42% Specificity: 90% PPV: 41% NPV: 90%	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	II
Okonofua et al, 1986	934	Singleton uncomplicated pregnancies attending a hospital antenatal clinic in UK, and who were sure of their LMP (n=100)	To compare SFH and US biometry in predicting SGA and LGA babies. SFH and US biometry done after 20 weeks in the third trimester. *Threshold*: Two consecutive values for SFH, BPD or AC > 90th centile of reference	SGA defined with BW < 10th centile, and LGA with BW > 90th centile	<u>SGA by SFH</u> Sensitivity: 71.4% Specificity: 85% PPV: 50% <u>LGA by SFH</u> Sensitivity: 33.3% Specificity: 85% PPV: 31.3% <u>SGA by US biometry</u>	Representative population Blinding not done/specified Test described adequately Reference test validated	CH	III

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
			curve (generated from sample of 30 healthy uncomplicated singleton pregnancies)		Sensitivity: 85.7% Specificity: 95.4% PPV: 66.7% <u>LGA by US biometry</u> Sensitivity: 66.7% Specificity: 95.4% PPV: 75%			
Ott et al, 1984	935	Pregnant women undergoing US examination within 72 hours of delivery in a medical center in USA (n=595)	To evaluate US biometry for detecting altered fetal growth. BPD and AC measured by US and EFW (Shepard's formula) calculated. *Threshold*: EFW > 1.5 SD for the reference curve.	Diagnostic accuracy results for predicting SGA (BW < 10thcentile for GA) and LGA (BW > 90th centile for GA) babies	<u>For SGA</u> Sensitivity: 89.9% Specificity: 78.8% PPV: 63.2% <u>For LGA</u> Sensitivity: 73.5% Specificity: 78.8% PPV: 59.6%	Retrospective study, population not representative Blinding not done/specified Test described adequately Reference test validated	CH	III

Fetal growth (effectiveness)

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
Neilson JP	566	Pregnant women around 14 wks of pregnancy randomly allocated to the experimental or control group using sealed, opaque and unnumbered envelopes (n=1639, 1 trial)	Tape measurement of SFH routinely measured after 28 weeks and plotted on a locally derived centile chart	Primary: complications associated with FGR or IUGR (intrauterine death, asphyxia hypoglycaemia) complications associated with macrosomia (CPD, caesarean for failure to progress, shoulder dystocia) complications associated with multiple pregnancy (preterm delivery, perinatal mortality) Secondary: other indices of maternal and perinatal mortality and morbidity, and indices of obstetric care including admission to hospital.	Peto Odds ratio with 95% CI Perinatal mortality 1.25 (0.38 - 4.08) Apgar score < 4 at 1 minute 0.93 (0.38 – 2.31) Apgar score < 4 at 5 minutes 1.04 (0.26 – 4.17) Labour induction for FGR 0.84 (0.44 - 1.59) Caesarean section for FGR 0.72 (0.31 – 1.67) Birthweight < 10th centile 1.34 (0.91 – 1.98) Admission neonatal unit 1.07 (0.69 – 1.65)	Methodology explained in detail Only 1 trial included	SR	1+
Smith-Bindman et al, 2002	936	Study population selected from a cohort of 1836 singleton pregnancies attending a medical centre in USA, and included all those who underwent two or more US examinations 2-17 wks apart during the study period (n=321)	To determine if fetal growth measured at serial US examination can predict neonatal morbidity. Results of US fetal biometry measurements obtained from computerized database and EFW calculated using HC, AC and FL	Comparison of risk between FGR group (n=24) and Normal FG (n=212) for - LBW (BW < 2500gms, < 1500 gms, < 5th centile and < 3rd centile for GA), preterm birth (< 37 wks), long hospital stay (> 4 days), admission in neonatal intensive care unit, and assisted ventilation required at birth. Risk was also calculated after adjustment for	LBW (BW < 2500 gms) 63% vs 16% RR: 3.9 (2.5, 6.0) Adj. OR: 16.9 (4.2, 68.1) LBW (BW < 1500 gms) 25% vs 3% RR: 8.8 (3.1, 25.2) Adj. OR: 17.6 (2.6, 122.0) LBW (BW < 5th centile) 25% vs 1% RR: 17.7 (4.7, 66.1) Adj. OR: 36.1 (3.9, 336.7) Preterm birth	Retrospective analysis of hospital database Blinding not specified Confounding variables controlled	CH	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
				confounding variables (maternal age, weight, height, race, parity, fetal sex, EFW)	50% vs 22% RR: 2.3 (1.4, 3.7) Adj. OR: 4.1 (1.2, 14.1) Long hospital stay 50% vs 19% RR: 2.6 (1.6, 4.2) Adj. OR: 6.2 (1.7, 22.6) Admission in NICU 46% vs 13% RR: 3.6 (2.1, 6.3) Adj. OR: 5.7 (1.5, 21.9)			
Stratton et al, 1995	937	Unselected mothers with singleton pregnancies and confirmed GA by a second trimester scan referred for third trimester US examination to a hospital in UK (n=285)	To compare outcomes in fetuses with US evidence of inadequate growth but born with BW > 10th centile for GA (Inadequate fetal growth group, n=75) with infants with normal US for fetal growth (Adequate fetal growth group, n=121).	Abnormal Doppler, induction of labour, meconium staining, need for intrapartum fetal blood sampling, operative vaginal delivery, caesarean section, Apgar score < 7 at 5 min and need for admission to neonatal ICU.	Meconium staining 23% vs 17% OR: 1.40 (0.64, 3.03) p = 0.36 Admission to neonatal ICU 20% vs 7% OR: 3.11 (1.19, 8.52) p < 0.05 Abnormal Doppler 7% vs 9% p > 0.05 Induction of labour 35% vs 34% p > 0.05 Cesarean section 16% vs 16% p > 0.05	Baseline characteristics of groups not compared Confounding variables not adjusted Blinding not done/specified	CH	2-
Zhang et al, 2004	938	English speaking women more than 18 years of age with singleton pregnancy, known LMP and GA < 18 wks in the screening arm of the RADIUS trial (multi-center trial) in USA, and who	To examine fetal growth and perinatal outcomes in pregnancies with isolated oligohydramnios (defined as AFI ≤ 5 cms). Comparison made	Preterm delivery (< 37 weks), caesarean delivery, Apgar score < 7 at 1 and 5 minutes, Duration of NICU stay, perinatal mortality, moderate and severe morbidity	GROUP 1 Preterm delivery 24.4% vs 13.2% RR: 1.9 (1.2, 3.1) Caesarean section 24% vs 29% RR: 0.9 (0.6, 1.3)	Baseline characteristics of two groups similar Blinding of outcome assessor Confounding variables controlled	CH	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		underwent US screening twice at 15-22 and 31-35 weeks (n=7549)	between OH and Normal AFI in two groups – Group 1 with associated maternal/fetal conditions like PROM, HT, DM, and Group 2 without such associated conditions		Apgar < 7 at 5 min 7.7% vs 3.1% RR: 2.2 (1.1, 4.7) Perinatal mortality 5.1% vs 1.2% RR: 4.1 (1.3, 13.4) Severe morbidity 7.7% vs 5.3% RR: 1.5 (0.5, 3.8) GROUP 2 Preterm delivery 3.5% vs 4.1% RR: 0.9 (0.3, 2.7) Caesarean section 19% vs 14% RR: 1.4 (0.8, 2.4) Apgar < 7 at 5 min 1.2% vs 1.2% RR: 1.0 (0.1, 7.0) Perinatal mortality 0% vs 0.5% RR: 0 Severe morbidity 1.2% vs 0.8% RR: 1.4 (0.2, 10.3)			
Biggio et al, 1995	[939]	Review of all computerized records of a tertiary hospital in USA (n=40065) *Cases*: pregnancies complicated by hydramnios after 20 wks gestation (n=370) *Controls*: all singleton pregnancies having	Hydramnios taken as AFI ≥ 25 cms or depth more than 8 cms measured in a single vertical pocket or sonographers subjective impression.	Comparison made for adverse perinatal outcomes (Perinatal mortality rate (PMR) per 1000 births, fetal anomalies, FGR, caesarean section, and diabetes), and confounding variables known to influence	PMR (per 1000 births) 49 vs 14 RR: 3.4 (2.2, 5.4) Adj RR: 3.8 (1.9, 7.3) Fetal anomalies 8.4% vs 0.3% RR: 25.4 (17.4, 37.2) Adj. RR: 18.2 (8.7, 38.2)	Nested case control Minimal chance of bias Blinding not specified Confounding variables controlled	CC	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		normal AF volume on US after 20 weeks (n=36425)		perinatal outcomes adjusted using regression model.	FGR 3.8% vs 6.7% RR: 0.6 (0.3, 0.9) Adj. RR: 0.5 (0.2, 1.1) Caesarean 47.0% vs 16.4% RR: 2.9 (2.6, 3.2)			
Bricker & Neilson,	575	The review includes all randomized and quazi-randomized controlled trials where routine Doppler US of umbilical artery and/or uterine artery was done in both unselected and low risk pregnant women (n=14338, 5 trials)	To assess the effectiveness of routine Doppler US on obstetric practice and pregnancy outcomes in unselected and low risk pregnancies	Primary outcome measures were induction of labour, caesarean section, preterm delivery < 28 and < 34 weeks, all deaths (perinatal, neonatal, and infant), neurodevelopment at 2 years of age, and maternal psychological effects	Routine Doppler US vs no/concealed/selective Doppler US Meta-analysis (4 trials) - no differences between the two group in antenatal admissions or other te of fetal well being, induction of labour, instrumental deliveries, caesarean section, neonatal interventions and perinatal mortal 3 trials report perinatal mortality fo fetuses/neonates without congenit anomalies, but there was heterogeneity of results (chi-squar 10.44, p < 0.025) with one trial finding increased perinatal mortalit in screened group (OR 3.31, 95% 1.37-2.53). Serial US and Doppler US versus selective US Single trial compared the two groups and no difference was found between them for all the primary outcomes. More babies in the screened group were of BW < 10th and < 3rd centile	Cochrane review Well addressed question and methodology explained in detail	SR	1++
Gardosi and Francis, 1999	567	Two similar catchment areas (distance from hospital, ethnicity and socio-economic background of population, number of referrals per year) of a	To evaluate the effect of a policy using serial SFH measurements plotted on CFGC (study group) compared with routine antenatal care policy of recording SFH	Primary outcomes: number of SGA (< 10th centile) and LGA (> 90th centile) babies detected antenatally in each group. Secondary outcomes: total number	Number of SGA detected antenatally 47.9% vs 29.2% OR: 2.23 (1.12, 4.45) Number of LGA detected antenatally	Non-randomized controlled trial Incomplete data for calculating diagnostic accuracy Blinding not specified		1-

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
		tertiary hospital in UK served by separate and non-overlapping groups of community midwives and GP's. *Study group:* singleton pregnancies (n=667) booked before 22 weeks GA and issued CFGC, *Control group:* consecutive singleton pregnancies (n=605) booked before 22 wks and delivered in the hospital	against women's GA (control group)	of investigations performed in each group including referrals to US department/pregnancy assessment unit, and admissions to the ward.	45.7% vs 24.2% OR: 2.63 (1.27, 5.45) <u>Induction of labour</u> 15.7% vs 16.7% OR: 0.93 (0.69, 1.26) <u>Preterm birth</u> 7.8% vs 6.4% OR: 1.23 (0.80, 1.88) <u>Admissions to SCBU</u> 3.3% vs 2.6% OR: 1.26 (0.65, 2.41) <u>Resuscitation at birth</u> 16.5% vs 14.4% OR: 1.18 (0.87, 1.56) <u>Fetal abnormality</u> 1.0% vs 1.5% OR: 0.70 (0.26, 1.90)			
Clausson et al, 2001	[940]	Details of all the live births recorded in the Swedish Birth Register between 1992-1995 after excluding those with congenital malformations, unknown gestational age, and insufficient information for calculating customized birth-weight centile. (n=326,377)	To determine if CFGC improves detection of SGA babies and association with adverse perinatal outcomes. Two standards for estimating birth weight constructed from database – a population one based on gender and gestational length, and an individually customized one with adjustment for maternal height, weight, parity and ethnic group.	Risks of stillbirth, neonatal death and Apgar score < 4 at 5 minutes compared in infants classified as SGA by the two standards to that of non-SGA infants. SGA defined as the lowest 10%, 5% or 2.5% of birth-weights in the population.	<u>SGA (pop) vs non-SGA (cust.)</u> Stillbirth OR: 1.2 (0.8, 1.9) Neonatal death OR: 0.9 (0.3, 2.3) Apgar < 4 at 5 min OR: 1.2 (0.9, 1.5) <u>SGA (cust.) vs non-SGA (pop.)</u> Stillbirth OR: 6.1 (5.0, 7.5) Neonatal death OR: 4.1 (2.5, 6.6) Apgar < 4 at 5 min OR: 2.2 (1.9, 2.7)	Population based cohort Baseline characteristics of two groups similar Confounding variables not controlled	CH	2+

Study	Ref.	Population	Intervention	Outcomes	Results	Comments	Study type	EL
					SGA (cust.) vs SGA (pop.) Stillbirth OR: 5.1 (4.3, 5.9) Neonatal death OR: 3.4 (2.4, 4.8) Apgar < 4 at 5 min OR: 2.0 (1.7, 2.3)			
Zhang et al, 2007	941	All recorded births with complete data for a period of 10 years (1992-2001) in the Swedish Birth Register. Apart from excluding those with congenital malformations, unknown gestational age, and insufficient information for calculating customized birth-weight centile (as in previous study), it also excluded births with GA < 28 weeks. (n=782,303)	To critically examine potential biases and artifacts underlying the use of CFGC. All the births were classified as non-SGA (both standards), SGA (cust.), SGA (pop.), or SGA (both), using the same standards as the above study	Risks of stillbirth, neonatal death and Apgar score < 4 at 5 minutes compared in infants classified as SGA by the two standards to that of non-SGA infants after controlling for confounding variables (gestational age and pre-pregnancy BMI)	SGA (pop) vs non-SGA (cust.) Stillbirth OR: 1.4 (1.1, 1.9) Adj. OR: 1.8 (1.3, 2.4) Neonatal death OR: 1.3 (0.9, 2.0) Adj. OR: 1.6 (1.0, 2.4) SGA (cust.) vs non-SGA (pop.) Stillbirth OR: 7.8 (6.9, 8.9) Adj. OR: 2.3 (2.0, 2.6) Neonatal death OR: 6.7 (5.5, 8.1) Adj. OR: 2.0 (1.6, 2.5) SGA (cust.) vs SGA (pop.) Stillbirth OR: 5.7 (5.2, 6.2) Adj. OR: 4.9 (4.4, 5.4) Neonatal death OR: 5.7 (4.9, 6.5) Adj. OR: 4.9 (4.3, 5.7)	Retrospective analysis of data from the population based cohort Baseline characteristics of two groups similar Confounding variables controlled	CH	2+

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(2003 version)

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