UK National Screening Committee

Department of Health

Fetal Anomaly Screening Programme - Screening for Down's Syndrome: UK NSC Policy recommendations 2007 – 2010: Model of Best Practice

1. **The UK National Screening Committee (UKNSC) recommends the following outcomes and benchmark timeframes for Down's syndrome screening programme in England:**

Programme Outcomes

- A detection rate (DR) for Down's syndrome of greater than 75% of affected pregnancies with a screen positive rate (SPR) of less than 3%.

  (*Benchmark timeframe: April 2007 to April 2010*)

- A detection rate (DR) of greater than 90% of affected pregnancies with a screen positive rate (SPR) of less than 2%.

  (Benchmark timeframe: by April 2010)

2. **Recommended screening strategies to achieve these outcomes are in paragraphs 9 to 22 and organisational implications are drawn out in paragraphs 23 to 31. Annex A summarises the key points and service issues on which the NHS locally may wish to take action.**

This advice builds on previous UK NSC policy recommendations for the period 2003 to 2007, which it supersedes.

Background

3. The Model of Best Practice[(1)] (MOBP) for England (2003) outlined current UK NSC recommendations for Down's syndrome screening which are that all women should be offered screening with a screen positive rate (SPR)[(2)] of less than 3% and a detection rate (DR) of more than 75%. This was determined after review of evidence from a number of publications particularly the HTA SURUSS report of 2003 [(3)]. The policy was supported by the Genetics White Paper[(4)], NICE guidance 2003[(5)] and the Maternity services NSF[(6)]. The aim is to give pregnant women choices with regard to screening.

4. The UK NSC is committed to reviewing new and emerging evidence to assess any possible improvements to the screening programme, and to keeping new technologies and screening strategies for Down's syndrome under review.

5. To establish evidence-based, best practice and advice for 2007 – 2010, the present policy was reviewed at four expert meetings during 2006 and early 2007. This included assessment of published evidence on new screening markers and

strategies and a series of workshops with experts, NHS professionals and service users to consider the implications. Recommended working standards to support the NHS on all aspects of this screening programme have been issued and are available from the Programme Centre [(7)].

UK NSC recommendations

6. The UK NSC recommends that screening should take place in the time window of 10 weeks+ 0 days to 20 weeks+ 0 days gestation using the strategies identified in this document. The preferred strategy, where women book for antenatal care sufficiently early, is that screening is completed by 13 weeks + 6 days gestation. There is presently insufficient evidence for screening strategies for Down's syndrome prior to 10 weeks of pregnancy. This will be kept under review.

7. It is of paramount importance that women can make an informed choice about whether they wish to undertake screening. Decision-making requires good quality information delivered in a timely manner and a national leaflet is available for this purpose [(8)]. It is recommended that this leaflet be used in consultations with women about screening for Down's syndrome.

Recommended Screening Programme Outcomes

8. The UK NSC recommended screening programme outcomes and benchmark timeframes are as follows:

Programme Outcomes

- A detection rate (DR) for Down's syndrome of greater than 75% of affected pregnancies with a screen positive rate (SPR) of less than 3%.

  (Benchmark timeframe: April 2007 to April 2010)

- A detection rate (DR) of greater than 90% of affected pregnancies with a screen positive rate (SPR) of less than 2%.

  (Benchmark timeframe: by April 2010)

Recommended Screening Strategies from 2007

9. The current evidence suggests that the following tests are acceptable and they are recommended to meet the outcome of a DR greater than 75% and SPR less than 3%.

10. **1st Trimester Combined – This should be the preferred method to aid early diagnosis. This is the preferred method as it supports screening being completed in one stage without the need for more than one attendance. It will also give a risk before 14 weeks of pregnancy allowing earlier decision making for parents.** The recent revision of the NICE clinical guideline on "Antenatal care: routine care for the healthy pregnant woman" also advises that the 1st trimester combined test is used. The evidence reviewed by the UK NSC shows that using

biochemistry or ultrasound alone before 13 weeks will not meet the 2007 recommended outcome.

11. This test (1st trimester combined) is undertaken before 13 weeks + 6 days of pregnancy and uses ultrasound Nuchal Translucency (NT) measurement, plus serum biochemistry testing to measure free beta hCG and PAPP-A. The optimal time to perform this test is between 11 weeks + 0 days to 13 weeks gestation. In this time window, blood samples can be taken from the pregnant woman at the same time as the NT can be measured.

12. NT should be performed at the time of the early dating scan if that is undertaken after 11 weeks + 0 days and before 13 weeks and 6 days gestation. If an early dating scan is undertaken prior to 11 weeks for any reason then a second appointment for a scan will need to be made to measure the NT.

13. **Integrated testing - This test requires the woman to attend at least twice for screening**, once before 13 weeks + 6 days and then again between 15 weeks + 0 days and 20 weeks + 0 days (2nd trimester). She has to wait until both samples have been processed for a final result. The test involves ultrasound NT measurement, plus serum biochemistry testing to measure PAPP-A (not hCG) in the 1st trimester, and 2nd trimester biochemistry testing to measure hCG (all types), uE_3 and AFP.

14. The optimal time for 1st trimester serum biochemistry tests for PAPP-A is between 10 weeks + 0 days and 12 weeks + 0 days. However, the full screening window for 1st trimester PAPP-A testing is between 10 weeks + 0 days and 13 weeks + 6 days gestation. Ultrasound NT is measured between 11 weeks + 0 days gestation and 13 weeks + 6 days gestation.

15. The screening window for the 2nd trimester serum testing is between 15 weeks + 0 days and 20 weeks + 0 days gestation.

16. **Serum Integrated testing - This test requires two attendances, one in the 1st and one in the 2nd trimester but does not include ultrasound NT.** The test involves women waiting between samples for a final result. 1st trimester serum biochemistry testing involves measurement of PAPP-A (not hCG) and 2nd trimester serum biochemistry testing measures hCG (all types), uE_3 and AFP.

17. The optimal time for 1st trimester serum biochemistry testing is between 10 weeks + 0 days and 12 weeks + 0 days. However, the full screening window is between 10 weeks + 0 days and 13 weeks + 6 days gestation.

18. The screening window for 2nd trimester serum biochemistry is between 15 weeks and 20 weeks + 0 days.

Testing in the second trimester for those women who book late

19. **Quadruple testing - A 2nd trimester test will always be required for those women who attend later in the pregnancy (this is usually around 15% of the pregnant population).** The 2nd trimester screening test that will just meet the 2007 recommended outcome is the quadruple test. This is a serum biochemistry test which

involves the measurement of four assays which may include hCG (all types), uE_3, AFP, and Inhibin A and is undertaken between 15 weeks 0 days and 20 weeks 0 days.

Threshold levels for risk measurements.

20. To ensure that the measurement of performance, quality assurance and decision-making are consistent nationally, individual results should be categorised as higher or lower risk and based on a cut-off of 1 in 200 at term for 2nd trimester screening strategies and 1 in 150 at term for 1st trimester screening strategies. This has been changed from the present 1 in 250. This change to the cut-off level will aid in meeting the 2007 and 2010 outcomes. The overall performance of the test for the screened population must be age-standardised to provide a true reflection of the DR and SPR. Assistance with this is provided free of charge by the support service, Down's Syndrome Screening Quality Assurance Support Service (DQASS), which is funded by the Programme Centre.

Quality Assurance.

21. Audit and monitoring are central functions of UK NSC National Screening Programmes and these help continually improve the quality of screening and ensure women receive the best available risk evaluation. It is recommended therefore that all screening strategies, including those using NT, are part of external quality assessment and assurance schemes. This includes participation in DQASS. Non-identifiable biochemistry and ultrasound NT patient data are sent to DQASS where the median values and performance of the screening test will be assessed against the recommended programme outcomes. DQASS issues a full report, with a summary report and letter to the Chief Executive of the Trust, and the relevant public health departments. It is recommended that all laboratories should be part of CPA, (Clinical Pathology Accreditation) and UK NEQAS (National External Quality Assessment Scheme).

Follow-on diagnostic procedures.

22. A confirmatory diagnostic service will be offered for all screen positive results. The main services in place at present are 2nd trimester diagnostic services (amniocentesis). A change to 1st trimester diagnostic services (CVS) will require commissioners to plan accordingly with the relevant stakeholders.

Organisational Implications of meeting programme outcomes for 2010

23. There are some base principles to consider when recommending and implementing a Down's syndrome screening programme.

- Approximately fifteen per cent of women will present too late in the pregnancy for first trimester tests and therefore only require a second trimester test.

- In Combined screening, the other 85% will require only this first trimester test.

- For Integrated and Serum Integrated strategies, approximately 85% of women will require testing in both the first and second trimester to ensure they have the full screening test.

NT measurement capacity

24. The UK NSC advises that a 1st trimester combined screening is the preferred option for the reasons given in paragraph 10 above. All Trusts presently provide early dating scans and NT measurement is already in place in 30% of these. The development of capacity to undertake NT measurement is a key area for the period 2007 – 2010. It is also important to develop the capacity to do NT scans as part of the Fetal Anomaly Screening Programme (FASP)[7] as they provide information about other potential abnormalities, and future clinical management of the pregnancy. The Programme Centre will be able to provide advice to support services in building capacity for NT.

Meeting the 2010 programme outcomes

Moving to 1st Trimester combined screening

25. For Trusts which currently only provide 2nd trimester biochemical screening, the move to 1st trimester combined screening would involve adding NT measurement onto the early ultrasound dating scan, and providing the 1st trimester analysis of PAPP-A. 1st trimester services do not require the analysis of AFP, uE3 or Inhibin A. Although combined screening will require the analysis of both PAPP-A and hCG, hCG is already costed into 2nd trimester biochemical services, so that costs can be transferred from one time window to the other. The cost of the ability to calculate risk is already being met by services.

26. A shift to the provision of a CVS diagnostic service will also be necessary. CVS uses the same equipment as that used for amniocentesis so the technical capacity to support a CVS service is already in place. Training of staff currently undertaking amniocentesis should be factored into planning. The accumulation of experience in the practice of CVS is difficult to quantify but should be considered when planning services.

Moving to Integrated testing

27. Presently only two Trusts in England offer this screening strategy, which does not provide the early risk assessment provided by 1st trimester combined screening. Services which only provide 2nd trimester biochemical screening would need to add NT measurement to the early ultrasound dating scan, and to introduce PAPP-A measurement in the first trimester. 2nd trimester biochemical testing for all women would also continue.

Moving to Serum Integrated

28. This screening strategy does not provide the early risk assessment provided by 1st trimester combined screening, and is used by only one English Trust at present.

29. If trusts wish to move to serum integrated screening, the introduction of PAPP-A measurement in the first trimester would be required. 2nd trimester biochemical testing for all women would also continue.

Quadruple testing for all women

30. This is the strategy for late bookers. Although it will not meet the 2010 recommended outcome, and only just meets the recommended outcome for 2007, there is presently no other screening strategy that will be available for those presenting later than 14 weeks gestation. If Inhibin A is used as the fourth, additional marker to be added to the Triple test, which many hospitals use, costs will vary depending on the ability to negotiate the price with suppliers.

Impact on diagnostic services

31. Achieving the 2010 outcome will give increased test accuracy and so will reduce the overall number of positive screening test results (SPR). This, in turn, will reduce the number of women receiving further counselling for higher risk results and also reduce the number of women needing follow-up diagnostic procedures and tests. This will reduce demand on diagnostic services from the screening programmes.

Developments to enable the NHS to deliver improved outcome measures from screening tests in the period after 2010

32. New strategies currently under review by the Health Technology Assessment (HTA) Programme will use the same serum biochemistry markers needed between 2007 and 2010, as outlined above, but require different methodologies to calculate risk. These strategies are known as Repeated Measure and Cross Trimester testing strategies. It is expected that these strategies will allow screening programmes to improve on the 2010 recommended outcome in the following few years.

33. It is expected that the basic infrastructure (outlined in Paragraph 34 below) which supports the capacity to achieve the improved 2010 programme outcomes will be able to accommodate these potential new strategies, when combined with new software to calculate risk. The changes required to currently available commercial risk calculation software will form part of the national Programme Centre's discussions with suppliers during 2008. Work to ensure that the basic infrastructure is in place by 2010, particularly the full introduction of NT scans by April 2010, will facilitate their introduction.

34. The base infrastructure for screening consists of the capacity to:-

1. undertake the dating of a pregnancy by ultrasound at an early stage of the pregnancy with the incorporation of the NT ultrasound measurement.
2. measure serum for PAPP-A in the first trimester i.e. before 14 weeks of pregnancy and ideally at 10 – 12 weeks
3. measure serum for AFP, hCG (all types) uE3 and Inhibin A in the second trimester i.e. after 15 weeks 0 days and 20 weeks 0 days. This is a particular need for those women presenting later in the pregnancy.
4. offer 1st trimester CVS and 2nd trimester amniocentesis diagnostic services

offer rapid testing for diagnosis i.e. QF – PCR and full karyotype in line with the recommended working standards issued by the national Programme Centre.

Further information can be obtained from:-

NHS Fetal Anomaly Screening Programme, Programme Centre, Unit G1, Innovation Centre, Rennes Drive, University of Exeter, Exeter, EX4 4RN. Tel: 01392 262396

References

1. Model of Best Practice 2003; Down's syndrome screening; DOH

2. The SPR is the number of women screened who are recalled for further diagnostic procedures. This is slightly different to the false positive rate, which is the number of women screened recalled for a diagnostic procedure less those women who have an affected pregnancy. SPR is a more accurate indicator of the resources required to support the screening programme. For example, it is the total number of women who will be offered a diagnostic procedure and who will require funding and resourcing when commissioning a service.

3. Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). HTA 2003; Vol.7: No.11

4. Genetics White Paper June 2003. 'Our inheritance, Our future – realising the potential of genetics in the NHS' Department of Health.

5. Antenatal care routine care for the healthy pregnant woman. Clinical Guideline October 2003. National Institute for Clinical Excellence.

6. National Service Framework for Children Young People and Maternity Services. Gateway reference 3779 2004.

7. Antenatal Screening – Working standards for Down's Syndrome Screening 2007.

8. This leaflet is available from the UK NSC Screening Office Tel: 0870 1555455 quoting ANSP01/07. It can also be downloaded from http://www.screening.nhs.uk/downs.

Abbreviations.

AFP – Alpha Feto Protein
CPA - Clinical Pathology Accreditation
CVS – Chrorionic Villus Sampling
DQASS – Down's syndrome Quality Assurance Support Service
DR – Detection Rate
FMCH – Fetal and Maternal Child Health sub group
FPR – False Positive Rate
HCG - Human Chorionic Gondatrophin
HTA – Health Technology Assessment
NEQAS – National External Quality Assessment Service
NT – Nuchal Translucency
PAPP-A – Pregnancy Associated Placental Protein A
QA – Quality Assurance
SPR – Screen Positive rate
uE3 – Unconjugated Estriol
UK NSC – UK National Screening Committee

QUICK REFERENCE SUMMARY **Annex A**

Fetal Anomaly Screening Programme - Screening for Down's Syndrome: UK NSC Policy recommendations 2007 – 2010: Model of Best Practice

1. Recommended Screening Programme Outcomes

Programme Outcomes

- A detection rate (DR) for Down's syndrome of greater than 75% of affected pregnancies with a screen positive rate (SPR) of less than 3%.

  (Benchmark timeframe: April 2007 to April 2010)

- A detection rate (DR) of greater than 90% of affected pregnancies with a screen positive rate (SPR) of less than 2%.

  (Benchmark timeframe: by April 2010)

2. Recommended screening strategies for 2007-2010

- **1st trimester - Combined testing. This is the preferred method to aid early diagnosis. This test requires only one visit for the woman and combines ultrasound NT measurement with serum biochemistry before 13 weeks + 6 days of pregnancy.**

- **Ist and 2nd trimester - Integrated testing** - This test requires the woman to attend at least twice for screening - once before 13 weeks + 6 days and again between 15 weeks + 0 days and 20 weeks + 0 days**.** The test involves ultrasound NT measurement plus serum biochemistry testing.

- **Ist and 2nd trimester - Serum Integrated testing** - This test requires the woman to attend twice for screening but does not include ultrasound NT.

- **2nd trimester - Quadruple testing –** This test is required for those women who attend later in the pregnancy.

3. During 2007-2010 – developments

During 2007-2010, services will wish to consider developing:

- Capacity to support measurements for Nuchal Translucency (NT) Scanning.
- Addition of NT measurement to early dating scan, where Trusts only provide 2nd trimester biochemical screening.
- Provision of 1st trimester analysis of PAPP-A and hCG.
- Shift to provision of CVS diagnostic service.
- Quadruple testing for women who present in the 2nd trimester (i.e. booking after 14/52), usually by adding Inhibin A tests to the existing triple test.