

*The following is an excerpt from the 8th Annual Report of the Confidential Enquiry into Stillbirth and Death in Infancy. The full report is available on [www.cemach.org.uk](http://www.cemach.org.uk)*

## **COMMENTARY: CLINICAL IMPLICATIONS OF ‘UNEXPLAINED’ STILLBIRTHS**

*The ‘unexplained’ stillbirth remains the biggest problem for all involved in maternity care. The qualitative review of the panel comments have identified a series of areas of concern. The EuroNatal study (Chapter 4) parallels these findings. CESDI invited Dr Jason Gardosi, Director of the West Midlands Perinatal Institute to write a response on how CESDI is best placed to take this topic forwards.*

The purpose of counting perinatal mortality rates and conducting confidential enquiries is ultimately to understand contributing factors and trends, and to seek ways of avoiding recurrence. However, the high proportion of stillbirths which are in the ‘unexplained’ category is not helpful to this endeavour. Surveys on perinatal mortality and reports of the Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) consistently find that about 70% of stillbirths are ‘unexplained’. This has become the single largest category in perinatal mortality statistics. While analysis of year-on-year trends suggests a gradual decline in perinatal mortality rates overall, the relative proportion of ‘unexplained’ stillbirths appears to be on the increase<sup>1</sup>.

### **Does ‘unexplained’ mean unavoidable?**

The preponderance of stillbirths in the ‘unexplained’ category occurs despite the three-tier classification used on CESDI Rapid Report Forms. This classification includes: (1) the pathophysiological classification of Wigglesworth<sup>2</sup>, (2) the Fetal and Neonatal Factor classification<sup>3</sup>, described by Bound *et al.* in 1956<sup>4</sup> and applied in the 1958 British Mortality Survey<sup>5</sup> and (3) the revised Aberdeen classification<sup>6</sup> described by Baird and Thomson<sup>7</sup> in 1954<sup>8</sup>.

In the CESDI ‘1 in 10’ enquiry, 10% of all singleton stillbirths in England and Wales in 1997 were examined, excluding congenital anomaly and weight <1000 g. Despite thorough review of the causes, these deaths were given a category other than ‘unexplained’ in only 17% of cases according to Wigglesworth, 16% by the Fetal and Neonatal Factor classification and 21% by the Aberdeen classification<sup>9</sup>. Yet in many instances, panel members commented on substandard management and considered that the death was potentially avoidable. Our current

classification system appears to work against the internal review by the clinicians involved in a case, or external, anonymised review by expert panels, seeking to establish what could have led to the loss.

Any classification system that throws up such a high proportion of ‘unexplained’ cases would appear to be failing to fulfil its purpose and failing to help in the quest to understand and reduce perinatal mortality. There is a danger that ‘unexplained’ is seen as synonymous with ‘unavoidable’, resulting in the conclusion that nothing can be done. The main aim of a classification system should be to shed light on the events and to inform on future management. Better understanding is important for counselling the affected parents and establishing a prognosis and a management plan for future pregnancies. There is also a need to link health promotion and death prevention initiatives to clinical observation and epidemiological research.

Studies using other classification systems for perinatal death report substantially lower rates of stillbirth in the ‘unexplained’ category. Whitfield’s study in Glasgow<sup>10</sup> found that only 15/67 (22%) of stillbirths remained unexplained, and a more recent report from Montreal suggested that 27% of antepartum deaths were unexplained<sup>11</sup>. Detailed analysis of cause of death in two Scandinavian studies left only 12% and 9%, unresolved or ‘unexplained’<sup>12,13</sup>. All of these studies include a category of small for gestational age (SGA) or fetal growth restriction (FGR).

### **Fetal weight and stillbirth**

The link between perinatal mortality and fetal growth restriction is obscured by definitions such as that by WHO for ‘low birth weight’ which has served its purpose but is now outdated wherever routine gestation dating by ultrasound is used. It lumps together two conditions, prematurity and growth restriction, with varying combinations of the two. Perinatal mortality statistics are collected in separate weight and gestational age groupings<sup>14</sup>, and such categories persist in England and Wales<sup>15</sup> as well as in Scotland<sup>16</sup>. Making comparisons *within* weight categories, i.e. controlling for birthweight<sup>17</sup>, can obscure the fact that many in-utero deaths include fetuses that are smaller than they should be at that gestational age. Nevertheless, even within the confines of the current classifications and the use of ‘low birth weight’ in an extended Aberdeen classification, an inferred category of ‘growth retardation’ emerges as the single most important component of stillbirth statistics, often occurring in mothers with no obstetric risk<sup>18</sup>.

The extent of the link between fetal weight and death becomes most apparent when weight is corrected for gestational age. Williams<sup>19</sup> analysed over 23 000 fetal deaths in California on population-based percentile curves and demonstrated a strong link between fetal weight for gestational age and demise. Analysis of the large Swedish birthweight register also demonstrated the strong links between smallness for

gestational age and fetal death<sup>20</sup>. Closer to home, in the absence of good denominator data, smaller, targeted studies in the Midlands confirmed the importance of a link, for stillbirths at all gestational ages<sup>21</sup> and for unexplained stillbirths at term<sup>22</sup>.

Although the exact time of fetal demise may not be known, it can in most instances be derived with sufficient accuracy to calculate a valid weight-for-gestational age percentile. A cessation of fetal activity in the third trimester tends to be reported early by mothers. Furthermore, in many instances labour commences spontaneously soon after fetal death. Many clinicians can recall agonising about an in-utero fetal death which resists attempts at induction of labour, but such cases are relatively infrequent. It is estimated that the average time interval between fetal death and spontaneous or induced delivery is 48 hours<sup>21</sup>, which is also consistent with histopathological evidence<sup>23</sup>. A median death-to-delivery interval of two days can be deduced from the gestational age at birth when calculating weight-for-gestational age percentiles for stillbirths<sup>21</sup>.

There is no evidence that dead fetuses, even when severely macerated, lose weight in utero. In addition, pathologists often observe that 'dry weight' measured just before postmortem tends to be *lower* than that recorded at delivery, as third space fluid – such as that which accumulated following congestive fetal heart failure – has had opportunity to drain. The weight at postmortem is therefore likely to be an underestimate of actual weight at time of death<sup>21</sup>, with weight at time of delivery being the best reflection of true fetal weight.

### **Diagnosis of growth restriction**

Smallness for gestational age (SGA) is not synonymous with fetal growth restriction (FGR) or intrauterine growth retardation (IUGR), as smallness may not be pathological, but the result of physiological/constitutional variation. Evidence of FGR in a stillborn fetus can be established in several ways:

- 1 Ultrasound imaging has allowed us to get a better understanding of normal growth, which occurs almost linearly in normal pregnancy<sup>24,25</sup>. Serial ultrasound biometry of the fetal abdominal circumference, or biophysical assessment (doppler flow) would establish the diagnosis of restricted growth. However, in most instances this information is not available; if it was, then it is likely that action would have been taken to deliver the fetus before in-utero demise, provided it was considered sufficiently mature.
- 2 Few would doubt that a higher rate of postmortems is desirable to help throw light on the causes of stillbirth. However, the quality of the postmortem and the standards used are important. There is evidence that, with the current classification, the proportion of 'unexplained' stillbirths is not substantially different in cases that had a postmortem and those that did not<sup>21</sup>. Pathologists have relied

on reference data from other stillborn babies<sup>26</sup> for individual organs as well as for whole body weights. But reference data from cadavers can hardly be regarded as a standard or 'norm', and the association between smallness and death can be missed. Careful histological examination of organs such as the heart and adrenals, and organ weight ratios, can help to determine whether growth restriction was present.

- 3 Birthweight can be linked to other measurements (e.g. length) to calculate a ratio (e.g. ponderal index). However, the validity and significance of ponderal index at various gestational ages, and for stillborn babies, has not been established.
- 4 Comparison can be made with a normal weight for gestational age standard; such reference curves have improved by the use of computerised databases and routine pregnancy dating with ultrasound which 'straighten' birthweight curves<sup>27</sup>. If a cohort of stillbirths has a disproportionate number of babies weighing less than, say, the tenth percentile, but is not significantly different in constitutional variables, then it can be reasonably deduced that the difference in size for gestation is due to a higher prevalence of growth restriction in the stillborn compared with the live-born group<sup>21</sup>.
- 5 Smallness of individual babies could still be due to constitutional variation. To avoid this, a lower birth weight ratio or percentile cut-off can be used, as in Montreal, where a definition of '25% underweight' (equivalent to the 2.4 centile) was applied<sup>28</sup>. However, the same group found that a higher centile category (2.5–10th) is also significantly associated with stillbirths<sup>11</sup> and this is confirmed in other studies<sup>29,30</sup>. It has also been argued that the severity of SGA varies with gestational age; stillbirths at earlier gestations are smaller and a lower centile cut-off should apply<sup>31,32</sup>. However for prevention, the recognition of a small baby remains essential, whatever cut-off limit is used. Varying the percentile limits below which a weight is considered small would obscure the observation that preterm babies that die are more severely affected, or, that the more severely affected tend to die more prematurely.
- 6 A customised or individualised birthweight standard allows inferences to be made about growth status, as constitutional variation in fetal weight due to factors such as maternal height and weight, ethnic group, parity and sex is adjusted for, while pathological factors such as smoking are excluded. Adjustments for such variables create a weight standard which better reflects FGR and its association with neonatal morphometric indices<sup>33</sup>, adverse pregnancy events<sup>34</sup> and perinatal mortality<sup>30</sup>. The link between stillbirth and growth failure is seen to be even stronger<sup>30</sup>. Calculation of customised centiles has to be done by computer. The software is freely available on the internet ([www.gestation.net](http://www.gestation.net)).

### **Detection and avoidability**

It is important for the health service and for clinicians in perinatal disciplines to learn from outcome, and to be aware that growth failure is

a substantial contributor to perinatal mortality. The purpose of a classification is to highlight the areas in need of attention to reduce mortality, and clearly a category of ‘fetal growth restriction’ is required. The majority of growth restriction is currently not detected because it is not looked for and because its importance is not recognised. Analysis of the ‘1:10’ stillbirth enquiries highlights the fact that in many instances, growth screening and assessment was considered inadequate. But even in the general population, routine growth screening strategies are failing – only about 25% of SGA babies are detected antenatally in an unselected population<sup>35</sup>. In a ‘low risk’ population, this can be as low as 16%<sup>36</sup>.

Although there is no in-utero treatment, fetal death following slow growth has to be considered as potentially avoidable. The majority of such deaths occur at mature gestations, and these babies are likely to do well if delivered in good condition. Appropriate surveillance of babies recognised as high risk is possible following the substantial improvements in maternal–fetal medicine, and will allow determination of the best time for delivery from an unfavourable intrauterine environment. The missing link is the screening and detection of which babies are at risk.

### **The role of antenatal care**

An acknowledgement of the importance of fetal growth – and the need for early detection – will define the priorities of antenatal care and question much of current practice. For example, the utility of risk assessment at the beginning of pregnancy must be in doubt in this regard, as most cases of growth failure occur in pregnancies with *no* risk factors. If a designation of ‘low risk’ at the beginning of pregnancy results in fewer visits, and less vigilance and attention to fetal well-being, then such pregnancies might be at a *higher* risk of fetal demise.

All pregnancies require a minimum standard of antenatal surveillance in the third trimester, with two main components:

- **Maternal perception:** the sensation of fetal movement is an important indicator of fetal well-being. Yet there is often insufficient counselling and emphasis on the need to be seen urgently if a reduction in fetal movements is felt. In addition, the test ordered for ‘decreased fetal movements’ is usually an antenatal CTG (non-stress test of the fetal heart rate), which is an inappropriate investigation, as it may provide false reassurance<sup>37</sup>. The antenatal CTG is one of the last parameters which becomes abnormal in the sequence of events leading to fetal demise. Ultrasound and doppler is indicated if fetal movements appear reduced<sup>38</sup>.
- **Clinical assessment:** first-line screening needs to include the systematic measurement and serial plotting of fundal height. Symphysio-fundal height measurement has had mixed reports in the

literature, but was often used to predict weight or gestational age, rather than to assess fetal growth. The measurement is often not done properly, or with incorrect technique, and is not even taught in many medical and midwifery schools. The (erroneous) expectation – that the measurement in centimetres should be equivalent to the gestational age in weeks – also leads to bias. However, standardised measurement, plotted on customised fundal height charts, and referral according to well-established criteria results in a significant increase in the detection of babies which are too small or too large<sup>39</sup>. Furthermore, this method results in *fewer* referrals for investigations for fetal well-being (such as ultrasound scan and doppler), as midwives are reassured when growth is proceeding normally.

Thus it is likely that the required service development would be cost-neutral, but would require the effort and resources to achieve a shift in emphasis towards a system of antenatal care that acknowledges the importance of this problem. Currently, fetal surveillance does not appear to feature prominently in discussions about the aims of maternity care. Better awareness of fetal growth would not only allow timely intervention to reduce intrauterine death, but in other cases forewarn of diminished reserve to ensure optimum intrapartum and neonatal management. Furthermore, knowledge of the prevalence of fetal growth failure would improve our understanding of the social, physiological and pathological factors affecting growth within a defined population, and provide a basis for future improvements in maternity services.

### Summary

Fetal growth failure is a precursor of many instances of ‘unexplained’ stillbirths. There is an urgent need to alter our current classification system and to raise awareness of the problem of growth restriction – both in the understanding of adverse outcome and in the development of better strategies for prevention.

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