Prevention of stillbirth

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Key content:

- Most of the variability in stillbirth risk is not due to maternal risk factors. Hence, modifying maternal risk factors, or screening women using maternal risk factors to assess risk has limited potential impact.
- The only intervention that prevents stillbirth is delivery. The overall risk of perinatal death is lowest at 39 weeks gestational age, and induction of labour at term does not increase a woman's risk of emergency caesarean section.
- The most promising approach to screening low risk women for stillbirth risk may be to improve identification of small for gestational age infants. However, there is an absence of high quality evidence around the optimal approach to achieving this goal.

Learning objectives

- To understand the relationship between maternal risk factors, obstetric complications and fetal size in relation to stillbirth risk.
- To understand the approach to fetal assessment and elective delivery as methods to prevent stillbirth.

Ethical issues

- Screening for stillbirth risk has the potential to do good by preventing deaths. However, if programmes of screening and intervention are developed, many more women may be harmed due to high false positive rates.

Introduction

Stillbirth is delivery of a baby showing no signs of life at or beyond a given gestational age threshold, or threshold of birth weight (see Smith & Fretts 2007 for review[1]). The thresholds employed vary internationally. In the UK, stillbirth requires delivery at or after 24 weeks and, using this threshold the absolute risk of stillbirth in the UK is approximately 1 in 200. About 99% of stillbirths in the world occur in low and middle income settings. Globally, the most effective way to prevent stillbirth would be to implement the same universal provision of antenatal and intrapartum care that is routinely available in high income countries. There are, obviously, multiple barriers to achieving this, and identifying the most cost effective elements of care to prevent stillbirths in low and middle income settings is an important focus in Global Health. However, there is a failure to recognise stillbirth as important. For example stillbirths did not feature in the Millenium Development Goals.

Stillbirth can be classified by the timing of fetal death in relation to the onset of labour: antepartum stillbirth is where death occurred prior to the onset of labour, and intrapartum is where death occurred during labour. In high income countries, <10% of stillbirths involve death of the baby during labour. Stillbirths can also be classified due to the presumed cause. However, it is only in a minority of cases where the cause of death is known with complete certainty. In the remainder, there is a full spectrum from highly probable causes with strong associations through to losses where no cause or risk factor can be identified. This spectrum is illustrated for stillbirths attributed to maternal disease in Figure 1. These issues lead to problems in classification, which are manifested by the presence of more than 40 current classification systems.

Preventing stillbirth can be considered in terms of modifying risk factors, use of antenatal interventions, management of complications of pregnancy, and the potential for population based

screening for stillbirth. This review focuses on antepartum stillbirths in late pregnancy in high income countries.

Strategies for preventing stillbirth

Maternal risk factors

Multiple maternal risk factors have been identified which are associated with the risk of stillbirth including nulliparity, advanced maternal age, and obesity (Table 1). However, a carefully conducted US case-control study, performed by the NICHD, demonstrated that all maternal risk factors which could be assessed at the time of the first antenatal visit (including non-demographic characteristics such as obstetric history, diabetes and multiple pregnancy) only accounted for 19% of the variability in the risk of stillbirth at the population level.[2] This key observation has two important implications: (i) there is limited scope for reducing the number of stillbirths by modifying maternal characteristics, and (ii) screening women based on assessment of maternal risk factors will only identify a minority of babies at risk. Clearly, individual women should be encouraged to correct risk factors associated with the risk of stillbirth, such as smoking and obesity. However, significant impacts on overall rates of stillbirth in the general population are unlikely to be achieved with programmes aimed solely at modifying maternal risk factors.

One recent observation of interest is the association between stillbirth and maternal sleep position. It has long been known that supine position results in compression of the maternal inferior vena cava, which leads to reduced uterine blood flow and fetal hypoxia. Hence, in clinical situations where a woman is in a supine position for more than a few minutes (e.g. late pregnancy ultrasound), left lateral tilt is usually employed to prevent caval compression. A case control study of stillbirth from New Zealand demonstrated an association between non left sided sleep position and stillbirth risk[3]. A case control study is currently in progress in the UK (MiNESS study). If the finding is confirmed, it is

possible that women may be actively recommended to sleep on their left side, and this could be a future population-based approach to reducing the number of stillbirths.

Antenatal interventions

The use of low dose aspirin in women deemed to be at high risk of pre-eclampsia has been shown to be associated with a modest reduction in the risk of stillbirth.[4] Otherwise, there are no antenatal interventions which have been shown to be effective. The meta-analysis of RCTs of aspirin does show that the intervention is not significantly associated with complications. Hence, it is reasonable to consider use of aspirin in women deemed to be at high risk. A recent RCT, the paper reporting the TIPPS trial, failed to show any benefit of low molecular weight heparin (LMWH) on the risk of pregnancy loss or placentally related complications among women with thrombophilia.[5] This result was in contrast to a meta-analysis of smaller trials which demonstrated a protective effect of antithrombotic therapy on the risk of perinatal death (60% reduction).[6] However, the TIPPS study also included a meta-analysis and concluded that the positive results previously observed were driven by single centre studies and were not observed in the multi-centre studies. Hence, there is not a strong basis for the use of LMWH as a means to prevent placentally-related complications such as stillbirth, although further research is required to rule out smaller treatment effect sizes.

Delivery

In many cases of stillbirth, death of the baby would be prevented by delivery. This would obviously not be the case for lethal anomalies associated with stillbirth, such as Edward's syndrome. It is also obvious that the reduced risk of stillbirth would have to be balanced with the risks of neonatal and infant mortality (and severe morbidity) associated with delivery. i.e. all stillbirths could be prevented by delivering all babies at 24 weeks and 0 days, however, the benefit would be swamped by the harm. Clearly the balance tends towards favouring delivery as gestational age progresses and modelling studies indicate that the overall risk of perinatal death may be lowest with delivery at 39

weeks gestational age.[7] The model reflects common sense: the risk of neonatal death does not fall further beyond 39 weeks, but on-going pregnancy beyond this point exposes the baby to the risk of stillbirth at or after 40 weeks (Figure 2). Consistent with the modelling, meta-analyses of RCTs demonstrate that routine induction of labour at term reduces the risk of perinatal death by 50%.[8] These observations make a case for offering induction of labour to all women. Any benefits arising from this would have to be balanced against the increased demands of maternity systems. However, the observations do suggest that a more liberal approach to induction of labour at term may be one approach to reduce stillbirths. Moreover, studies of screening and intervention should focus on predicting risk of stillbirth at term, as there is a safe and effective intervention to mitigate the risk in women who screen positive.

Managing complications of pregnancy

Stillbirth is associated with many common complications of pregnancy, including fetal growth restriction, pre-eclampsia, antepartum haemorrhage, and reduced fetal movements. As discussed above, the primary intervention to prevent stillbirth is delivery of the baby. Hence, managing these and other complications of stillbirth is primarily focused on how to target this intervention in a way that prevents the maximum number of stillbirths and causes the minimal harm. The issues can be illustrated with the ultrasonic assessment of high risk pregnancies. A Cochrane review indicates that use of umbilical artery Doppler is associated with a reduced risk of perinatal death in high risk women.[9] As an ultrasound scan is, self-evidently, not a therapeutic intervention, this observation indicates that knowledge of the umbilical artery Doppler reduces the risk of death by some combination of (i) encouraging delivery of a compromised fetus which would otherwise have been managed conservatively, or (ii) encouraging expectant management of a healthy fetus where delivery would have exposed the baby to a greater risk of death through prematurity. Multiple other methods of fetal assessment have been described, including other Doppler measurements (middle cerebral artery, ductus venosus, umbilical vein), ratios of Doppler indices (e.g. middle cerebral artery

to umbilical artery Doppler) other ultrasound measurements (biophysical profile, placental assessment), and cardiotocography (CTG), which can be interpreted either visually or using a computerised analysis. There is less trial evidence regarding many of the above. However, a multicentre trial (TRUFFLE) comparing ductus venosus Doppler and computerised assessment of the CTG is about to be reported. However, this study is focused on preventing adverse outcomes in the context of severe, early onset growth restriction, rather than late pregnancy stillbirths. The current state of evidence regarding the management of small for gestational age fetuses, including those with suspected fetal growth restriction, is presented in the RCOG Greentop Guideline, *The investigation and management of the small for gestational age fetus*.

Existing trial evidence suggests that use of non-computerised CTG in antenatal assessment of the fetus shows a strong trend towards increasing the risk of perinatal death (relative risk for potentially preventable death associated with use of CTG = 2.46, 95% CI 0.96 to 6.30).[10] This is presumably by false reassurance. For example, a woman presents with reduced fetal movements, the CTG is normal and she is reassured, sent home and the baby subsequently dies in utero. In this case, the clinical presentation gave more information about the true risk status of the fetus than the CTG. Trials comparing computerised with conventional antenatal CTG show a strong trend towards better outcomes with the computerised assessment (relative risk for any perinatal death = 0.2, 95% CI: 0.04 to 0.88 and relative risk for potentially preventable death = 0.23, 95% CI: 0.04 to 1.29).

Taking the above together, it would be reasonable to recommend a liberal use of induction of labour at or after 39 weeks in the presence of factors associated with stillbirth. Prior to 39 weeks, the risk of stillbirth must be balanced against the risks of intervention, a balance that will tend to favour delivery the closer the woman is to term. Given the trial evidence, it is difficult to understand why many units still use non-computerised antenatal CTG when making these decisions.

Screening pregnant women for stillbirth risk

For the reasons outlined above, programmes which aim to reduce the population burden of stillbirth substantially will need to be able to prevent losses among women who lack obvious risk factors. One approach to this is to identify small for gestational age (SGA) fetuses. Approximately half of all stillbirths appear to be SGA.[11] Audits of perinatal deaths have indicated that undiagnosed SGA is a common association with stillbirth.[12;13] If the fetus is known to be SGA, the risk of stillbirth is reduced by 50% compared with cases where the SGA is not recognised.[11] These characteristics are the basis for considering improved screening for SGA as one of the most promising approaches. A randomised controlled trial has demonstrated that routine planned delivery of SGA infants at ~37 weeks' gestational age was not associated with an increased risk of adverse maternal or fetal outcome,[14] hence a safe intervention is available to prevent stillbirths at term.

It is possible, however, to exaggerate the potential effect of improved screening for SGA on population rates of stillbirth. Currently, routine care identifies about 1 in 4 small babies. Any new method of screening will reduce stillbirth rates by the effect of detecting the other 75% of SGA babies which are not identified. Taking the example of customized assessment of symphyseal fundal height (SFH), one trial and one observational study have demonstrated that use of this approach identifies about 1 in 4 of the cases of SGA which are currently missed.[15;16] Even this figure is slightly exaggerated as both studies appeared to define being small by SFH measurement as prenatal diagnosis as SGA. In reality, prenatal diagnosis would only be regarded as true if confirmed by ultrasound and, in reality, ultrasound will not identify all small babies correctly. However, taking the 1 in 4 figure at face value, and assuming that prenatal identification of SGA reduces the risk of stillbirth by 50%, the predicted proportion of stillbirths prevented is 0.5 x 0.25 x 0.5 = 6%. However, this figure also assumes that no units are currently using this method of screening at present. Just over half of UK units are already using customized assessment of symphyseal fundal height. Hence, implementation of this across the UK would be expected to prevent less than 5% of the ~4000

stillbirths occurring in the UK each year. Hence, reducing the numbers of stillbirths due to SGA will require (i) better methods of population-based screening for true fetal growth restriction, and (ii) better management of cases of SGA which are identified.

Uterine artery Doppler flow velocimetry in mid gestation is associated with stillbirth due to fetal growth restriction, but this test tends to be associated with stillbirths occurring at extreme preterm gestational ages, and is only weakly associated with the risk of stillbirth near term.[17] Another approach to screening for SGA infants is universal ultrasound in the third trimester. This is not currently recommended as meta-analyses of RCTs have failed to demonstrate any beneficial effect on pregnancy outcome.[18] However, the trials of universal ultrasound in late pregnancy have a number of methodological issues, in particular that they were designed in the absence of high quality information of the diagnostic effectiveness of ultrasound as a screening test in low risk women, and none of the trials of screened coupled ultrasound with a clearly effective package of intervention: these issues have been reviewed in detail elsewhere.[19] We have completed a prospective cohort study of ~4,500 unselected nulliparous women with singleton pregnancies,[20] and this study will report high quality data on the diagnostic effectiveness of universal ultrasound to screen for both SGA and neonatal morbidity in 2015.

While there are clearly problems in preventing stillbirths which are SGA, there at least the potential for antenatal screening. However, preventing stillbirth of normally grown babies is an even greater problem. One approach may be to develop better blood tests (biomarkers) for placental function. Even apparently normally grown stillbirths exhibit histopathological abnormalities in the placenta.[1] Development of tests to identify underlying placental dysfunction which are associated with stillbirth in the absence of SGA/FGR may be one approach to preventing these losses.

How do we know what works, and what does not?

Clinical guidelines generally change when there is strong evidence to support change. Although stillbirth is one of the more common serious complications of pregnancy, the absolute risk remains low. Consequently, it is very difficult to design trials that are sufficiently large to address the effects of interventions. For example, sample size calculations demonstrate that if a screening test identified 5% of the population who had a likelihood ratio for stillbirth of 10, and if this screening test was coupled with an intervention which reduced the risk of stillbirth by 50%, a randomised controlled trial would require ~130,000 women to be powered to detect the effect. In contrast, the current Cochrane review of routine ultrasonography in low risk women has ~27,000. Hence, confident statements that routine ultrasound does not reduce the risk of stillbirth are misleading.

One way to approach this problem in the future would be to modify the way we design RCTs of screening, an area which has previously been reviewed.[19] Another is to consider interventional trials which randomise at the level of hospitals: these include cluster RCTs and stepped wedged RCTs which have, again, been reviewed in detail elsewhere.[21]

Conclusions

Stillbirth is a devastating complication of pregnancy which affects ~4000 families in the UK each year. Impacting on overall rates of stillbirth will require improving care of low risk women, principally, development of better methods for identifying the low risk women who has a high risk conceptus. In the meantime, increased awareness of the problem is likely to improve outcomes, for example, through (i) better management of babies with problems, such as SGA, and (ii) targeted use of indicated delivery, the primary disease modifying therapy.

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Legends for Figures

Figure 1.

Illustration of the spectrum of certainty regarding maternal disease as a "cause" of fetal death. For 5 of the events, the actual mechanism resulting in death of the baby is unknown, although there are increasingly strongly associated predisposing factors. In case 6, the mechanism leading to disease is completely understood. ALT denotes alanine transaminase, and GA denotes gestational age. Reproduced with permission from a report of an NICHD workshop.[22]

Figure 2.

The perinatal risk index associated with delivery at a given week of gestational age at term. This is a calculation of the combined risk of antepartum stillbirth, intrapartum stillbirth and neonatal death associated with a given week of delivery at term. This is calculated using a conditional probability tree. The perinatal mortality rate cannot be used to summarise the risk, as the three different types of event have different denominators – see Smith 2005[23] for review. Figure reproduced with permission from Smith, 2001.[7]

Figure 1

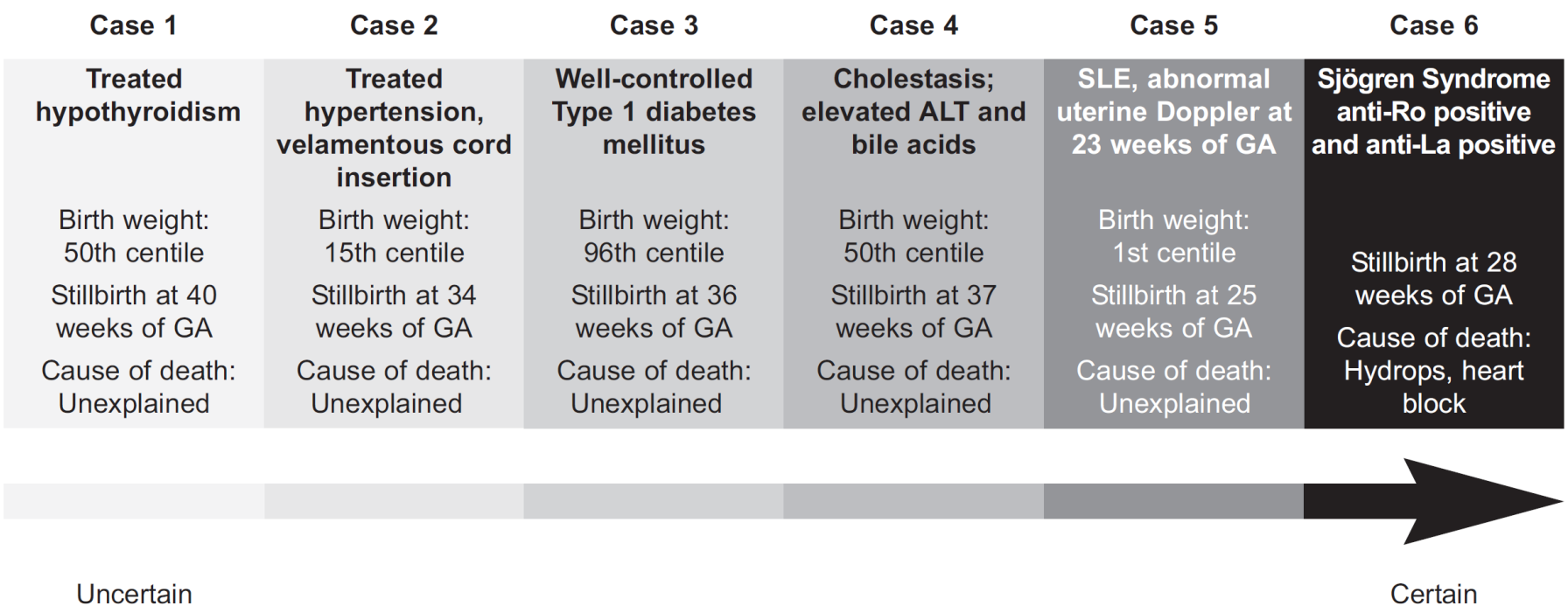
Case 1
Case 2
Case 3
Case 4
Case 5
Case 6
Treated hypothyroidism
Birth weight: 50th centile
Stillbirth at 40 weeks of GA
Cause of death: Unexplained
Treated hypertension, velamentous cord insertion
Birth weight: 15th centile
Stillbirth at 34 weeks of GA
Cause of death: Unexplained
Well-controlled Type 1 diabetes mellitus
Birth weight: 96th centile
Stillbirth at 36 weeks of GA
Cause of death: Unexplained
Cholestasis; elevated ALT and bile acids
Birth weight: 50th centile
Stillbirth at 37 weeks of GA
Cause of death: Unexplained
SLE, abnormal uterine Doppler at 23 weeks of GA
Birth weight: 1st centile
Stillbirth at 25 weeks of GA
Cause of death: Unexplained
Sjögren Syndrome anti-Ro positive and anti-La positive
Stillbirth at 28 weeks of GA
Cause of death: Hydrops, heart block
Uncertain
Certain

Figure 2

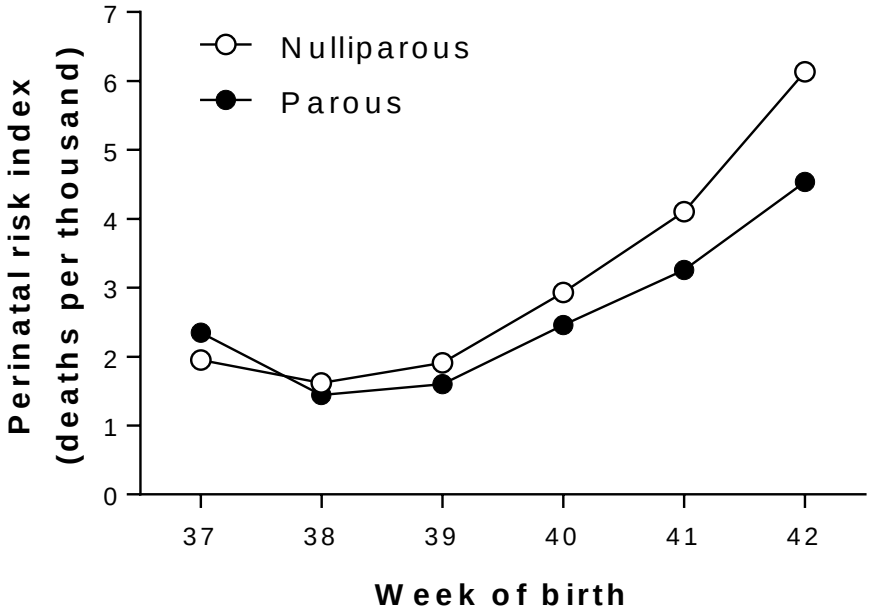
Perinatal risk index
(deaths per thousand)
Nulliparous
Parous
0
1
2
3
4
5
6
7
37
38
39
40
41
42
Week of birth

Table 1. Maternal characteristics associated with the risk of stillbirth from the NICHD case control study.

Characteristic	**Adjusted Odds ratio**	**95% CI**
Non-Hispanic black race/ethnicity	2.12	1.41 to 3.20
Previous stillbirth	5.91	3.18 to 11.00
Nulliparity + previous losses at <20 weeks'	3.13	2.06 to 4.75
Nulliparity, no previous losses	1.98	1.51 to 2.60
Diabetes mellitus	2.50	1.39 to 4.48
Maternal age 40 years or older	2.41	1.24 to 4.70
Maternal AB blood type	1.96	1.16 to 3.30
History of drug addiction	2.08	1.12 to 3.88
Smoking	1.55	1.02 to 2.35
Obesity/overweight	1.72	1.22 to 2.43
Not living with a partner	1.62	1.15 to 2.27
Multiple pregnancy	4.59	2.63 to 8.00

CI denotes confidence interval. Data from The Stillbirth Collaborative Research Network Writing Group, 2011.[2] See publication for adjustment and referent categories. The definition of stillbirth in this analysis uses the gestational age threshold 20 weeks.