Screening and prevention of stillbirth

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Abstract (150 words)

Stillbirth is delivery of a baby at or after 24 weeks of gestational age (UK definition) showing no signs of life. It affects almost 1 in 200 pregnancies and is the single major cause of perinatal death. Stillbirth is associated with a wide range of maternal demographic characteristics, but most of the variation in stillbirth risk is independent of these characteristics. Stillbirth is the end point of multiple processes, but the single most common cause is probably placental dysfunction. Stillbirth is associated with a range of biochemical and ultrasonic predictors, but there is limited evidence to support population based screening. However, the evidence based is weak due by use of poorly characterised screening tests, the failure to couple risk assessment with a clearly effective intervention for those who screen positive, and inadequate study sample sizes. Basic research needs to identify better predictors, and clinical trials need to adopt more rigorous methodology.

Key words:

Stillbirth, screening, intervention, ultrasound, biomarkers.

1. Introduction

The 2016 Lancet *Ending Preventable Stillbirth Series* indicated that the UK was in about the middle of the range of 49 high income countries in relation to stillbirth rates, and had one of the slowest rates of decline in stillbirth.[1] The absolute risk of stillbirth from 24 weeks onwards is 3-5 per 1,000, i.e. about the same as the total risk of death in the first year of life. Moreover, a significant proportion of stillbirths potentially could have been prevented if the babies had been identified as high risk, i.e. cases where the cause of death was not a major congenital anomaly and where the death occurred at a gestational age associated with a low risk of infant mortality.[2] A recent study, supported by the James Lind Alliance, reported the top research priorities in relation to stillbirth. This study elicited 1275 responses from 574 participants (equally divided between professionals and non-professionals) and identified several priorities (out of 300 indicative unanswered questions) directly related to screening, (e.g. Priority #5, Does ultrasound assessment of fetal growth in the third trimester reduce stillbirth?), and 4 others which were also relevant (e.g. Priority #6, Would increasing the frequency of umbilical artery Doppler scanning during pregnancy reduce stillbirth?).[3] The top 11 recommendations are listed (Table 1). The aim of the current review is to consider current practice in relation to screening for stillbirth, and how improved methods of screening may be developed and evaluated.

1.1 Epidemiology of stillbirth

Stillbirth is defined as delivery of a baby in the perinatal period which fails to show any signs of life. The definition of the start of the perinatal period varies between countries. In the USA it is 20 weeks of gestational age (wkGA) and in the UK it is 24wkGA.[2] The rate of stillbirth in high income countries varies from 1.3 per 1,000 to 8.8 per 1,000, with an average of 3.5 per 1,000.[1] The clear majority of stillbirths in high income countries are the result of intra-uterine fetal death prior to the onset of labour (antepartum stillbirth).[2] Deaths occurring during labour (intrapartum stillbirths) account for 5-10% of all stillbirths in high income countries but account for a much larger proportion of losses in low and middle income countries (LMIC).[4] A range of maternal characteristics have been associated with the risk of stillbirth. One of the most systematic and methodologically sound analyses of such risk factors was performed by the NICHD's Stillbirth Collaborative Research network.[5] Their analysis of risk factors identifiable at the start of pregnancy is tabulated (Table 2).

1.2 Causes and classification of stillbirth

Aside from the sub-division of stillbirths into intrapartum and antepartum, losses can also be classified according to the presumed cause. However, this process is complicated by the fact that

relatively few losses have a completely understood cause of death. The remainder have varying degrees of uncertainty in the mechanism(s) leading to death. This is illustrated in Figure 1 in relation to ascribing cause of death in the presence of a range of maternal medical conditions.

A diverse – if not bewildering – array of classification systems have been developed.[1] One of the main characteristics which determines variation between the systems is the extent to which they will attribute a given associated condition or finding as being the cause of death. For example, an unexpected and unexplained stillbirth of an infant at 39 weeks where the baby's birth weight was on the 2rd percentile for sex and gestational age might be defined as unexplained in one classification system and as being due to fetal growth restriction (FGR) in another. In a sense, both classifications are correct. The actual cause of death is unknown, hence the loss is strictly unexplained. However, it is known that birth weight <3rd percentile is associated with a 10-fold risk of stillbirth at term.[6] Hence, it is very likely that the baby's death was related to its size. The subject of classification of stillbirth is reviewed in detail elsewhere.[7]

In the context of screening, one of the key associations for stillbirth is poor fetal growth. It is estimated that between 30 and 50% of stillbirths are associated with low birth weight percentile, and this is assumed to reflect FGR, which is in turn presumed to be related, in a large proportion of cases, to placental dysfunction.[2] This association is important in the context of screening, as a number of tools exist to quantify both fetal growth and placental function.

2. Screening for stillbirth

The first element of screening is to differentiate a population into those at high risk of the condition and those at low risk. The analysis and interpretation of screening statistics can be complicated. Particular problems in the context of stillbirth are as follows.

(i) stillbirth is the end result of diverse pathological processes. Hence, no one test is likely to be highly sensitive for the condition overall.

(ii) stillbirth can occur across the whole range of gestational age. As the primary means to prevent stillbirth is to deliver the baby, the consequences of inappropriate intervention differ profoundly: at 24 weeks outcomes are generally extremely poor, whereas at 40 weeks, outcomes are generally extremely good.

(iii) stillbirth is relatively uncommon, hence, any sub-type of stillbirth is less common still. For example, if 40% of stillbirths are due to FGR and the risk of stillbirth in a country is 4 per 1,000, the absolute risk of stillbirth associated with FGR is 1.6 per 1,000. Normally, a test with a positive likelihood ratio of 20 would be regarded as an excellent screening test. However, the positive predictive value of this test in such a population would be about 3%. Consequently, 97% of screen

positive women would not experience the event of interest. It follows, therefore, that if an intervention based on such a test caused any harm to false positives, that a programme of screening and intervention would be likely to cause harm despite a strong screening test and an effective intervention.

3. Maternal risk factors

The maternal characteristics which are associated with the risk of stillbirth have been tabulated (Table 2). However, collectively, these associations explained just 19% of the variability in the risk of stillbirth. Hence, programmes of screening and intervention which focus on maternal risk factors will have a relatively limited capacity to reduce the numbers of stillbirth. Another key element of maternal risk are the associations with gestational diabetes mellitus (GDM). There are a series of maternal characteristics which place a woman at increased risk of GDM (Table 3). A recent detailed review of a representative sample of unexpected stillbirths of normally formed infants at term in the UK, conducted by the national perinatal mortality surveillance system, MBRRACE-UK, found that failure to screen for GDM was one of the three most common potentially preventable characteristics observed which might have resulted in the loss being avoided.[8]

3.1 Clinical factors associated with stillbirth risk

Reduced fetal movements (RFM) is one of the key symptoms associated with the risk of stillbirth. This subject has been reviewed in detail elsewhere.[9] Failure of medical and midwifery staff to respond appropriately to RFM was one of the other major potentially preventable causes of stillbirth in the MBRRACE-UK review described above.[8] The RCOG in the UK has issued a guideline for the management of women who present with reduced movements.[10] Another major symptom associated with stillbirth risk is antepartum haemorrhage. In the absence of placenta praevia or cervical pathology, this is likely to represent bleeding from the placenta, and may be a harbinger of later abruption. Finally, acquired disorders of pregnancy (such as GDM or pre-eclampsia) could be associated with maternal symptoms. Management is based on specific testing for the condition in question.

3.2 Response to women with symptoms associated with stillbirth risk

At preterm gestational ages, fetal monitoring is indicated. Generally, the first line of assessment is cardiotocography (CTG, also called a non-stress test in the USA). Interestingly, the RCOG Guideline on RFM does not recommend computerised CTG,[10] which utilises objective analysis of the trace, including computerised assessment of beat to beat variability. However, the Cochrane reviews

indicate no benefit of using non-computerised CTG (and a trend towards harm) compared with using nothing, and a reduced risk of perinatal death using computerised CTG analysis compared with non-computerised CTG (see Smith 2015, for review).[11] Hence, computerised CTG is a reasonable first step. The next level of assessment is an ultrasound scan. This is done if there are other risk factors present, but will also be done in low risk women who are presenting with their second (or greater) episode of RFM. The key evidence-based measurement in high risk pregnancies is Doppler flow velocimetry of the umbilical artery. However, generally, fetal biometry and amniotic fluid measurement would also be performed, sometimes with additional Doppler measurements (middle cerebral artery). The evidence base supporting these supplementary measurements is poor: this is a key area for further research and multiple recommendations of the prioritisation exercise for stillbirth research touched on this area.

At term, induction of labour should be considered for women presenting with RFM. At 37-38 weeks, induction is still associated with increased risks of perinatal morbidity and should only be offered if fetal assessment is non-reassuring, there are other risk factors or if there have been multiple episodes of RFM. However, perinatal outcome is optimal at 39-41 weeks and induction should be considered for any women presenting with RFM at ≥39 weeks. Epidemiological evidence exists that universal induction at 39 weeks would reduce overall rates of stillbirth.[12] However, for women with a single episode of RFM, who have no other risk factors, and who want to avoid intervention, it is reasonable not to induce labour, as the absolute risk of stillbirth is likely to be <1%. The basis for this statement is that the background risk of stillbirth at term is 1-2 per 1,000 and it is unlikely that a single episode of RFM in an otherwise low risk women is associated with a >5-fold risk of stillbirth.

4. Biochemical predictors of stillbirth risk

A range of biochemical tests have been associated with the risk of stillbirth. Most of these are maternal blood tests but, historically, urine tests were also evaluated. Many of the associations described were secondary analyses of measurements made for the purposes of screening for unrelated conditions, such as neural tube defects and Down's syndrome.

4.1 Pregnancy associated plasma protein A (PAPP-A)

PAPP-A is a protease for insulin like growth factor binding proteins 4 and 5, and it is produced by the placenta. Its primary application has been for screening for Down's syndrome. However, it was shown that low first trimester PAPP-A was associated with stillbirth risk and that the association was due to losses related to placental dysfunction.[13;14] A systematic review concluded that PAPP-A was a

"good predictor of stillbirth related to placental dysfunction disorders".[15] In the UK, an RCOG Guideline recommends methods for further monitoring of women found to have low PAPP-A in the first trimester of pregnancy.[16]

4.2 Alpha fetoprotein (AFP)

AFP is a fetal oncotic protein. High maternal serum levels are associated with structural fetal anomalies (neural tube defects and abdominal wall defects) and low levels are associated with Down's syndrome. High levels in the second trimester are associated with the risk of stillbirth in normally-formed babies, but the associations are stronger for losses occurring at extreme preterm gestational ages.[17] Hence, intervention to prevent such losses is problematic. The association is thought to be related to abnormal permeability of the placenta, hence increased passage of the protein across the placental barrier. Interestingly, unexplained raised maternal serum AFP is associated with a diverse series of abnormalities on subsequent placental pathological examination where the pregnancy was complicated.[18]

4.3 Others

A range of other biochemical tests have been associated with the risk of FGR and stillbirth. Some of these were in widespread use prior to the advent of ultrasound, such as measurement of oestrogens in maternal urine. Others have been more recently identified as potential screening tests for pre-eclampsia, in particular pro- and anti-angiongenic proteins circulating in the mother's blood, such as PlGF, sFlt-1, and eEng. Studies have described some promising associations with the angiogenic regulators.[19] However, the relative rarity of stillbirth (compared with preeclampsia and preterm birth) make it a more difficult subject to address. Cohort studies have to be larger in order to be able to detect associations. Moreover, if a measurement has a positive likelihood ratio of 10, which would usually be regarded as a good screening test, it would only have a positive predictive value of <5%, and much lower still if performed later in pregnancy.

Biochemical tests have great potential as a screening tool for stillbirth when combined with ultrasound. However, any such potential will not be adequately evaluated unless studies are sufficiently powered to detect associations. Moreover, interventional studies will present huge challenges and will require addressing significant methodological considerations (see below).

5. Ultrasonic assessment of stillbirth risk

The first use of ultrasound to estimate the weight of the fetus was described in 1975.[20] Subsequently, multiple other methods were described to assess fetal well-being, including biophysical measurements (activity, breathing movements, tone and liquor volume) and ultrasonic Doppler flow velocimetry of fetal and utero-placental arteries and veins. Research focused on both the diagnosis of fetal compromise in women who had presented with complications and/or those known to have risk factors, and also on trying to identify which apparently low risk women had occult fetal compromise. The body of work quickly led to RCTs of universal screening of low risk women using late pregnancy ultrasound. A meta-analysis of these trials (latest version is Bricker et al 2015[21] including data from a total of 34,980 women recruited to 13 trials), reported no maternal or fetal benefit of screening. A previous version of this meta-analysis (which had very similar conclusions) led NICE to conclude in their 2008 Guideline on Antenatal Care[22] that women should not have routine late pregnancy ultrasound scans.

In the same Guideline, NICE indicated that further studies on the diagnostic effectiveness of universal ultrasound as a screening method in the general population should be considered a priority. It may seem counterintuitive that NICE would declare universal screening to be ineffective but then to propose further studies on the diagnostic effectiveness of the screening test. This apparent anomaly is explained by closer examination of the studies included in the meta-analysis. Ultimately, all meta-analyses, however appropriately conducted, are only as good as the trials included. Issues with the 13 trials in the Cochrane review are as follows: (i) the individual trials used different definitions of screen positive, (ii) none of the definitions had been evaluated in a level 1 study of diagnostic effectiveness prior to being employed in the screening study, i.e. all of the individual interventional studies were designed and conducted in the absence of high quality quantitative information about the performance of the screening test, (iii) none of the trials had a standardised intervention for those who screened positive, other than to reveal the test or to perform further scans. Finally, even the meta-analysis itself is under-powered. The 2016 Lancet *Ending Preventable Stillbirth Series* reported sample size calculations for trials of screening and intervention for stillbirth. These looked at the statistical power assuming very optimistic values of screening test performance (5% of the population identified with a positive likelihood ratio of 10) and intervention (50% reduction) based on the incidence of stillbirth (1 in 200). The sample size required (90% power, alpha 0.05, two sided) was 131,000.[1] Hence, the meta-analysis has only about a quarter of the sample size required for even a very good screening test coupled with a highly effective intervention. Consequently, despite the fact that ultrasound has been used for >40 years to assess fetal well-being, and despite the fact that it is the primary method for assessing and

monitoring high risk pregnancies, there is an absence of evidence in relation to its utility in screening low risk women.

Universal ultrasound has been assessed as a means of detecting small for gestational age (SGA) infants in a level 1 study of diagnostic effectiveness (i.e. where the result of the research scans was blinded) including ~4,000 first pregnancies.[23] The rate of detection of SGA infants was 20% with selective use of ultrasound and 57% with universal scanning. However, for every one additional true positive result, there were two additional false positives with universal scanning. Moreover, of a range of ultrasonic indicators of FGR, only one differentiated between SGA infants and the risk of perinatal morbidity. Fetuses which were SGA on scan and had reduced growth velocity of the abdominal circumference (compared with the 20 week scan) were at increased risk of morbidity compared with normal sized fetuses, whereas SGA was not associated with the risk of morbidity if the growth velocity was normal. A meta-analysis has also demonstrated that high resistance patterns of Doppler flow velocimetry in the uterine arteries in mid-gestation are a good predictor of stillbirth related to placental dysfunction.[15] However, the studies revealed the result of the scan, which complicates assessment of the association.

Many private ultrasound providers have started offering late pregnancy ultrasound scans. There is, therefore, *ad hoc* screening at present with very little evidence regarding the balance of risks and benefits. Late pregnancy ultrasound has the potential to cause harm. False positive diagnoses can lead to unnecessary intervention and, in particular, early term delivery. While this is a valuable and evidence based intervention in certain contexts, such as pre-eclampsia, infants born at 37-38 weeks are at increased risk of short term morbidity,[24] and even have poorer achievement at school.[25] Hence, *ad hoc* screening and intervention has the potential to cause short and long term harm through iatrogenic late preterm and early term birth. This has recently been recognised in France, where routine ultrasound was implemented in the absence of supportive evidence. Screening did not appear to confer any benefit, but false positive diagnosis of SGA was associated with a greater than 3-fold increase in the risk of medically-indicated preterm birth.[26] This does not indicate that universal screening is futile. However, these findings underline the importance of understanding what elements of prenatal ultrasonic assessment of the fetus in a low risk pregnancy are informative of risk, and what interventions can be applied to mitigate the risk without causing harm.

6. Interventions to prevent stillbirth

6.1 Medical interventions

6.1.1 Aspirin

Low dose aspirin has been widely evaluated as a method for preventing placentally-related complications in pregnancy and, in particular, pre-eclampsia. Aspirin acts by irreversibly inhibiting the enzyme cyclo-oxygenase (COX), which is a key point in the biochemical synthesis of prostanoids, including thromboxane. Aspirin selectively blocks platelet prostanoid production as they lack a nucleus and cannot synthesise further COX following the irreversible binding with aspirin. The Cochrane review contains 14 trials containing 33,098 women, and demonstrates an 14% reduction in the risk of stillbirth or neonatal death.[27] Hence, aspirin should be considered for all women at risk of stillbirth. Typically, it would be started at 12 weeks and discontinued at 36 weeks. There is preliminary evidence from the pre-eclampsia literature to suggest that starting the treatment prior to 16 weeks may be associated with greater risk reduction.[28]

6.1.2 Low molecular weight heparin

Given the success of aspirin and given some published associations between maternal thrombophilia and stillbirth risk, many groups have considered the use of LMWH as a preventative treatment for women at increased risk of stillbirth. It is regarded as a strongly indicated therapy in some situations, such as anti-phospholipid syndrome, where it has the additional benefit of reducing the risk of maternal venous thrombo-embolism. A series of small trials appeared to show a benefit of the treatment on perinatal outcome.[29] However, a subsequent multicentre study demonstrated no beneficial effect of LMWH.[30] A caveat to this is that even that study was only powered to detect very major effects of LMWH. The confidence intervals around the effect from the trial include reductions in stillbirth risk which would be regarded as clinically significant. The current status of LMWH is, therefore, that it's use should primarily be considered to prevent maternal venous thrombo-embolism and that further studies are required before its use is recommended for the primary aim of preventing fetal complications.

6.1.3 Nitric oxide donors and selective phosphodiesterase inhibitors

Nitric oxide, a gaseous mediator of smooth muscle relaxation, is thought to have a key role in the control of placental development, with a deficit of nitric oxide effects postulated to be a determinant of abnormal placentation.[31] This has led to studies evaluating methods for increasing nitric oxide. Broadly, these fall into two categories: (i) nitric oxide donors, and (ii) selective phosphodiesterase inhibitors. Many nitric oxide donors have been developed for treatment of cardiovascular disease, such as angina and heart failure. A number of studies have evaluated nitric oxide donors in high risk populations. These have generally been small scale single centre studies and some have generated positive results.[32;33] However, further large scale multicentre trials are required prior to introduction of these agents in the management of high risk women. Selective

phosphodiesterase inhibitors were first developed for cardiovascular applications. But early experience in healthy volunteers led to an unanticipated effect on male erectile function, and a range of these drugs is available for erectile dysfunction. The best known is sildenafil citrate (known commercially as Viagara), and the evidence supporting a beneficial effect of this drug in the context of early onset FGR has been reviewed.[34] Currently, a multicentre RCT is in process, STRIDER, which seeks to assess the effect of sildenafil citrate in pregnancies complicated by early onset severe FGR. The field may also develop into the evaluation of other selective PDE inhibitors with longer half-life, and the use of the drug in pregnancies at high risk of FGR by their screening results, but prior to the disease onset.

6.1.4 Others

A range of other specific therapies exist, which are at various stages of evaluation but are not likely to be in routine clinical use in the very near future. These include the use of supplemental oxygen[35] and gene therapy.[36] Both of these approaches face significant logistical issues. Gene therapy has been evaluated in animal models and is currently being assessed for acceptability and feasibility in the context of severe, early onset FGR.

Finally, optimal management of co-existing medical conditions is an indirect way to reduce the risk of stillbirth associated with maternal disease. The obvious example is diabetes mellitus, both gestational and pre-existing. The risk of perinatal mortality reduces with better control. Although diabetes is the obvious example, it is plausible that optimal medical therapy would improve perinatal outcome with other maternal medical conditions, such as thyroid disease, connective tissue disorders etc.

6.2 Delivery to prevent stillbirth

At present, the only intervention which has a major effect on the risk of stillbirth is delivery. The effect of this clearly depends on (i) the background risk of stillbirth, and (ii) the gestational age, as GA is the major determinant of the risk of neonatal death. At term, the risk of neonatal death is extremely low, particularly following exclusion of deaths due to anomalies. However, the weekly risk of stillbirth is stable from 24 onwards and then rises at term and postterm. Combining analysis of declining risk of neonatal death and increasing and cumulative risk of stillbirth, it has been estimated that the risk of perinatal death is lowest at around 39 weeks.[12] Hence, one approach to preventing term stillbirths would simply be to induce labour in all women at 39 weeks. This approach is supported by a Cochrane review, which indicates that routine induction of labour at term and post

term reduces the risk of perinatal mortality by ~70%.[37] However, most would feel that this level of intervention would be excessive in relation to the number of deaths prevented. Nevertheless, this background should inform attitudes in general. If a woman feels strongly that she should be induced at 39 weeks or later, it is probably not unreasonable to agree to the request assuming the healthcare system is sufficiently well resourced. Furthermore, a low threshold for induction of labour should be applied to women with concerning symptoms or investigations. If a woman presents with reduced fetal movements (RFM) at 34 weeks, induction of labour would only be considered if there were confirmatory tests indicating other concerns. However, at 39 weeks and beyond, it would be entirely reasonable to induce labour for RFM. This would be especially the case if the woman actively wanted induced, and it would be appropriate if the woman was neutral and expressed the sentiment of so many "I just want what is best for my baby". However, many women are keen to avoid induction. In such cases, an open discussion is required. Women who decline induction can be reassured that, with a single episode of RFM, no associated risk factors, and reassuring monitoring, the absolute risk of a stillbirth remains low. It is essential in all these discussions that the woman's own attitudes and preferences are a foundation for the discussion. A key element for any such discussion would be to contradict the misconception that induction of labour increases the risk of caesarean section. A systematic review indicates that it results in a lower risk of caesarean delivery.[38] Moreover, a recent RCT has shown no increase in the risk of caesarean section when labour was induced at 39 weeks in a group of women with a high background risk of caesarean (nulliparous women aged 35y or greater).[39]

6.3 Modifying maternal risk factors for stillbirth

A number of the maternal characteristics associated with stillbirth risk are potentially modifiable. Numerous studies have demonstrated higher rates of stillbirth among smokers, and a causal association is plausible. It follows, therefore, that smoking cessation is likely to reduce the risk of stillbirth. Given the problems of conducting RCTs of interventions to prevent stillbirth (see below), it is unlikely that there will ever be level 1 evidence to support the use of smoking cessation as a means to prevent stillbirth. Nevertheless, given the background and given that this represents an absence of evidence, rather than evidence of absence, recommending that mothers participate in smoking cessation would be an appropriate approach. Similarly, raised body mass index is both directly associated with stillbirth in epidemiological studies and is also a risk factor for a cause of stillbirth, namely, GDM. Weight reduction should be considered for women who are obese and are planning pregnancy. Dieting through calorific restriction is controversial in pregnancy. However, women who are obese should be referred to a dietician and approaches which might improve

outcomes include reducing quantities of sugar intake, controlling portion sizes, eating more fresh fruit and vegetables, and the maintenance of healthy levels of activity through pregnancy.

A number of epidemiological studies have shown associations between maternal sleep position and the risk of stillbirth. These have demonstrated increased risks of stillbirth with supine sleep position, and it is speculated that this may be due to reduced blood supply to the uterus through caval compression (i.e. a pressure effect of the gravid uterus on the inferior vena cava). Further studies aiming to confirm or refute the association are in progress. If these confirm the association with maternal sleep position, there may be a case for a public health campaign to modify maternal sleep position as a means to reduce stillbirth risk. This is analogous with sudden infant death syndrome: epidemiological studies demonstrated an association with prone infant sleeping positon and SIDS, and a public health campaign was followed by an extraordinarily rapid decline in rates of SIDS in the UK.[40]

7. Evaluating novel methods for screening and prevention of stillbirth.

Despite huge expenditure of time and resources, there is no clear approach to screening women for stillbirth risk. Numerous studies have described possible methods for screening, including biochemical tests and ultrasound scans. However, none has been clearly shown to be effective in randomised controlled trials. The negative results of the trials do not necessarily indicate that ultrasound is futile. As discussed above, there are multiple issues in relation to the meta-analysis of RCTs of universal ultrasound. It is essential, therefore, that any future trials learn the lessons from previous trials and address new methods of screening using a methodologically rigorous approach. Key elements in designing new RCTs to prevent stillbirth are as follows: (i) the eligible population, (ii) the screening test to be employed and its diagnostic effectiveness, (iii) the timing of randomisation, namely, before or after application of the screening test, (iv) the intervention, (v) the control group, (vi) the primary and secondary outcomes, (vii) the sample size, (viii) the possibility of randomising at the level of hospitals, e.g. using a cluster RCT or stepped wedge RCT, (ix) the potential use of an adaptive trial design, (x) whether an initial smaller scale feasibility study is required, and (xi) the feasibility of the study, including manpower, skills mix, and quality assurance of the screening test. Many of these issues have previously been discussed in more depth elsewhere.[41]

8. Summary

Stillbirth in the single major determinant of perinatal death. In high income countries, ≥90% follow death of the baby prior to the onset of labour, and in this setting typical absolute rates are 3-4 per 1,000. Stillbirth is the end result of diverse processes, hence a single perfect screening test is unlikely

to be developed. Currently, women are assessed for their risk of stillbirth at the time of first attendance for antenatal care, and then are re-assessed during the pregnancy either at routine visits or when they present with symptoms which are associated with increased risk of stillbirth (such as reduced fetal movements). A range of methods have been developed to estimate the risk of stillbirth and associated conditions (such as FGR). Currently, investigations such as ultrasound are only applied to women who have risk factors or attend with complications. However, the possible utility of universal ultrasound has been poorly evaluated. About one third of all stillbirths occur at term and these are, potentially, the most readily preventable as there is a safe and effective intervention, namely, induction of labour, which reduces the risk of perinatal death by 70%. A key challenge is how to identify the women at increased risk of stillbirth and who would benefit from this intervention, from the general healthy population. In this way, losses could be prevented without causing unacceptably high rates of intervention.

Conflicts of interest.

GS receives/has received research support from GE, Roche and GSK. GS has been paid to attend advisory boards by GSK and Roche. GS has acted as a paid consultant to GSK. GS has received support to attend a scientific meeting from Chiesi. GS is named inventor in a patent submitted by GSK (UK), for novel application of an existing GSK compound for the prevention of preterm birth (PCT/EP2014/062602). GS has acted as an expert witness. GS is a member of a Data Safety Monitoring Committee for a trial of an RSV vaccine in pregnancy, being run by GSK.

Legend for Figure.

Figure 1. Representation of the continuum of uncertainty in ascribing cause for stillbirth, using the example of losses associated with maternal medical conditions. ALT denotes alanine transaminase; GA denotes gestational age. Reproduced with permission from a report of an NICHD workshop (Reddy et al., Obstet Gynecol 2009;114:901-914).

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Practice points

- Maternal risk factors do not perform well as a screening test for stillbirth. Many stillbirths occur to low risk women
- Common issues with quality of care in relation to stillbirth prevention include failure of effective screening or treatment of GDM, reduced fetal movements, or poor fetal growth
- Non-computerised antenatal cardiotocography has little role in assessing fetal well being, and may provide false reassurance about stillbirth risk in women presenting with reduced movements
- Induction of labour can safely be considered from 39 weeks onwards, even in relatively low risk women. It will prevent subsequent stillbirth, and is not associated with an increased risk of caesarean delivery.
- Women at risk of stillbirth should be treated with low dose aspirin from 12 to 36 weeks. Low molecular weight heparin should primarily be used to prevent maternal thrombo-embolism and its use to prevent stillbirth will largely be confined to randomised controlled trials

Research agenda

- Design, feasibility and optimal design of an RCT of universal ultrasound, and the effect of universal ultrasound scanning
- The best ultrasonic markers of likely intra-uterine fetal death in women presenting with complications
- The ability of biomarkers to differentiate between women with normal and abnormal placental function
- The relationship between placental pathology and adverse pregnancy outcome, and methods for diagnosing specific placental pathological processes in the antenatal period (e.g. blood tests for recognised placental disease processes)
- The mechanisms leading to placental dysfunction

Multiple choice questions

Question 1.

In relation to the epidemiology of stillbirth:

(a) the absolute risk of all cause stillbirth in high income countries is <1 in 1000

(b) globally, i.e. combining low, middle and high income countries, ≤10% of stillbirths follow intrapartum intra-uterine fetal death

(c) maternal risk factors explain more than 50% of the variation in stillbirth risk in the USA

(d) more than 90% of stillbirths are associated with fetal growth restriction

(e) if a post mortem has been performed, a minority of stillbirths have a clear and well-defined cause of death

Answers: (a) F (b) F (c) F (d) F (e) T

Explanation of answers: (a) The average rate for a high income country is 3-4 per 1,000 and all rates fall within the range 1-9 per 1,000 **(b)** In high income countries, intrapartum stillbirth does account for 5-10% of all stillbirths. However, the proportion is much high in low and middle income countries and 98-99% of all stillbirths occur in such countries **(c)** Overall, it is estimated that <20% of the variation in stillbirth risk is explained by maternal characteristics. **(d)** The exact proportion of stillbirths estimated to be due to growth restriction depends on the method used, but generally it is in the region of 30-50%. Hence, better screening for growth restriction would only impact on a minority of stillbirths. **(e)** The cause of most stillbirths is not known. There are many associations, particularly in relation to placental histopathology. However, many of these are also seen in completely normal pregnancies. Hence, the actual cause of death is not known for many stillbirths.

Question 2

In relation to biochemical markers of stillbirth risk:

(a) low levels of PAPP-A in the first trimester are associated with an increased risk of stillbirth due to placental causes

(b) the use of urinary oestriol was shown to be ineffective in an appropriately powered randomised controlled trial

(c) elevated levels of maternal serum AFP are associated with stillbirth due to neural tube defects and anterior abdominal wall defects, but are not predictive of the risk of loss in normally formed infants

(d) low levels of PAPP-A in the third trimester have been shown to be associated with the risk of unexplained stillbirth

(e) measurement of the sFlt-1/PlGF ratio should be performed in women presenting with reduced fetal movements

Answers: (a) T (b) F (c) F (d) F (e) F

Explanation of answers: (a) A PAPP-A level of <0.4 multiples of the median is associated with an increased risk of stillbirth and the majority in this group are associated with fetal growth restriction, placental abruption or preeclampsia **(b)** The use of biochemical tests of placental function were both introduced and withdrawn in the absence of clear evidence of effectiveness (or ineffectiveness) **(c)** Raised msAFP is associated with these structural abnormalities but elevated second trimester levels are also associated with an increased risk of non-anomalous stillbirth, particularly at early gestational ages and associated with placental causes **(d)** the data on PAPP-A and stillbirth relate to first trimester measurement, and there is an absence of evidence in relation to late pregnancy measurements **(e)** the sFlt-1/PlGF ratio has been described as a test for maternal pre-eclampsia, but there is limited evidence regarding its association with stillbirth.

Question 3.

In relation to induction of labour:

(a) Induction can safely be performed at any stage of pregnancy from 37 weeks onwards

(b) Level 1 evidence indicates that induction of labour results in a 10-15% reduction in the risk of caesarean delivery

(c) Level 1 evidence indicates that induction of labour at term and postterm reduces the risk of perinatal mortality by ≥50%

(d) Level 1 evidence indicates that, among nulliparous women aged 35 and above, routine induction of labour had no effect on the risk of caesarean delivery.

(e) It should not be considered in a woman presenting at 40 weeks gestational age with her first presentation with reduced fetal movements.

Answers: (a) F (b) T (c) T (d) T (e) F

Explanation of answers: (a) Delivery at 37-38 weeks is referred to early term. It is associated with increased risks of short term and long term complications. Hence, it is generally only indicated if the balance of risks of expectant management exceed these risks. **(b)** Although induction of labour is associated with higher rates of caesarean delivery in observational studies, the reverse is apparent in RCTs. This suggests that the observational associations are due to confounding by the indication for induction. **(c)** This is a key finding of the meta-analysis. The explanation is that once a baby is delivered it is no longer at risk of stillbirth. Hence, shortening the pregnancy reduces the risk of stillbirth. However, from 38 weeks onwards, there is no further decline in the risk of neonatal death with advancing gestational age. **(d)** This was the key finding of the 35/39 trial, published in NEJM 2016. **(e)** Elective induction (i.e. without a medical indication) can be considered from 39 weeks onwards. Reduced fetal movements commonly precede stillbirth. Hence, induction of labour should be offered to women who present with reduced fetal movements from 39 weeks onwards.

Question 4.

In relation to universal late pregnancy ultrasound:

(1) Level 1 evidence indicates that universal late pregnancy ultrasound reduces the risk of perinatal morbidity related to fetal growth restriction

(2) The meta-analysis of RCTs of universal late pregnancy ultrasound has >90% power to detect a 50% reduction in the risk of stillbirth in screen positive women, assuming a positive likelihood ratio of 10 or greater

(3) Has been implemented in some countries despite clear positive evidence of clinical effectiveness

(4) Could not plausibly cause harm, directly or indirectly.

(5) If performed at 28 and 36 weeks, increases the detection of SGA infants by about 3-fold compared with selective use of ultrasound.

Answers: (a) F (b) F (c) T (d) F (e) T

Explanation of answers: (a) The current meta-analysis of RCTs fails to demonstrate any benefits of universal ultrasound. **(b)** The current meta-analysis is too small to be adequately powered to detect a reduction in perinatal death with plausible estimates of screening test and interventional effectiveness. **(c)** A number of countries have implemented universal late pregnancy ultrasound in the absence of trial evidence. **(d)** False positive diagnoses have

significant potential to cause harm. For example, if a woman has a scan and the baby is wrongly diagnosed as being large for dates, she is at increased risk of emergency caesarean during labour. **(e)** A level 1 study of diagnostic effectiveness published in the Lancet is 2015 demonstrated a 20% rate of detection with selective ultrasound and a 57% rate of detection with universal ultrasound. However, for every 1 additional true positive for SGA, there were 2 additional false positives.

Figure

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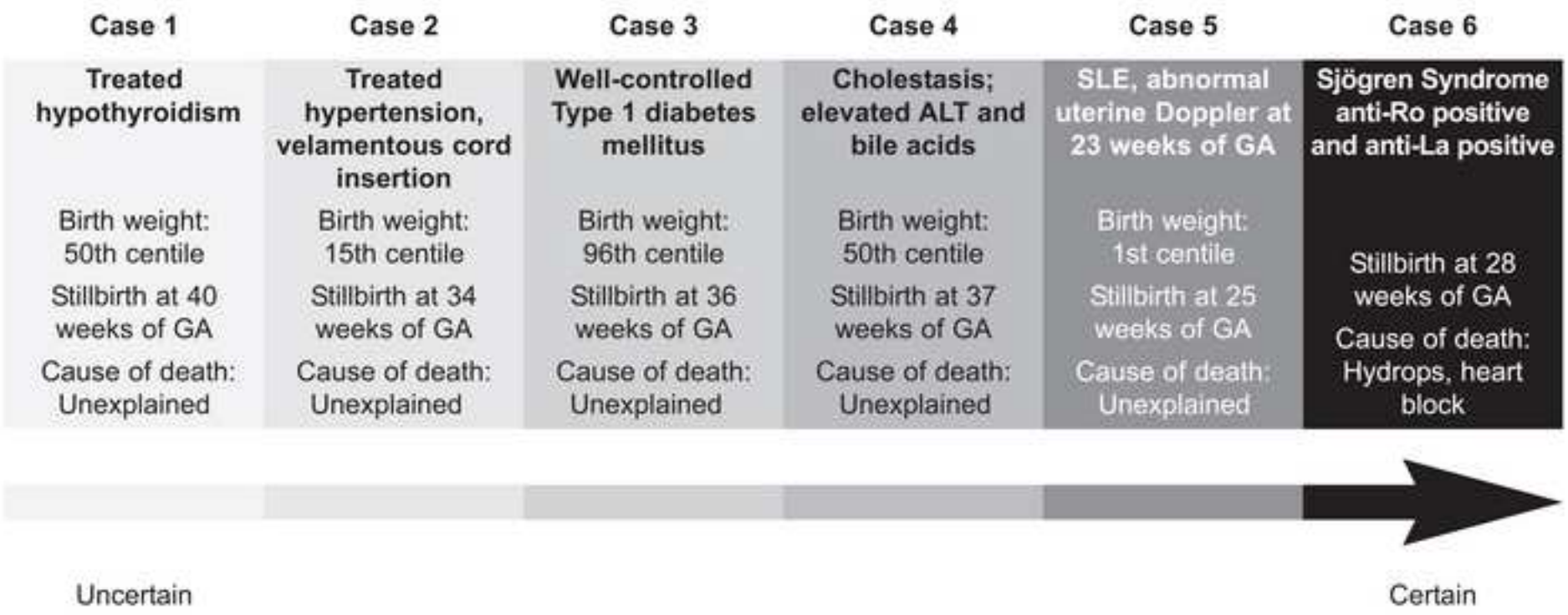

Table 1. Top 11 research priorities from a stillbirth priority setting partnership

Research questions
How can the structure and function of the placenta be assessed during pregnancy to detect potential problems and reduce the risk of stillbirth?
Does ultrasound assessment of fetal growth in the third trimester reduce stillbirth?
Do modifiable 'lifestyle' factors (e.g. diet, vitamin deficiency, sleep position, sleep apnea, lifting and bending) cause or contribute to stillbirth risk?
Which investigations identify a fetus at risk of stillbirth after a mother believes she has experienced reduced fetal movements?
Can the wider use of existing tests and monitoring procedures, especially in later pregnancy, and the development and implementation of novel tests (biomarkers) in the mother or in early pregnancy, help prevent stillbirth?
What causes stillbirth in normally grown babies?
What is the most appropriate bereavement and postnatal care for both parents following a stillbirth?
Which antenatal care interventions are associated with a reduction in the number of stillbirths?
Would more accessible evidence-based information on signs and symptoms of stillbirth risk, designed to empower women to raise concerns with healthcare professionals, reduce the incidence of stillbirth?
How can staff support women and their partners in subsequent pregnancies, using a holistic approach to reduce anxiety, stress and any associated increased visits to healthcare settings?
Why is the incidence of stillbirth in the UK higher than in other similar high-income countries, and what lessons can we learn from this?

Text quoted verbatim from Heazell et al, 2015 (reference 3)

Table 1. Maternal risk factors for stillbirth.

Characteristic	Adjusted Odds ratio	95% confidence interval
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

Data from reference 5 (see publication for details of multivariate analysis and referent categories). Stillbirth defined on basis of ≥20 weeks gestational age threshold.

Table 2. Maternal risk factors for gestational diabetes mellitus

Maternal risk factors for gestational diabetes mellitus
Body mass index >30 kg/m2
Previous macrosomic infant (>4.5kg)
Previous gestational diabetes
First degree relative with diabetes
Ethnic origin associated with high incidence of diabetes