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Predicting and preventing stillbirth at term

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ABSTRACT

Stillbirth at term affects ~1 per 1000 pregnancies at term in high income countries. A range of maternal characteristics are associated with stillbirth risk. However, given the low *a priori* risk of stillbirth, the vast majority of women with clinical risk factors would not experience a stillbirth in the absence of intervention. Stillbirth is the end point of multiple pathways, including both fetal growth restriction and fetal overgrowth. In most term stillbirths there is no mechanistic understanding of the cause of death and a sizeable proportion are completely unexplained. Term stillbirth is potentially preventable by early delivery, providing a rationale for screening. "Omic" analyses of blood taken prior to the onset of some of the conditions associated with stillbirth may help identify women at high risk and allow the potentially harmful intervention of early term medically indicated delivery to be targeted to the pregnancies most likely to benefit.

Introduction

Stillbirth at term is a tragedy for the parents and, in terms of healthy years of life lost, should be regarded as a very high priority for prevention. Less than 10 % of stillbirths have a congenital anomaly[1] and, if the risk had been identified, delivery would have prevented the event. The problems for prediction and prevention are (a) stillbirth is relatively uncommon at term (1.2 per 1000 in the UK in 2021[1]), (b) stillbirth is the end point of multiple different pathophysiological pathways and it is unlikely that a single test will be highly predictive of all types,[2] and (c) the main intervention, early term delivery, causes short and long term harm to healthy infants who were not at high risk.[3] The aim of this review is to outline the main issues to consider in the context of trying to predict and prevent term stillbirth, and the focus of the review will be the situation in high income countries, as the nature of the problem differs profoundly by geography.

Epidemiology of term stillbirth

The absolute risks of different forms of stillbirth vary internationally.[4] In high income settings the risk of stillbirth in labor is extremely low whereas intrapartum stillbirth (IPSB) at term is one of the major causes of perinatal death in low- and middle- income settings.[2] In the UK, about one quarter of all stillbirths occur at term; the absolute risk of term stillbirth is just over one per thousand and the great majority of losses involve fetal death (FD) prior to the onset of labor (antepartum stillbirth, APSB).[1] Moreover, term stillbirth rates have fallen in recent years whereas rates of stillbirth in the preterm period have remained stable.[1] Reasons are uncertain but this may due to national care bundles for stillbirth prevention which focus on interventions at term.[5] The Netherlands had one of the fastest rates of decline in stillbirth in a 2016 comparison, which followed a national initiative to reduce the risk of perinatal death.[4]

Causes of term stillbirth

Advancing gestational age

As stillbirth can only occur when a woman is pregnant, the duration of pregnancy is itself a determinant of stillbirth risk. Considering the extreme example, if all women were delivered at the gestational age (GA) threshold used to define stillbirth, the stillbirth rate would be zero. However, as these deliveries would occur at an extreme preterm gestational age, the overall risk of perinatal death (stillbirth or early neonatal death) would be extremely elevated. However, as the risk of neonatal death falls with advancing weeks of GA (wkGA) there comes a point when the risk of perinatal death is lower if all women are delivered at the given gestational age: a modelling study estimated that 39wkGA was the week of pregnancy with the lowest overall risk of perinatal death.[6] An additional consideration is that the weekly risk of stillbirth increases with advancing gestational age after 39wkGA. An important methodological point is that the risk of APSB at a given week of gestational age should be estimated by the ratio of the number of stillbirths in the given

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week to the number of on-going pregnancies at the start of the given week, rather than the number of births in the given week (see Smith[7] for review). The risk can be modelled using time to event analytic approaches and these demonstrate a stable risk of stillbirth between 37 and 39wkGA and a steady rise in the weekly risk from 40wkGA onwards.[6] The mechanism linking advanced GA and stillbirth is unknown but it is thought to be related to a decline in placental function post term which could be due to placental cellular senescence.[8]

Fetal growth restriction

Early onset fetal growth restriction (FGR) is well recognized as a major cause of stillbirth and is often associated with evidence of uteroplacental insufficiency (identified by high resistance patterns of flow in the umbilical and/or uterine arteries), which is caused by impaired trophoblast invasion of the decidual and myometrial resistance vessels. FGR is a major cause of preterm birth, and is commonly associated with severe, early onset preeclampsia. However, analysis of the relationship between birth weight percentile and stillbirth risk also demonstrates associations between small for GA (SGA) birth weight at term and the risk of both APSB and IPSB. A complicating factor when analyzing the relationship between birth weight percentile and stillbirth risk is that there may be significant loss of fetal weight in the interval between FD and delivery and this may tend to cause an apparent but artificial increase in the strength of the association with SGA. This may be less of an issue at term where the likelihood of a very long interval between FD and delivery is lower. Analyses of Scottish and US data demonstrated that the risk of stillbirth was higher at both extremes of birth weight.[9,10] Overall, about 30 % of term stillbirths could be attributed to being either SGA or large for GA (LGA).[9]

Other placental causes of term stillbirth

The placenta can be a direct cause of stillbirth in the contexts of placental abruption (i.e. separation of the placenta prior to delivery of the fetus) or massive fetomaternal hemorrhage. However, the placenta is also implicated in the etiology of stillbirth in cases where its role is not so obvious. Studies of the placenta in cases of term stillbirth have identified many different associations with placental histopathological abnormalities. A Dutch study estimated that about 80 % of stillbirths at term were associated with placental histopathological abnormalities, with approximately half of cases demonstrating hypoplasia, infarction, or villous immaturity. [11]A US study compared cases of term stillbirths and controls and also reported increased frequency of villous immaturity and infarction, as well as including vascular thrombi in the chorionic plate, avascular villi, single umbilical artery and inflammatory changes).[12] Interpreting the results of these studies can be problematic due to inconsistencies in the conduct and reporting of placental histopathology which may be overcome by use of an international consensus statement and protocol. [13]

Diabetes mellitus (GDM)

Pre-gestational diabetes is a well-recognised risk factor for stillbirth. Thus, women with type 1 or type 2 diabetes have increased fetal surveillance in the antenatal period and are routinely offered early term delivery. Gestational diabetes (GDM) with effective treatment is not associated with an increased risk of stillbirth.[14] However, there is evidence that untreated or inadequately treated gestational diabetes increases stillbirth risk. First, women who are diagnosed with GDM for the first time in their second pregnancy have higher rates of stillbirth in the preceding pregnancy. [15] Second, the risk of unexplained stillbirth is increased among infants with a birth weight percentile >97th %. [9,10] Third, surveys of unexplained term stillbirth have identified failures in screening or treatment of GDM as an association.[16] Currently, GDM is usually detected by screening. In the USA, a 50 g non-fasting glucose challenge test is used at 24–28 weeks of gestation and women who screen positive have a 100 g fasting oral glucose tolerance test (OGTT). In the UK, women are screened based on risk factors and diagnosis is made by a 75 g fasting OGTT. However, no screening approach will have 100 % sensitivity. It follows, therefore, that development of more sensitive, specific, and readily implementable screening tests for GDM may be one approach to reduce rates of stillbirth.

Previous cesarean delivery

Rates of cesarean delivery have steadily increased over recent years. Hence, overall, an increasingly large proportion of the pregnant population has had a previous cesarean delivery. It was first shown in 2003 that a history of previous caesarean was associated with an increased risk of stillbirth[17] and a meta-analysis has confirmed the association.[18] The elevated risk is timed to the end of pregnancy;[17] hence, delivery at around 39 weeks of gestation is one approach to mitigate the risk. However, as this will often be achieved by a repeat cesarean delivery it is essential that the mother's plans for future pregnancies are taken into account, as pregnant women with high numbers of previous caesarean deliveries face elevated risks of maternal mortality and severe morbidity related to abnormal placental attachment.[18]

Other

There are a wide range of rarer causes of stillbirth, and these are reviewed elsewhere.[2] However, many stillbirths are "unexplained". What proportion of stillbirths is classified as unexplained varies markedly between studies. The different findings may represent variation in the level of postmortem analysis of the fetus and placenta. However, the proportion of unexplained stillbirths is also determined by the classification system. The proportion of cases where there is complete mechanistic understanding of why a baby died is relatively small. In most stillbirths, cause is attributed to associated factors which are known to be more commonly observed in cases of stillbirth. For example, if placental pathology demonstrates villous immaturity some classification systems would then attribute the stillbirth to a placental cause. However, this ignores the fact that placental histopathological abnormalities are commonly observed in pregnancies with normal outcomes.[19]

Predictors of term stillbirth

Clinical predictors

A recent individual patient data meta-analysis of five case control studies addressed clinical risk factors for late preterm stillbirth (28 to 36 weeks) and term stillbirth (37 weeks and beyond).[20] Statistical analysis demonstrated that the associations were similar for both stillbirth types and the authors created a statistical model for stillbirth prediction which had an area under the curve of 0.84 (95 % CI 0.82 to 0.86). A caveat to the apparently strong clinical prediction is the retrospective nature of the analysis and the propensity of case control studies to be affected by recall bias. Nevertheless, the analysis does provide a summary of clinical features associated with stillbirth which were observed in a sample which consisted of a heterogenous group of participants. The significant associations are listed in Table 1.

Ultrasonic predictors

Given its relative rarity, few studies have shown direct associations between ultrasonic markers and the risk of term stillbirth. However, there is a very extensive literature on the relationship between ultrasound and other outcomes which are associated with stillbirth, such as fetal growth restriction and preeclampsia. It has been shown that a high resistance pattern of blood flow in the mother's uterine arteries in mid-gestation is associated with an increased risk of stillbirth at term [21]. However, this measurement tends to be more strongly predictive of stillbirths associated with FGR and preeclampsia and these tend to occur at earlier gestational ages. A single, very early study showed a strong association between ultrasonic indicators of accelerated placental maturation (patterns of calcification in the placenta) and the risk of perinatal death at term. [22] More recently, it has been suggested that the ratio of two Doppler indices, called the cerebral perfusion ratio (the ratio

Table 1
Maternal characteristics significantly associated with the risk of stillbirth using individual patient data meta-analysis from five case control studies.

Characteristic		aOR (95 % CI)
Maternal age		
	35–39	1.55 (1.09–2.22)
	>=40*	1.83 (0.99–3.37)
BMI		
	Per 5 kg/m^3 increase	1.46 (1.17–1.80)
Ethnicity		
	Black	2.38 (1.09–5.20)
Parity		
	0	1.92 (1.25–2.95)
	3	1.91 (1.03–3.55)
	>=4*	1.54 (0.77–3.07)
Treatment for mental health disorder		
	Present	1.62 (1.05–2.51)
Smoking		
	Beyond 12 weeks	1.92 (1.26–2.93)
	Second hand	1.42 (1.05–1.91)
Preterm antenatal care		
	Inadequate*	2.56 (0.93–7.04)
	Intermediate	1.62 (1.03–2.55)
Antepartum hemorrhage		
	Present	1.81 (1.16–2.83)
Fetal hiccoughs		
	Present	**0.43 (0.34–0.55)**
Vigorous fetal movements		
	Once	2.81 (1.90–4.17)
	More than once	0.62 (0.47–0.83)
Preterm fetal movements		
	Increased strength	**0.10 (0.07–0.16)**
	Increased frequency	**0.39 (0.17–0.86)**
	Decreased frequency	4.20 (2.44–7.22)
Term fetal movements		
	Increased strength	**0.27 (0.18–0.40)**
	Decreased frequency	2.04 (1.34–3.11)
Sleep		
	Supine position	3.14 (1.86–5.30)
	Other/unknown position	2.71 (1.64–4.50)
	Out of bed at night	**0.54 (0.39–0.73)**

Protective factors are indicated in bold
Data from Thompson et al 2023[20] and redrawn with permission.
aOR denotes adjusted odds ratio and CI denotes confidence interval.
See original publication for referent categories and non-significant associations.
*Associations were included where the 95 % CI of the aOR crossed unity if there was a trend towards an association and it had been significant at a less extreme level of category in an ordinal scale.

of the pulsatility indices in the middle cerebral and umbilical arteries) is predictive of the risk of stillbirth [23] and a randomized controlled trial (TRUFFLE 2, ISRCTN76016200) is currently evaluating this method in the management of late fetal growth restriction. A prospective cohort study addressing predictors of neonatal morbidity at term in infants which were small for gestational age (a proxy for stillbirth) indicated that the ultrasonic feature which best discriminated between healthy SGA infants and those having complications was the growth velocity of the abdominal circumference between 20wkGA and 36wkGA.[24]

Biochemical predictors

In the era before the widespread introduction of ultrasound, a number of biochemical tests of placental function were employed in assessing the "fetoplacental unit", including measurement of urinary estriol.[25] However, these methods were largely abandoned following the introduction of ultrasound. More recently, secondary analysis of maternal serum proteins measured for the assessment of Down syndrome risk identified associations with the risk of other complications of pregnancy, including fetal growth restriction and stillbirth, in later pregnancy, and the associations are reviewed elsewhere.[26] Low levels of pregnancy associated plasma protein A (PAPP-A) have been shown to be weakly associated with the overall risk of stillbirth but strongly associated with the risk of stillbirth due to placental dysfunction.[27] In the UK, women with low levels of PAPP-A are recommended to have uterine artery Doppler in mid-gestation. Those with elevated patterns of resistance undergo frequent surveillance with ultrasound, while those with normal uterine blood flow are also scanned for growth at 32wkGA and 36wkGA. Analysis of rates of stillbirth following implementation of the national care bundle which recommended this approach demonstrated evidence of a reduction in stillbirth rates.[5]

Prevention of term stillbirth

There is currently only one disease modifying intervention which reduces the risk of stillbirth, namely, iatrogenic delivery. Ideally, this is achieved by induction of labor. Delivery by planned cesarean delivery reduces the risks of intrapartum complications during vaginal birth but is associated with increased risks of neonatal respiratory morbidity and with complications in future pregnancies, including stillbirth. [18] Delivery reduces stillbirth risk both by abbreviating the duration of pregnancy and by preventing the baby being exposed to the later weeks of gestational age when the risk of stillbirth per unit time increases. A large scale randomized controlled trial in the USA demonstrated that, among low risk nulliparous women, induction of labor at 39 weeks reduced the risk of cesarean delivery and hypertensive disorders of pregnancy with no difference in composite perinatal morbidity. [28] The trial was too small to address the effect on the risk of perinatal death but a Cochrane review of randomized controlled trials has shown that routine induction of labor at term is associated with a 70 % decrease in the risk of stillbirth. [29] A caveat to this is that elective delivery at early term gestational age (37 and 38 weeks) is associated with a range of short and long-term complications for the infant and, if elective delivery in the absence of a medical indication is contemplated, it is better performed at 39wkGA. [3] This will, however, result in potentially avoidable stillbirths at 37 and 38wkGA. The current view is that causing a small amount of harm to a very large numbers of infants (who would not have been stillborn at 37 or 38wkGA) outweighs the gain achieved by early term delivery through preventing a small number of deaths. However, different individuals may assess the same evidence and draw opposite conclusions.

Researching term stillbirth

The foregoing points to the potential utility of research. Induction of labor is a life-saving intervention for infants who are at high risk of stillbirth. However, early term induction of labor could be a cause of lifelong harm to healthy infants. Hence, better methods to identify the fetuses at highest risk of stillbirth could allow the intervention to be targeted to those who would benefit most.

Challenges in researching stillbirth

A major issue when trying to study term stillbirth is that it is relative uncommon, affecting just over 1 per 1000 pregnancies. This means that for prospective studies to have enough cases of stillbirth, tens of thousands of women would have to be recruited. A rule of thumb when evaluating a new diagnostic test is that there should be 10 cases for each predictor studied. Taken at face value this would require a sample size of 40,000 to 50,000 to evaluate a panel of five novel predictors of term stillbirth. However, even this is optimistic. Stillbirth is not a condition *per se*. It is a descriptive term for delivery of an infant showing no signs of life, having died *in utero*. As is the case for deaths of children and adults, death of a fetus is the end point of multiple different pathophysiological processes. This is reflected in the association with birth weight percentile. Stillbirth rates are highest in very small infants, relatively low in the normal range, and increase again in those which are LGA. [9] Within the appropriate for gestational age birth weight group, there are multiple placental histopathological markers which are associated with the condition. [12,13] Moreover, as discussed above, in many cases, the cause of stillbirth is unexplained or only partially explained. When evaluating a biomarker, it is likely only going to be predictive of stillbirths due to

specific pathophysiological pathways. This then makes the conduct of studies to address stillbirth even more difficult. For example, if we assume that 25 % of term stillbirths are explained by fetal growth restriction, there might be only 3 such cases per 10,000 women studied. Hence, to have 10 cases per predictor, a study could have to recruit >150,000 women to evaluate just five predictors. However, there are statistical approaches that may help which can deal with less than 10 events per predictor. [30]

Use of proxies

One approach to overcoming these issues is to study non-lethal cases of complications which are associated with stillbirth. It may be a reasonable assumption that factors which predict cases of birth weight less than the 3rd percentile where the baby experienced complications in the neonatal period are also likely to be predictive of the risk of stillbirth associated with FGR. However, as discussed above, it is not fully understood why one fetus with a very low weight percentile dies and another survives. Nevertheless, some clinical approaches to reducing the risk of stillbirth involve an assumption of a relationship between lethal and non-lethal manifestation of complications leading to stillbirth. For example, the UK's national care bundle, Saving Babies Lives, recommends delivery of fetuses with an estimated weight <3rd percentile at 37 weeks and those <10th percentile and no other features of concern at 39 weeks (https://www.england.nhs.uk/long-read/saving-babies-lives-version-3). For researchers trying to develop novel tests which could be predictive of stillbirth, studying severe fetal growth restriction, preeclampsia with severe features, placental abruption, and severe macrosomia where the baby survives could be informative and is more likely to be feasible than studying deaths related to the same conditions. Another potential approach would be to develop tests which are informative of the risk of placental histopathological abnormalities which are associated with stillbirth. Ultimately, however, any such tests would have to be validated on very large sample sizes which included enough cases of stillbirth associated with the given pathophysiological pathway.

Future directions

Imaging

Ultrasound has been the mainstay of medical efforts to identify fetuses at increased risk of stillbirth and the field is reviewed in detail elsewhere. [31] Perhaps the most promising future direction for imaging is the use of magnetic resonance imaging (MRI). [32] This modality has the advantage of being less affected by maternal obesity, although it is affected by fetal movements. MRI has capacity to study both the fetus and placenta and can yield information, such as estimates of oxygen levels, which could be associated with stillbirth. A limitation on achieving the full potential of MRI in pregnancy has been safety issues with contrast agents; however, newer agents have been developed which may be safer in pregnancy and the potential for MRI in fetal assessment has been recently reviewed. [33] A remaining limitation is the expense of performing and reporting MRI, the duration and experience of the procedure, and requirement for specialized expertise. For these reasons it is unlikely that MRI will be a first line tool for fetal assessment unless the conduct and reporting of the procedure can be made briefer and more cost-effective.

Wearable devices

Wearable devices have impacted on many areas of medicine outside of Obstetrics. However, the fetus generates multiple different signals *in utero* which could potentially be detected by passive sensors, including fetal heart sounds, electrical signals such as fetal ECG and kinetic signals caused by fetal movements. [34] Some of these modalities could be combined to give functional information. For example, the time interval between the R wave of the ECG and the first heart sound could yield information of the electro-mechanical function of the fetal heart. As the science of signal detection and processing matures, combined with technological developments in portable electronic devices, passive detection of fetal signals has potential for clinical utility. One issue affecting this is maternal obesity, which is both associated with stillbirth and dampens signals arising from the baby. Another potential approach is wearable devices which utilize active signal acquisition, such as the use of an array of ultrasound transducers. A concern with this approach would be the potential for prolonged exposure of the fetus to ultrasound to cause harm to fetal organs, for example through heating. Nevertheless, wearable devices may be a major area for future research in stillbirth prevention. This would address a commonly expressed parental concern about the burden of being asked to be aware of fetal movements, which can be a source of anxiety.

Biomarkers

Rapid technological development in the field of biomarker discovery has generated tools which have may dramatically improve our ability to predict pregnancy complications. The major contributor to this is the development of "omics". These are technology platforms which analyze a given category of compound, such as proteins or metabolites. The analysis is generally not targeted at one specific pathway or biological function but rather spans diverse pathways and functions. This makes the approach ideal for situations where the mechanism leading to the disease is unknown, which is the case for most pregnancy complications leading to stillbirth. Previously, one approach to identifying new biomarkers would be to apply omic technologies to the placenta, as this organ is presumed to be key in determining many of the complications associated with stillbirth. Analyses of the placenta could then highlight a pathway or specific molecules which were associated with the condition in the placenta. If the molecule is secreted, then it is worth testing whether maternal circulating concentrations of the molecule were predictive of complications. An example of this approach was the use of placental RNA-seq to identify follistatin-like-3 (FSTL3) as a predictor of preeclampsia and FGR.[35]

More recently, however, there has been rapid technological development of methods which can perform omics in the mother's blood. [36] Table 2 lists a range of omic methods which can be applied to these samples. One advantage of this approach is that, if a non-placental molecule is predictive of a condition, it can still be detected by direct study of the mother's blood. Another is ease of access. Maternal blood is the key substrate for predictive tests and findings made in the mother's blood are likely to be directly predictive of complications whereas a placental molecule may be strongly associated with a given outcome but the elevated levels in the placenta are not reflected in elevated levels in serum or plasma. It is likely that the coming years will see a massive expansion in promising candidate biomarkers for conditions associated with stillbirth and the challenge will be to determine whether the same markers are also predictive of the lethal manifestation of these conditions and, if so, whether the diagnostic test accuracy is sufficiently high that it can overcome the very low *a priori* risks of most types of term stillbirth.

Conclusions

Stillbirth at term is a readily preventable tragedy. However, large scale prevention requires identifying which low risk women are at high risk of a relatively rare event. Technological developments hold the promise of generating novel predictive approaches for the conditions associated with term stillbirth. The challenge will be to construct clinical trials which can show that screening using these approaches is safe and effective.

Disclosure

In the last three years, GS has received research support from Roche Diagnostics, Illumina and Pfizer (fetal growth, restriction and

Table 2
Omic methods which can be applied to blood for the identification of novel biomarkers

Omic category	Analysis	Source	Comments
DNA	Sequence	Serum or plasma	
	Methylation	Maternal leukocytes	
	Chromatin state/ modification	Circulating trophoblast	
	Metagenomics		
RNA	Quantification of transcript abundance	Serum or plasma	Includes small and long RNAs, latter includes coding, non-coding and circular
		Maternal leukocytes	
		Circulating trophoblast	
		Exosomes or microvesicles	
	Metagenomics		
Proteins	Quantification of circulating protein levels	Serum or plasma	Can be achieved using ligands (aptamers or antibodies) or chromatography followed by mass spectrometry
Metabolites	Quantification of products of metabolism	Serum or plasma	Can be achieved using chromatography followed by mass spectrometry or nuclear magnetic resonance Can be focused on a subset of metabolites, such as lipidomics

preeclampsia, preterm birth and infection). GS has been a paid consultant to GSK (preterm birth) and has been a member of a Data Monitoring Committee for GSK trials of RSV vaccination in pregnancy. GS is currently a member of a Data Monitoring Committee for Moderna trials of RSV vaccination in pregnancy. Current or recent government or charity grant support: MRC, NIHR, Wellcome Trust & Wellcome Leap.

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