PREVENTING STILLBIRTH: A REVIEW OF SCREENING AND PREVENTION STRATEGIES

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Abstract

Stillbirth is a devastating pregnancy complication that still affects many women, particularly from low and middle-income countries. It is often labelled as 'unexplained' and therefore unpreventable, despite the knowledge that placental dysfunction has been identified as a leading cause of antepartum stillbirth. Currently, screening for pregnancies at high-risk for placental dysfunction relies on checklists of maternal risk factors and serial measurement of symphyseal-fundal height to identify small for gestational age fetuses. More recently, the first-trimester combined screening algorithm developed by the Fetal Medicine Foundation has emerged as a better tool to predict and prevent early-onset placental dysfunction and its main outcomes of preterm preeclampsia, fetal growth restriction and stillbirth by the appropriate use of Aspirin therapy, serial growth scans and induction of labour from 40 weeks for women identified at high-risk by such screening. There is currently no equivalent to predict and prevent late-onset placental dysfunction, although algorithms combining an ultrasound-based estimation of fetal weight, assessment of maternal and fetal Doppler indices and maternal serum biomarkers show promise as emerging new screening tools to optimize pregnancy monitoring and timing of delivery to prevent stillbirth. In this review we discuss the strategies to predict and prevent stillbirths based on first-trimester screening as well as fetal growth and wellbeing assessment in the second and third trimesters.

Keywords

Stillbirth; Fetal growth restriction; Screening; Prevention; Biomarkers; Placental dysfunction

Introduction

Stillbirth is defined as a fetal demise that occurs in the second half of pregnancy and before birth, whether it happens antepartum or after the onset of labour. There are variations in the threshold that is used to define a stillbirth with gestational age ranging from 20 to 28 weeks [1]. However, early stillbirths occurring before 28 weeks are not commonly reported in low-income countries. In 2015 it was estimated that about 2.6 million women experienced a stillbirth, which represents a burden of 7000 fetal deaths every day or 18.4 stillbirths/1000 births [2]. The vast majority of stillbirths (98%) occurred in low and middle-income settings, with 75% of all stillbirths recorded in sub-Saharan Africa and south Asia, where half of these fetal deaths were diagnosed intrapartum. In contrast, the stillbirth rate is 3.4/1000 births in developed countries, with only 10% presenting as intrapartum stillbirths.

Many stillbirths are still labelled as ‘unexplained’, which is also often incorrectly interpreted to infer that these stillbirths were not preventable. Less than 10% of stillbirths are associated with congenital abnormalities, whereas other causes such as maternal infection, malnutrition or obesity, diabetes, prolonged pregnancy or placental dysfunction are all potentially modifiable [2]. The most recent estimates suggest that the majority - at least 60% - of antepartum stillbirths are a consequence of placental dysfunction in high-income countries [3]. Screening for pregnancies at high-risk of placental dysfunction in the first trimester is conventionally based on the assessment of maternal risk factors through antenatal checklists, even though risk algorithms combining maternal factors, ultrasound markers and serum biomarkers have been developed and validated. The identification of fetuses at high-risk for stillbirth in later pregnancy is usually based on estimation of fetal weight, as poor fetal growth is a marker of placental dysfunction. The rationale for this strategy relies on the finding of a higher-than-expected percentage of small for gestational age (SGA) babies in stillbirths [4, 5]. However new evidence challenges this conventional approach.

In this review we will discuss the strategies to predict and prevent stillbirths based on first-trimester screening, fetal growth and assessment of fetal wellbeing.

First trimester screening for pregnancies at high-risk for placental dysfunction

The current checklist-based approach to risk assessment

The majority of international societies recommend the use of a checklist system based on maternal risk factors to identify high-risk pregnancies [6-8]. For instance, a checklist of major risk factors (previous preeclampsia (PE), chronic hypertension etc) and moderate risk factors (nulliparity, advanced maternal age etc) is proposed by the National Institute for Health and Care Excellence (NICE) and the American College of Obstetricians and Gynecologists (ACOG) to identify women at high-risk for developing PE [6, 7]. However, the sensitivity and specificity of these checklist-based systems are poor – for example, the NICE screening method only achieves detection rates of 30% for all PE and 40% for preterm PE at a 10% screen-positive rate [8, 9]. The individual risk conferred by each risk factor is not taken into consideration - for example, maternal age and chronic hypertension are inappropriately considered as equally important (Fig. 1). Continuous variables such as maternal age or Body Mass Index (BMI) are classified in arbitrary categories, where for example a woman is considered low risk at 39 years of age, but becomes high risk on her 40th birthday. There is no factor that can mitigate the risk of presenting an adverse outcome – for example, normal weight or a history of previous uneventful pregnancies are not taken into account to reduce a woman’s risk. The interaction between the risk factors to further increase or decrease the

likelihood of developing the complication is not considered. In many instances, the woman must have developed the disorder in a previous pregnancy to be considered at high-risk. Finally, these checklists fail to produce an individual numerical estimate of risk, which precludes individualisation of care for the woman.

The basis for the Fetal Medicine Foundation (FMF) screening algorithm

To overcome the weaknesses of checklist-based screening, new algorithms have been developed to identify pregnancies at high-risk of placental dysfunction. In these algorithms each risk factor is given an individual positive or negative weight and the interactions between these factors are accounted for in order to estimate the woman's personal numerical risk of developing placental dysfunction and related adverse outcomes. The first-trimester FMF algorithm is based on a competing risk approach, which uses the individual relative contribution of each demographic (age, weight etc), medical (chronic hypertension, previous PE etc), biochemical (serum biomarkers) and biophysical (blood pressure, uterine artery Doppler) risk factors to estimate a woman's individual risk of developing an adverse outcome related to placental dysfunction such as PE (Fig. 1) [10]. The competing risk approach is able to account for treatment paradox (sometimes known as intervention bias), where a woman predicted to be at high risk of PE may not develop PE because she gives birth before she reaches the gestation at which she was destined to develop the disorder (Fig. 2). Under these circumstances, the model may be incorrectly assumed to have been inaccurate, but the use of statistical truncation in a competing risk model accounts for this phenomenon.

The FMF screening algorithm for PE

The FMF algorithm has been externally validated to be accurate and head-to-head comparisons have shown the superiority of the FMF algorithm as compared to the conventional checklist-based method [8-11]. In the Screening PRogram for PE (SPREE) study, the first-trimester FMF algorithm combining maternal factors, mean arterial pressure, uterine artery pulsatility index and serum placental growth factor (PlGF) showed a significantly higher detection rate for PE than the NICE checklist-based method [9, 10]. Indeed, the FMF combined screening identifies 75% of women with preterm PE <37 weeks and 41% of women with term PE ≥37 weeks at a 10% screen-positive rate [12]. The improved sensitivity allows the effective use and targeting of medical resources and the increased specificity reduces the inappropriate stigmatisation of women as being at high-risk. Other models have also been proposed to predict PE in the first trimester, but very few have been externally validated or shown to be effective in clinical trials [8, 13]. The individualised risk provided by such algorithm enables personalised care and improves the patient's

compliance to medication. In the SPREE study, only 23% of women identified as high-risk for PE by the NICE method used Aspirin throughout pregnancy [9], whereas the compliance reached 85% for most high-risk women identified by the FMF algorithm in the Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial [14].

Efficacy of the FMF screening algorithm for placental dysfunction

As discussed previously, most prediction models were developed using conventional sensitivity and specificity analysis without taking into account the treatment paradox – the impact of elective birth on avoiding subsequent stillbirth. It is therefore not surprising that most conventional prediction models have shown poor performance for predicting stillbirth. Most of the screening algorithms also treat PE, fetal growth restriction (FGR) and stillbirth as separate diseases rather than considering them as pregnancy outcomes that are frequently caused by the same disorder – placental dysfunction. Similarly, in adult life, headache, visual disturbances and poor balance are outcomes (or symptoms) of the same disorder – brain cancer. In keeping with this relationship between disorder and outcomes, effective screening for PE should also be useful at predicting all outcomes of placental dysfunction including FGR and stillbirth. In the SPREE study, the first-trimester FMF combined screening identified 46% of SGA neonates <10th centile born at <37 weeks, but only 20% of those born at ≥37 weeks [15].

Efficacy of the FMF screening program in preventing adverse pregnancy outcomes

The first-trimester FMF algorithm combined with the use of targeted low dose Aspirin therapy is effective in predicting and preventing preterm PE [16]. The ASPRE trial demonstrated a 62% reduction in the rate of preterm PE after prescription of prophylactic Aspirin therapy at 150 mg daily from 11-14 to 36 weeks' gestation for women identified at high-risk for PE by the first-trimester FMF algorithm [14]. However, the prophylactic use of Aspirin had no effect on the rate of term PE. One hypothesis is that Aspirin delays the gestational age at delivery with PE, counteracting the effect of Aspirin on the development of term PE due to a shift of high-risk pregnancies from the preterm period into cases with term PE (Fig. 3) [17]. Use of Aspirin in the high-risk group in the ASPRE study was also associated with a 40% reduction of SGA birth <10th centile at <37 weeks, but had no impact on the incidence of SGA birth at ≥37 weeks [15]. Therefore, screening for SGA birth <10th centile by the FMF combined screening followed by appropriate Aspirin prophylaxis could also have an impact on reducing preterm SGA birth, but would not be expected to impact on term SGA births.

Clinical effectiveness of the FMF screening programme in a routine healthcare setting

Efficacy studies are undertaken under ideal research trial conditions and may not be transferable to a routine healthcare setting without evaluation of clinical effectiveness in such an environment. In one such study, researchers looked at clinical outcomes before and after the implementation of the combined FMF algorithm with subsequent Aspirin prophylaxis, serial scans at 28 and 36 weeks, and induction of labour from 40 weeks for women identified at high-risk. They used interrupted time series analysis, which accounts for confounders and temporal trends, to demonstrate an 80% reduction of preterm PE [18]. They also demonstrated a 45% reduction of term SGA birth <10th centile which was attributed to the scheduled elective birth of high-risk pregnancies at 40 weeks of gestation, precluding the development of failed fetal growth in the post-term period [19]. The same authors evaluated the impact of these improvements in pregnancy outcomes on the prevalence of perinatal death (PND) rate – combining stillbirth after 24 weeks and neonatal death (NND) within 28 days of birth [20]. The perinatal death rate was reduced from 4.46/1000 to 2.78/1000 births with a screening program based on the NICE checklist versus the FMF combined screening. Specifically, there was a 70% reduction in PND associated with PE and/or FGR resulting in a fall in PND rates from 1.73/1000 to 0.48/1000 births (Fig. 4). It is therefore apparent that outcomes of pregnancies complicated by placental dysfunction might be improved by the implementation of first-trimester FMF combined screening and subsequent prophylactic Aspirin therapy, ultrasound monitoring and elective birth at 40 weeks' gestation in high-risk women in routine clinical practice.

Second trimester screening for pregnancies at high-risk for placental dysfunction

Ashoor *et al.* proposed a second-trimester algorithm for the prediction of stillbirths related to placental dysfunction defined by PE and/or a birthweight <10th centile. The detection rate of the algorithm combining maternal risk factors, uterine artery Dopplers and estimated fetal weight (EFW) at 19-24 weeks' gestation was 62% at a 10% false-positive rate (70% at <37 weeks versus 29% at ≥37 weeks) for stillbirths related to placental dysfunction [3]. The authors propose a two-stage screening strategy to prevent stillbirths related to placental dysfunction, based on the first-trimester PE screening and targeted Aspirin use in the high-risk group followed by the second-trimester screening to identify pregnancies at high-risk for stillbirth between 24 and 37 weeks' gestation and offer close monitoring and optimal timing of delivery. If first and second-trimester combined screening might detect the majority of early-onset placental dysfunction, there is no equivalent screening tool for late-onset placental dysfunction [21].

Other screening models for pregnancies at risk of stillbirth

There is expert consensus that the existing stillbirth prediction models are not yet suitable for clinical practice and to inform decision-making, and that there are limitations to their application [22-24]. In a systematic review including all stillbirth prediction models developed up to 2019, nearly all models showed a high-risk of bias due to the handling of missing data and the low number of events (stillbirths) in the population used to develop the model [22]. Unfortunately, the authors excluded studies that used the first-trimester combined test for PE as a screening tool for stillbirth and models that reported composite outcome including stillbirth. Moreover, women identified at high-risk by the prediction models are likely to be delivered earlier, before stillbirth happens, which introduces a treatment paradox. This further reduces the number of events and the performance of the models developed in observational studies [22]. A general criticism about existing prediction models is that they often lack internal validation [22-24]. In the same review, a limited number of the identified models had been internally validated and none were able to be externally validated in an independent dataset [22]. Allotey *et al.* recently published an individual participant data (IPD) meta-analysis with the objective of performing an external validation of the existing stillbirth prediction models on a large cohort of women to increase the number of events [24]. Of the 40 identified models, only 3 could be included in the IPD due to the non-availability of the model equations and the lack of data on key variables used in most published models. The authors concluded that none of these models could be recommended for clinical practice and that further research was needed to develop and validate more robust prediction models. Another limitation of existing prediction models is that stillbirth is the endpoint or outcome of conditions other than placental dysfunction. It is therefore possible that several models would be required for different phenotypes of stillbirth, i.e. those due to placental dysfunction or diabetes for example [24].

Later pregnancy interventions to reduce stillbirth

Rationale for screening based on fetal weight assessment

The majority of SGA neonates with birthweight <10th centile are delivered at term [25]. The rationale for fetal size assessment is based on the association between perinatal mortality and SGA birth [25]. In recent studies, a birthweight <10th centile was found in 30%-40% of stillbirths and there was a 3 to 4-times higher rate of birthweight <10th centile among stillbirths than livebirths [5, 26]. On the basis of this association, screening for SGA has been universally implemented in an attempt to reduce adverse outcomes by offering close monitoring and optimizing timing of birth for SGA fetuses. In routine antenatal care, detection of SGA fetuses usually relies on serial measurement of symphyseal-fundal height [27]. If suspicion arises, targeted or selective ultrasound evaluation of fetal growth and wellbeing is

undertaken [27]. This strategy is still widely used even though it has been demonstrated that a policy of universal third-trimester ultrasound screening increases the detection rate of SGA fetuses [28, 29].

Estimation of absolute fetal weight

Fetal ultrasound biometry is measured to calculate the estimated fetal weight (EFW). There are many published formulae based on single or multiple parameters to estimate the fetal weight, but it has been demonstrated that the best formula is the Hadlock formula, which uses head circumference, abdominal circumference and femur length [30]. The Hadlock formula can predict the birthweight within 10% in about 80% of singleton and 70% of twin pregnancies [31, 32].

Estimation of fetal weight centile

Here, the estimation of gestational age must be accurate in order to establish the fetal weight centile. Pregnancy dating by the last menstrual period is not always reliable and as a result, pregnancy dating by fetal crown-rump length (CRL) at 8-14 weeks or by the head circumference if the CRL is over 84mm is the preferred method [33].

The obtained EFW is then plotted against a fetal size reference chart to obtain a fetal weight centile for gestational age [33]. There is a lack of consensus about the optimal fetal size reference chart to establish the EFW centile for the gestational age. Charts provide different centiles for the same EFW and therefore variable rates of SGA fetuses in the same population.

National reference charts correspond to the geography of a particular country and are usually constructed retrospectively based on measured neonatal birthweight rather than EFW by ultrasound assessment [34]. There are 2 main problems associated with this retrospective approach to establishing fetal size reference charts. First they usually include non-healthy pregnancies with occult morbidities that might impact fetal growth, but not result in fetal demise [35]. Secondly, they contain very few preterm cases and even then, the birthweight of preterm babies is likely to be influenced negatively by the pathology that triggered prematurity [36]. To overcome this issue, Nicolaides *et al.* developed a fetal weight reference chart for all fetuses of a given gestational age, including those remaining in utero by using ultrasound EFW [36]. Using this approach, they demonstrated that previous fetal weight reference charts underestimated fetal weight because there were an increased proportion of SGA fetuses in the preterm birth cohort [36]. More importantly, it seems peculiar that the country of origin or the maternal passport might account for a difference in fetal growth. The biological explanation for a difference in growth by geographical location is

more likely to be related to environmental, socio-economic and nutritional factors rather than ethnicity or nationality per se [35].

International fetal size reference standard charts are not descriptive but prescriptive. In other words, they are constructed prospectively and show how fetuses should grow in a healthy population at low risk for adverse pregnancy outcomes and fetal growth impairment [33, 35]. Two international standards, the WHO sponsored study and the INTERGROWTH - 21st project, have been developed prospectively based on low-risk pregnancies from both high- and low-income countries [37, 38]. The INTERGROWTH - 21st project showed that fetal growth is similar across the world in low-risk pregnancies and would be the preferred fetal size reference standard in our opinion [35].

Customized charts are adjusted for variables that affect fetal growth such as maternal weight, height, ethnicity and parity [39]. The advocates of customized charts argue that these variables are physiological, while others consider them as proxy markers for adverse pregnancy outcomes that should not be used to normalise poor fetal growth. For example, ethnicity is associated with socio-economic status and education that are risk factors for poor maternal health and stillbirth [35]. By defining a set 10% SGA rate in a population, customization does not take into consideration the variations in maternal malnutrition that would account for higher rates of underweight neonates in low versus high-income countries [35]. The implementation of these customized fetal size charts has not shown a reduction in the stillbirth rate in the UK [40].

Fetal growth velocity

Fetal growth velocity assessment on serial scans has also been proposed to identify placental dysfunction, but the benefit of this approach is uncertain. In a large series of 44,000 pregnancies undergoing routine ultrasound evaluation at 19-24 and 35-37 weeks, the performance of screening for SGA neonates by a single scan at 35-37 weeks was not improved by adding fetal growth velocity between the second and third trimesters [41]. Similarly, fetal growth velocity was not predictive of adverse perinatal outcome in the TRUFFLE-2 study that prospectively evaluated more than 800 fetuses with severe FGR at 22-37 weeks' gestation [42].

Small-for-gestational age (SGA) versus Fetal Growth Restriction (FGR)

SGA fetuses are found in 30% to 40% of all stillbirths [5, 26]. However, the relationship between birthweight and the risk of stillbirth is known to weaken with advancing gestational age (Fig. 5). In recent studies, about 65% to 70% of stillbirths before 32 weeks had a birthweight <10th centile, whereas only 25% to 35% of stillbirths after 37 weeks were SGA

[3-5]. Moreover, the body weight of stillbirth fetuses decreases through maceration in utero and by dehydration between delivery and autopsy, suggesting that the true prevalence of SGA in stillbirth is not as high as previously estimated and is more likely to be around 20% to 25% [43]. These findings would suggest that the majority of stillbirths at term typically occur in normally grown fetuses [5, 26]. SGA corresponds to the statistical deviation of fetal size from a reference standard, with a threshold that is usually set below the 10th centile. Most SGA babies are constitutionally small with no increased risk for adverse outcomes. In contrast, FGR is a functional disorder caused by placental dysfunction that prevents the fetus from reaching its growth potential. FGR is thus far more strongly associated with adverse perinatal outcomes than SGA [44]. Until recently, there was no consensus on the definition of a FGR fetus in the literature. In 2016, a Delphi expert consensus for FGR was established on a combination of fetal biometry with functional indices including fetal and maternal Dopplers (Table 1). Different criteria are used to diagnose early- and late-onset FGR depending on the gestational age at onset of placental dysfunction before or after 32 weeks. This consensus definition recognises - for the first time - that late-onset FGR can be diagnosed in fetuses with an EFW above the 10th centile by the combination of a reduced fetal growth velocity and abnormal fetal Dopplers [44].

Early-onset and late-onset FGR

As compared to late-onset FGR, early-onset FGR is less frequent (0.5%-1.0% versus 5%-10%), is more often associated with PE and presents with a higher weight deficit and more frequent abnormal fetal Doppler indices. Both early- and late-onset FGR are associated with significant perinatal morbidity and mortality, but early-onset FGR fetuses have more severe hypoxia resulting in high morbidity and mortality rates [21, 34, 45, 46]. Early and late-onset FGR are two different presentations of the same disease - placental dysfunction. This can be explained by the changes in fetal nutritional and respiratory demands with advancing gestational age. Nutritional requirements follow a logarithmic increase throughout pregnancy, whereas there is an exponential rise in fetal respiratory demands with advancing gestation (Fig. 6) [34, 47, 48]. Therefore, early-onset placental dysfunction has a predominant effect on fetal growth before compromising respiratory needs, resulting with fetal stunting as a key feature of the disorder. With early-onset FGR, low fetal respiratory needs can be sustained for several weeks by the dysfunctional placenta. In contrast, late-onset FGR develops at a time when respiratory demands are maximal and nutritional demands have reached a plateau. As a consequence, late-onset FGR will have a major impact on respiratory function before it will affect fetal growth. Hypoxemia will thus develop in a fetus with a falsely reassuring ‘appropriate size’ for gestational age, and may confer an increased risk of stillbirth from hypoxemia in a matter of hours or days. Placental dysfunction can thus present early

with SGA from malnutrition evolving over days/weeks or late with stillbirth from acute hypoxemia.

Management of FGR

Early-onset FGR

Screening for early-onset PE and FGR can be achieved by the first-trimester FMF combined algorithm. In the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) study, the management of early-onset FGR diagnosed between 26 and 32 weeks' gestation was based on a combination of both computerized cardiotocography (cCTG) and fetal umbilical and ductus venosus (DV) Doppler assessment to guide decision about timing of birth [49]. The authors demonstrated a 95% survival without neurological impairment at 2 years of age when the decision to deliver was based on the combination of cCTG and/or late DV changes – mandating the use of this approach for early-onset FGR [50].

Late-onset FGR

If the first-trimester FMF combined algorithm can detect the majority of early-onset FGR, there is no equivalent screening tool for late-onset FGR [21]. The main challenges near term are (1) to differentiate constitutionally small fetuses from growth restricted fetuses affected by placental dysfunction among the cohort of SGA babies (reduce false-positives) and (2) to identify normal-sized fetuses affected by placental dysfunction (reduce false-negatives). It has been demonstrated that a low cerebroplacental ratio (CPR) in the third-trimester is an independent predictor of stillbirth and adverse perinatal outcome [51-53], but its efficacy to improve the prediction of adverse perinatal outcome in routine antenatal care remains unascertained [21, 52, 54]. Serum biomarkers such as PlGF and soluble fms-like tyrosine kinase-1 (sFlt1) are widely used to predict and diagnose PE [55, 56], but their routine assessment at 35-37 weeks' gestation has shown a poor performance to predict adverse pregnancy outcomes in both SGA and appropriate for gestational age (AGA) fetuses [57].

It is likely that new algorithms combining maternal risk factors, EFW, maternal and fetal Dopplers and/or serum biomarkers might improve the detection rate of stillbirth and FGR near term [58]. An example of such an approach was proposed by Akolekar *et al.* In their study of 45,000 singleton pregnancies, they stratified fetuses into 4 categories of risk based on a third-trimester scan assessment of EFW, uterine, umbilical and middle cerebral artery Dopplers [59]. The first step identified very low-risk fetuses with an EFW ≥40th centile, then the second step discriminated between 3 categories of risk (high, intermediate and low) for fetuses with an EFW <40th centile. The frequency of subsequent pregnancy monitoring was tailored in line with those 4 risk categories. This approach showed a better performance than

an EFW <10th centile alone to predict adverse perinatal outcome. In the absence of definitive evidence for EFW and Doppler parameters assessment, several international societies have taken a pragmatic approach to their use in the management of late-onset FGR. An example of such guidance is the Saving Babies Lives Care Bundle version 2 (SBLCBv2) recommendations in the UK. SBLCBv2 recommends birth from 37 weeks, 39 weeks, 41 weeks or specialist Maternal-Fetal Medicine referral based on findings from EFW and Doppler assessment at term (Fig. 7) [60].

Conclusion

Placental dysfunction is the major cause of antepartum stillbirth. It has been demonstrated that screening for pregnancies at high-risk for early-onset placental dysfunction can be successfully achieved by the first-trimester FMF combined algorithm. Stillbirth, PE and FGR have to date been treated as distinct diseases rather than as outcomes of predominantly a single disorder - placental dysfunction. It is therefore not surprising that management of pregnancies at high-risk of placental dysfunction with Aspirin therapy, serial ultrasound monitoring and elective birth at 40 weeks is associated with improved pregnancy outcomes for preterm PE, SGA birth and stillbirth. Early-onset FGR can be easily diagnosed by the ultrasound estimation of fetal weight and its prognosis can be improved by a combination of both computerized cardiotocography and fetal Doppler assessment to guide decision about timing of birth. In late-onset FGR, the relationship between birthweight and the risk of stillbirth weakens with advancing gestational age because of the divergent increase in nutritional versus metabolic demands of the fetus. The evidence presented in this review demonstrates that screening algorithms for late-onset FGR should not be limited to ultrasound estimation of fetal weight, but also include maternal Dopplers and maternal serum biomarkers of placental dysfunction as well as fetal Doppler indices of hypoxaemia to achieve better pregnancy outcomes.

Funding

None.

Conflicts of Interest

None.

Table 1 Delphi consensus-based definitions for early and late-onset FGR in absence of congenital anomalies (adapted from Gordijn *et al*. [44])

Early FGR: GA <32 weeks	**Late FGR: GA ≥32 weeks**
AC/EFW <3rd centile *or* UA-AEDF	AC/EFW <3rd centile
or	*Or at least 2 out of 3 of the following*
1. AC/EFW <10th centile *combined*	1. AC/EFW <10th centile
with	2. AC/EFW crossing centiles >2
2. UtA-PI >95th centile *and/or*	quartiles on growth centiles *
3. UA-PI> 95th centile	3. CPR <5th centile *or* UA-PI >95th centile

AC: Fetal abdominal circumference; AEDF: Absent end-diastolic flow; CPR: Cerebroplacental ratio; EFW: Estimated fetal weight; FGR: Fetal growth restriction; GA: Gestational age; PI: Pulsatility index; UA: Umbilical artery; UtA: Uterine artery.

* Growth centiles are non-customized centiles. Reprinted from Ultrasound Obstet Gynecol, Vol 48(3), Gordijn, S.J., Beune, I.M., Thilaganathan, B., Papageorghiou, A., Baschat, A.A., Baker, P.N., Silver, R.M., Wynia, K. and Ganzevoort, W., Consensus definition of fetal growth restriction: a Delphi procedure, 333-339, Copyright (2016), with permission from John Wiley and Sons, reproduction with permission.

FIGURES

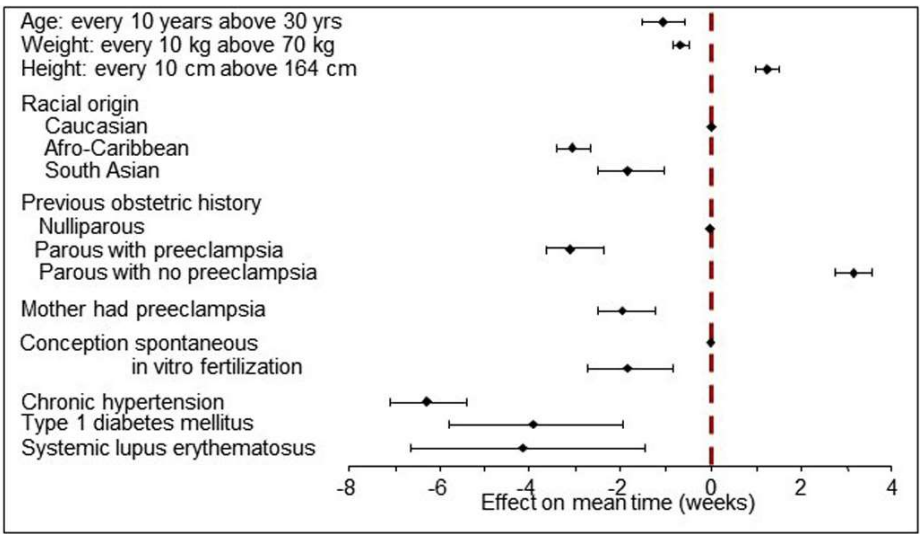

Figure 1 The basis for the Fetal Medicine Foundation (FMF) screening algorithm. In the FMF algorithm each demographic (age, weight etc), medical (chronic hypertension, previous obstetric history etc), biochemical (serum biomarkers) and biophysical (blood pressure, uterine artery Doppler) risk factor is given an individual positive or negative weight and the interactions between these factors are accounted for in order to estimate the woman's personal numerical risk of developing preeclampsia (PE). For example the risk conferred by chronic hypertension is higher than that conferred by advancing maternal age. Adapted from Chaemsaithong *et al*. [8]. Reprinted from Am J Obstet Gynecol, Vol 226(2s), Chaemsaithong, P., D.S. Sahota, and L.C. Poon, *First trimester preeclampsia screening and prediction*, S1071-S1097.e2, Copyright (2022), with permission from Elsevier

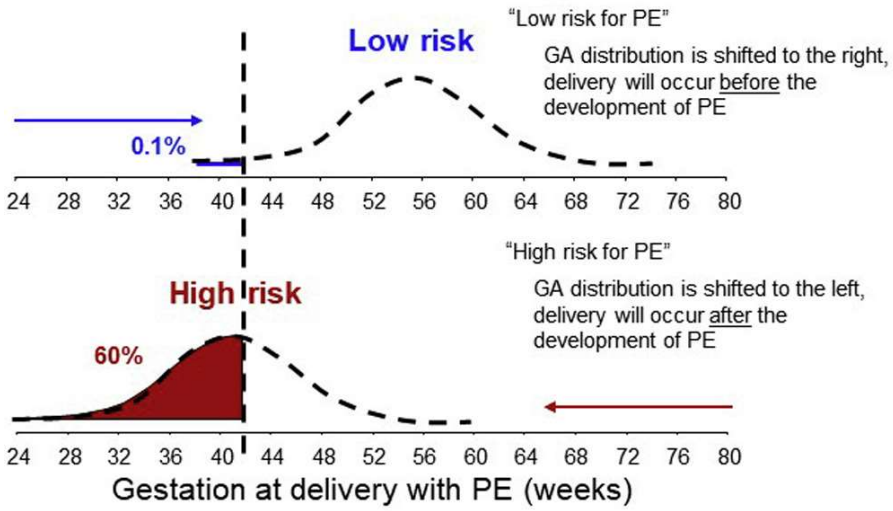

Figure 2 The Fetal Medicine Foundation screening algorithm is based on a competing risk approach. For each woman, the competing risk model gives the Gaussian (GA) distribution of gestational age at delivery with preeclampsia (PE). In women with a low risk for PE, the gestational age distribution is shifted to the right. Thus, in most pregnancies, delivery will occur before the development of PE. In women with a high risk for PE, the gestational age distribution is shifted to the left, indicating that PE is likely to occur before delivery. Adapted from Chaemsaithong *et al*. [8]. Reprinted from Am J Obstet Gynecol, Vol 226(2s), Chaemsaithong, P., D.S. Sahota, and L.C. Poon, *First trimester preeclampsia screening and prediction*, S1071-S1097.e2, Copyright (2022), with permission from Elsevier

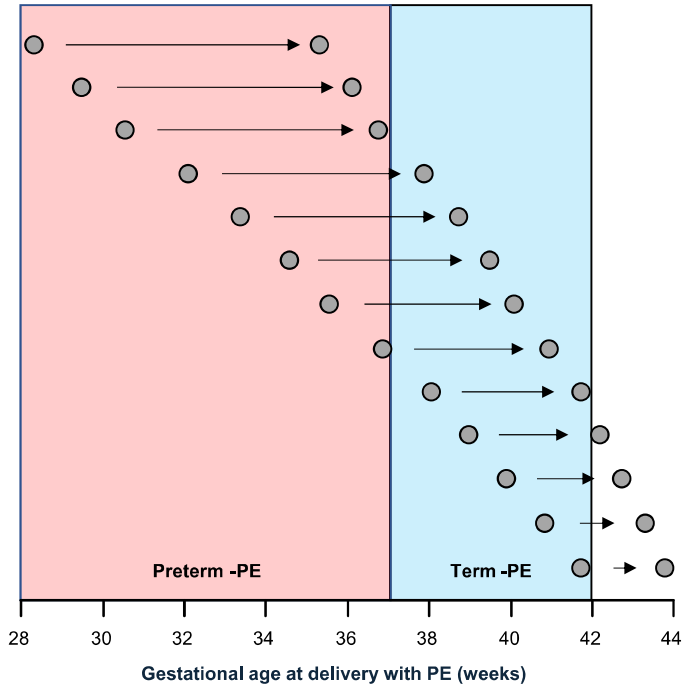

Figure 3 Aspirin delays the development of preeclampsia. The Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial demonstrated a reduction in the rate of preterm preeclampsia (PE) after prescription of prophylactic Aspirin therapy for women identified at high-risk for PE by the first-trimester Fetal Medicine Foundation algorithm [14]. However, the prophylactic use of Aspirin had no effect on the rate of term PE. One hypothesis is that Aspirin delays the gestational age at delivery with PE, counteracting the effect of Aspirin on the development of term PE due to a shift of preterm PE cases for high-risk pregnancies into cases with term PE. Adapted from Wright *et al.* [17]. Reprinted from Am J Obstet Gynecol, Vol 220(6), Wright, D. and K.H. Nicolaides, Aspirin delays the development of preeclampsia, 580.e1-580.e6, Copyright (2019), with permission from John Wiley and Sons, reproduction with permission.

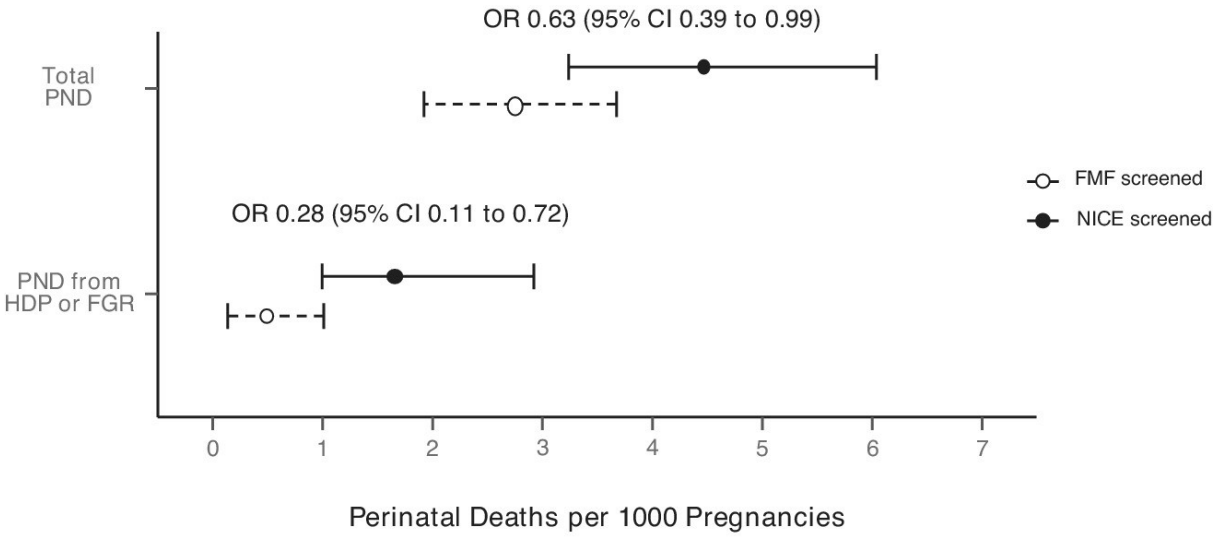

Figure 4 This graph shows absolute rates (95% confidence intervals) of perinatal death (PND) in women who underwent National Institute for Health and Care Excellence (NICE) or Fetal Medicine Foundation (FMF) first-trimester screening for preeclampsia, stratified by whether there was a diagnosis of hypertensive disorders of pregnancy (HDP) and/or fetal growth restriction (FGR). Adapted from Liu *et al*. [20].

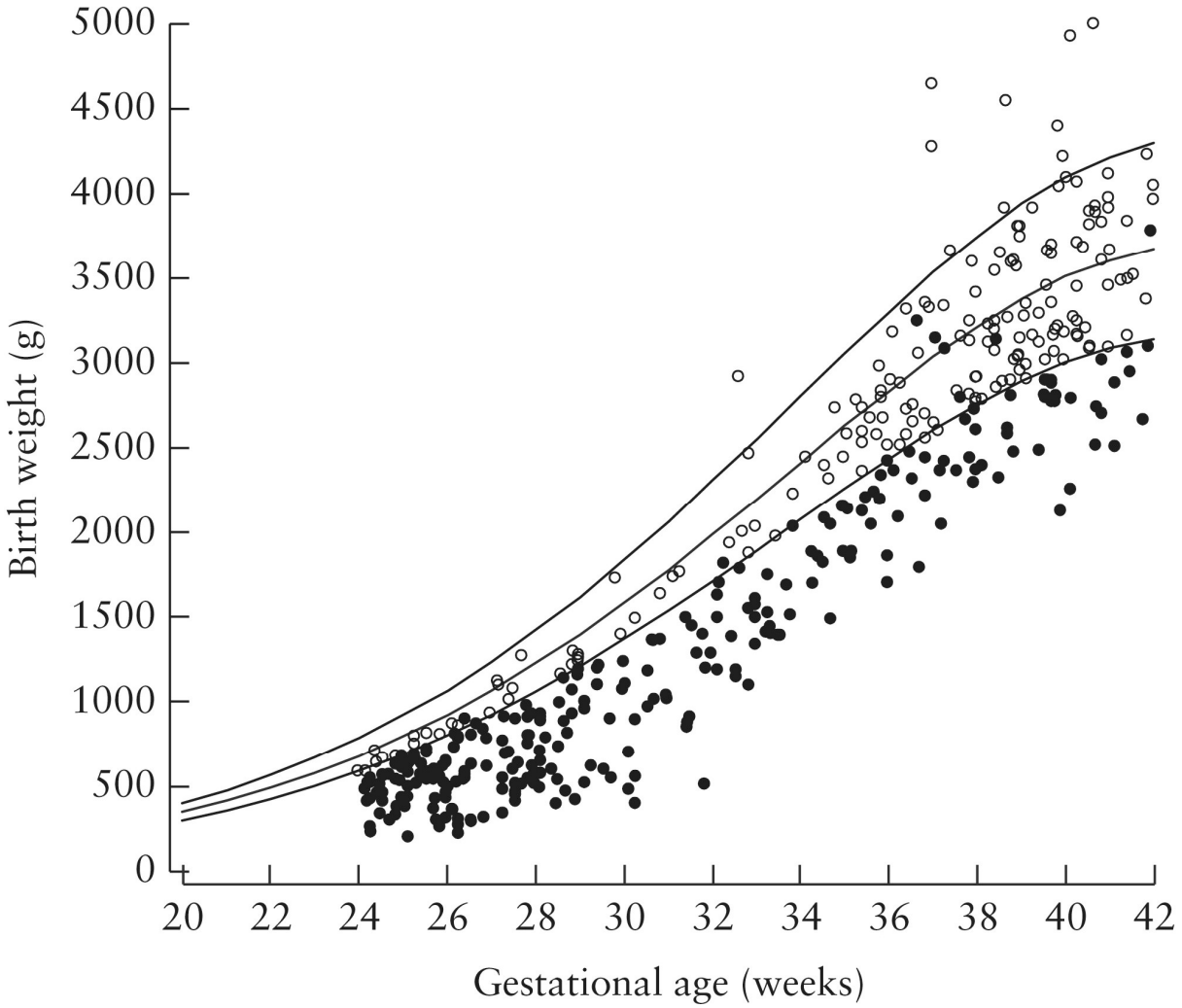

Figure 5 Gestational age and birthweight distribution of antepartum stillbirths, plotted on the reference range developed by Nicolaides *et al.* [36] and demonstrating the median, 90th and 10th percentiles. The black dots represent the stillbirths related to placental dysfunction because the baby was small-for-gestational age or the pregnancy was complicated by preeclampsia (60% of all antepartum stillbirths). The white dots represent the stillbirths due to other causes or unexplained (40% of all antepartum stillbirths). Placental dysfunction was associated with 72% of antepartum stillbirths <37 weeks, whereas only 33% of antepartum stillbirths at term were associated with placental dysfunction. Adapted from Ashoor *et al.* 2022 [3]. Reprinted from Ultrasound Obstet Gynecol, Vol 59, Ashoor, G., Syngelaki, A., Papastefanou, I., Nicolaides, K.H. and Akolekar, R., Development and validation of model for prediction of placental dysfunction-related stillbirth from maternal factors, fetal weight and uterine artery Doppler at mid-gestation, 61-68, Copyright (2022), with permission from John Wiley and Sons, reproduction with permission.

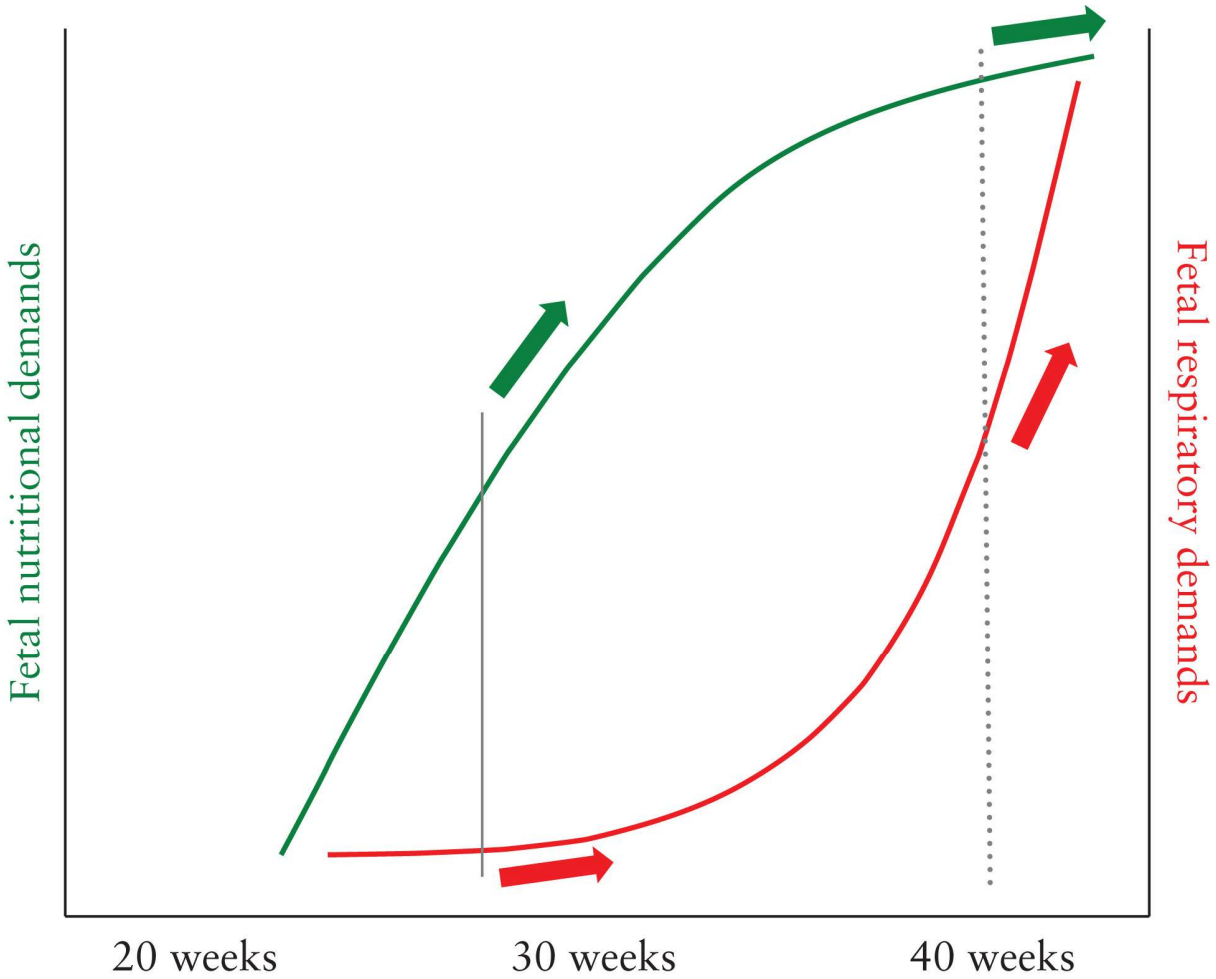

Figure 6 Increase in fetal nutritional (green line) and respiratory (red line) demands with advancing gestation. Early-onset placental dysfunction (vertical gray solid line) will impact at a time when fetal nutritional demands (green arrows) rise exponentially and therefore will have a disproportionate effect on fetal growth compared with development of fetal hypoxemia and demise. Placental dysfunction at term (vertical gray dotted line) will impact at a time when fetal respiratory needs (red arrows) rise exponentially and therefore likely to compromise fetal wellbeing before fetal growth is impaired. Reprinted from Ultrasound Obstet Gynecol, Vol 52, Thilaganathan, B., Ultrasound fetal weight estimation at term may do more harm than good, 5-8, Copyright (2018), with permission from John Wiley and Sons, reproduction with permission.

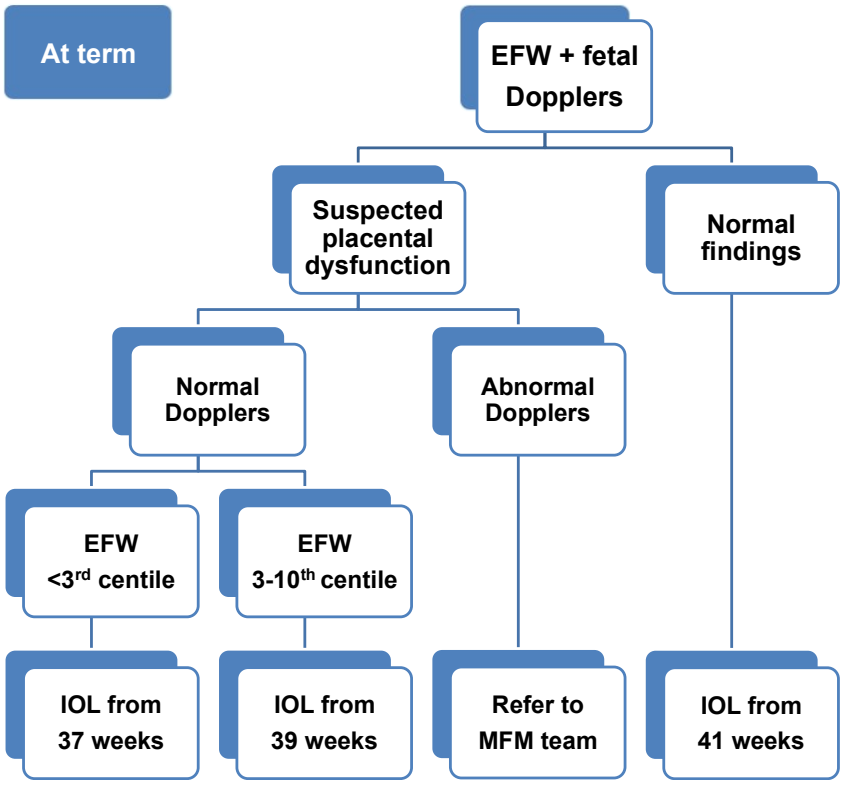

Figure 7 Recommendation of the National Health Service in the UK published in the 2nd version of the Saving Babies Lives Care Bundle to detect placental dysfunction and guide decisions about timing of birth based on estimated fetal weight (EFW) and fetal Dopplers assessment at term.
EFW:Estimated fetal weight; IOL: Induction of labour; MFM: Maternal-Fetal Medicine.

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