First trimester prediction and prevention of adverse pregnancy outcomes related to poor placentation

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Purpose of review
To summarize recent research findings related to first trimester prediction and prevention of adverse pregnancy outcomes associated with poor placentation. Recent publications related to prediction and prevention of preeclampsia, intrauterine growth restriction (IUGR) and stillbirth were reviewed.

Recent findings
Researchers continue to identify markers that will help predict pregnancies that go on to develop preeclampsia through screening at $11–13^{+6}$ weeks. A number of multivariate algorithms describing risks for preeclampsia have been published and some of these have been validated in independent populations. A large randomized controlled trial has proven the efficacy of a first trimester prediction – prevention programme for preeclampsia with an 80% reduction in prevalence of disease leading to delivery less than 34 weeks. Screening tools for IUGR and stillbirth are less advanced and require further validation in other populations. The value of these models in preventing disease still needs to be demonstrated.

Summary
Significant progress has been made in developing predictive and preventive strategies which can affect the prevalence of severe early-onset preeclampsia. This approach could be adopted for population-based screening aiming to prevent this disease.

Keywords
intrauterine growth restriction, mean arterial blood pressure, placental protein A, preeclampsia, prenatal screening, stillbirth, uterine artery Doppler

INTRODUCTION

Combined first trimester screening provides an effective means of screening for aneuploidy and has been widely adopted and performs well at a population level [1]. This test has formalized the concept of routine risk assessment at an early stage ($11–13^{+6}$ weeks) of pregnancy with inclusion of a variety of demographic, biophysical and biochemical parameters in a single risk algorithm [2]. This provides a foundational platform for assessment of risk related to other adverse obstetric outcomes with the potential to intervene and reduce the prevalence of these diseases.

One triad of adverse outcomes that are often recognized as having a similar aetiological base are maternal preeclampsia, foetal intrauterine growth restriction (IUGR) and placental abruption – which commonly leads to stillbirth. A number of groups have reported a variety of investigational tools that may help predict these disorders – with varying levels of efficacy, state of validation and demonstration of effective preventive intervention. Most progress has been made in the prediction and prevention of early-onset preeclampsia, wherein a highly effective and validated predictive model has been defined which has been successfully coupled to a preventive intervention leading to a significant reduction in the prevalence of disease [3▪,4▪▪]. In comparison, models for prediction of IUGR and stillbirth are generally less effective and no formal advantage of first trimester prediction and prevention has been demonstrated [5,6].

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KEY POINTS

- Preeclampsia, IUGR and stillbirth share similar causes associated with placental impairment.
- Common markers may be used to screen for these conditions.
- Algorithms for prediction of early-onset preeclampsia are highly effective and have been widely validated.
- A large randomized trial (ASPRE) has successfully demonstrated that prediction and prevention of early-onset preeclampsia should be offered to all pregnant women.
- Further work is needed for validation of predictive algorithms for IUGR and stillbirth and to demonstrate that pregnancies associated with these outcomes can be prevented.

Here, we review the progress that has been made in first trimester prediction and prevention of disorders commonly associated with impaired placentation.

GENERAL PRINCIPLES OF PREDICTION AND PREVENTION

Although the majority of pregnant women have an uncomplicated pregnancy leading to spontaneous and normal term vaginal delivery, a significant proportion are impacted by an adverse event that will potentially affect their or their child's future health. The spectrums of risks are diverse: Extreme preterm delivery (which affects 1–2% of pregnancies) can lead to death, short and/or long-term morbidity of the infant [7]. Gestational diabetes (affecting >10% of our obstetric population) appears to be less significant in the short term – impacting risks of macrosomia and complicating delivery – but is associated with increased risks of type II diabetes in mothers and obesity, diabetes, cardiovascular disease and metabolic syndrome in children in the longer term [8]. Conditions such as preeclampsia and IUGR have the potential to lead to a whole range of outcomes –- being associated with both preterm delivery and longer term disease in mothers and babies [9].

Most adverse obstetric outcomes have complex underlying causes, which are often incompletely understood. Pathogenesis is, however, often multifactorial and heterogeneous so predictive models that encompass a number of pathways are likely to perform better than those focused on one aspect of a disease. The investigational parameters that are most predictive of different adverse outcomes vary and there will be a need for some rationalization of the screening process to avoid it becoming too complex and costly. A similar problem impacts reporting of risk – as each algorithm will define its own screen positive group leading to a large proportion of women being defined at high risk of one or another adverse outcome. Measurement of investigational parameters needs to be standardized and quality assured and results often need to be presented in a statistical format as raw data are impacted by natural population variation. The multivariate algorithms that are used are typically complex, requiring large independent populations for validation before research findings are translated into clinical practice [10▪].

PREDICTION AND PREVENTION OF PREECLAMPSIA

Preeclampsia affects 3–7% of pregnancies and is recognized as being responsible for 60 000 maternal deaths and 500 000 premature births worldwide each year [11]. Placental disease is a central component of this disease and delivery of the placenta (and therefore the baby) leads to acute resolution; although this is of benefit to the mother, it conflicts with the best course for the neonate – who generally benefits from remaining in utero until the anticipated date for confinement. The pathophysiology of early-onset preeclampsia can be defined in stages [12]; poor implantation and placental insufficiency lead to placental hypoxic and the production of local angiogenic markers. These cause endothelial dysfunction that in turn results in peripheral vasoconstriction and end organ damage reflected in the symptoms and signs of this disease. First trimester prediction and prevention are attractive as they potentially allow intervention before the development of symptoms associated with disease.

Several first trimester algorithms for the prediction of early-onset (delivery <34 weeks) preeclampsia have been developed although they have not all been successfully validated in independent populations [13]. One algorithm, involving the assessment of maternal characteristics, the biophysical markers mean arterial pressure and uterine artery pulsatility index and the biochemical markers pregnancy-associated placental protein A (PAPP-A) and placental growth factor (PlGF), has been successfully validated in a number of independent populations [3▪,14,15▪]. These have demonstrated that 89% of cases of preeclampsia less than 32 weeks, 75% of cases less than 37 weeks and 47% of cases more than 37 weeks can be identified for a fixed 10% false positive rate [3▪]. This algorithm was then used as the basis for defining risk in an unselected population screened across

Table 1. Prevalence of preeclampsia in aspirin and placebo-treated high-risk cohorts in the ASPRE trial

	Aspirin ($n=798$)	Placebo ($n=822$)	Risk reduction (P)
Preeclampsia with delivery <32 weeks	3 (0.4%)	15 (1.8%)	78% ($P<0.01$)
Preeclampsia with delivery <37 weeks	13 (1.6%)	35 (4.3%)	63% ($P<0.01$)
Preeclampsia with delivery ≥37 weeks	53 (6.6%)	59 (7.2%)	5% ($P=$n/s)
All preeclampsia	66 (8.3%)	94 (12.5%)	34% ($P=0.03$)

Data from [4▪▪].

13 European centres as part of a multicentre trial examining the effectiveness of aspirin (150 mg PO nocte) in the prevention of preeclampsia [4▪▪]. The ASPRE trial recruited 26 941 patients including 1776 women defined as being high risk who were randomized to prophylactic aspirin ($n=878$) or placebo ($n=898$). The trial demonstrated a significant 62% reduction in the primary outcome; preeclampsia leading to delivery less than 37 weeks (Table 1) [4▪▪]. The prevalence of disease leading to very early (<34 weeks) delivery was reduced by 78%, supporting the findings of a previous cohort study. The prevalence of disease more than 37 weeks was not significantly impacted by the prevention programme. Moreover, the authors reported a 34% reduction in preeclampsia through effective screening and prevention. Treatment was more effective when compliance was more than 90% – which supports the process of screening prior to prophylaxis rather than merely offering universal prophylaxis. Interestingly, a secondary analysis has shown that women with a diagnosis of chronic hypertension appear to be resistant to prophylactic aspirin therapy [16].

Although the prediction and prevention of early preeclampsia has been very successful, preventing a significant number of preterm births, 75% of disease occurs more than 37 weeks [17]. Neither the screening programme (47% sensitivity) nor the preventive intervention (5% nonsignificant reduction in prevalence) seems to be particularly effective for this cohort of women. There is an increasing amount of data that support differing causes leading to early and late forms of disease [18▪]. The current screening strategy, involving assessment of uterine artery Dopplers and the biochemical markers PaPP-A and PlGF, is focused around placental function. Aspirin, which was originally prescribed on the basis of preventing platelet activation and hypercoagulation within the placenta, also appears to affect angiogenesis (PlGF) and placental implantation. Further improvements in the screening strategy and prediction of late-onset preeclampsia will likely require inclusion of better markers of endothelial dysfunction. Prospective tools include measurement of inflammatory markers such as hsCRP, assessment of retinal artery diameters and blood flow and assessment of carotid artery intimal thickness – but none have been incorporated and validated in screening algorithms to date [19–22].

Prevention of late-onset preeclampsia will also require different prophylactic strategies. Metformin, prescribed in a randomized controlled trial for the prevention of gestational diabetes, appears to give a 50% reduction in the prevalence of preeclampsia [23]. The use of metformin for prevention of preeclampsia is supported by in-vitro work that has demonstrated improved endothelial function, vasodilatation and induction of angiogenesis [24▪▪]. The challenge with prescription of metformin relates to the high rate of gastrointestinal side-effects which is likely to affect compliance [25]. Other drugs that have been proposed for the prevention of preeclampsia include Pravastatin – because of the similarities between this disease process and atherosclerosis [26]. This is the subject of several ongoing clinical trials. Another alternative that has been assessed in in-vitro work is proton pump inhibitors. These drugs appear to have several benefits: reducing sFlt and sENG levels, protecting endothelial function and causing local vasodilatation [27▪▪]. There is some clinical evidence that sFlt levels are reduced in women exposed to proton pump inhibitors during their pregnancy and these drugs have no obvious teratogenic effect and are used to complement aspirin for cardiovascular protection in later adult life [28]. Trials testing the hypothesis that statins or proton pump inhibitors may be able to prevent preeclampsia in high risk women are urgently needed.

Research attempting to identify alternative biomarkers for preeclampsia continues. Recent proteomic studies suggest that various matrix metalloproteinases (MMP-2, MMP-7 and MMP-9) are key factors in the pathogenesis of preeclampsia [29,30]. The potential value of adding MMP-9 to the first-trimester screening algorithm for preeclampsia was tested by Poon *et al.* [31] but showed no additional value. Other inflammatory markers such as Interlukin-1β have been reported to be increased

in early-onset preeclampsia [32]. Cell-free foetal DNA may also be increased in affected pregnancies and expression of several microRNAs (miR-1233, miR-210, miR-144, miR-517–5p, miR-518b and miR-520 h) has been reported to be altered in pre-eclamptic pregnancies [33,34]. Further work is needed to confirm these findings in other population groups.

PREDICTION AND PREVENTION OF INTRAUTERINE GROWTH RESTRICTION

IUGR – which can be defined as a failure to reach genetic growth potential – is another common complication of pregnancy. In its most severe, early-onset form, the foetus may die before reaching a point of viability or, if delivered extremely preterm, be affected by attendant morbidity [35]. Late-onset IUGR is more insidious and difficult to define but can also lead to stillbirth and is associated with foetal distress in labour and neonatal encephalopathy [36]. Approximately 1/3 of cases of IUGR are associated with preeclampsia; a proportion that rises when focusing on early-onset disease [37▪]. Once again, the phenotypes associated with different gestational ages appear to differ; early-onset IUGR being associated with placental insufficiency and late-onset IUGR being associated with placental failure [38,39]. Reported data on the prediction of IUGR can be difficult to interpret as a variety of endpoints are used to define IUGR and some studies distinguish between maternal cohorts affected by preeclampsia, whereas others do not make this distinction. Given the likely different causes of early-onset and late-onset disease, it is probably unreasonable to anticipate that a single first trimester test will perform equally in both cohorts.

The 'bar' for screening efficacy for IUGR was set by Poon *et al.* [40] who reported that 55.5% of preterm and 44.3% of term pregnancies that had a foetus more than 5th centile birth weight could be detected using the same investigational tools as had been described in screening for ePET. The test was based on maternal characteristics, uterine artery Doppler and maternal blood pressure and the biochemical markers PaPP-A and PlGF. In contrast to the work that this group has produced screening for preeclampsia, there are no reported studies that have validated this algorithm in other populations. One small Egyptian study did, however, support the findings, describing 100% sensitivity for IUGR with 95.5% specificity using Uterine Artery Doppler and PaPP-A for screening [41]. The potential therapeutic intervention for early-onset IUGR (a disease of placental insufficiency) is the same as that for early-onset preeclampsia – namely aspirin. The value of aspirin for prophylaxis against IUGR was recognized in meta-analysis many years ago – although there are as yet no large studies linking first trimester prediction of IUGR to successful prophylactic intervention [42].

Other groups, most notably the team in Barcelona, have also focussed on the development of first trimester predictive models for IUGR [37▪]. This algorithm has a similar format, including maternal characteristics, biophysical parameters and biochemical markers – although the biochemistry differed – including sFLT1 rather than PaPP-A. The outcome definitions used by this research group are also different – defining early-onset and late-onset IUGR with a 34-week cut-off and using a different definition for foetal growth restriction. This group reported an 86.4% detection rate (at a 10% false positive rate) for early IUGR [37▪]. The detection rate for late-onset IUGR was 65.8%. The area under receiver operating charcteristics for screening were 0.93 and 0.76, respectively. Once again – this extremely promising screening model needs external validation. The authors have also continued to look at the value of repeated measures – using uterine artery Doppler and PlGF measures in both the first and second trimesters of pregnancy – although they did not find these to be more valuable than either an isolated first or isolated second trimester approach [43].

The value of sFlt in first trimester screening is supported by other data. Inan *et al.* [44] reported that Prokineticin-1 (also described as endocrine gland VEGF) is increased in IUGR (85.7% sensitivity for 72.5% specificity) and Takenaka *et al.* [45] have demonstrated that first trimester mRNA levels of VEGF receptor 1 levels are significantly upregulated in pregnancies affected by IUGR [mean (SD) 2.63 (0.34) vs. 2.18 (0.54); $P = 0.01$]. Ultrasound assessment of placental volume does not appear to be as valuable (25% sensitivity for 90% specificity) and biochemical evaluation of placental function therefore appears to be preferred [46]. Similarly, the addition of other biophysical measures, such as measurement of ophthalmic artery pulsitility index – does not appear to add to the performance of uterine artery Doppler assessment [47]. One recent interesting finding is that Lipoxin A2 levels are decreased in pregnancies that develop foetal growth restriction. Lipoxin A2 modulates the inflammatory response and it has been suggested that this plays an anti-inflammatory and proangiogenic role during placental implantation [48]. The potential value of this in a multivariate screening model is that it assesses a different aetiological pathway and may therefore increase sensitivity. It is also interesting to note that aspirin impacts Lipoxin metabolism and may have an action through this pathway.

Identification and/or quantitation of cell free nucleic acids is rapidly becoming established as a primary screening technique for chromosomal and single gene disorders [49]. This technology could potentially be expanded to measure changes in mRNA and/or miRNA expression which may be representative of altered placental function [50]. These markers may reflect changes in the maternal compartment – either as means of compensation for or response to placental abnormality or changes found directly in foetal/placental gene expression (measuring foetal or placental-specific cell-free nucleic acids). This is an exciting area of research that has not yet reached a point of clinical implementation. To date, most research has focused on the third trimester either through placental biopsy (after delivery) or in maternal blood (after development of clinically apparent disease). Markers of fetal hypoxia have been clearly indentified as have markers of maternal cardiovascular disease [51,52]. There are fewer data related to the first trimester involving maternal blood samples taken prior to the onset of clinical disease; in one study, focused on quantification of C19MC miRNAs that are thought to be placental specific, there appeared to be miRNA changes associated with early-onset preeclampsia but no change in relation to the later development of IUGR [53].

PREDICTION AND PREVENTION OF STILLBIRTH

Millions of babies are stillborn each year [54]. In developing economies, almost half of these losses occur in the intrapartum period, an event that is much rarer, but not absent from the statistical data of developed nations. Placental diseases (maternal hypertension, foetal growth restriction and placental abruption) account for the majority of antepartum stillbirths. Prevention of stillbirth has been defined as a priority for improvement in obstetric care and early prediction and prevention of associated complications (hypertension and IUGR) would contribute to this [55].

In 2014, Conde-Agudelo *et al.* [56] published a systematic review and meta-analysis of literature reporting first and second trimester predictive models for stillbirth. The review included examples of models based on the performance of a single biomarker (e.g. alphafetoprotein and PaPP-A), ultrasound-based tools (e.g. uterine artery Doppler, nuchal translucency and ductus venous Doppler), markers of chronic disease (e.g. antiphospholipid antibodies, thyroid function tests and maternal haemoglobin), as well as various combinations of these tools. The list of models that were assessed is very extensive, but very few showed significant value. Among these were PaPP-A measurement (<0.4 MoM) in the first trimester, examining the specific outcome of stillbirth related to placental abruption; with positive and negative likelihood ratios of 15.1 and 0.3, respectively (sensitivity of 75% and specificity of 95%) [56]. This finding, limited to one study, contrasted with the more generic review of seven studies for all causes of stillbirth – which had a positive likelihood ratio of 2.7 and a negative likelihood ratio of 0.9 (sensitivity of 14% for specificity of 95%). Uterine artery Doppler also appears to be an effective screening tool for the identification of stillbirth related to growth restriction or placental abruption at less than 32 weeks – although the data for first and second trimester assessment are reported together. Sensitivities for these outcomes were more than 80% for 90% specificity [56]. This meta-analysis sets the benchmark for ongoing comparison of test development.

As stillbirth is rare, affecting approximately one in 200 pregnancies that progress beyond 12 weeks, datasets that develop and validate predictive models have to be very large. Small datasets typically have very few cases and are unable to draw conclusions about the effectiveness of screening parameters [57]. Two large population-based studies were recently published by the same group – testing slightly different screening algorithms [6,58▪]. In the first article, the authors reported findings in a series of 76 897 women screened at $11–13^{+6}$ weeks gestation [6]. The cohort included 268 (0.35%) women who later had a stillbirth – and 157 (0.21%) of these were deemed to be due to a placental cause. The algorithm was based on maternal characteristics, PaPP-A MoM, uterine artery pulsitility index MoM and the foetal ductus venosus pulsatility index. Foetal nuchal translucency thickness and maternal serum βhCG MoM did not make a significant contribution to the model. The algorithm had 40% sensitivity for all stillbirth and 55% for stillbirth related to placental abnormalities (at a false positive rate of 10%). Within those cases that had a placental abnormality – the test predicted 64% of those that resulted in foetal death less than 32 weeks compared to only 42% of those where death occurred at least 37 weeks.

In their second study, this research group reported on a subgroup of 45 225 pregnancies from the original cohort who also had PlGF measured [58▪]. The study included 227 (0.49%) women who had a stillbirth and 131 of these were deemed to be related to impaired placentation. In this study, with inclusion of PlGF, PaPP-A dropped out of the risk algorithm. The final algorithm had 42% sensitivity for all stillbirth and 61% for stillbirth

related to placental impairment (at a false positive rate of 10%). Within those cases that had a placental abnormality – the test predicted 71% of those that resulted in foetal death less than 32 weeks compared to only 46% of those where death occurred more than 37 weeks. In summary, these studies suggest that a significant proportion of pregnancies that continue to be affected by stillbirth can be predicted at $11–13^{+6}$ weeks. The test algorithm is particularly suited to pregnancies affected by placental impairment that result in stillbirth less than 32 weeks. PlGF is a slightly better discriminator than PaPP-A – improving algorithmic performance in this group by 7%.

A meta-analysis of studies that have examined the impact of low-dose aspirin suggests that this prophylactic intervention can reduce rates of perinatal death as well as reducing rates of maternal preeclampsia [59]. Given that more than half of stillbirths are related to impaired placentation and that 70% of these can now be predicted at 12 weeks, it would be appropriate to take this forward in a trial linking prediction and prevention with a view to reducing rates of stillbirth. The ASPRE trial, which reported the effect of low-dose aspirin following prediction of a high-risk group for early-onset preeclampsia, showed a nonsignificant difference in rates of miscarriage and stillbirth after recruitment to the two groups – but it should be noted that the study was designed for this primary outcome measure and the algorithm being tested related to early-onset preeclampsia not stillbirth [4▪▪].

CONCLUSION

Considerable progress has been made in screening for common adverse outcomes associated with placental impairment. There is now good evidence that a robust algorithm is available to screen for early-onset preeclampsia that has been validated in a variety of populations. This is of particular relevance as prophylactic intervention for prevention of early (<37 weeks) preeclampsia has now been shown to lead to a very significant reduction in the prevalence of disease when coupled to a programme of first trimester risk prediction. The cause of late-onset preeclampsia is likely different and consequently a first trimester algorithm that is based on the assessment of placental function is not as effective in predicting a high-risk group. It is also interesting that aspirin does not seem to be as effective in this late-onset cohort – likely because of similar reasons.

Algorithms that are used to screen for IUGR are less well developed. Comparison of approaches is often difficult as researchers include and discriminate between different patient groups and use different criteria to define growth restriction. The algorithms generally appear to be less effective – which may also reflect differences in cause. It is, however, becoming apparent that measurement of PlGF and sFlt is likely more important than in preeclampsia assessment. Only a limited number of studies have had enough power to develop algorithms that screen for stillbirth. These now need validation in other populations. Although aspirin should be an effective intervention for both IUGR and stillbirth – this also needs to be demonstrated prospectively.

It is likely that cases of preeclampsia, IUGR and stillbirth will be defined as being at increased risk through more than one algorithm and one of the challenges that remains is how to combine the findings of these three risk equations to define a single screen positive group, minimizing the anxiety associated with a false positive result while avoiding false negative reports.

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Conflicts of interest

There are no conflicts of interest.

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