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Opinion

From first-trimester screening to risk stratification of evolving pre-eclampsia in second and third trimesters of pregnancy: comprehensive approach

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Introduction

Pre-eclampsia is a heterogeneous, multiorgan disorder of pregnant women, affecting ~2–5% of all pregnancies[1,2]. It is one of the leading causes of maternal and perinatal morbidity and mortality worldwide and the only effective treatment is delivery[1–3]. The current diagnostic criteria for pre-eclampsia include hypertension after 20 weeks of gestation, coupled with new onset of one or more of the following: significant proteinuria, renal insufficiency, impaired liver function, neurologic complications, hematologic complications or disturbed uteroplacental and/or fetoplacental perfusion[4–6]. Identification of women at risk for developing pre-eclampsia, timely referral to specialist care, prophylaxis, early detection of disease and active monitoring of women with confirmed or suspected pre-eclampsia are essential for improving maternal and neonatal outcome[4,7]. However, the clinical presentation of pre-eclampsia is extremely variable. This impacts the specificity and reliability of clinical assessments for diagnosing pre-eclampsia and predicting its evolution[8].

Pre-eclampsia is defined as early-onset when it leads to delivery < 34 weeks of gestation and late-onset when it occurs ≥ 34 weeks of gestation. It is also subclassified as preterm or term, depending on whether the onset occurs < 37 weeks or ≥ 37 weeks of gestation, respectively[9]. Subclassification of pre-eclampsia is particularly important as early-onset pre-eclampsia is more likely than term pre-eclampsia to be associated with placental insufficiency, with potentially quite different clinical manifestations[10]. Although maternal morbidity is often more significant amongst women with early-onset pre-eclampsia, late-onset pre-eclampsia can also manifest with severe complications for both mother and fetus[11,12].

Placental dysfunction is associated with an imbalance in the maternal blood of angiogenic and antiangiogenic factors, including placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1)[13–15]. Circulating levels of the antiangiogenic protein, sFlt-1, are increased in women with pre-eclampsia, whilst levels of the proangiogenic factor, PlGF, are decreased before the onset of clinical disease[13,14,16,17]. The sFlt-1/PlGF ratio is also elevated in women with a confirmed diagnosis of pre-eclampsia, and the value of this ratio in short-term prediction in women with clinical suspicion of pre-eclampsia has been demonstrated[18,19]. Therefore, measurement of angiogenic markers, either alone or combined as part of the sFlt-1/PlGF ratio, has significant value in pre-eclampsia prediction[19,20].

Large studies have demonstrated that first-trimester screening using a combination of maternal history and characteristics, measurements of maternal mean arterial pressure (MAP), uterine artery pulsatility index (PI) and angiogenic markers, such as PlGF, can identify effectively pregnancies that will go on to develop preterm pre-eclampsia[21]. Furthermore, administration of low-dose aspirin to women identified as being high risk using this approach reduces significantly the rate of preterm pre-eclampsia[22,23]. Widespread implementation of this combination of first-trimester prediction and prevention has the potential to have a significant impact on the prevalence of early-onset and preterm pre-eclampsia[21,23,24]. However, it is important to recognize that this approach is less effective at predicting and preventing pre-eclampsia developing at > 37 weeks of gestation[21,23]. Prediction of both the development and evolution of late-onset pre-eclampsia remains a major obstetric challenge and unmet medical need. However, recent studies suggest that further assessment of angiogenic markers and other risk factors throughout the second and third trimesters of pregnancy can help with early identification and improve the management of this form of the disease[25,26].

Currently, there is no consensus on the optimum strategy to link first-trimester screening for pre-eclampsia with appropriate second- and third-trimester strategies regarding prediction, early detection and likely evolution of pre-eclampsia. The aims of this Opinion paper are to outline the current evidence for first-trimester pre-eclampsia screening and the evidence supporting risk stratification throughout the second and third trimesters of pregnancy, and to propose a potential model linking these tools.

First-trimester screening and prevention of pre-eclampsia

The objective of first-trimester screening is to identify women at high risk for preterm pre-eclampsia as well as to provide reassurance to women identified as being at low risk of developing the disease. Identification of high-risk women allows focused and timely prophylactic prescription of low-dose aspirin with the intention of reducing the risk of disease. Administration of low-dose aspirin to high-risk women is supported by several international guidelines, although the recommended dose varies[4,6]. However, many centers do not use a combined first-trimester screening approach and, as a result, determination of risk is often based on maternal history alone. There is considerable variation in advice for screening based on maternal history, with some guidelines describing only a limited number of risk factors[4,27]. Such screening strategies show only moderate performance for the prediction of pre-eclampsia[28]. Inclusion in risk assessment of additional common features, such as nulliparity and obesity, may increase the sensitivity of the assessment, but result in lower specificity[29]. Application of the National Institute for Health and Care Excellence (NICE) guidelines demonstrated only a 40% detection rate for preterm pre-eclampsia, leading to a significant underestimation of the number of women at risk of preterm pre-eclampsia who would benefit from aspirin prophylaxis[30].

Using a multivariate algorithm for first-trimester screening has several advantages. Such an approach focuses screening assessment on the timepoint at which prophylaxis is most beneficial, allows incorporation of multiple risk factors and allows risk factors to be weighted according to the strength of their association. Several comparisons of these approaches have demonstrated improved screening performance when using a multivariate algorithm compared with maternal factors alone[30–32].

Several groups have reported the efficacy of multivariate screening algorithms for prediction of pre-eclampsia, and the difficulties in developing and validating these tools have been discussed elsewhere[33]. One algorithm that is used widely and has been validated by other groups was produced by The Fetal Medicine Foundation (FMF). Poon *et al.*[34] initially proposed this algorithm based on the use of a combination of maternal demographics, medical and obstetric history, mean uterine artery PI, MAP and maternal serum levels of PlGF and pregnancy-associated plasma protein-A (PAPP-A) between 11 and 13 weeks of gestation[34]. In each case, measured values are converted to multiples of the expected median (MoM), adjusting for individual maternal and gestational characteristics. Using multivariate logistic regression analysis that combines maternal factors and the MoM values, the test identifies > 90% of cases of early-onset pre-eclampsia at a 5% false-positive rate[34].

Subsequent iterations of the FMF algorithm have incorporated a competing-risks model that combines maternal factors and the aforementioned risk factors with the prior distribution of gestational age at delivery with pre-eclampsia and various combinations of biomarker MoM values. This is used to derive a patient-specific risk of delivery with pre-eclampsia at < 37 weeks of gestation. The current model was developed in a mixed population of 35 948 women with singleton pregnancy attending a routine visit at one of two UK hospitals, and a combination of maternal factors, uterine artery PI, MAP and PlGF can predict 90% of cases of early-onset pre-eclampsia, 75% of preterm pre-eclampsia and 41% of term pre-eclampsia, at a screen-positive rate of 10%[31,35]. The model has been validated prospectively by the same research group in two large multicenter trials (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) and Screening Programme for Preeclampsia (SPREE)), involving more than 40 000 women[21,32]. Inclusion of serum PAPP-A did not improve the performance of the screening algorithm[35]. However, in the absence of serum PlGF, a combined test of maternal factors, uterine artery PI, MAP and serum PAPP-A predicted 70% of preterm pre-eclampsia[31]. Other groups have developed and validated algorithms that have similar forms and that are also available freely to clinicians as online calculators or mobile applications. The Fetal Medicine Barcelona research group have used both PlGF and sFlt-1 as angiogenic markers in their model and also report detection rates of ~90% for early-onset pre-eclampsia in cohorts of 9462 and 4621 women[36,37].

The role of aspirin in the prevention of pre-eclampsia has been the subject of much debate and the etiology of the disease and the mechanism of action of aspirin are still not understood completely[38]. The recent ASPRE trial[21] was designed to investigate the effect of night-time administration of 150 mg aspirin from 11 + 0 to 14 + 6 weeks until 36 weeks in pregnancies identified using the FMF first-trimester screening strategy as being at high risk for preterm pre-eclampsia. During the trial, the first-trimester screening algorithm detected 77% of cases of preterm pre-eclampsia. In total, 26 941 women with singleton pregnancy were screened and 2971 (11%) were determined to be at high risk of pre-eclampsia. Of the 798 women randomized to aspirin, 13 (1.6%) developed pre-eclampsia, compared with 35 (4.3%) of the 822 women randomized to placebo. These results suggest that daily administration of 150 mg aspirin significantly reduces the risk of developing preterm pre-eclampsia (by 62%; odds ratio (OR), 0.38 (95% CI, 0.20–0.74)), without increasing the rate of placental abruption[23]. A non-significant reduction of 82% (OR, 0.18 (95% CI, 0.03–1.03)) was also achieved for the risk of early-onset pre-eclampsia (< 34 weeks) in the aspirin-treated group compared with the placebo group. However, it should be noted that only a very small number of cases with pre-eclampsia < 34 weeks of gestation were observed[23]. Importantly, the beneficial effect of aspirin in the prevention of preterm pre-eclampsia is dependent on patient compliance with the treatment regimen. *Post-hoc* analysis of the data suggests that the reduction in preterm

pre-eclampsia may be ~75% if compliance is ≥ 90%. However, when the proportion of prescribed tablets taken was < 90%, the risk reduction was only ~40%[39]. It is also worth noting that a further subanalysis of the data found that there was no beneficial effect of aspirin in the prevention of preterm pre-eclampsia in a subgroup of pregnancies with chronic hypertension[40].

A recent meta-analysis including 16 trials, with a combined total of 18 907 participants, also demonstrated that daily administration of ≥ 100 mg aspirin at ≤ 16 weeks of gestation reduced the rate of preterm pre-eclampsia by ~65%[41]. Although these studies indicate that the optimal time for initiating aspirin administration is ≤ 16 weeks, it is worth noting that additional studies have suggested that low-dose aspirin started after 16 weeks may still be associated with a modest reduction in pre-eclampsia (relative risk, 0.81 (95% CI, 0.66–0.99); 0.81 (95% CI, 0.63–1.03); and 0.90 (95% CI, 0.83–0.98))[42–44]. Further research is needed to investigate whether late administration of low-dose aspirin confers any benefit in the prevention of pre-eclampsia.

The data provided by these recent publications indicate that a strategy based on first-trimester screening for pre-eclampsia and administration of ≥ 100 mg per day of aspirin to high-risk women would be useful in reducing their risk of pre-eclampsia. There are insufficient data to recommend stopping treatment earlier than 36 weeks. Implementation of first-trimester prediction and prevention of early-onset pre-eclampsia is likely to be cost-effective, as the additional costs required to screen the population are recovered through reductions in neonatal admission and length of stay in neonatal intensive care units[45,46].

Statement

- A combination of maternal factors, uterine artery PI, MAP and serum PlGF as part of the FMF algorithm is optimal for first-trimester screening for preterm pre-eclampsia in all pregnant women.
  - Other screening methods based on maternal history, such as those recommended by the American College of Obstetricians and Gynecologists (ACOG) or NICE, are inferior regarding detection rate and false-positive and false-negative rates.
  - PAPP-A can be considered for inclusion in the algorithm in the absence of PlGF.
- Aspirin should be recommended at 100–150 mg per day to women classified as high risk based on first-trimester screening results, starting at 11 + 0 to 14 + 6 weeks and concluding at 36 weeks.
- Universal prescription of aspirin to all pregnant women is not recommended.

Risk stratification and prediction of pre-eclampsia in second and third trimesters of pregnancy

Women classified as being at high risk of developing pre-eclampsia based on first-trimester screening need to be followed up regularly throughout pregnancy in order to ensure early detection of evolving pre-eclampsia and to monitor compliance with aspirin treatment. Regular antenatal pregnancy care is also important in women classified as low risk, as pre-eclampsia, especially late-onset disease, as well as other pregnancy-associated disorders, can still occur in this population. There is a paucity of literature evaluating the optimal frequency and content of follow-up visits[47]. Below, we summarize the evidence from several studies investigating the prediction of pre-eclampsia in the second and third trimesters of pregnancy using sFlt-1 and PlGF biomarkers, uterine artery PI or the combination of maternal factors, uterine artery PI, MAP and serum biomarkers, as well as evidence from studies demonstrating the value of potential risk stratification algorithms in these women.

Predictive value of sFlt-1 and PlGF

Numerous studies have demonstrated the value of both sFlt-1 and PlGF in the short-term prediction, diagnosis and evolution of pre-eclampsia[48–52] and their use as a ratio (sFlt-1/PlGF) in the diagnosis of early- and late-onset pre-eclampsia has also been investigated. A multicenter case–control study, including a total of 1149 women with singleton pregnancy (of whom 877 were used to construct normal ranges for the sFlt-1/PlGF ratio throughout pregnancy), compared 234 women with pre-eclampsia with a matched cohort of 468 women with normal pregnancy outcome[53]. Visits from subjects at a gestational age ≥ 20 + 0 weeks were included and sFlt-1 and PlGF measurements were taken at the first visit following confirmation of pre-eclampsia. This study demonstrated that a sFlt-1/PlGF ratio ≥ 85 yielded a positive likelihood ratio (LR+) of 176 (95% CI, 24.88–1245) for the diagnosis of early-onset pre-eclampsia (20 + 0 to 33 + 6 weeks), whilst a ratio ≥ 110 resulted in a LR+ of 13 (95% CI, 7.34–23.0) for the diagnosis of late-onset pre-eclampsia (≥ 34 + 0 weeks)[53]. It is worth noting that the authors used a different approach to data analysis from that recommended for first-trimester screening, using fixed, population-based, analyte cut-offs to categorize patients as high or low risk.

The PROGNOSIS study[19], a prospective observational study conducted in 14 countries, was designed to investigate the value of using the sFlt-1/PlGF ratio to predict the absence of pre-eclampsia within 1 week and to predict the presence of pre-eclampsia within 4 weeks in women with clinical suspicion of pre-eclampsia. This study included pregnant women ≥ 18 years of age at 24 + 0 to 36 + 6 weeks of gestation with clinical suspicion of pre-eclampsia. Women with established pre-eclampsia were excluded (Table 1). The prevalence of pre-eclampsia in the validation cohort of this study ($n = 550$) was 17.8%. This study demonstrated a negative predictive value (NPV) of 99.3% (95% CI, 97.9–99.9%) for a sFlt-1/PlGF ratio cut-off of ≤ 38 for ruling out the occurrence of pre-eclampsia within 1 week in women with signs and symptoms suggestive of pre-eclampsia. The positive predictive value (PPV) of a sFlt-1/PlGF ratio > 38 for ruling in the occurrence of pre-eclampsia within 4 weeks was 36.7% (95% CI, 28.4–45.7%). The PPV for the occurrence of a combined endpoint

Table 1 Inclusion and exclusion criteria for PROGNOSIS study[65]

Criteria contributing to clinical suspicion of PE*
New onset of elevated BP†
Aggravation of pre-existing hypertension
New onset of protein in urine‡
Aggravation of pre-existing proteinuria
PE-related symptoms
Epigastric pain
Excessive edema, severe swelling (face, hands, feet)
Headache
Visual disturbances
Sudden weight gain (> 1 kg per week in third trimester)
PE-related findings
Low platelets
Elevated liver transaminases
(Suspected) intrauterine growth restriction
Abnormal uterine perfusion detected by Doppler sonography with mean PI > 95th percentile in second trimester and/or bilateral uterine artery notching
Exclusion criteria
Manifest PE
Proteinuria ≥ 2+ by dipstick urinalysis (or ≥ 0.3 g protein/24 h or ≥ 30 mg/dL protein in spot urine or spot urine protein/creatinine ratio ≥ 30 mg protein/mmol creatinine) AND reproducible elevated BP (≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic) or current antihypertensive treatment
HELLP syndrome
Concomitant participation in another clinical study
Treatment with an investigational medicinal product during 90 days prior to enrollment

HELLP, hemoylsis, elevated liver enzymes and low platelet count; PE, pre-eclampsia; PI, pulsatility index. *Presence of at least one of these clinical criteria for suspicion of pre-eclampsia was required for inclusion in PROGNOSIS. †Including levels that would not be defined as hypertension (≥ 140 mmHg systolic blood pressure (BP) and/or ≥ 90 mmHg diastolic BP). ‡Including levels that would not be defined as proteinuria (any protein in urine considered sufficient).

of pre-eclampsia/eclampsia/hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome and maternal and/or fetal adverse outcome within 4 weeks was 65.5% (95% CI, 56.3–74.0%)[19].

An exploratory *post-hoc* analysis of data from 550 women participating in the PROGNOSIS study also demonstrated that a sFlt-1/PlGF ratio ≤ 38 can rule out pre-eclampsia within 4 weeks with a NPV of 94.3% (95% CI, 91.7–96.3%)[54]. Evidence from this analysis also suggests that there is value in performing repeat measurements when using the sFlt-1/PlGF ratio: women who developed pre-eclampsia had a significantly larger median increase in the sFlt-1/PlGF ratio at 2 weeks (Δ31.22) and at 3 weeks (Δ48.97) post-initial visit, compared with those who did not (Δ1.45 and Δ2.39, respectively; $P < 0.001$)[54].

Subsequently, the PROGNOSIS Asia study also demonstrated the value of the sFlt-1/PlGF ratio for the short-term prediction of pre-eclampsia in pregnant Asian women with suspected pre-eclampsia[55]. The inclusion criteria for this study were similar to those used for the PROGNOSIS study (excessive edema, severe swelling, headache and sudden weight gain were not included as pre-eclampsia-related symptoms). In this study, a sFlt-1/PlGF ratio cut-off of ≤ 38 was shown to have an NPV of 98.6% (95% CI, 97.2–99.4%) for ruling out pre-eclampsia within 1 week and a ratio > 38 demonstrated a PPV of 30.3% (95% CI, 23.0–38.5%) for ruling in pre-eclampsia within 4 weeks in a cohort of 700 evaluable women. The PPV for the occurrence of a combined endpoint of pre-eclampsia/eclampsia/HELLP syndrome, maternal and/or maternal or fetal adverse outcomes within 4 weeks was 65.0% (95% CI, 56.6–72.8%)[55].

These studies indicate that sFlt-1 and PlGF represent valuable biomarkers for the short-term prediction and detection of evolving pre-eclampsia in women with clinical signs and symptoms of the disorder, demonstrating a high NPV for ruling out pre-eclampsia, although the PPV remains relatively low. Use of these markers may aid clinicians in the identification of women who require intensive monitoring, and help them in decision-making regarding instigation of timely admission and administration of necessary treatment. The ability to rule out evolving pre-eclampsia is of particularly high clinical value. Indeed, NICE has been recommending since 2016 the use of the sFlt-1/PlGF ratio, or the PlGF marker alone, to help rule out pre-eclampsia in women presenting with signs and symptoms of the disorder between 20 + 0 and 34 + 6 weeks of gestation[56]. A number of studies have examined the cost-effectiveness of triaging women suspected of having pre-eclampsia with this test and have shown that adoption of this tool potentially reduces the cost burden to the healthcare system[57,58].

Risk stratification in asymptomatic 'high-risk' women

Recent studies have attempted to investigate the performance of algorithms incorporating angiogenic biomarkers to stratify patient risk for developing pre-eclampsia during the second half of pregnancy. As the prediction and prevention model of first-trimester screening appears to be most effective in preventing early-onset pre-eclampsia, it could be argued that monitoring should focus on disease occurring at 28–32 weeks of gestation through assessment at 24–28 weeks[23]. Measurement of angiogenic biomarkers could be applied to the whole population or could be limited to those identified as being at high risk using first-trimester screening (extending the screen-positive rate as described in the first-trimester screening section) or through assessment of other parameters, such as uterine artery PI, at the time of the routine 18–22-week morphology scan. At 24–28 weeks, differences in sFlt-1 and PlGF values between women with normal outcome and those destined to develop early-onset pre-eclampsia are usually already apparent[13].

A recent study by Herraiz *et al.*[59] investigated the value of a tiered risk-stratification model, in which asymptomatic women classified initially as low or high risk based on maternal factors were rescreened using uterine artery Doppler PI at 18–22 weeks of gestation. Women considered to be at high risk of developing pre-eclampsia based on maternal factors and uterine artery Doppler PI were selected for intensive follow-up

at 24–28 weeks using measurement of the sFlt-1/PlGF ratio to help predict pre-eclampsia and fetal growth restriction[59,60]. The area under the receiver–operating characteristics curve (AUC) in these women was 0.98 (95% CI, 0.97–1.00) for sFlt-1/PlGF ratio at 24–28 weeks in the detection of early-onset pre-eclampsia or fetal growth restriction requiring delivery < 32 weeks, with a detection rate of 100% (95% CI, 78.5–100.0%) at a false-positive rate of 19.4% (95% CI, 14.8–25.0%)[60]. This approach to assessment appears to be very effective, providing an accurate assessment of the risk of developing early-onset pre-eclampsia and fetal growth restriction, and thereby allowing optimization of perinatal care. This strategy could also potentially be used as a complementary approach to first-trimester screening, to reduce the false-positive rate. Further studies are needed to demonstrate the value of such an approach for improving maternal and fetal outcome.

Risk stratification in asymptomatic, unselected or 'low-risk' women

Several studies have also investigated the use of sFlt-1 and PlGF in risk stratification in women considered to be at low risk for developing pre-eclampsia or who have no clinical suspicion of the disorder. The FMF provides an online algorithm for screening asymptomatic, unselected women for pre-eclampsia during the second and third trimesters of pregnancy. This combines maternal factors, uterine artery PI, MAP and serum PlGF, utilizing the competing-risks approach. It was developed in 7748 women attending a routine hospital visit at 19–24 weeks of gestation. The model predicted 99%, 85% and 46% of cases of pre-eclampsia with delivery at < 32, < 37 and ≥ 37 weeks, respectively, at a false-positive rate of 10%. This was superior to the predictive performance achieved using maternal factors alone, which predicted 52%, 47% and 37% of cases of pre-eclampsia with delivery at < 32, < 37 and ≥ 37 weeks, respectively[25].

This algorithm was further validated in a prospective follow-up study of 16 254 unselected women. The model identified 100% of cases of pre-eclampsia at < 32 weeks of gestation, compared with 35% identified when screening with maternal factors and MAP alone. It identified 90% of pre-eclamptic cases between 32 + 0 and 35 + 6 weeks. This indicates that assessment of risk for pre-eclampsia at 19–24 weeks of gestation can stratify the population into high-risk women, who are likely to develop pre-eclampsia at < 32 weeks and require intensive monitoring at 24–31 weeks, intermediate-risk women, who are likely to develop pre-eclampsia at 32–36 weeks and require reassessment at 32 weeks, and low-risk women, who require only standard antenatal care until 36 weeks[61].

A study assessing the sFlt-1/PlGF ratio as a screening test for pre-eclampsia in 4099 unselected, nulliparous women recruited to the Pregnancy Outcome Prediction (POP) study found that, at 28 weeks of gestation, a sFlt-1/PlGF ratio cut-off of > 38 demonstrated a similar PPV both in women with high and in those with low prior risk of disease (based on maternal factors or abnormal uterine artery PI at 20 weeks of gestation) (33% *vs* 31%; $P = 0.91$)[62]. Women who had a ratio > 85 had a nearly 60% risk of delivering preterm with pre-eclampsia. Among low-risk women at 36 weeks of gestation, a sFlt-1/PlGF ratio ≤ 38 had a NPV for severe late-onset pre-eclampsia of 99.2% (95% CI, 98.9–99.6%). These data demonstrate that measurement of the sFlt-1/PlGF ratio also provides clinically useful prediction of the risk of pre-eclampsia in women considered to be at low risk for developing the disorder. These authors also suggested that one strategy for reducing the burden of morbidity associated with pre-eclampsia could be to screen all nulliparous women at 36 weeks using maternal risk factors and the sFlt-1/PlGF ratio, increase surveillance in screen-positive women and, if necessary, induce labor before the development of severe disease[62]. However, prospective randomized controlled trials (RCTs) are needed to demonstrate that use of the ratio is capable of reducing morbidity and improving outcome.

With regards to risk assessment in the third trimester of pregnancy, the FMF have developed a risk algorithm for assessment at 35 + 0 to 36 + 6 weeks of gestation in a population of 13 350 women with singleton pregnancy attending for routine antenatal care. This model, which uses a combination of maternal factors, MAP, serum PlGF and sFlt-1, demonstrated 70% detection of term pre-eclampsia compared with detection of 28% of cases using maternal factors alone[63].

Interestingly, a study by Tan *et al.*[64] compared the predictive value of a model using a combination of maternal factors and serum PlGF and sFlt-1 with the performance of the sFlt-1/PlGF ratio alone in order to stratify asymptomatic unselected women into high-, intermediate- and low-risk groups during the third trimester of pregnancy. This prospective observational study, including 8063 women attending a routine third-trimester ultrasound scan at 31–34 weeks of gestation, demonstrated similar performance of the sFlt-1/PlGF ratio and the combined model for predicting pre-eclampsia with delivery < 4 weeks. The AUC was 0.988 (95% CI, 0.981–0.994) for the sFlt-1/PlGF ratio, compared with 0.987 (95% CI, 0.979–0.995) for the combined model. This demonstrates the equivalence of using either an algorithm incorporating PlGF and sFlt-1 or use of the sFlt-1/PlGF ratio for identifying women in the third trimester at high risk for developing pre-eclampsia with delivery within 4 weeks[64]. When screening for delivery with pre-eclampsia ≥ 4 weeks after assessment up to 40 weeks of gestation, the combined model demonstrated an AUC of 0.884 (95% CI, 0.854–0.914), compared with an AUC of 0.818 (95% CI, 0.775–0.860; $P < 0.0001$) for the sFlt-1/PlGF ratio in this unselected population[62].

The studies presented here indicate that these different risk-stratification strategies may show clinical value in predicting pre-eclampsia during the second and third trimesters of pregnancy. However, RCTs are needed to demonstrate improvement in maternal and neonatal outcome in high-risk and especially in low-risk populations.

Statement*

- A sFlt-1/PlGF ratio ≤ 38 can be used to rule out the occurrence of pre-eclampsia within 1 week in women with clinical signs and symptoms suggestive of pre-eclampsia. A sFlt-1/PlGF ratio ≥ 85 is useful to aid in the diagnosis of early-onset pre-eclampsia.
- Risk assessment should be performed during the second and third trimesters in all pregnant women irrespective of first-trimester screening results. Uterine artery Doppler measurement should be performed at 18–22 weeks of gestation.
- In asymptomatic women considered to be at high risk for pre-eclampsia based on either first-trimester screening or uterine artery Doppler at 18–22 weeks, the sFlt-1/PlGF ratio can be measured at 24–28 weeks.
- Alternatively, uterine artery Doppler measurements at 19–24 weeks can be combined with other investigative tools, including maternal factors, MAP and angiogenic biomarkers, as part of a risk-assessment algorithm, such as the FMF combined model. This assessment can be repeated at 30–34 and 35–37 weeks of gestation, depending on the patient's risk.
- Risk assessment should be performed in all pregnant women at 36 weeks of gestation, regardless of previous risk classification. This can be performed by measurement of the sFlt-1/PlGF ratio or by using a combined algorithm approach at 35–37 weeks of gestation.
- Women initially identified by first-trimester screening as being high risk for developing pre-eclampsia should be considered high risk for the duration of the pregnancy.
- Women initially classified as being low risk based on first-trimester screening, with abnormal uterine artery Doppler (PI > 95th percentile) at 18–22 weeks, or who are subsequently classified as high risk based on screening with the FMF algorithm at 19–24 weeks, should subsequently be classified as high risk and monitored accordingly.

*Diagnosis of pre-eclampsia should be made based on clinical criteria, according to appropriate guidelines. The decision to deliver the baby should not be based on the sFlt-1/PlGF ratio alone, but on the ratio in addition to standard diagnostic and clinical criteria.

Comprehensive approach to screening, prediction, prevention and management of pre-eclampsia from first to third trimester

This article has reviewed a number of different approaches founded on research that has improved our understanding of the pathogenesis of pre-eclampsia, allowing the development of predictive tools that can be used to prevent or better manage the disease. There is no single test that provides a solution for all forms of pre-eclampsia. Therefore, we propose a potential strategy for optimal management of pre-eclampsia throughout the clinical continuum (Figure 1). Individual sections of this process have been validated with various levels of evidence. Combined first-trimester screening has been shown to be effective at predicting early-onset pre-eclampsia in a number of large cohort studies and there is high-grade evidence from a RCT that aspirin given to high-risk women provides effective prophylaxis against this form of disease.

Whilst first-trimester prediction and prevention can have a significant impact on the prevalence of early-onset disease, it does not identify the majority of pregnancies that present with late-onset disease or modify the prevalence of term pre-eclampsia. Different approaches to screening through the second and third trimesters have been reported and, largely, these have not followed on from first-trimester prediction and prevention. These strategies have demonstrated the potential value of angiogenic biomarkers (sFlt-1 and PlGF) and sonographic markers (uterine artery Doppler) but it is not completely clear how high-risk pregnancies should be selected, what combination of tools are best used for risk prediction, what is the most appropriate gestational age for testing

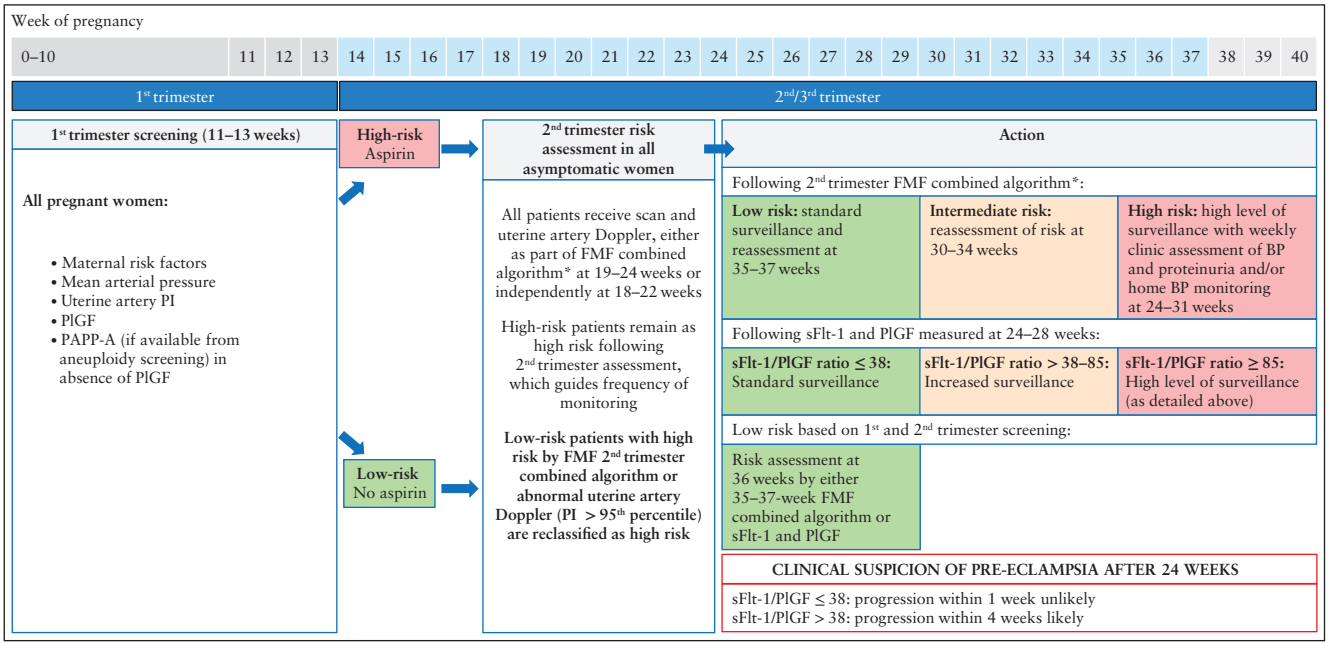

Figure 1 Proposed model linking screening, prediction and management of pre-eclampsia throughout pregnancy. *FMF combined algorithm for screening utilizes combination of maternal factors, uterine artery pulsatility index, mean arterial pressure and angiogenic biomarkers. BP, blood pressure; FMF, Fetal Medicine Foundation; PAPP-A, pregnancy-associated plasma protein-A; PI, pulsatility index; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

and whether management can be altered to improve maternal and neonatal outcome. To our knowledge, there have been no RCTs that have examined this pathway and such studies are urgently needed.

Data from several cohort studies have shown that the sFlt-1/PlGF ratio can be used to triage patients suspected through clinical review of having pre-eclampsia. Expert recommendations for the clinical value of such biomarkers, including indications for use, impact of test results on clinical management and cost-effectiveness analysis, have been developed. This is despite the fact that there has been no demonstration of improvement in clinical outcome. There is, therefore, an urgent need for prospective interventional trials investigating the usefulness of these biomarkers, alone or in combination with other predictive tools, in this situation.

Conclusions

Pre-eclampsia and associated hypertensive disorders of pregnancy are leading causes of maternal and perinatal morbidity and mortality worldwide and, currently, the only treatment is delivery. However, the ability to identify those women at high risk of developing preterm pre-eclampsia in early pregnancy, who would benefit from administration of low-dose aspirin, has the potential to reduce significantly the rate of preterm pre-eclampsia. In addition, follow-up of these women in the second and third trimesters of pregnancy, and effective risk stratification to identify women who require more intensive surveillance, will aid with early detection of pre-eclampsia, enabling referral to specialist centers and timely delivery and liaison with the neonatal team, if necessary. This is expected to improve clinical maternal and neonatal outcomes. Angiogenesis-related biomarkers – sFlt-1 and PlGF – have been shown to have clinical value, aiding in the prediction, diagnosis and risk stratification of pre-eclampsia. In this Opinion paper, we have outlined the evidence demonstrating the clinical value of sFlt-1 and PlGF, in combination with maternal factors and/or other biomarkers, throughout the duration of pregnancy. Based on the available evidence, we have outlined a potential model to link first-trimester screening for preterm pre-eclampsia with appropriate pre-eclampsia management strategies in the second and third trimesters of pregnancy. Further clinical trials are needed to demonstrate the benefits of such a strategy, in terms of perinatal and maternal risk reduction and resource optimization.

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