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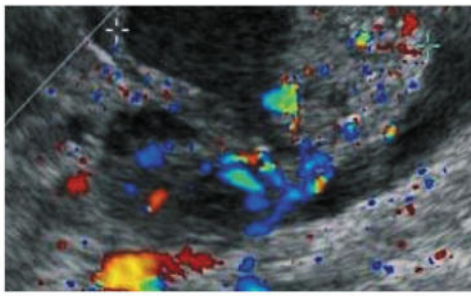

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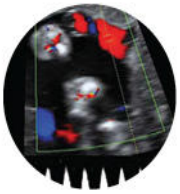

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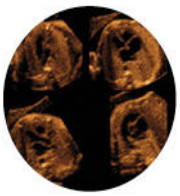

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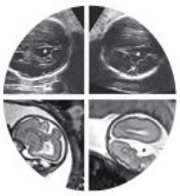

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From first-trimester screening to risk stratification of evolving pre-eclampsia in the second and third trimesters of pregnancy: a comprehensive approach

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ABSTRACT

Preeclampsia and associated hypertensive disorders of pregnancy represent a leading cause of global maternal and neonatal morbidity and mortality. Identification of women at high risk for developing preterm-preeclampsia and prophylaxis with low-dose aspirin has the potential to significantly reduce the rate of preterm-preeclampsia. In addition, risk assessment and monitoring of women in the second and third trimester of pregnancy, to aid in early detection of evolving disease, timely referral to specialist care, and active monitoring of women with confirmed or suspected preeclampsia is essential for improving maternal and neonatal outcomes. The angiogenesis-related biomarkers sFlt-1 and PlGF have been shown to have clinical value to aid in the prediction, diagnosis, and risk stratification of preeclampsia when used either alone or in combination with other risk factors. However, currently there is no consensus on the optimum strategy to link first trimester screening for preterm-preeclampsia with appropriate second and third trimester risk assessment strategies. This opinion paper will outline the current evidence for first trimester preeclampsia screening and prevention, as well as the evidence for various risk stratification approaches for detection of evolving preeclampsia through the second and third trimesters of pregnancy, and proposes a potential model integrating these tools.

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Introduction

Preeclampsia 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 preeclampsia include hypertension after 20 weeks of gestation, coupled with new onset of one or more of the following conditions: 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 preeclampsia, timely referral to specialist care, prophylaxis for preeclampsia prevention, early detection of disease and active monitoring of women with confirmed or suspected preeclampsia is essential for improving maternal and neonatal outcomes[4, 7]. However, the clinical presentation of preeclampsia is extremely variable. This impacts the specificity and reliability of clinical assessments for diagnosing preeclampsia and predicting its evolution[8].

Preeclampsia is defined as early-onset when it leads to delivery at <34 weeks of gestation and late-onset when it occurs ≥34 weeks of gestation. Preeclampsia is also sub-classified as preterm or term depending on whether the onset occurs <37 weeks or ≥37 weeks of gestation, respectively[9]. Sub-classification of preeclampsia is particularly important as early-onset preeclampsia is more likely to be associated with placental insufficiency than term-preeclampsia and, therefore, with potentially different clinical manifestations[10]. Although maternal morbidity is often more significant amongst women who have the early-onset subtype, late-onset preeclampsia can also manifest with severe complications for both the mother and fetus[11, 12].

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Placental dysfunction is associated with an imbalance of angiogenic and anti-angiogenic factors circulating in maternal blood, including placental growth factor (PlGF), and soluble fms-like tyrosine kinase 1 (sFlt-1)[13-15]. Circulating levels of the anti-angiogenic protein sFlt-1 are increased in women with preeclampsia, whilst levels of the pro-angiogenic factor PlGF are decreased before the onset of clinical disease[13, 14, 16, 17]. The ratio of sFlt-1/PlGF is also elevated in women with a confirmed diagnosis of preeclampsia and the value of the sFlt-1/PlGF ratio in short-term prediction in women with clinical suspicion of preeclampsia has also been demonstrated[18, 19]. Therefore, measurement of angiogenic markers either alone, or combined as part of the sFlt-1/PlGF ratio, have significant value in preeclampsia 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, uterine artery pulsatility index (PI) and angiogenic markers, such as PlGF, can effectively identify pregnancies that will go on to develop preterm-preeclampsia[21]. Furthermore, administration of low-dose aspirin to women identified as being high risk using this approach significantly reduces the rate of preterm-preeclampsia[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-preeclampsia[21, 23, 24]. However, it is important to recognize that this approach is less effective at predicting and preventing preeclampsia developing at >37 weeks of gestation[21, 23]. Prediction of both the development and evolution of late-onset preeclampsia 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

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pregnancy will 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 preterm-preeclampsia with appropriate second and third trimester strategies regarding prediction, early detection and likely evolution of preeclampsia. The aims of this opinion paper are to outline the current evidence for first trimester preeclampsia screening, the evidence supporting risk stratification through the second and third trimesters of pregnancy, and to propose a potential model linking these tools.

First trimester screening and prevention of preeclampsia

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

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significant underestimation of the number of women at risk of preterm-preeclampsia during the pregnancy who would otherwise benefit from aspirin prophylaxis[31]. Using a multivariate algorithm for first trimester screening has several advantages. Such an approach focuses screening assessment to the time point where 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[31-33].

Several groups have reported the efficacy of multivariate screening algorithms for prediction of preeclampsia, and the difficulties in developing and validating these tools have been discussed elsewhere[34]. One algorithm that is widely used and has been validated by other groups is produced by the Fetal Medicine Foundation (FMF). Poon et al. initially proposed this algorithm based on the use of a combination of maternal demographics, medical and obstetric history, mean uterine artery pulsatility index (PI), mean arterial pressure (MAP), and maternal serum levels of PlGF and pregnancy-associated plasma protein A (PAPP-A) between 11–13 weeks of gestation[35]. 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 preeclampsia at a 5% false-positive rate[35].

Subsequent iterations of the FMF algorithm have incorporated a competing-risk model that combines maternal factors and the aforementioned risk factors with the prior distribution of gestational age at delivery with preeclampsia and various combinations of biomarker MoM values. This is used to derive patient-specific risks of delivery with preeclampsia at

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<37 weeks of gestation. The current model was developed in a mixed population of 35,948 women with singleton pregnancies 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 early-onset preeclampsia, 75% of preterm-preeclampsia and 41% of term-preeclampsia, at a screen-positive rate of 10%[32, 36]. The model has been prospectively validated 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, 33].

Inclusion of serum PAPP-A did not improve the performance of the screening algorithm[36]. 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-preeclampsia[32].

Other groups have developed and validated algorithms that have similar forms and that are also freely available 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 preeclampsia in cohorts of 9462 and 4621 women[37, 38].

The role of aspirin in the prevention of preeclampsia has previously been the subject of much debate and the etiology of disease and mechanism of action of aspirin are still not completely understood[39]. The recent ASPRE trial was designed to investigate the effect of night-time administration of 150 mg of aspirin from $11–14^{+6}$ weeks until 36 weeks in pregnancies identified as high risk for preterm-preeclampsia using the FMF first trimester screening strategy. The first trimester screening algorithm detected 77% of cases of

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preterm-preeclampsia during the ASPRE study[21]. During the ASPRE trial 26,941 women with singleton pregnancy were screened and 2971 (11%) were determined to be at high risk of preeclampsia. Of the 798 women randomized to aspirin, 13 (1.6%) developed preeclampsia compared with 35 (4.3%) of the 822 women randomized to placebo. These results suggest that daily administration of 150 mg of aspirin significantly reduces the risk of developing preterm-preeclampsia by 62% (odds ratio [OR]=0.38; 95% confidence interval [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 very early-onset preeclampsia in the aspirin-treated group compared with placebo. However, it should be noted that only a very small number of cases with preeclampsia <34 weeks of gestation were observed[23]. Importantly, the beneficial effect of aspirin in the prevention of preterm-preeclampsia is dependent on patient compliance to the treatment regimen. Post hoc analysis of the data suggests that the reduction in preterm-preeclampsia may be ~75% if adherence to medication is ≥90%. However, when the proportion of prescribed tablets taken was <90%, risk reduction was only ~40% [40]. It is also worth noting that a further sub-analysis of the data found that the beneficial effect of aspirin in the prevention of preterm-preeclampsia did not apply in a subgroup of pregnancies with chronic hypertension[41].

A recent meta-analysis, including sixteen trials and a combined total of 18,907 participants, also demonstrated that administration of ≥100 mg aspirin at ≤16 weeks of gestation reduced the rate of preterm-preeclampsia by ~65%[42]. Although these studies indicate that the optimal time for initiating aspirin administration is ≤16 weeks of gestation, 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 preeclampsia (relative risk=0.81 [95% CI, 0.66–0.99]; 0.81 [95% CI, 0.63–1.03]; 0.9 [95% CI, 0.83–0.98])[43-45]. Further research is needed to

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investigate whether late administration of low-dose aspirin confers any benefit in the prevention of preeclampsia.

The data provided by these recent publications indicate that a strategy based on first-trimester screening of preeclampsia and administration of ≥100 mg per day of aspirin to high-risk women would be useful to reduce the risk of preeclampsia in these women. There is insufficient data to recommend stopping treatment earlier than 36 weeks. Implementation of first trimester prediction and prevention of early-onset preeclampsia is likely to be cost-effective, as the additional costs required to screen the population are recovered through a reduction in neonatal admission and in the length of stay in neonatal intensive care units[46, 47].

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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-preeclampsia in all pregnant women.
    - Other screening methods based on maternal history, such as those recommended by ACOG or NICE, are inferior regarding detection rate, and false-positive and -negative rate.
    - 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 11–14^{+6} weeks and concluding at 36 weeks.
- Universal prescription of aspirin to all pregnant women is not recommended.

Risk stratification and prediction of preeclampsia in the second and third trimesters of pregnancy

Women classified as high risk for developing preeclampsia based on first trimester screening need to be followed up regularly throughout pregnancy in order to ensure early detection of evolving preeclampsia and to monitor compliance to aspirin treatment. Regular antenatal pregnancy care is also important in women classified as low risk, as preeclampsia,

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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[48]. The evidence from several studies investigating the use of the sFlt-1 and PlGF biomarkers, the uterine artery PI, or the combination of maternal factors, uterine artery PI, MAP and serum biomarkers in the prediction of preeclampsia, as well as studies demonstrating the value of potential risk stratification algorithms, in women in the second and third trimesters of pregnancy are summarized below.

Predictive value of sFlt-1 and PlGF

Numerous studies have demonstrated the value of sFlt-1 and PlGF to aid in the short-term prediction, diagnosis and evolution of preeclampsia[49-53].

The use of the sFlt-1/PGF ratio for the diagnosis of early- and late-onset preeclampsia have been investigated. A multicenter case-control study including a total of 1149 women with singleton pregnancy compared 234 women with preeclampsia with a matched cohort of 468 women with normal pregnancy outcome[54]. Normal ranges for the sFlt-1/PlGF ratio throughout pregnancy were constructed. For the case-control study, visits from subjects at a gestational age of ≥20^{+0} weeks were included and sFlt-1 and PlGF measurements were taken at the first visit following confirmation of preeclampsia diagnosis. This study demonstrated that an sFlt-1/PlGF ratio ≥85 yielded a positive likelihood ratio (LR+) of 176 (95% CI, 24.88–1245) for the diagnosis of early-onset preeclampsia (20–33^{+6} weeks), whilst a ratio ≥110 resulted in a LR+ of 13 (95% CI, 7.34–23.0) for the diagnosis of late-onset preeclampsia (34^{+0} weeks)[54]. It is worth noting that the authors have used a different approach to data analysis to that described for first trimester screening; here they have used fixed, population based, analyte cut-offs to categorize patients as high or low risk.

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The PROGNOSIS study, 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 preeclampsia within 1 week and predict the presence of preeclampsia within 4 weeks in women with clinical suspicion of preeclampsia. This study included pregnant women ≥18 years of age at 24–36^{+6} weeks of gestation. Women with established preeclampsia were excluded from the study (Table 1). The prevalence of preeclampsia 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 an sFlt-1/PlGF ratio cut-off of ≤38 for ruling out the occurrence of preeclampsia within 1 week in women with signs and symptoms suggestive of preeclampsia. The positive predictive (PPV) value of an sFlt-1/PlGF ratio >38 for ruling in the occurrence of preeclampsia within 4 weeks was 36.7% (95% CI, 28.4–45.7). The PPV for the occurrence of a combined endpoint of preeclampsia/eclampsia/ hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome, maternal and/or fetal adverse outcomes 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 has also demonstrated that an sFlt-1/PlGF ratio of ≤38 can rule out preeclampsia within 4 weeks with an NPV of 94.3% (95% CI, 91.7–96.3)[55]. Evidence from this analysis also suggests that there is value in performing repeat measurements when using the sFlt-1/PlGF ratio. These data show that women who developed preeclampsia had a significantly larger median increase in the sFlt-1/PlGF ratio at 2 weeks (Δ31.22) and 3 weeks (Δ48.97) post-initial visit, compared with those who did not (Δ1.45 and Δ2.39, respectively; $p<0.001$)[55].

Subsequently, the PROGNOSIS Asia study has also demonstrated the value of the sFlt-1/PlGF ratio for the short-term prediction of preeclampsia in pregnant Asian women with

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suspected preeclampsia. The inclusion criteria for this study were similar to those used for the PROGNOSIS study (only severe persistent epigastric pain and new onset of visual disturbances were considered as potential preeclampsia-related symptoms). In this study an 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 preeclampsia within 1 week and a ratio >38 demonstrated a PPV of 30.3% (95% CI, 23.0–38.5) for ruling in preeclampsia within 4 weeks in a cohort of 700 evaluable women. The PPV for the occurrence of a combined endpoint of preeclampsia/eclampsia/HELLP syndrome, maternal and/or maternal or fetal adverse outcomes within 4 weeks was 65.0% (95% CI, 56.6–72.8)[56].

These studies indicate that sFlt-1 and PlGF represent valuable biomarkers for short-term prediction and detection of evolving preeclampsia in women with clinical signs and symptoms of the disorder, demonstrating a high NPV for ruling out preeclampsia, although the PPV remains limited. Use of these markers may aid clinicians in decision-making to help identify women who require intensive monitoring, instigate timely admission and administer necessary treatment. In particular, the ability to rule out evolving preeclampsia is of high clinical value. Indeed, NICE has been recommending the use of the sFlt-1/PlGF ratio, or the PlGF marker alone, to help rule out preeclampsia in women presenting with signs and symptoms of the disorder between 20–34^{+6} weeks of gestation since 2016[57]. A number of studies have examined the cost effectiveness of triaging women suspected of having preeclampsia with this test and have shown that adaptation of this tool potentially reduces the cost burden to the healthcare system[58, 59].

Risk stratification in asymptomatic 'high-risk' women

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Recent studies have attempted to investigate the performance of algorithms incorporating angiogenic biomarkers to stratify patient risk for developing preeclampsia 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 preeclampsia, it could be argued that monitoring should focus on disease occurring from 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 above) 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 preeclampsia are usually already apparent[13].

A recent study by Herraiz et al. investigated the value of a tiered risk stratification model in which asymptomatic women initially classified as low or high risk based on maternal factors were re-screened using uterine artery Doppler PI at 18–22 weeks of gestation[60]. Women considered to be high risk for the development of preeclampsia 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 preeclampsia and fetal growth restriction[60, 61]. Follow-up measurement of the sFlt-1/PlGF ratio at 24–28 weeks in women identified as high risk for developing preeclampsia demonstrated an area under the receiver operating characteristics curve (AUC) of 0.98 (95% CI, 0.97–1.00) for detecting early-onset preeclampsia 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)[61]. This approach to assessment appears to be very effective, providing an accurate assessment of

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the risk of developing early-onset preeclampsia and fetal growth restriction, 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 outcomes.

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 preeclampsia or who have no clinical suspicion of the disorder. The FMF provides an online algorithm for screening asymptomatic, unselected women for preeclampsia during the second and third trimesters of pregnancy. This combines maternal factors, uterine artery PI, MAP and serum PlGF utilizing the competing-risk 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 preeclampsia 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 preeclampsia 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 preeclampsia at <32 weeks of gestation, compared with 35% identified when screening with maternal factors and MAP alone. The model identified 90% of preeclamptic cases between 32^{+0} and 35^{+6} weeks. This indicates that assessment of risk for preeclampsia at 19–24 weeks of gestation can stratify the

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population into high-risk women, who are likely to develop preeclampsia at <32 weeks and requiring intensive monitoring at 24–31 weeks, intermediate-risk women, who are likely to develop preeclampsia between 32–36 weeks and require reassessment at 32 weeks, and low-risk women who only require standard antenatal care until 36 weeks[62].

A study assessing the sFlt-1/PlGF ratio as a screening test for preeclampsia in 4099 unselected, nulliparous women recruited to Pregnancy Outcome Prediction (POP) study found that, at 28 weeks of gestation, an sFlt-1/PlGF ratio cut-off of >38 demonstrated a similar PPV in women with both high and low prior risk of disease (based on maternal factors or abnormal uterine artery PI at 20 weeks of gestation) (33% versus 31%, respectively; p=0.91)[63]. Women who had a ratio of >85 had nearly 60% risk of delivering preterm with preeclampsia. Among low-risk women at 36 weeks of gestation, an sFlt-1/PlGF ratio ≤38 had an NPV for severe late-onset preeclampsia of 99.2% (95% CI, 98.9–99.6). These data have demonstrated that measurement of the sFlt-1/PlGF ratio also provides clinically useful prediction of the risk of preeclampsia in women considered to be at low risk for developing the disorder. These authors also suggest that one strategy for reducing the burden of morbidity associated with preeclampsia 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[63]. However, prospective randomized clinical trials (RCTs) are needed to demonstrate that the 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 35–36^{+6} weeks of gestation in a population of 13,350 women with singleton pregnancies attending routine antenatal care. This model, which uses a combination of maternal factors, MAP, serum PlGF and sFlt-1, demonstrated a 70%

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detection of term-preeclampsia compared with detection of 28% of cases using maternal factors alone[64].

Interestingly, a study by Tan et al. has 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[65]. This prospective observational study, including 8063 women attending a routine third trimester ultrasound scan at 31–34 weeks of gestation, demonstrated an analogous performance of the sFlt-1/PlGF ratio and the combined model for predicting preeclampsia 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 and the use of the sFlt-1/PlGF ratio for identifying women in the third trimester at high risk for developing preeclampsia with delivery within 4 weeks[65]. When screening for delivery with preeclampsia at ≥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.[63]

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

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- An sFlt-1/PlGF ratio cut-off of ≤38 can be used to rule out the occurrence of preeclampsia within 1 week in women with clinical signs and symptoms suggestive of preeclampsia. An sFlt-1/PlGF ratio ≥85 is useful to aid in the diagnosis of early-onset preeclampsia.
- Risk assessment should be performed during the second and third trimester 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 preeclampsia based on either first trimester screening or on 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 as high risk for developing preeclampsia by first trimester screening should be considered as high risk for the duration of the pregnancy.
- Women initially classified as low risk based on first trimester screening with an 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

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19–24 weeks, should subsequently be classified as high risk and monitored accordingly.

*Diagnosis of preeclampsia 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 in addition to standard diagnostic and clinical criteria.

A comprehensive approach to screening, prediction, prevention and management of preeclampsia from first to third trimester

This article has reviewed a number of translational processes founded on research that has improved our understanding of the pathogenesis of preeclampsia, 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 preeclampsia, therefore a potential strategy for optimal management of preeclampsia throughout the clinical continuum has been proposed (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 preeclampsia in a number of large cohort studies and there is high-grade evidence from an 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-preeclampsia. Different approaches to screening through the second and third trimesters have been reported, and these have largely not followed on from first trimester prediction and prevention. These

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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, the most appropriate gestational age for testing, or whether management can be altered to improve maternal and neonatal outcomes. To our knowledge there are no RCTs that have examined this pathway and these studies are urgently needed.

Data from several cohort studies has shown that the sFlt-1/PlGF ratio can be used to triage patients suspected of having preeclampsia through clinical review. 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 outcomes. Therefore, there is 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

Preeclampsia 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-preeclampsia in early pregnancy, who would benefit from administration of low-dose aspirin, has the potential to significantly reduce the rate of preterm-preeclampsia. In addition, follow-up of these women in the second and third trimester of pregnancy, and effective risk stratification to identify women who require more intensive surveillance, will aid with early detection of preeclampsia, referral to specialist centers and timely delivery and liaison with

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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 to aid in the prediction, diagnosis and risk stratification of preeclampsia. During 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 this available evidence, we have outlined a potential model to link first trimester screening for preterm-preeclampsia with appropriate preeclampsia management strategies in the second and third trimester 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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Figure legend

Figure 1: A proposed model linking screening, prediction and management of preeclampsia through all stages of pregnancy

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

* The FMF combined algorithm for screening utilizes a combination of maternal factors, uterine artery pulsatility index, mean arterial pressure and angiogenic biomarkers

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Table 1: Inclusion and exclusion criteria for the PROGNOSIS study[66]

Criteria contributing to the clinical suspicion of preeclampsia[a]

• New onset of elevated blood pressure[b]
• Aggravation of pre-existing hypertension
• New onset of protein in urine[c]
• Aggravation of pre-existing proteinuria
• Preeclampsia-related symptoms:
  o Epigastric pain
  o Excessive edema, severe swelling (face, hands, feet)
  o Headache
  o Visual disturbances
  o Sudden weight gain (>1kg per week in the third trimester)
• Preeclampsia-related findings:
  o Low platelets
  o Elevated liver transaminases
  o (Suspected) intrauterine growth restriction
  o Abnormal uterine perfusion detected by Doppler sonography with mean PI >95th percentile in the second trimester and/or bilateral uterine artery notching

Exclusion criteria
• Manifest preeclampsia   o Proteinuria ≥2+ by dipstick urinalysis (or ≥0.3 g protein/24 hours or ≥30 mg/dL protein in spot urine or spot urine protein/creatinine ratio ≥30 mg

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protein/mmol creatinine) AND reproducible elevated blood pressure (≥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 the 90 days prior to enrollment

HELLP, hemoylsis, elevated liver enzymes and low platelet count

[a]The presence of at least one of these clinical criteria for suspicion of preeclampsia was required for inclusion in the study.

[b]Not required to be defined hypertension (≥140 mmHg systolic and/or ≥90 mmHg diastolic)

[c]Not required to be defined proteinuria (any protein in the urine considered sufficient)

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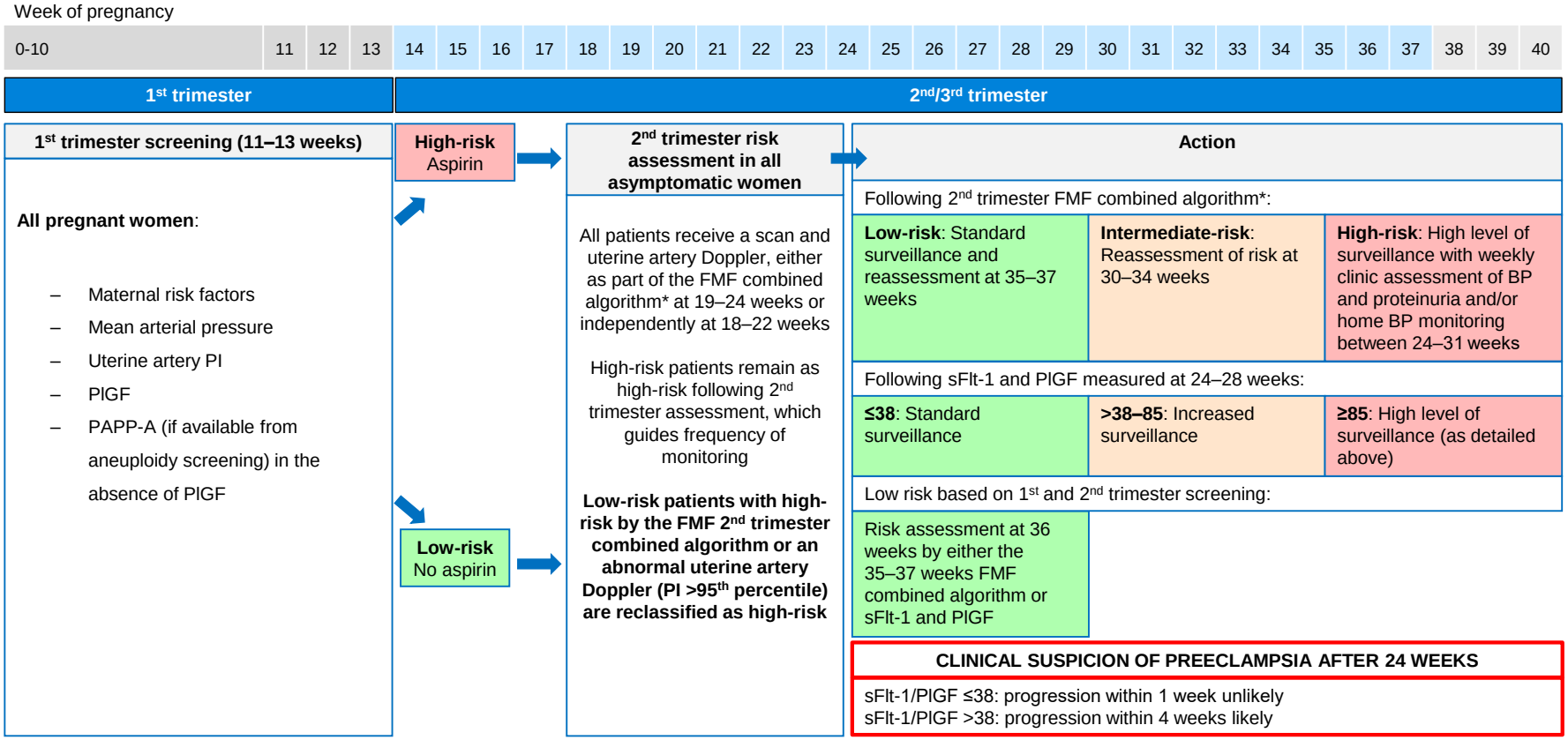

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