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Clinical utility of sFlt-1 and PlGF in screening, prediction, diagnosis and monitoring of pre-eclampsia and fetal growth restriction

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Abstract

Preeclampsia (PE) is characterized by placental and maternal endothelial dysfunction, and associated with fetal growth restriction (FGR), placental abruption, preterm delivery and stillbirth. The angiogenic factors soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF) are altered in pregnancies complicated by placental-related disorders. In this review, we summarize existing literature examining the performance of maternal PlGF, sFlt-1 and sFlt-1/PlGF ratio for a) screening and diagnosing PE, b) predicting PE development in the short term, c) monitoring established PE and d) predicting other placental-related disorders. We also discuss the performance of PlGF and the sFlt-1/PlGF ratio for predicting PE in twin pregnancies. For first trimester screening, a more accurate way of identifying high-risk women than current practices is to combine PlGF levels with clinical risk factors and ultrasound markers. To support diagnosis of PE later in pregnancy, the sFlt-1/PlGF ratio has advantages over PlGF because it has a higher pooled sensitivity and specificity for diagnosing and monitoring PE. The sFlt-1/PlGF ratio has clinical value because it can rule out the development of PE in the subsequent 1–4 weeks after the test. Once diagnosis of PE is established, repeated measurement of sFlt-1 and PlGF can help monitor progression of the condition and may inform clinical decision-making around optimal time for delivery. The sFlt-1/PlGF ratio is useful for predicting FGR and preterm delivery, but the association between stillbirth and the angiogenic factors remains unclear. The sFlt-1/PlGF ratio can also be used to predict PE in twin pregnancies, although different sFlt-1/PlGF ratio cut-offs to those of singleton pregnancies should be applied for optimal performance. In summary, PlGF, sFlt-1 and the sFlt-1/PlGF ratio are useful for screening, diagnosing, predicting, and monitoring placental-related disorders in singleton and twin pregnancies; we propose further integration of these angiogenic factor tests in clinical practice.

INTRODUCTION

Preeclampsia (PE) is a complex disorder characterized by poor placental function and maternal endothelial dysfunction (Figure 1).[1, 2] PE can deteriorate into eclampsia (a severe complication of PE, characterized by maternal seizures) or HELLP syndrome (maternal hemolysis, elevated liver enzymes and low platelet count), which are leading causes of maternal morbidity and mortality.[3-6] PE is also associated with adverse fetal outcomes, including fetal growth restriction (FGR), preterm delivery and stillbirth.[7, 8] Globally, PE is estimated to affect 2–8% of pregnancies and is responsible for >70,000 maternal deaths and >500,000 fetal deaths every year.[9, 10]

FGR is defined as the failure of the fetus to reach its genetically determined growth potential.[11] This condition is diagnosed using ultrasound, and is defined as an estimated fetal weight of <10th percentile for gestational age.[12, 13] FGR increases the risk of fetal morbidity and mortality and long-term ill health in adulthood.[12, 14-18] The main treatment for PE and/or FGR is delivery of the fetus and the pathological placenta, thus PE and FGR are among the leading causes of preterm delivery.[19]

PE rarely develops before 20 weeks' gestation, and is often classified as early-onset (<34 weeks' gestation) or late-onset (≥34 weeks' gestation).[20-22] Early-onset PE is associated with a higher risk of adverse maternal and fetal outcomes than late-onset PE.[23] PE symptoms include *de novo* hypertension, proteinuria and/or evidence of maternal acute kidney injury, pulmonary edema, liver dysfunction, neurological features, hemolysis, thrombocytopenia, or FGR.[22] Although there is no cure for PE, being able to effectively screen, diagnose, predict and monitor PE development is important as it allows for the implementation of preventative clinical management strategies.[24] For example, several studies have demonstrated that treating women who have a high risk of developing PE with low-dose aspirin starting early in pregnancy can reduce the risk of developing the preterm forms of the disease and associated adverse outcomes.[25-28]

The American College of Obstetricians and Gynecologists (ACOG), the National Institute for Health and Care Excellence (NICE) and the International Society for the Study of Hypertension in Pregnancy (ISSHP) recommend screening pregnant women for PE in the first trimester based on the following maternal risk factors: diagnosed with PE or hypertension in a previous pregnancy; having chronic hypertension or kidney disease; having pre-pregnancy diabetes mellitus or autoimmune disease; primiparity or multiple pregnancy or pregnancy being conceived by assisted reproductive technology; mother aged >35 years or having a pre-pregnancy body mass index of >30 kg/m^2; pregnancy interval of >10 years; or a family history of PE (Table 1).[10, 23, 29-31] These organizations further advise that high-risk women are offered low-dose aspirin to try to prevent the onset of PE (Table 1).[10, 23, 31] It is recommended that women with a diagnosis of PE are monitored closely for the development of severe PE, eclampsia and HELLP syndrome and their fetuses should be monitored for the development of FGR.[22]

Certain circulating maternal blood pro-angiogenic and anti-angiogenic factors, such as placental growth factor (PlGF) and soluble fms-like tyrosine kinase 1 (sFlt-1), respectively, are altered in pregnancies complicated by PE, FGR, preterm delivery and stillbirth.[11, 32-38] Altered levels of sFlt-1 and PlGF are observed when abnormal placentation occurs, leading to insufficient remodeling of maternal spiral arteries and placental ischemia.[11, 32] The hypoxic placenta releases elevated concentrations of anti-angiogenic factors, such as sFlt-1, to promote peripheral vasoconstriction and raise maternal blood pressure, increasing the flow of oxygenated maternal blood through the intervillous space.[39] Meanwhile, concentrations of pro-angiogenic factors, such as PlGF, are substantially reduced due to inhibition by sFlt-1.[39] The imbalance of sFlt-1 and PlGF contributes to the clinical manifestation of PE, and alterations in these angiogenic factors can often be detected before the onset of clinical symptoms.[11, 32-38] According to the 2021 ISSHP guidelines, angiogenic imbalance (i.e. an increased maternal sFlt-1/PlGF ratio or decreased maternal PlGF) is a diagnostic criterion for *de novo* PE, where maternal and fetal outcomes differ considerably to preeclampsia

superimposed on chronic hypertension.[40] Therefore, gestational hypertension combined with uteroplacental dysfunction, e.g. angiogenic imbalance, is defined as *de novo* PE.[10] The NICE 2016 guidelines, the Danish Society for Obstetrics and Gynecology 2018 guidelines, the European Society of Cardiology 2018 guidelines, the German Society of Obstetrics and Gynecology, the Austrian Society of Obstetrics and Gynecology, the Swiss Society for Obstetrics and Gynecology 2019 guidelines and the Spanish Society of Gynecology and Obstetrics 2020 guidelines recommend measuring the maternal sFlt-1/PlGF ratio to help diagnose and/or predict PE development.[41-45]

The purpose of this review is to summarize the existing literature examining the performance of maternal sFlt-1 and PlGF levels and the sFlt-1/PlGF ratio in PE.

Angiogenic imbalance underlying PE and placental-related disorders

sFlt-1 is an anti-angiogenic factor that is important for the regulation of angiogenic homeostasis during pregnancy.[1] sFlt-1 concentration steadily increases during the third trimester but increases prematurely in women who go on to develop PE and in women with pregnancies complicated by FGR.[46] Circulating maternal sFlt-1 has been reported to increase approximately 5 weeks before the onset of symptoms.[46] sFlt-1 binds to PlGF, and a recent study suggests that lower circulating levels of PlGF are largely mediated by excess circulating sFlt-1.[47] PlGF is a pro-angiogenic factor that is expressed in the placenta and enhances the actions of vascular endothelial growth factor-A (VEGF-A), which is essential for placental vascular development.[1] Maternal PlGF concentration increases initially, peaking in mid-gestation and then gradually decreases toward term.[46, 48] This decrease in PlGF concentration is known to occur prematurely in women who go on to develop PE and is often detectable before the onset of symptoms.[37] Increasing levels of sFlt-1 and decreasing levels of PlGF result in an increasing sFlt-1/PlGF ratio, thus the sFlt-1/PlGF ratio can be a useful tool for predicting and/or diagnosing placental-related disorders, including PE, FGR, stillbirth and preterm birth.[49] Other anti-angiogenic factors, such as soluble endoglin, have previously been investigated as biomarkers for diagnosis and prediction of PE, but have not been implemented in clinical practice.[46, 50]

Using PlGF in the first trimester to screen for PE

A key objective of first trimester screening is to identify women at high risk of developing PE later in pregnancy so that suitable preventative strategies can be put in place. At present, many centers do not use a combined first-trimester screening approach.[20] Identification of women at high risk of developing PE is often based on assessment of clinical risk factors only, as recommended by the ACOG 2018 and NICE 2019 guidelines.[29, 31] Combining clinical risk factors, maternal blood pressure (including mean arterial pressure [MAP]), mean uterine artery pulsatility index (MUTPI) measurements, and maternal angiogenic biomarkers into an algorithm may be a more accurate way of identifying high-risk women.[20, 51]

One of the most robust PE screening algorithms has been developed by the Fetal Medicine Foundation (FMF) and uses a combination of clinical risk factors, maternal age, MAP and MUTPI measurements and maternal PlGF to identify high-risk women in the first trimester (Figure 2).[20, 52-54] The FMF algorithm was initially developed in almost 36,000 pregnant women attending a UK hospital and has since been validated in two large multicenter trials.[20, 28, 53] The FMF algorithm for screening for PE can also be adapted for use later in pregnancy to assess the risk of developing the disease based on a combination of clinical risk factors, maternal age, MAP, MUTPI, and maternal PlGF measurements.[52] The International Federation of Gynecology and Obstetrics recommends that all pregnant women should be screened for PE early in pregnancy by assessing both clinical risk factors and maternal biomarkers.[7]

sFlt-1 is not useful for screening for PE during the first trimester, as levels of sFlt-1 only begin to increase at 21–24 weeks of gestation in women who go on to develop PE.[46]

Using PlGF to diagnose and predict PE in the second and third trimester

The normal decrease in maternal PlGF levels toward the end of pregnancy often occurs prematurely in women who develop PE; therefore, regular measurement of maternal circulating PlGF levels may

help to diagnose PE promptly and before clinical onset of the disease.[37, 55] In support of this, a meta-analysis of 40 studies (3189 cases of PE *vs* 89,498 pregnant controls at <14 weeks, ≥14 weeks or ≥19 weeks to term) reported that low maternal PlGF levels of 80–120 pg/mL were able to diagnose PE with a pooled sensitivity of 78%, a pooled specificity of 88%, a pooled positive likelihood ratio of 6.3 and a pooled negative likelihood ratio of 0.26 (Table 2).[37]

In addition, the prospective, multicenter PETRA trial reported that low PlGF levels (≤100 pg/mL) in women presenting at <35 weeks' gestation with suspected PE had a sensitivity of 76%, a specificity of 69% and a negative predictive value (NPV) of 53% for predicting a final diagnosis of PE at any time.[35] A secondary analysis of the PETRA trial showed that low PlGF levels (≤100 pg/mL) were significantly associated with increased risk for a composite maternal adverse outcome compared with normal PlGF levels (6.2% *vs* 1.9%), and had a sensitivity and specificity of 86.8% and 34.3%, respectively, for predicting a composite maternal outcome.[56]

Low maternal PlGF levels can also predict the development of PE in women with suspected PE. The prospective, multicenter PELICAN study showed that, for 287 women presenting at <35 weeks' gestation with suspected PE, a PlGF concentration of <5th percentile for gestation had a sensitivity of 96%, a specificity of 55% and an NPV of 98% for predicting the development of PE requiring delivery within the next 14 days (Table 2).[48] In the same cohort of women, a PlGF concentration of <100 pg/mL predicted PE requiring delivery within 14 days with a sensitivity of 96%, a specificity of 56% and an NPV of 98% (Table 2).[48]

To assess the diagnostic accuracy of PlGF measurements in a real-world setting, the PARROT trial examined whether knowledge of the woman's PlGF concentration decreased the time taken by clinicians to diagnose PE in women with suspected PE.[55] In this study, 11 maternity units were assigned to blocks that represented an intervention initiation time that occurred at 6-week intervals throughout the trial; the units were assigned either to the intervention group or to receive usual

care with additional concealed testing depending on their allocated block.[55] The study found that the availability of the PlGF test result significantly reduced the median time for clinical confirmation of PE from 4.1 to 1.9 days (*P*=0.027) and significantly lowered the incidence of severe maternal adverse outcomes (as defined by the fullPIERS consensus*, P*=0.043) but did not significantly alter adverse fetal outcomes.[55] In addition, no differences between groups in gestational age at delivery were observed in this study (mean difference = 0.52 weeks).

Using the sFlt-1/PlGF ratio to diagnose and predict PE in the second and third trimester

Several cut-off thresholds for the sFlt-1/PlGF ratio have been established using receiver operating characteristic (ROC) analysis (Table 2). Verlohren *et al*. validated a set of gestational dependent cut-offs for the diagnosis of PE.[57] For early-onset PE (<34 weeks' gestation), an sFlt-1/PlGF ratio cut-off of ≤33 ruled out PE at the time of the test with a sensitivity of 95.0% and a specificity of 94.0%, and a cut-off of ≥85 diagnosed PE with a sensitivity of 88.0% and a specificity of 99.5%. For late-onset PE (≥34 weeks' gestation), an sFlt-1/PlGF ratio cut-off of ≤33 ruled out PE at the time of the test with a sensitivity of 89.6% and a specificity of 73.1%, and a cut-off of ≥110 diagnosed PE with a sensitivity of 58.2% and a specificity of 95.5%. Later, Herraiz *et al*. reported that using an sFlt-1/PlGF ratio cut-off of >95th percentile at 24–28 weeks' gestation identified 100% of the women at high risk of PE who went on to develop the early-onset form of the disease in a prospective, observational study of 5601 pregnant women (Table 2).[13]

Employing the sFlt-1/PlGF ratio can also predict the development of PE and/or adverse fetal outcomes in the short term in women with suspected PE. PROGNOSIS was a prospective study conducted at 30 sites across 14 countries and recruited women with suspected PE at 24+0–36+6 weeks' gestation.[58] The study validated an sFlt-1/PlGF ratio cut-off of ≤38 for ruling out the development of PE within 1 week of the test with a sensitivity of 80.0%, a specificity of 78.3% and an NPV of 99.3% (Table 2). The study also showed an improvement in prediction, compared with clinical variables, of an sFlt-1/PlGF ratio cut-off of >38 for ruling in the development of PE within 4 weeks of

the test with a sensitivity of 66.2%, a specificity of 83.1% and a positive predictive value (PPV) of 36.7% (Table 2). These sFlt-1/PlGF ratio cut-offs were then validated in 764 pregnant Asian women in the PROGNOSIS Asia study (Table 2).[59] Zeisler *et al*. later carried out exploratory post-hoc analysis of the data collected during the PROGNOSIS study and reported that applying an sFlt-1/PlGF ratio cut-off of ≤38 ruled out the onset of PE for up to 4 weeks with a high NPV of 94.3% (Table 2).[60] Moreover, the INSPIRE trial reported that clinical examination combined with an sFlt-1/PlGF ratio of >38 was able to identify 100% of the women who developed PE in the subsequent week and post-hoc analysis found that an sFlt-1/PlGF ratio of ≥85 was able to rule in PE developing within the next 4 weeks with a PPV of 71.4% (Table 2).[61, 62]

In a prospective pilot study that included 50 pregnant women at risk for developing PE, Soundararajan *et al*. found that women with a high-risk sFlt-1/PlGF ratio (>85) were more likely to have PE with severe features (90.9% *vs* 8.00%, *P*<0.001), a higher composite maternal adverse outcome rate (18.2% *vs* 0%, *P*=0.04), and to deliver at an earlier gestational age (32.6 *vs* 37.4 weeks, *P*=0.001) compared with women with a low-risk sFlt-1/PlGF ratio (<33).[63] Similarly, Leaños-Miranda *et al*. reported that pregnant women with PE who had a severe imbalance of angiogenic factors (sFlt-1/PlGF ratio ≥85) had significantly higher rates of preterm delivery, delivery within 14 days of the test, and infants that were small for gestational age (SGA) compared with women with PE who had no imbalance (sFlt-1/PlGF ratio ≤38) or a mild imbalance (sFlt-1/PlGF ratio >38–<85) of angiogenic factors (*P*<0.001).[64] Indeed, Tan *et al*. reported that screening for delivery due to PE within 4 weeks of assessment at 31–34 weeks' gestation by combining maternal risk factors with sFlt-1 and PlGF values performed similarly to using the sFlt-1/PlGF ratio alone.[65]

The sFlt-1/PlGF ratio has been shown to have a similar sensitivity to PlGF for prediction and diagnosis of PE, but a higher specificity (Table 2).[37, 58-62, 66-68] Consequently, many of the current guidelines recommend using the sFlt-1/PlGF ratio to aid in the diagnosis of PE.[10, 41-45]

Using PlGF and the sFlt-1/PlGF ratio to monitor disease progression in established PE

Following a diagnosis of PE, monitoring maternal sFlt-1 and PlGF levels may help to predict the interval between diagnosis of PE and delivery, which would allow for the implementation of clinical management strategies. In a secondary analysis of an observational cohort study, Zeisler *et al*. investigated the correlation between the sFlt-1/PlGF ratio and the time to delivery and reported that women with suspected PE at 24+0–36+6 weeks' gestation had a 2.9 fold greater likelihood of imminent delivery (i.e., delivery on the day of the test) if their sFlt-1/PlGF ratio was >38, when compared with pregnant women with lower sFlt-1/PlGF ratios.[69] The sFlt-1/PlGF ratios determined in the primary analysis were not available to investigators or patients until study completion; as such, the results did not influence clinical decision-making.[58]

In addition, several studies have taken serial measurements of sFlt-1/PlGF ratios once PE has been diagnosed to examine the time between diagnosis and delivery. Baltajian *et al*. conducted an observational study in which sFlt-1 and PlGF concentrations were recorded weekly from admission to delivery in pregnant women admitted to hospital with suspected PE; the mean number of days from admission to delivery was six (range: 0–35) for women with an sFlt/PlGF ratio ≥85 at admission and 14 (range: 0–39) for women with an sFlt/PlGF ratio <85 at admission (P<0.001).[70] In addition to shorter time to delivery, the rate of increase in anti-angiogenic state was more pronounced in women with adverse outcomes compared with those without adverse outcomes.[70] Similarly, Schaarschmidt *et al*. took serial measurements of sFlt-1 and PlGF from women with confirmed early-onset PE and confirmed late-onset PE from admission until delivery.[71] Compared with those who had late-onset PE, women with early-onset PE had greater daily increases in sFlt-1 levels (11% *vs* 3% per day, respectively, P<0.05), greater daily decreases in PlGF levels (21% *vs* 10% per day, respectively, P=0.30) and much higher daily increases in the sFlt-1/PlGF ratio (23% *vs* 8% per day, respectively, P<0.05). Likewise, Peguero *et al*. measured sFlt-1 and PlGF levels in women with confirmed early-onset PE at admission and just before delivery and reported that longitudinal changes in maternal

sFlt-1 levels were more pronounced in pregnancies with early-onset severe PE *vs* uncomplicated pregnancies (median increase: 1047 *vs* 342 pg/mL/day, respectively; *P*=0.04) and the median time from admission to delivery was shorter (4 days *vs* 16 days, respectively).[72] Daily increments in the sFlt-1 and sFlt-1/PlGF ratio values measured following PE diagnosis were associated with shorter time to delivery, and women with steeper increases in sFlt-1 had a significantly shorter time to delivery (*P*<0.001), with earlier gestational age at delivery.[72] In a cohort of 84 women diagnosed with PE before 37 weeks' gestation, Meler *et al*. reported very low PlGF levels (<12 pg/mL) in 87.5% of women diagnosed before 28 weeks' gestation, 78.4% of women diagnosed between 28 and 32 weeks' gestation, and 41% of women diagnosed after 32 weeks' gestation, with a sensitivity of 76.9% and NPV of 76.9% for predicting maternal complications.[73] Importantly, in some cases of severe or early-onset PE, PlGF concentrations may be lower than the detection limit of many commercially available PlGF assays (1.9–9 pg/mL); therefore, measurement of PlGF alone may not be a useful tool for prognosis of early-onset PE.[41, 73] However, these findings support the characterization of PE as a progressive disorder.[71]

PE is frequently accompanied by adverse maternal and fetal outcomes. The fullPIERS model can help to determine which women with confirmed PE will have adverse maternal outcomes and is designed to be used at any stage of pregnancy.[29] The model is based on a combination of maternal risk factors and clinical findings including gestational age, presence of chest pain or dyspnea, oxygen saturation, platelets, creatinine and aspartate transaminase/alanine aminotransferase ratio.[74] The fullPIERS model has been validated in several populations and is currently recommended by NICE guidelines.[29] Ukah *et al*. assessed whether adding maternal PlGF concentration improved the performance of the fullPIERS model; the study reported an area under the curve (AUC) of 0.67 (95% confidence interval [CI], 0.58–0.76), lower than that previously reported for the fullPIERS model alone (AUC >0.75).[75] Median gestational age at delivery was lower in the extension cohort, for which maternal PlGF concentrations were available, compared with the original fullPIERS cohort (33.9 *vs* 36.9 weeks).[75]

Nevertheless, a Spanish multicenter study demonstrated that using an algorithm based on maternal PlGF levels to determine the optimal delivery time for women with late-onset preterm PE resulted in a lower rate of progression to severe PE (adjusted relative risk [ARR] = 0.5; 95% CI, 0.33–0.76; *P*=0.001) without an increase in neonatal morbidity (ARR = 0.77; 95% CI, 0.39–1.53; *P*=0.45).[76] In this study, median gestational age at delivery was the same in the revealed cohort, in which deliveries were planned based on maternal PlGF concentrations, compared with the concealed cohort, in which deliveries were managed under standard of care (37 *vs* 37 weeks).[76]

Using PlGF and the sFlt-1/PlGF ratio to predict FGR

Placental dysfunction is associated with FGR and often occurs alongside PE.[13] Pregnancies that result in FGR have a similar angiogenic factor profile to pregnancies complicated by PE.[38] They are characterized by low levels of PlGF throughout pregnancy, particularly in the first trimester, and higher median sFlt-1/PlGF ratios than gestation-matched pregnancies; therefore, knowledge of maternal sFlt-1 and PlGF levels may help predict which pregnancies will be complicated by FGR.[11, 33, 38, 77] Importantly, the sFlt-1/PlGF ratio reflects the degree of placental dysfunction alone and cannot differentiate fully between different clinical presentations of placental dysfunction, such as PE and FGR. Additional tools, such as ultrasound, biophysical methods, and additional biomarkers, are required to make a differential diagnosis.

In a study that examined 47 biomarkers, maternal PlGF levels were the best predictor of delivery of an SGA neonate (defined in this study as both constitutionally small and pathologically small [FGR] neonates) in women presenting at 20+0–34+6 weeks' gestation with suspected PE.[78] Low maternal PlGF concentrations (<100 pg/mL) had a sensitivity of 93.2% and an NPV of 89.7% for predicting an SGA fetus, outperforming ultrasound prediction, which yielded a sensitivity of 71.2% (95% CI, 57.9–82.2%) and an NPV of 78.5% (95% CI, 67.8–86.9%).

An elevated sFlt-1/PlGF ratio has been reported in pregnancies complicated by FGR and are particularly elevated in cases of early-onset or severe FGR.[11, 79] The sFlt-1/PlGF ratio was shown to perform similarly to PlGF levels for predicting adverse outcomes, including FGR, in a systematic review of 33 studies.[80] Moreover, an observational study of pregnancies complicated by early-onset FGR reported that an elevated sFlt-1/PlGF ratio (>38) could be measured from 4 weeks before delivery in most (73%) of the cases of FGR included in the study; extreme sFlt-1/PlGF ratio values (≥655) could be measured in the 48 hours before delivery in 65% of the pregnancies complicated by FGR and PE, but in only 8% of pregnancies complicated by FGR only.[36]

Combining the sFlt-1/PlGF ratio with other clinical investigations can also help predict FGR. Gaccioli *et al*. reported that combining ultrasound measurements of the fetus with the sFlt-1/PlGF ratio at 28 weeks' gestation (using a cut-off of >5.78) provided a positive likelihood ratio for premature delivery of an SGA fetus of 41.1, with a sensitivity of 38.5% and a specificity of 99.1% (Table 2).[81] Combined ultrasonic estimated fetal weight and sFlt-1/PlGF ratio screening provided a higher positive likelihood ratio (41.1 *vs* 5.9) and higher specificity (99.1% *vs* 92.2%) for predicting premature delivery of an SGA fetus compared with ultrasonic estimated fetal weight alone, but lower sensitivity (38.5% *vs* 46.2%).[81] Furthermore, in a real-world data analysis of women with symptoms of PE, an AUC of 88.7% was obtained for prediction of maternal and/or fetal adverse outcomes, where the sFlt-1/PlGF ratio was combined with all available clinical information.[82] Notably, Ciobanu *et al*. reported that the addition of PlGF, sFlt-1, MUTPI, umbilical artery pulsatility index and fetal middle cerebral artery pulsatility index, to maternal factors and fetal biometry only marginally improved the predictive performance for the delivery of an SGA neonate compared with maternal factors and fetal biometry alone.[83]

Using PlGF and the sFlt-1/PlGF ratio to predict preterm delivery

Both PlGF and the sFlt-1/PlGF ratio have been examined for their association with spontaneous and iatrogenic preterm delivery. In women presenting with suspected PE at 20+0–35+0 weeks' gestation,

low maternal PlGF levels strongly correlated with early delivery.[35] Specifically, a maternal PlGF concentration of ≤100 pg/mL predicted preterm delivery with a sensitivity of 81.0% and a specificity of 85.3% (Table 2). A PlGF level within normal range (>100 pg/mL) was associated with pregnancy progressing closer to term, even if the women went on to develop PE. Similarly, Salahuddin *et al*. assessed the association between maternal sFlt-1 and PlGF levels and adverse maternal and fetal outcomes, including premature delivery, in 412 pregnant women with suspected PE and 434 pregnant women without PE.[84] The study reported that women who had an adverse outcome had a significantly higher sFlt-1, a significantly lower PlGF and consequently, a significantly higher sFlt-1/PlGF ratio than women who did not. The sFlt-1/PlGF ratio also negatively correlated with the timing of delivery. Consistent with the two aforementioned studies, Rana *et al*. reported that an sFlt-1/PlGF ratio cut-off of ≥85 yielded a sensitivity of 72.9% and a specificity of 94.0% for the development of a range of adverse pregnancy outcomes, including preterm delivery, in women at <34 weeks' gestation.[85] During the study, delivery occurred within 2 weeks of admission in 86.0% of women with an sFlt-1/PlGF ratio of ≥85 compared with only 15.8% of women with an sFlt-1/PlGF ratio <85 (hazard ratio = 15.2; 95% CI, 8.0–28.7). Similarly, in a population of pregnant women with chronic hypertension, Heimberger *et al*. reported that women with an sFlt-1/PlGF ratio ≥85 had a higher prevalence of preterm delivery compared with those with an sFlt-1/PlGF ratio <85.[86]

Using PlGF and the sFlt-1/PlGF ratio to predict stillbirth

The association between maternal angiogenic factors and the risk of stillbirth has been examined in several systematic reviews but remains unclear. Heazell *et al*. performed a systematic review of 21 studies including 100,687 pregnancies involving 740 stillbirths and reported that, of the four biochemical tests examined (PlGF, human placental lactogen, estriol and uric acid), PlGF was the most accurate at predicting stillbirth, with a diagnostic odds ratio (OR) of 49.2 (95% CI, 12.7–191).[87] Conversely, a systematic review performed by Townsend *et al*. reported that maternal age, parity and prior adverse pregnancy outcome were better predictors of stillbirth than any of the biomarker

tests examined, including PlGF.[88] However, in a systematic review of 12 studies including 71,668 women, Jacobs *et al.* reported no clear evidence for a consensus between sFlt-1 levels in the first trimester and adverse pregnancy outcomes.[89]

Using PlGF and the sFlt-1/PlGF ratio to predict complications in twin pregnancies

Women with twin pregnancies are more likely to develop PE than women with singleton pregnancies (OR 4.07; 95% CI, 3.65–4.54).[90] sFlt-1, PlGF and the sFlt-1/PlGF ratio have demonstrated utility in predicting PE or predicting delivery due to PE in twin pregnancies.[91, 92] In a European multicenter study of 49 twin pregnancies and 292 gestation-matched singleton pregnancies, it was observed that women with twin pregnancies complicated by PE had a similar angiogenic factor profile to that of women with singleton pregnancies complicated by PE; however, ROC analysis provided an optimal sFlt-1/PlGF ratio cut-off of 53 for diagnosing PE in twin pregnancies.[92] Applying this cut-off resulted in a sensitivity of 94.4% and specificity of 74.2% for diagnosing PE in twin pregnancies, whereas applying the singleton cut-off values of 33 and 85 gave sensitivities of 100% and 83.3% and specificities of 67.7% and 80.6%, respectively. Conversely, in a retrospective study of 164 twin pregnancies with suspected PE, an sFlt-1/PlGF ratio cut-off of <38 was used to rule out delivery due to PE within 1 week with an NPV of 98.8% and within 2 weeks with an NPV of 96.4%.[91] Furthermore, De La Calle *et al*. analyzed data from three prospective studies (PROGNOSIS, STEPS, and a multicenter case-control study) and reported that reference ranges for the sFlt-1/PlGF ratio were comparable in twin and singleton pregnancies until 29 weeks' gestation, but were then higher in twin pregnancies until birth.[57, 58, 68, 93-95]

Hayes-Ryan *et al*. reported that women with twin pregnancies who developed PE have significantly lower PlGF levels compared with controls across all gestational intervals from 12+0 to 36+6 weeks' gestation.[96] Moreover, this difference can be observed several weeks before the onset of clinical symptoms of PE.[96] Dröge *et al.* also reported significantly lower PlGF levels in women with twin pregnancies who developed PE compared with controls ($P \leq 0.001$), in addition to significantly lower

PlGF levels in women with twin pregnancies who developed PE compared with singleton pregnancies who developed PE ($P \leq 0.001$).[92] Therefore, measurement of PlGF alone may have potential as an aid in predicting PE in women with twin pregnancies.

sFlt-1, PlGF and the sFlt-1/PlGF ratio have also been examined for their association with adverse maternal and fetal outcomes in twin pregnancies. Rana *et al*. reported that the angiogenic factor profile was altered in women with twin pregnancies who had subsequent adverse outcomes when compared with those who did not; the median [25th–75th percentile] sFlt-1 level was elevated (11,461.5 pg/mL [8794.0–14,847.5] *vs* 7495.0 pg/mL [3498.0–10,482.0], respectively, P=0.0004), the median PlGF level was reduced (162.5 pg/mL [98.0–226.5] *vs* 224.0 pg/mL [156.0–449.0], respectively, P=0.005) and the median sFlt-1/PlGF ratio was elevated (74.2 [43.5–110.5] *vs* 36.2 [7.1–71.3], respectively, P=0.0005).[97]

CONCLUSIONS

Maternal PlGF, sFlt-1 and the sFlt-1/PlGF ratio show good performance for screening and diagnosing PE, for predicting PE development in the short term, for monitoring established PE and for predicting other placental-related disorders. In particular, the sFlt-1/PlGF ratio is clinically useful in guiding management of pregnant women with unclear symptoms of PE, as it has a high NPV and can therefore rule out PE in the subsequent 1–4 weeks. The sFlt-1/PlGF ratio also shows good performance for predicting PE in twin pregnancies. The sFlt-1/PlGF ratio may be preferred over PlGF alone because PlGF decreases with disease severity and in cases of severe or early-onset disease, PlGF concentrations may be lower than the detection limit of commercially available PlGF assays. In cases of early-onset PE, measurement of PlGF alone is not a useful tool and may limit monitoring of disease progression. There remains a need for further integration of tests for these angiogenic factors in clinical practice.

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Author contributions

All authors proposed the concept and/or content of this review, provided references for inclusion, contributed to the writing, editing and/or critical review, and approved the final version for submission.

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FIGURE LEGENDS

Figure 1 Pathophysiology and features of PE[1, 2]

PE is associated with placental dysfunction and altered maternal sFlt-1 and PlGF concentrations. PE can result in a range of adverse maternal outcomes including maternal hypertension, proteinuria, cerebral edema and liver dysfunction, and a range of adverse fetal outcomes including fetal growth restriction, prematurity and stillbirth.

AT1-AAs, agonistic angiotensin II type 1 receptor autoantibodies; NK, natural killer cells; PE, preeclampsia; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase 1. This figure was adapted from Stepan et al. 2020, and originally printed by Wang et al. 2009.

Figure 2 Proposed model for screening, prediction, and monitoring PE in pregnant women[20]

*FMF combined algorithm for the early identification of women with a high risk of developing PE. The algorithm uses a combination of maternal factors, uterine artery PI, mean arterial pressure and angiogenic factors to create an individualized risk score. BP, blood pressure; FMF, Fetal Medicine Foundation; PAPP-A, pregnancy-associated plasma protein-A; PI, pulsatility index; PE, preeclampsia; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1. This figure was adapted from Poon et al. 2020.

TABLES

Table 1 Summary of maternal risk factors and recommendations for prevention of PE outlined by the ACOG, NICE and ISSHP guidelines

Guideline	**ACOG 2018[31]**	**NICE 2019[29]**	**ISSHP 2021[10]**
Maternal risk factors for PE			
High risk factors	• Diagnosis of PE in a previous pregnancy • Multi-fetal gestation • Renal disease • Autoimmune disease • Diabetes mellitus (type 1 or type 2) • Chronic hypertension	• Diagnosis of hypertensive disease during a previous pregnancy • Chronic kidney disease • Autoimmune disease (e.g., antiphospholipid syndrome) • Diabetes mellitus (type 1 or type 2) • Chronic hypertension	• Diagnosis of PE in a previous pregnancy • BMI >30 kg/m^2 • Chronic hypertension • Pregestational diabetes mellitus • Chronic kidney disease (including kidney transplanted women) • Systemic lupus erythematosus/ antiphospholipid syndrome • Receipt of assisted reproductive treatments
Moderate risk factors	• First pregnancy • Maternal age ≥35 years • BMI >30 kg/m^2 • Family history of PE • Sociodemographic characteristics • Personal history factors	• First pregnancy • Maternal age ≥40 years • Pregnancy interval of >10 years • BMI ≥35 kg/m^2 at first visit • Multi-fetal pregnancy	• First pregnancy • Maternal age >40 years • Multi-fetal pregnancy • Prior placental abruption • Prior stillbirth • Prior fetal growth restriction
Recommendations for prevention of PE			

	For women at high risk of developing PE, low-dose aspirin (81 mg/day) should be initiated between 12–28 weeks of gestation (optimally before 16 weeks) and should be continued daily until delivery. Low-dose aspirin should be considered for women with >1 moderate risk factor for PE.	Advise pregnant women at high risk of developing PE, or with >1 moderate risk factor for PE, to take 75–150 mg/day aspirin from 12 weeks of gestation until delivery.	For women at increased risk of developing PE, low-dose aspirin is recommended, to be taken at bedtime, preferably before 16 weeks of gestation and discontinued by 36 weeks. After multivariable screening, aspirin should be given at a dose of 150 mg/night. After screening with clinical risk factors and blood pressure, aspirin should be given at a dose of 100–162 mg/day.

ACOG, American College of Obstetricians and Gynecologists; BMI, body mass index; ISSHP, International Society for the Study of Hypertension in Pregnancy;

NICE, National Institute for Health and Care Excellence; PE, preeclampsia

Table 2 PlGF and the sFlt-1/PlGF ratio cut-offs and accuracy for diagnosing and predicting PE and associated adverse outcomes

Diagnose/ predict/rule out PE	*PlGF cut-off*	*Sensitivity (95% CI), %*	*Specificity (95% CI), %*	*PPV (95% CI), %*	*NPV (95% CI), %*	*Positive likelihood ratio (95% CI)*	*Negative likelihood ratio (95% CI)*	*Reference (study)*
Diagnose PE in asymptomatic women (Meta-analysis subset, 6 studies, g=various)	80–120 pg/mL	78 (67–86)	88 (75–95)	-	-	6.3 (2.7–14.7)	0.26 (0.16–0.42)	[37]
Diagnose PE in asymptomatic women (Meta-analysis subset, 12 studies, g=various)	50–150 pg/mL	74 (64–82)	85 (78–90)	-	-	4.8 (3.1–7.6)	0.31 (0.21–0.45)	[37]
Diagnose PE requiring delivery within 14 days in women with suspected PE (*n*=287, g=20+0–<35+0 weeks)	<5th percentile for gestation	96 (89–99)	55 (48–61)	43 (36–51)	98 (93–99.5)	2.1 (1.8–2.5)	0.07 (0.02–0.22)	[48] (PELICAN)
Diagnose PE requiring	<100 pg/mL	96 (89–99)	56 (49–63)	44 (36–52)	98 (93–99.5)	2.2 (1.9–2.6)	0.07 (0.02–0.22)	[48] (PELICAN)

delivery within 14 days in women with suspected PE (*n*=287, g=20+0–<35+0 weeks)								
Predict adverse outcome	*PlGF cut-off*	*Sensitivity (95% CI), %*	*Specificity (95% CI), %*	*PPV (95% CI), %*	*NPV (95% CI), %*	*Positive likelihood ratio (95% CI)*	*Negative likelihood ratio (95% CI)*	*Reference (study)*
Predict delivery of an SGA fetus in women with suspected PE (*n*=274, g=20+0–34+6 weeks)	<100 pg/mL	93.2 (83.5–98.1)	52.2 (39.7–64.6)	63.2 (52.2–73.3)	89.7 (75.8–97.1)	2.0 (1.5–2.5)	0.13 (0.05–0.34)	[78] (PELICAN, further analysis)
Predict preterm delivery in women with suspected PE (*n*=753, g=20+0–35+0 weeks)	≤100 pg/mL	81.7 (NR)	85.3 (NR)	93.5 (NR)	64.5 (NR)	-	-	[35]
Diagnose/ predict/rule out PE	*sFlt-1/PlGF ratio cut-off*	*Sensitivity (95% CI), %*	*Specificity (95% CI), %*	*PPV (95% CI), %*	*NPV (95% CI), %*	*Positive likelihood ratio (95% CI)*	*Negative likelihood ratio (95% CI)*	*Reference (study)*

Diagnose PE in high and low risk women (Meta-analysis, 15 studies, *n*=20, 121, g=various)	various	80 (68–88)*	92 (87–96)*	-	-	10.5 (6.2–18.0)*	0.22 (0.13–0.35)*	[67] (SaPPPhirE)
Rule out early-onset PE (*n*=1149, g=20+0–33+6 weeks)	≤33[†]	95.0 (89.8–100)	94.0 (90.5–100)	-	-	15.8 (9.13–27.5)	0.05 (0.02–0.13)	[57]
Rule in early-onset PE (*n*=1149, g=20+0–33+6 weeks)	≥85[†]	88.0 (81.3–100)	99.5 (97.7–100)	-	-	176 (24.88–1245)	0.12 (0.07–0.21)	[57]
Rule out late-onset PE (*n*=1149, g>34+0 weeks)	≤33[†]	89.6 (84.2–100)	73.1 (68.3–100)	-	-	3.33 (2.71–4.10)	0.14 (0.09–0.24)	[57]
Rule in late-onset PE (*n*=1149, g>34+0 weeks)	≥110[†]	58.2 (50.7–100)	95.5 (92.9–100)	-	-	13 (7.34–23.0)	0.44 (0.36–0.54)	[57]
Rule out early-onset PE/FGR in women with suspected PE	>95[th] percentile	100 (78.5–100)	80.6 (75.0–85.2)	24.1 (15.0–36.5)	100 (97.9–100)	5.2 (4.0–6.7)	-	[13]

(*n*=14, g=24+0–28+0 weeks)								
Rule out late-onset PE/FGR in women with suspected PE (*n*=37, g=24+0–28+0 weeks)	>95th percentile	40.5 (26.3–56.5)	92.9 (87.7–96.0)	57.7 (38.9–74.5)	86.7 (80.7–91.1)	5.7 (2.9–11.4)	-	[13]
Rule out PE developing within 1 week of test in women with suspected PE (*n*=550, g=24+0–36+6 weeks)	≤38	80.0 (51.9–95.7)	78.3 (74.6–81.7)	-	99.3 (97.9–99.9)	-	-	[58] (PROGNOSIS)
Rule in PE developing within 4 weeks of test in women with suspected PE (*n*=550, g=24+0–36+6 weeks)	>38	66.2 (54.0–77.0)	83.1 (79.4–86.3)	36.7 (28.4–45.7)	-	-	-	[58] (PROGNOSIS)
Rule out PE developing within 1 week	≤38	76.5 (58.8–89.3)	82.1 (79.0–85.0)	17.9 (12.1–25.2)	98.6 (97.2–99.4)	4.28 (3.34–5.48)	0.29 (0.16–0.53)	[59] (PROGNOSIS Asia)

of test in women with suspected PE (*n*=700, g=20+0–36+6 weeks)‡								
Rule in PE developing within 4 weeks of test in women with suspected PE (*n*=700, g=20+0–36+6 weeks)‡	>38	62.0 (49.7–73.2)	83.9 (80.8–86.7)	30.3 (23.0–38.5)	95.1 (93.0–96.8)	3.86 (2.99–4.98)	0.45 (0.34–0.61)	[59] (PROGNOSIS Asia)
Rule out PE developing within 2 weeks of test in women with suspected PE (*n*=550, g=24+0–36+6 weeks)	≤38	78.0 (62.4–89.4)	81.1 (77.5–84.4)	25.0 (17.8–33.4)	97.9 (96.0–99.0)	4.14 (3.25–5.27)	0.27 (0.15–0.48)	[60] (PROGNOSIS post-hoc analysis)
Rule out PE developing within 3 weeks of test in women with suspected PE	≤38	70.0 (56.8–81.2)	82.4 (78.8–85.7)	32.8 (24.8–41.7)	95.7 (93.3–97.5)	3.99 (3.1–5.14)	0.36 (0.25–0.54)	[60] (PROGNOSIS post-hoc analysis)

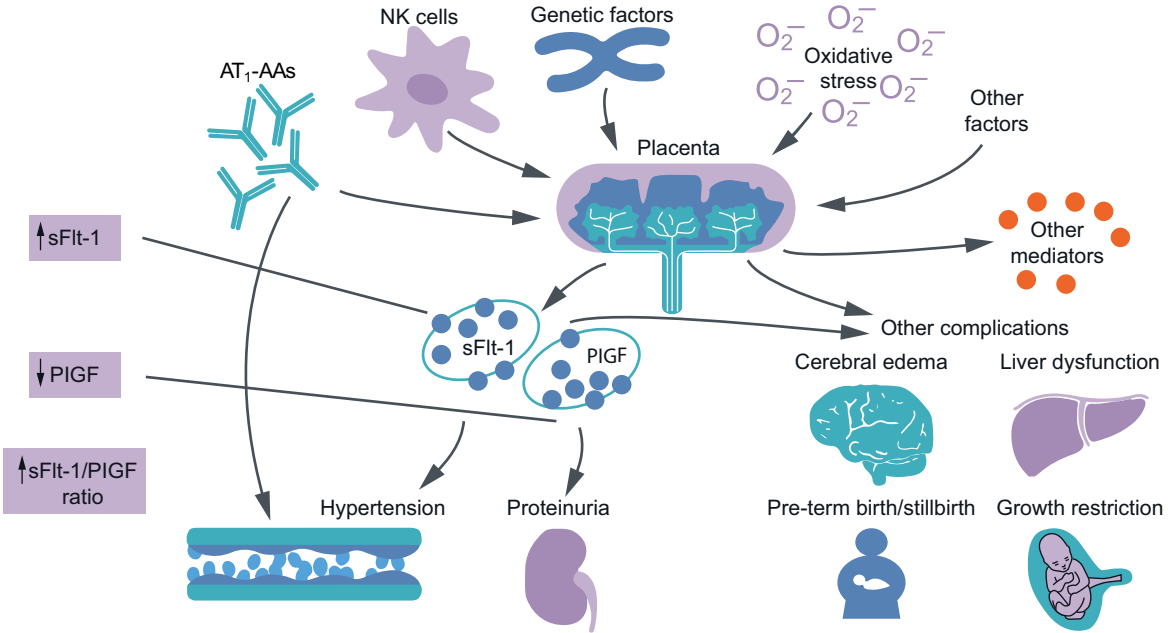
(*n*=550, g=24+0–36+6 weeks)								
Rule out PE developing within 4 **weeks of test in women with suspected PE (*n*=550, g=24+0–36+6 weeks)**	≤38	66.2 (54.0–77.0)	83.1 (79.4–86.3)	36.7 (28.4–45.7)	94.3 (91.7–96.3)	3.91 (3.02–5.07)	0.41 (0.29–0.56)	[60] (PROGNOSIS post-hoc analysis)
Rule in PE developing within 1 **week of test in women with suspected PE (*n*=370, g=24+0–37+0 weeks)**	>38	100 (85.8–100)	77.8 (70.6–83.9)	40.0 (27.6–53.5)	100 (97.1–100)	-	-	[61] (INSPIRE)
Rule in PE developing within 4 **weeks of test in women with suspected PE (*n*=186, g=24+0/7–36+6/7 weeks)**	≥85	57.1 (39.4–73.7)	94.7 (89.8–97.7)	71.4 (51.3–86.8)	-	-	-	[62] (INSPIRE post-hoc analysis)

Predict/rule out adverse outcome	*sFlt-1/PlGF ratio cut-off*	*Sensitivity (95% CI), %*	*Specificity (95% CI), %*	*PPV (95% CI), %*	*NPV (95% CI), %*	*Positive likelihood ratio (95% CI)*	*Negative likelihood ratio (95% CI)*	*Reference (study)*
Rule out adverse fetal outcomes within 1 week of test in women with suspected of PE (*n*=690, g=20+0–36+6 weeks)‡	≤38	80.0 (61.4–92.3)	81.8 (78.7–84.7)	16.7 (11.0–23.8)	98.9 (97.6–99.6)	4.40 (3.46–5.60)	0.24 (0.12–0.50)	[59] (PROGNOSIS Asia)
Rule in adverse fetal outcomes within 4 weeks of test in women with suspected of PE (*n*=690, g=20+0–36+6 weeks)‡	>38	61.6 (52.5–70.2)	88.1 (85.2–90.7)	53.5 (45.0–61.8)	91.2 (88.5–93.4)	5.19 (3.99–6.76)	0.44 (0.35–0.55)	[59] (PROGNOSIS Asia)
Predict preterm delivery of an SGA fetus (*n*=3981, g=28 weeks)	>5.78§,**	38.5 (21.1–59.3)	99.1 (98.7–99.3)	21.3 (11.6–35.8).	99.6 (99.3–99.8)	41.1 (23.0–73.6)	0.62 (0.46–0.84)	[81]

Predict delivery of an SGA fetus associated with PE or perinatal morbidity or mortality (*n*=3747, g=36 weeks)	>38**	37.9 (26.1–51.4)	97.8 (97.3–98.3)	21.6 (14.5–30.8)	99.0 (98.6–99.3)	17.5 (11.8–25.9)	0.63 (0.52–0.78)	[81]
Predict adverse outcome in women with PE (*n*=176, g<34+0 weeks)	≥85	72.9 (NR)	94.0 (NR)	-	87.3 (NR)	-	0.29 (NR)	[85]

*Pooled sensitivity and specificity values are reported; [†]The sFlt-1/PlGF ratio cut-off values were derived and validated for the Elecsys sFlt-1/PlGF assay only; [‡]Gestational week 18+0 in Japan; [§]an sFlt-1/PlGF ratio cut-off of >38 was not used as it would represent an extremely elevated ratio at 28 weeks' gestation; **reported values are for an elevated sFlt-1/PlGF ratio combined with a suspicion of SGA (<10th percentile for gestational age) determined by ultrasound scan measurements.

CI, confidence interval; g, gestational age at time of test; n, number of participants in study; NPV; negative predictive value; NR, not reported; PE, preeclampsia; PlGF, placental growth factor; PPV, positive predictive value; sFlt-1, soluble fms-like tyrosine kinase 1; SGA, small for gestational age.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Other mediators
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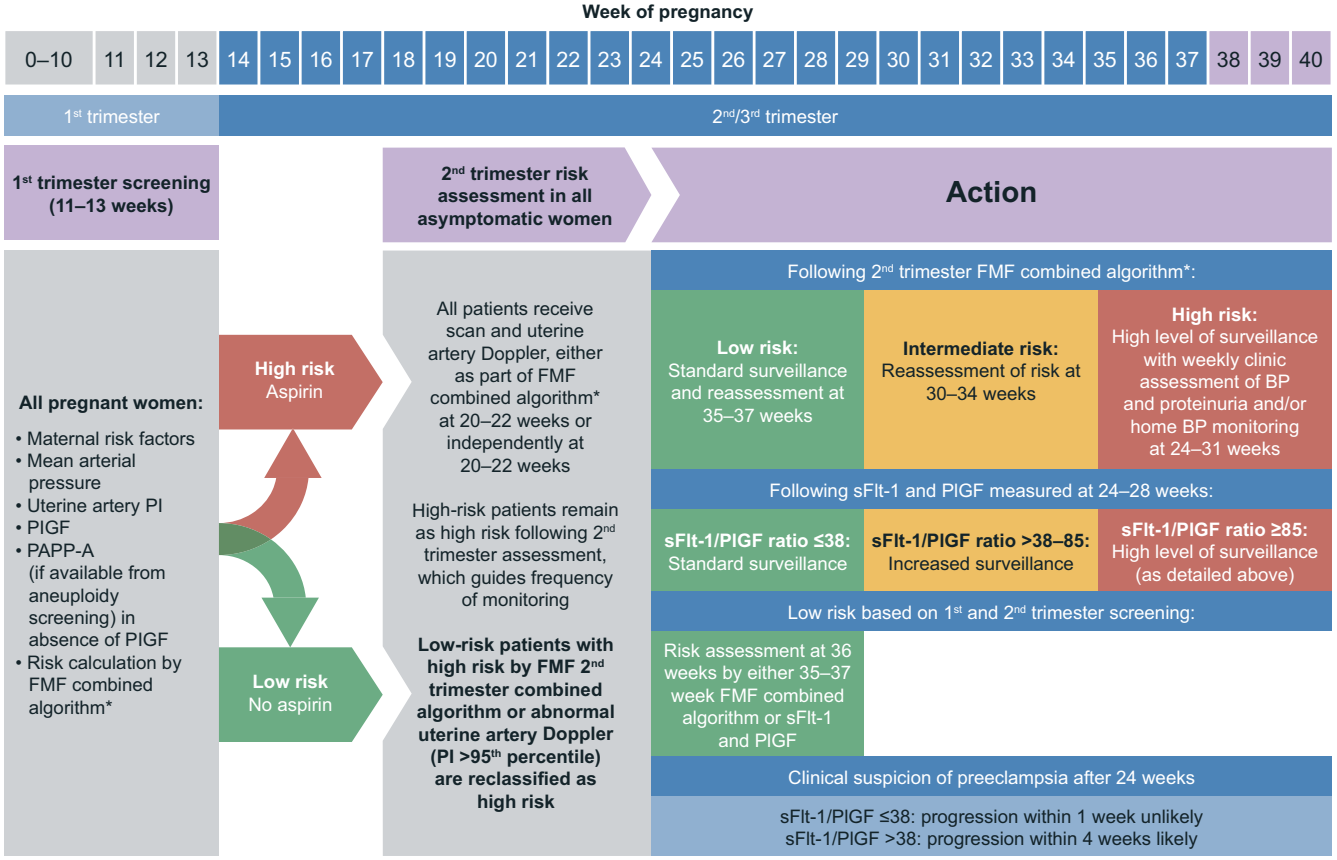
↓PIGF
Cerebral edema
Liver dysfunction
↑sFlt-1/PIGF ratio
Hypertension
Proteinuria
Pre-term birth/stillbirth
Growth restriction


Week of pregnancy
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1st trimester
2nd/3rd trimester
1st trimester screening (11–13 weeks)
2nd trimester risk assessment in all asymptomatic women
Action
All pregnant women:
• Maternal risk factors
• Mean arterial pressure
• Uterine artery PI
• PIGF
• PAPP-A (if available from aneuploidy screening) in absence of PIGF
• Risk calculation by FMF combined algorithm*
High risk
Aspirin
Low risk
No aspirin
All patients receive scan and uterine artery Doppler, either as part of FMF combined algorithm* at 20–22 weeks or independently at 20–22 weeks
High-risk patients remain as high risk following 2nd trimester assessment, which guides frequency of monitoring
Low-risk patients with high risk by FMF 2nd trimester combined algorithm or abnormal uterine artery Doppler (PI >95th percentile) are reclassified as high risk
Following 2nd trimester FMF combined algorithm*:
Low risk: Standard surveillance and reassessment at 35–37 weeks
Intermediate risk: Reassessment of risk at 30–34 weeks
High risk: High level of surveillance with weekly clinic assessment of BP and proteinuria and/or home BP monitoring at 24–31 weeks
Following sFlt-1 and PlGF measured at 24–28 weeks:
sFlt-1/PlGF ratio ≤38: Standard surveillance
sFlt-1/PlGF ratio >38–85: Increased surveillance
sFlt-1/PlGF ratio ≥85: High level of surveillance (as detailed above)
Low risk based on 1st and 2nd trimester screening:
Risk assessment at 36 weeks by either 35–37 week FMF combined algorithm or sFlt-1 and PlGF
Clinical suspicion of preeclampsia after 24 weeks
sFlt-1/PlGF ≤38: progression within 1 week unlikely
sFlt-1/PlGF >38: progression within 4 weeks likely