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Opinion

Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice

Introduction

Pre-eclampsia (PE) is a leading cause of maternal and fetal/neonatal morbidity and mortality worldwide. Clinical diagnosis and definition of PE is commonly based on the measurement of non-specific signs and symptoms, principally hypertension and proteinuria[1–3]. However, due to the recognition that measurement of proteinuria is prone to inaccuracies and the fact that PE complications often occur before proteinuria becomes significant, most recent guidelines also support the diagnosis of PE on the basis of hypertension and signs of maternal organ dysfunction other than proteinuria[3–5]. Furthermore, the clinical presentation and course of PE is variable, ranging from severe and rapidly progressing early-onset PE, necessitating preterm delivery, to late-onset PE at term. There may be associated intrauterine growth restriction (IUGR), further increasing neonatal morbidity and mortality. These features suggest that the classical standards for the diagnosis of PE are not sufficient to encompass the complexity of the syndrome. Undoubtedly, proper management of pregnant women at high risk for PE necessitates early and reliable detection and intensified monitoring, with referral to specialized perinatal care centers, to reduce substantially maternal, fetal and neonatal morbidity[6,7].

In the decade since Maynard *et al.*[8] reported that excessive placental production of soluble fms-like tyrosine kinase receptor-1 (sFlt-1), an antagonist of vascular endothelial growth factor and placental growth factor (PlGF), contributes to the pathogenesis of PE, extensive research has been published demonstrating the usefulness of angiogenic markers in both diagnosis and the subsequent prediction and management of PE and placenta-related disorders. Various reports have demonstrated that disturbances in angiogenic and antiangiogenic factors are implicated in the pathogenesis of PE and have possible relevance in the diagnosis and prognosis of the disease.

Increased serum levels of sFlt-1 and decreased levels of PlGF, thereby resulting in an increased sFlt-1/PlGF ratio, can be detected in the second half of pregnancy in women diagnosed to have not only PE but also IUGR or stillbirth, i.e. placenta-related disorders. These alterations are more pronounced in early-onset rather than late-onset disease and are associated with severity of the clinical disorder. Moreover, the disturbances in angiogenic factors are reported to be detectable prior to the onset of clinical symptoms (disease), thereby allowing discrimination of women with normal pregnancies from those at high risk for developing pregnancy complications, primarily PE[9–30].

Plasma concentrations of angiogenic/antiangiogenic factors are of prognostic value in obstetric triage: similar to the progressively worsening clinical course observed in women with early-onset PE, changes in the angiogenic profile leading to a more antiangiogenic state can be found. Current definitions of PE are poor in predicting PE-related adverse outcomes. A diagnosis of PE based on blood pressure and proteinuria has a positive predictive value of approximately 30% for predicting PE-related adverse outcomes[31]. Estimation of the sFlt-1/PlGF ratio allows identification of women at high risk for imminent delivery and adverse maternal and neonatal outcome[23,30,32–35]. Moreover, it has also been shown that the time-dependent slope of the sFlt-1/PlGF ratio between repeated measurements is predictive for pregnancy outcome and the risk of developing PE, and repeated measurements have been suggested[36]. However, the 'optimal' time interval for a follow-up test remains unclear. Finally, high values are closely related to the need to deliver immediately[22,23,37].

Additionally, in normal and complicated pregnancies, angiogenic factors are correlated with Doppler ultrasound parameters, mainly uterine artery (UtA) indices[38–42]. Combining the sFlt-1/PlGF ratio with UtA Doppler ultrasound, at the time of diagnosis of early-onset PE, has prognostic value mainly for perinatal complications, being limited for the prediction of maternal complications[37,43]. The additional measurement of the sFlt-1/PlGF ratio has been shown to improve the sensitivity and specificity of Doppler measurement in predicting PE[44–48], supporting its implementation in screening algorithms.

Whereas studies on the predictive efficacy of the sFlt-1/PlGF ratio in the first trimester have yielded contradictory results[49], reports on the use of this marker as an aid in prediction from the mid trimester onwards have led to its suggested use as a screening tool, especially for identifying all women developing PE and requiring delivery within the subsequent 4 weeks[50–52].

This short review of the literature highlights that measurement of the sFlt-1/PlGF ratio has the potential to become an additional tool in the management of PE, particularly as automated tests that allow rapid and easy measurement of these markers are now widely available. Nevertheless, although these markers were incorporated recently into the German guidelines[53], no formal recommendation regarding how to use sFlt-1,

PlGF or the sFlt-1/PlGF ratio has been established in any official protocol.

The purpose of this paper is to answer questions that are frequently asked around the use of the sFlt-1/PlGF ratio in the diagnosis and prediction of PE and regarding the implications for clinical practice, in particular, 'When?' and 'In which women?' should the sFlt-1/PlGF ratio be measured and, 'What should be done with the results?', and to provide guidance to educate physicians on the use of the sFlt-1/PlGF ratio in clinical practice. To achieve this, international experts in the use of angiogenic markers have strived to develop a consensus statement on the clinical use of the sFlt-1/PlGF ratio and the consequential management in pregnant women with suspected PE or at a high risk of developing PE.

Consensus statement

This consensus statement aims to apply a 'risk for developing PE algorithm' to two different patient populations:

- women with signs and symptoms of PE and
- asymptomatic women at high risk of developing PE.

At the outset, it should be emphasized that: 1) the sFlt-1/PlGF ratio has not been evaluated as a screening test and 2) the sFlt-1/PlGF ratio does not replace other techniques to monitor high-risk patients. Furthermore, decisions regarding delivery are not based solely on the sFlt-1/PlGF ratio, but are always made in the context of other established techniques and clinical signs and symptoms. Finally, most of the studies on the sFlt-1/PlGF ratio have been performed using the Elecsys® assay and the cut-off levels described in this guidance have been validated so far only for this assay[18,54].

Gestational age-specific sFlt-1/PlGF ratio cut-offs of > 85 ($20 + 0$ to $33 + 6$ weeks) and > 110 ($34 + 0$ weeks to delivery) have been shown to be highly suggestive of PE[55]. The same study identified a cut-off of 33 for exclusion of PE (sensitivity, 95%; specificity, 94%). However, no insight was gained regarding the likelihood of these women developing PE over the course of their pregnancy. In the PROGNOSIS study[56,57], a single sFlt-1/PlGF ratio cut-off (< 38) was validated to rule out reliably PE within 1 week (negative predictive value $> 96\%$) and rule in PE (≥ 38) within 4 weeks (positive predictive value $> 25\%$). The cut-offs for the sFlt-1/PlGF ratio used in this Opinion are based on these studies, adjusted for both early and late gestational age (Table 1).

Use of the sFlt-1/PlGF ratio in women with signs and symptoms of pre-eclampsia

This population includes both women with suspicion of PE (Table 2) and women with PE already confirmed. The criteria contributing to suspicion of PE (adopted from the inclusion criteria in the PROGNOSIS and PreOS study[56]) are very 'open', covering any suspicion of PE, and are in line with usual clinical experience.

According to the described cut-off values of the sFlt-1/PlGF ratio, three 'subgroups' of women have to be considered:

- sFlt-1/PlGF ratio < 38: these women will most likely not develop PE for at least 1 week;
- sFlt-1/PlGF ratio > 85 (early-onset PE) or > 110 (late-onset PE): these women are very likely to have PE or another form of placental insufficiency;
- sFlt-1/PlGF ratio 38–85 (early-onset PE) or 38–110 (late-onset PE): these women do not have a definite diagnosis of PE but are highly likely to develop PE within 4 weeks.

sFlt-1/PlGF ratio < 38

Women with an sFlt-1/PlGF ratio < 38 do not have PE at the time of the test and in all likelihood will not develop PE for at least 1 week; it is thereby of great value for reassuring the clinician and the patient. This cut-off is irrespective of gestational week and predictive performance is not improved by gestational-age-adapted cut-offs. More than 80% of patients will be in this patient group; therefore, clinicians are able to exclude the majority of patients and focus on those who need more attention and care. How to manage this group can be left to the clinician's discretion. No further determinations are needed unless a new suspicion arises.

Statement 1: sFlt-1/PlGF < 38

sFlt-1/PlGF ratio < 38 rules out PE, irrespective of gestational age, for at least 1 week. Further management is according to the clinician's discretion.

sFlt-1/PlGF ratio > 85 (early-onset PE) or >110 (late-onset PE)

Women with an elevated sFlt-1/PlGF ratio > 85 (early-onset PE) or > 110 (late-onset PE) are highly likely to have PE or some form of placenta-related disorder and should be managed according to local practice/guidelines. A severely elevated sFlt-1/PlGF ratio (> 655 in early-onset PE; > 201 in late-onset PE) is associated closely with the need to deliver within 48 hours[22,23,37] and should prompt extra surveillance in an appropriate clinical setting. In early-onset PE, antenatal corticosteroids to accelerate fetal lung maturation should be considered strongly.

Statement 2: sFlt-1/PlGF ratio > 85 (early-onset PE) or > 110 (late-onset PE)

Diagnosis of PE or placenta-related disorder is highly likely. Management according to local guidelines.
Severely elevated sFlt-1/PlGF ratios (> 655 at $< 34 + 0$ weeks; > 201 at $\geq 34 + 0$ weeks) are associated closely with the need to deliver within 48 h. Close surveillance and (if < 34 weeks) prompt initiation of antenatal corticoids to accelerate fetal lung maturation are mandatory.

Table 1 Soluble fms-like tyrosine kinase receptor-1 (sFlt-1)/placental growth factor (PlGF), ratio cut-offs for prediction and diagnosis of pre-eclampsia (PE) in singleton pregnancy

	Cut-off		
Utility of sFlt-1/PlGF ratio	*Early onset (< 34 weeks)*	*Late onset (≥ 34 weeks)*	*Reference*
Suspicion of PE	38	38	Zeisler *et al.*[57]
Diagnosis of PE	85	110	Verlohren *et al.*[55]

Table 2 Criteria contributing to suspicion of clinical diagnosis of pre-eclampsia (PE)

Clinical signs and symptoms
De-novo elevated blood pressure*
Aggravation of pre-existing hypertension
De-novo protein in urine†
Aggravation of pre-existing proteinuria
One or more other reason(s) for clinical suspicion of PE:
PE-related symptoms
Epigastric pain
Excessive edema /severe swelling (face, hands, feet)
Headache
Visual disturbances
Sudden weight gain (>1 kg/week in third trimester)
PE-related findings
Low platelets
Elevated liver enzymes
(Suspected) intrauterine growth restriction
Abnormal uterine artery Doppler (mean PI > 95th centile in second trimester and/or bilateral notching)

*Standard definition of hypertension (≥140 mmHg systolic and/or ≥ 90 mmHg diastolic) need not apply. †Standard definition of proteinuria need not apply. PI, pulsatility index.

A repeat measurement of the sFlt-1/PlGF ratio may help to distinguish whether a patient is at moderate, high or very high risk of developing a complication, such as PE, depending on the dynamics of the increased sFlt-1/PlGF ratio. In women with relatively stable test results, the physician can be confident that the woman will not deteriorate rapidly. In these cases a follow-up sFlt-1/PlGF test in 2 weeks may be considered. However, it is still not possible to determine how these women will progress after this point and the trend indicating pathology is unknown.

Statement 3: sFlt-1/PlGF ratio > 85 (early-onset PE) or > 110 (late-onset PE), repeat measurement

Re-measure after 2–4 days to determine trend and follow up according to clinician's discretion depending on severity.
The test frequency can be adapted to the clinical situation and trend in sFlt-1/PlGF ratio dynamics.

sFlt-1/PlGF ratio 38–85 (early-onset PE) or 38–110 (late-onset PE)

Women with an sFlt-1/PlGF ratio of 38–85 (early-onset PE) or 38–110 (late-onset PE) do not have PE at the time of the test. Although the majority will not develop PE, these women may be at risk for developing PE within 4 weeks and should be monitored more closely, although the time interval for a follow-up test remains unclear. In one study in pregnant women in early gestation (< 34 weeks), 100% of women in this intermediate zone had a preterm birth, even in the absence of PE[58]. Therefore, these women should be considered as high risk and more intensive follow-up is required, depending on gestational age.

Statement 4: sFlt-1/PlGF ratio 38–85 (early-onset PE) or 38–110 (late-onset PE)

The sFlt-1/PlGF ratio provides information about the patient before the onset of overt signs and symptoms. An sFlt-1/PlGF ratio of 38–85 or 38–110 provides extra information as to which women are at moderate risk or at high risk of developing PE within 4 weeks. Current PE or a placenta-related disorder can be ruled out, but women are at (high) risk (especially in the early-onset group).
Early onset: Consider a follow-up sFlt-1/PlGF test in 1–2 weeks, according to the individual clinical situation. Results are to be treated accordingly.
Late onset: An intermediate result of the sFlt-1/PlGF ratio is suggestive of impending placental dysfunction. Consider lowering the threshold for induction of delivery.

In women with confirmed PE, measurement of the sFlt-1/PlGF ratio does not provide additional diagnostic information, but it can be useful for prognostic purposes, in a similar way to that described in Statements 2 and 3.

Statement 5:

The sFlt-1/PlGF ratio has been proven as an aid in diagnosis for PE.
In a woman with PE already confirmed (high blood pressure and proteinuria) the sFlt-1/PlGF ratio may be useful to determine the severity of the disorder.

Use of the sFlt-1/PlGF ratio in asymptomatic women at high risk of pre-eclampsia

This group includes:

- women with established criteria associated with an increased risk of developing PE;
- women who are identified to be at risk as a result of a UtA Doppler examination;
- women with any perceived increased risk of PE.

Women at higher risk of PE based on established criteria obviously need to be followed up more carefully and UtA Doppler may be considered. An estimation

of the sFlt-1/PlGF ratio should be performed in those asymptomatic women considered to be high risk based on history or abnormal UtA Doppler. The optimal time for starting measurement of the sFlt-1/PlGF ratio in these high-risk patients is 24–26 weeks, given that at this time point the differences in the values of the sFlt-1/PlGF ratio between women with normal outcome and those destined to develop early PE are usually already significant. Those women with a normal sFlt-1/PlGF test result can be reassured that PE can be ruled out for at least 1 week but not for the whole pregnancy, and therefore serial measurements should be considered. Currently, there are no recommendations regarding time interval for a follow-up test. Conversely, women with abnormal sFlt-1/PlGF ratios should be considered as having suspected PE and should be managed accordingly.

Using the sFlt-1/PlGF ratio for clinical management: general considerations

- Maternal complications cannot be avoided completely but women at high risk can be hospitalized.
- No data exist on the usefulness of the sFlt-1/PlGF ratio to avoid maternal complications.
- No data exist to show that maternal outcome is better now than it was before use of the sFlt-1/PlGF ratio.
- No randomized controlled trials have been performed to test the usefulness of the sFlt-1/PlGF ratio regarding maternal or fetal outcomes.
- The test should be used in the population in which it is most reasonable, i.e. in the high-risk population. The economics and resource utilization need to be considered too.

Conclusions

The diagnostic and predictive value of the sFlt1/PlGF ratio in patients at risk of placenta-related disorders, i.e. PE, HELLP syndrome, IUGR and stillbirth, has been shown in the recent literature and estimation of the sFlt-1/PlGF ratio has become an additional tool in the management of these disorders, primarily PE. Repeat measurements of the sFlt-1/PlGF ratio are suggested to improve individual risk assessment in these patients, but this has to be proven by further studies.

To date, the use of sFlt-1, PlGF or the sFlt-1/PlGF ratio has not been incorporated into official guidelines. In this statement, we have aimed to give good clinical practice guidance for implementation of this method into the management algorithm of pregnant women. Use of the sFlt-1/PlGF ratio may help to optimize care by improving management of women with suspected PE.

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