Consensus statement on the potential implementation of the sFlt-1/PlGF ratio in women with suspected pre-eclampsia

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Pre-eclampsia is one of the leading causes of maternal and perinatal mortality and morbidity worldwide, and places a significant burden on the South African (SA) healthcare system. The soluble fms-like tyrosince kinase (sFlt-1)/placental growth factor (PlGF) ratio can serve as a diagnostic aid for PE, and should be used in combination with clinical judgement and other ancillary tests. The Preeclampsia Advisory Board was convened on 31 March 2017, with experts in the field of PE from various hospitals and universities around the country in attendance. An international expert gave insight into best practices from countries that have implemented the Elecsys immunoassay sFlt-1/PlGF ratio. Others recommend that the sFlt-1/PlGF ratio be implemented in clinical practice when clinical diagnosis is in doubt in patients with suspected PE, in the interests of avoiding unnecessary hospitalisation and interventions. The strength of the test lies in its negative predictive value in ruling out PE. Ruling out PE could drive cost savings, as fewer women would be needlessly admitted to hospital, and there could, in addition, be fewer iatrogenic preterm deliveries, which are associated with considerable morbidity and cost. As most data are derived from high-income countries, multicentre studies are required to assess the clinical performance of this test within the context of SA.

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Pre-eclampsia (PE) is one of the leading causes of maternal and perinatal mortality and morbidity worldwide.[1-3] It complicates between 2 and 8% of pregnancies globally; however, there is wide variation across different regions of the world.[2,3] South Africa (SA), as a low- and middle-income country (LMIC), experiences the brunt of most complications associated with PE, in comparison with high-income countries.[4] Hypertensive disorders of pregnancy are responsible for approximately 25 000 maternal deaths in Africa annually.[5] A Canadian study estimated that for every woman who dies, another 20 suffer severe morbidity.[6] Ninety-nine percent of pre-eclampsia-associated maternal deaths occur in LMICs.[2] PE is associated with one-quarter of stillbirths and neonatal deaths in LMIC countries, and is a common cause of preterm births.[2]

PE is characterised by the presence of hypertension and proteinuria after 20 weeks' gestation.[7,8] Most recent guidelines also support the diagnosis of PE on the basis of hypertension and signs of maternal organ dysfunction, other than proteinuria (Table 1).[9-11] This is as a result of the variable clinical presentation and course of the disease, as well as the fact that PE complications often occur before proteinuria becomes significant.[10] Blood

Table 1. The revised ISSHP definition of PE 2014 [11]

Hypertension developing after 20 weeks' gestation and the coexistence of one or more of the following new onset conditions:

1. Proteinuria
2. Other maternal organ dysfunction:
- renal insufficiency (creatinine >90 µmol/L)
- liver involvement (elevated transaminases and/or severe right upper quadrant or epigastric pain)
- neurological complications (examples include eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied by clonus, severe headaches when accompanied by hyperreflexia, persistent visual scotomata)
- haematological complications (thrombocytopenia, DIC, haemolysis)
3. Uteroplacental dysfunction:
- fetal growth restriction

ISSHP = International Society for the Study of Hypertension in Pregnancy; PE = pre-eclampsia.

pressure and proteinuria have low sensitivity and specificity in terms of predicting the course of the disease, and/or adverse maternal and perinatal outcomes.[12,13] Their diagnostic value is also limited when women have pre-existing hypertension and/or proteinuria (e.g. in chronic renal disease).[14]

The pathogenesis of PE is not fully understood. New research has demonstrated that there is altered angiogenesis and an increase in circulating antiangiogenic factors in PE.[13,15] Soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) are proteins released by the placenta into the circulation of pregnant women and have been demonstrated to be deranged in PE.[14-17] PlGF is a member of the vascular endothelial growth factor family, and plays a role in angiogenesis, trophoblast invasion and subsequent transformation of the maternal spiral arteries.[18,19] Soluble fms-like tyrosine kinase-1, a soluble form of VEGF receptor -1, binds and scavenges circulating vascular endothelial growth factor (VEGF) and PlGF, thus antagonising the action of these pro-angiogenic proteins.[16,17,20,21]

Several studies have demonstrated that circulating levels of sFlt-1 and PlGF are altered in women with PE.[13-16] Maternal serum concentrations of sFlt-1 and PlGF are altered before the onset of clinical signs and symptoms of PE, and correlate with disease severity.[15,22-24] The sFlt-1 levels increase approximately 5 weeks before the onset of PE, and remain elevated compared with those in unaffected women,[15] while PlGF levels are significantly lower in women who later develop PE.[15,23,25,26] Elevated sFlt-1 and diminished PlGF levels are more significantly altered in women with an early- rather than late-onset PE and in women in whom PE is associated with small-for-gestational-age babies.[15,25,27] The sFlt-1/PlGF ratio is an index of pro- and anti-angiogenic activity that reflects alterations in both biomarkers. This ratio seems to be a better predictor of PE than either measure alone.[28-30]

The sFlt-1/PlGF ratio allows the identification of women at high risk for imminent delivery, whereas measurements of blood pressure and proteinuria are poor indicators of the severity of the disease, clinical course and the impact on maternal and fetal morbidity and mortality.[12,31] Extremely elevated sFlt-1/PlGF values have been shown to be closely related to the need for immediate delivery.[31]

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

The sFlt-1/PlGF ratio has been recommended as a diagnostic aid for PE, and should be used in combination with clinical judgement and other diagnostic tests.[30,32,33]

Three subgroups of women can be defined based on the sFlt-1/PlGF ratio (Fig. 1):[10]

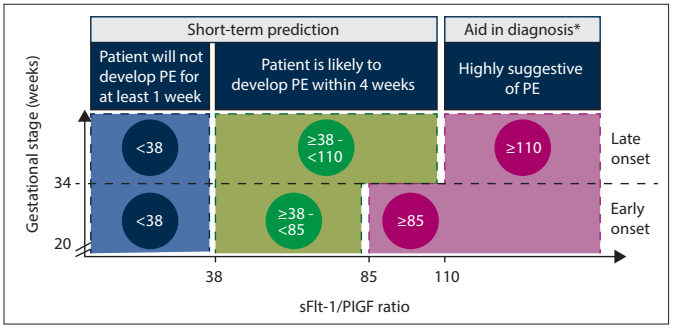

Fig. 1. Using gestational age-specific cut-offs, the sFlt-1/PlGF ratio can aid in the diagnosis and short-term prediction of PE. (PE = pre-eclampsia; PlGF = placental growth factor; sFlt-1 = soluble fms-like tyrosine kinase-1.)
**Used in addition to other accepted diagnostic tools, and clinical information.*

- sFlt-1/PlGF ratio <38: these women will most likely not develop PE for at least 1 week.[10,30]
- 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-based disorder.[32]
- 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.[34]

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 a week.[10,30,33] The great majority of patients will fall into this category (negative predictive value of 99.3% (95% confidence interval (CI) 97.9 - 99.9, for PE developing in the next week). This allows clinicians to exclude the majority of patients and to focus on the patients who need appropriate attention and care.[11] The sFlt-1/PlGF ratio will therefore likely improve clinical decisions with respect to hospitalisation v. outpatient monitoring, and the intensity of outpatient monitoring.[30]

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 accordingly.[10,32] Moreover, a severely elevated sFlt-1/PlGF ratio (>655 in early-onset PE; >201 in late-onset PE) is closely associated with the need to deliver within 48 hours. These patients should be managed in an

appropriate clinical setting, and the administration of antenatal corticosteroids to accelerate fetal lung maturation should be seriously considered in early-onset PE.[10]

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

Women with a sFlt-1/PlGF ratio of 38 - 85 (early-onset PE) or 38 - 110 (late-onset PE) are unlikely to have PE at the time of the test. Although the majority of these patients will not develop PE, these women may be at risk for developing PE within 4 weeks, and should be more closely monitored.[10]

sFLT-1/PlGF ratio has the potential for cost-saving in clinical practice

An economic analysis (for the UK) on the use of the sFlt-1/PlGF ratio test suggested that introduction of the test could reduce the number of women hospitalised by more than half (56%). Reduction of hospitalisation was the driver of cost-savings, and it was found that the additional cost of the test was more than offset by a saving in inpatient resource use.[35] The NICE [National Institute for Health and Care Excellence] economic model also demonstrated significant cost-savings compared with standard clinical assessment, particularly for women presenting with suspected PE before 35 weeks' gestation (approximately GBP2 488 saving).[33,36]

The Preeclampsia Advisory Board meeting took place at the Roche offices in Midrand on 31 March 2017. In attendance were experts in the field of PE from various hospitals and universities around the country. The National Health Laboratory Service (NHLS) and the Department of Health (DoH) were also represented. Dr M Vatish, an international expert, gave insight into best practices from countries that have successfully implemented the Elecsys immunoassay sFlt-1/PlGF ratio. The purpose of the meeting was:

- to discuss the burden of disease, economic and clinical impact of PE on the SA healthcare system
- to determine the clinical positioning and value of the Elecsys immunoassay sFlt-1/PlGF ratio in the SA context in relation to current management interventions
- to learn best practices from countries that had clinical utility for the test.

Consensus statements

Statement 1: Pre-eclampsia places a significant burden on the SA healthcare system.

Pre-eclampsia places a ignificant economic burden on healthcare systems.[35,37] The mortality and morbidity for women and children affected by PE and its complications are a major burden, particularly in LMICs.[2,38] SA has a high incidence of PE compared with most European and North American countries.[3] Furthermore, pre-eclampsia and in particular eclampsia contribute significantly to serious maternal and perinatal mortality in SA.[39-41] Two studies, one in Limpopo Province and another at Groote Schuur Hospital, Cape Town, found that the most common reasons for obstetric intensive care unit (ICU) admissions were PE and eclampsia.[42,43] Possible reasons for PE and eclampsia's significant contribution to maternal mortality and the perinatal morbidity rate are a lack of proper antenatal care, late referrals, poor transport facilities, limited specialist obstetrician and critical-care specialist support, long distances to the referral hospital and inadequate emergency obstetric care at referral centres close to patient residences.[42] Neonatal resources in SA are limited and oversubscribed.[43,44] As a result and in most instances, neonates with birth weights of 800 - 1000 g are not ventilated. The severity of PE, late presentation for medical care as well as birthweight and gestational age restriction for ventilation all contribute to high neonatal mortality rates.[43,44]

Statement 2: The sFlt-1/PlGF ratio test is recommended in clinical practice when the clinical diagnosis is in doubt in patients with suspected PE, in the interests of avoiding unnecessary hospitalisation and unnecessary intervention. The emphasis would be on utilising the negative predictive value of sFlt-1/PlGF ratios to rule out PE.

In the PROGNOSIS study, a single sFlt-1/PlGF ratio cut-off value of 38 was identified as having important negative predictive value.[30] An sFlt-1/PlGF ratio <38 was validated to reliably rule out PE within 1 week, and had a negative predictive value of 99.3% (95% CI; 97.9 - 99.), with 80.0% sensitivity (95% CI; 51.9 - 95.7) and 78.3% specificity (95% CI; 74.6 - 81.7).[10,30,33]

In routine clinical practice, PE may be over-diagnosed, and suspected PE may be over-investigated and treated.[45] The PreOS study demonstrated that use of sFlt-1/PlGF ratio test influences clinical decision-making in routine clinical practice towards appropriate hospitalisation in a considerable proportion of women with suspected PE.[45] Reducing inappropriate hospital admissions is an important goal, in order to avoid unnecessary stress and anxiety for the patient, and to reduce the financial burden for the healthcare provider. The wider adoption of the sFlt-1/PlGF ratio test in maternity care could assist with decision-making in clinical care. Patients deemed low risk can be reassured, and avoid unnecessary hospitalisation.[45] Instances of immediate delivery of the fetus could also be reduced, with resultant fewer premature babies requiring neonatal ICU admission.[33]

Statement 3: Identifying the clinically suspicious PE group needs to be contextualised to SA circumstances. Criteria relevant and appropriate to the country's settings should be specified, regarding when the sFlt-1/PlGF ratio should be implemented, so as to provide clear guidelines as to when the assay could provide the most benefit.

It was suggested that sFlt-1/PlGF ratio test be used in patients who do not present with classic symptoms of PE, and when the diagnosis is uncertain – criteria similar to those utilised in the PreOS and PROGNOSIS studies (Table 2). [46,47]

Statement 4: It would be important for the test results to be promptly available, in order to derive maximum savings from hospitalisation costs, and to minimise patient anxiety. In order for the sFlt-1/PlGF ratio to be a valuable aide in conjunction with clinical assessment and other tests, laboratories would need to ensure that test results are available within 24 hours.

Under optimal conditions, the established turnaround time of the Elecsys immunoassay sFlt-1/PlGF ratio test is about 18 minutes.[33] In order to be of additional clinical value, laboratories need to prioritise the sFlt-1/PlGF ratio test results.

Conclusion

Various studies have shown the clinical utility of the sFlt-1/PlGF ratio test in the context of ruling in or ruling out PE when the diagnosis is in doubt, in patients with suspected disease. The strength of the test lies in its negative predictive value to rule out PE. Ruling out PE could drive cost savings, as fewer women would be admitted to hospital unnecessarily, and additionally, there would be fewer PE-associated iatrogenic preterm deliveries, which contribute considerably to perinatal morbidity and mortality. As most current data are derived from high-income countries, multicentre studies are required to assess the clinical performance of this test within the context of SA.

Table 2. Criteria contributing to suspicion of clinical diagnosis of PE[46,47]

Clinical signs and symptoms
a. New onset of elevated blood pressure (does not need to be defined hypertension (≥140 mm Hg systolic and/or ≥90 mm Hg diastolic).
b. New onset of hypertension (does not need to be defined proteinuria – any protein in the urine is sufficient)
c. Aggravation of pre-existing hypertension
d. New onset of protein in urine
e. New onset of proteinuria
f. Aggravation of pre-existing proteinuria
g. One or more other reason(s) for clinical suspicion of PE (see i. and ii. below)
i. Pre-eclampsia-related symptoms:
1. Epigastric pain
2. Excessive oedema/severe swelling, (face, hands, feet)
3. Severe or atypical headaches
4. Visual disturbances
5. Sudden weight gain (>1 kg/week in the third trimester)
ii. PE-related findings:
1. Low platelets
2. Elevated liver transaminases
3. (Suspected) intrauterine growth restriction
4. Abnormal uterine perfusion detected by Doppler sonography with mean pulsatility index >95th percentile in the second trimester and/or bilateral uterine artery notching

PE = pre-eclampsia.

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