# Pre-eclampsia Prediction Panel

## Introduction to Pre-eclampsia

Hypertensive disorders are the most common medical problems encountered in pregnancy, affecting up to15% of pregnancies and accounting for approximately 25% of antenatal admissions. Notably Pre-eclampsia (PE) is a major cause of maternal and fetal or neonatal mortality and morbidity. The disorder complicates 5%-7% of all pregnancies [1]. Each year, an estimated 50,000 women die from PE worldwide [2]. If Pre-eclampsia is not diagnosed and closely monitored, it can lead to potentially life-threatening complications including Eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low platelets), disseminated intravascular coagulation, stroke, or organ dysfunction.

Diagnostic criteria for PE are new onset of hypertension (systolic BP ≥140 mmHg, or diastolic BP ≥90 mmHg atleast on 2 determinations) and proteinuria (≥300 mg/day) after 20 weeks of gestation. A diagnosis of PE based on blood pressure and proteinuria has positive predictive value of approximately 30% for predicting PE related adverse outcomes. 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]. 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.

Till date, no treatment is available to prevent PE or hinder at least progression of the disease. The only causal therapy of PE is delivery. Current management is focused on close monitoring of these pregnancies in combination with treatment of hypertension and inducing (early) delivery when indicated. Although no therapeutic or preventive strategy is available yet, clinical experience suggests that early detection, monitoring and supportive care are beneficial to the mother and the fetus. To optimize this, reliable prediction of PE would be helpful allowing closer prenatal monitoring, timely diagnosis and timely intervention.
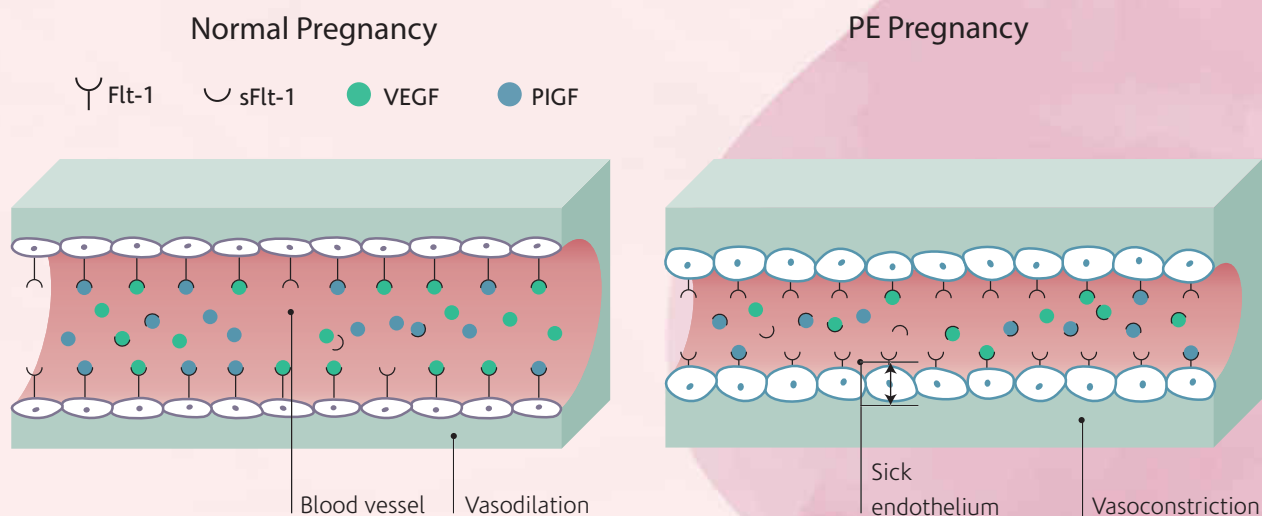
Various clinical studies have reported that routine clinical measurement of soluble Fms-like tyrosine kinase-1 (sFlt-1), Placental Growth F-actor (PlGF), and sFlt-1/PlGF ratio may be particularly beneficial for the prediction of PE and in the differential diagnosis of patients with atypical presentation of PE. sFlt-1 and PlGF may predict the onset of PE, eclampsia or HELLP some weeks before the actual onset of the disease, this would mean that these angiogenic factors may help physicians to diagnose the disease earlier compared to the traditional diagnosis of PE [4,5].

# Pathophysiology

PE appears to progress in two stages: The first, pre-clinical stage is characterized by poor placentation, resulting from insufficient endovascular invasion of fetal extravillous cytotrophoblasts into the maternal spiral arterioles. The second stage of PE, the clinical manifestation of PE, reflects generalized endothelial dysfunction, resulting in vasoconstriction and end organ damage.

The cause of pre-eclampsia is not fully understood, but there is growing evidence that angiogenic growth factors such as PlGF and sFlt-1 play a major role in the development of pre-eclampsia. sFlt-1 is able to bind both Vascular Endothelial Growth Factor (VEGF) and PlGF. Being free in serum, it may diminish binding of these pro-angiogenic factors to their receptors. In patients with PE increased sFlt-1 is associated with decreased free VEGF and PlGF resulting in a net anti-angiogenic state causing endothelial dysfunction. Of note, sFlt-1 concentrations are high 5-6 weeks prior to onset of PE. Concentrations of free VEGF and PlGF are also found to be low several weeks prior to clinical manifestation. Increased levels of sFlt-1 and reduced levels of PlGF herald the onset of PE, whereas the ratio of sFlt-1/PlGF, an index reflecting changes in both biomarkers, is a better predictor of PE than either measure alone [6]. The intra-individual rate of change of the sFlt 1/PlGF ratio is highly predictive of overall PE risk [7]. Severity of disease and time of onset (early onset vs late onset PE) seem to correlate with the dimension of change in either sFlt-1 or PlGF serum levels.

## Increased sFlt-1 and decreased PlGF are linked to reduced blood flow to the placenta

### Normal Pregnancy

Y Flt-1    ∪ sFlt-1    ● VEGF    ● PlGF

Blood vessel | Vasodilation

### PE Pregnancy

Sick endothelium | Vasoconstriction

**In PE, blood flow is reduced to the placenta and may lead to fetal growth restriction**

Powe et al (2011). Circulation 123: 2856-2869

PE: Preeclampsia; PlGF: Placental growth factor; sFlt-1: Soluble fms-like tyrosine kinase-1
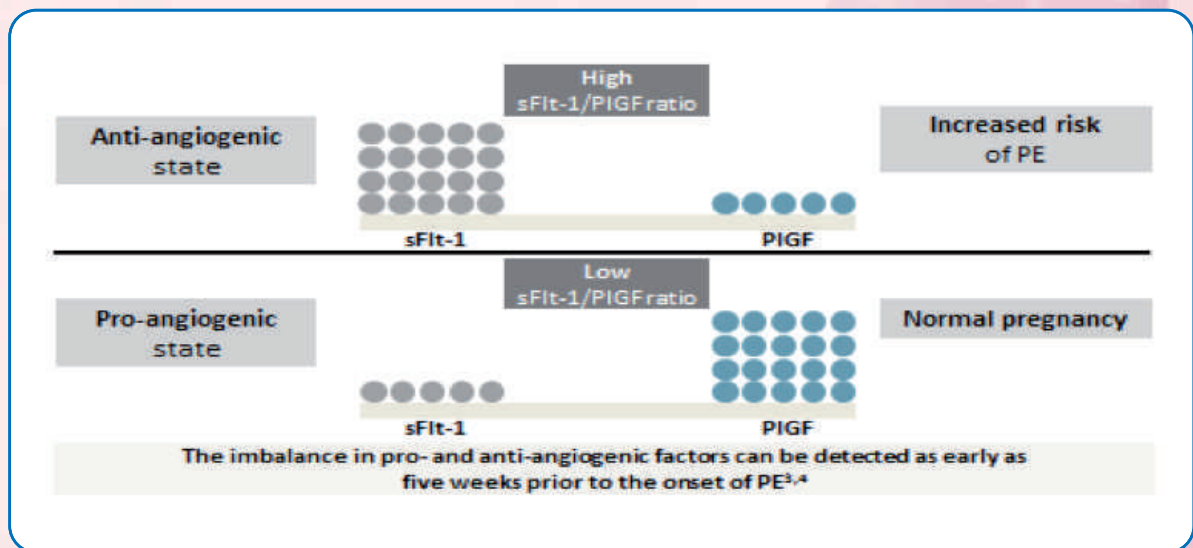
Figure 2: PE is associated with an imbalance of sFlt-1 and PlGF

## Prognosis Study[5]

PROGNOSIS (Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study) was designed to investigate the value of using the sFlt-1:PlGF ratio for the short term prediction of the presence or absence of preeclampsia in women with clinical suspicion of the syndrome. 1273 patients with suspected pre-eclampsia in the gestational age of 20-34 weeks were enrolled in the study. An sFlt-1:PlGF ratio of 38 or lower had a negative predictive value (i.e., no preeclampsia in the subsequent week) of 99.3% (95% confidence interval [CI], 97.9 to 99.9), with 80.0% sensitivity (95% CI, 51.9 to 95.7) and 78.3% specificity (95% CI, 74.6 to 81.7). The positive predictive value of an sFlt-1:PlGF ratio above 38 for a diagnosis of preeclampsia within 4 weeks was 36.7% (95% CI, 28.4 to 45.7), with 66.2% sensitivity (95% CI, 54.0 to 77.0) and 83.1% specificity (95% CI, 79.4 to 86.3). The study concluded that sFlt-1:PlGF ratio of 38 or lower can be used to predict the short-term absence of preeclampsia in women in whom the syndrome is suspected clinically.

## How to use sFlt-1/PlGF ratio?

At the outset, it is emphasized that:

1. The sFlt-1/PlGF ratio has not been evaluated as a screening test.

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.
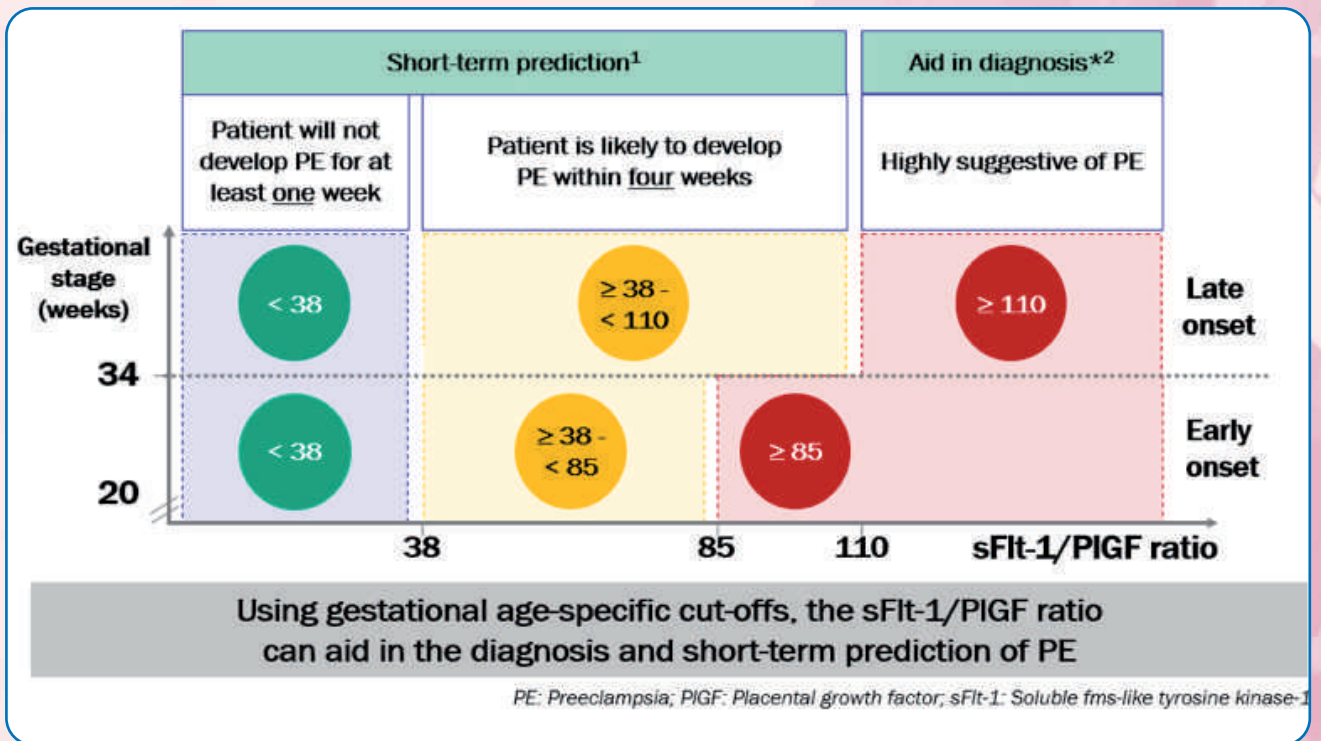
## NICE Recommendations, 2016

sFlt-1/PlGF ratio when used with standard clinical assessment and subsequent clinical follow-up, show promise in helping to diagnose (rule-in) pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation [8].

Suspicion of clinical diagnosis of PE may be based on one or more of the following criteria:

- New onset of elevated BP
- Aggravation of pre-existing hypertension
- New onset of protein in urine
- Aggravation of preexisting 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).
  - PE-related findings: low platelets, elevated liver transaminases, IUGR or abnormal uterine perfusion detected by Doppler sonography with mean PI > 95th percentile in second trimester and /or bilateral notch.

## How to interpret the results?



Short-term prediction[1] | Aid in diagnosis*[2]

| Patient will not develop PE for at least one week | Patient is likely to develop PE within four weeks | Highly suggestive of PE |

Late onset: < 38 | ≥ 38 - < 110 | ≥ 110

Early onset: < 38 | ≥ 38 - < 85 | ≥ 85

Gestational stage (weeks): 34, 20

sFlt-1/PlGF ratio: 38, 85, 110

Using gestational age-specific cut-offs, the sFlt-1/PlGF ratio can aid in the diagnosis and short-term prediction of PE

PE: Preeclampsia; PlGF: Placental growth factor; sFlt-1: Soluble fms-like tyrosine kinase-1

- sFlt-1/PlGF ratio, an sFlt-1/PlGF ratio < 38 rules out PE for at least one week, irrespective of gestational age, providing reassurance to the physician and the patient. With more than 80% of patients belonging to this patient group, clinicians are able to exclude the majority of patients, keeping them in routine antenatal care, and focus on those who need more attention and care[9]

- an sFlt-1/PlGF ratio above 85 (early onset PE) or above 110 (late onset PE) is highly indicative of PE[9]

- sFlt-1/PlGF ratio, an sFlt-1/PlGF ratio 38–85 (early onset PE) or 38–110 (late onset PE) provides extra information as to which women are at moderate risk or at high risk of developing PE within four weeks[9]

## Conclusion

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. The test should be used in the population in which it is most reasonable, i.e., in the high-risk population.

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