Role of sFlt-1 and PlGF Ratio in the Diagnosis, Prediction and Prognosis of Pre-eclampsia: A Review of Literature with Highlights from Real World Indian Experience

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ABSTRACT

Pre-eclampsia (PE) is a globally prevalent complication of pregnancy whose prevalence in India is near the higher value of the global average. The diagnosis and prediction of PE is currently based on nonspecific clinical signs such as hypertension and proteinuria. PE is associated with significant morbidity and mortality for the mother as well as the fetus. Placental growth factor (PlGF) and soluble Fms-like tyrosine kinase 1 (sFlt-1) are key factors in the pathophysiology of PE. In PE patients, sFlt-1 levels increase and PlGF levels fall, resulting in an elevation of the sFlt-1/PlGF ratio. A recent NICE recommendation has included sFlt-1 PlGF ratio for the diagnosis of early PE. The sFlt-1/PlGF ratio appears to be an important triage tool in patients at risk of placenta-related disorders, in the second half of pregnancy, and also helps stratify those likely to develop adverse fetal outcomes from the others. The diagnostic strategy for PE is based on a dual cut-off. The suggested cut-offs between 20+0 and 33+6 weeks are ≤33 and ≥85 for rule-out and rule-in of PE respectively, and the values for 34+0 weeks and beyond are ≤33 and ≥110 respectively. A preliminary analysis of a study being conducted in India showed that the usage of sFlt-1/PlGF ratio resulted in continuation of stable pregnancies beyond 37 weeks without increase in perinatal mortality. Implementation of sFlt-1/PlGF ratio in the diagnostic process may help in optimizing care by improving management of women with suspected PE.

Keywords: Pre-eclampsia; sFlt-1; PlGF; sFlt-1/PlGF ratio; Diagnosis and prediction.

INTRODUCTION AND EPIDEMIOLOGY

Pre-eclampsia (PE) is a pregnancy-related hypertensive disorder, which is characterized by elevated blood pressure and proteinuria, and can progress to multiple organ system involvement. The clinical definition of PE, as given by the Royal College of Obstetricians and Gynaecologists[1] and International Society for the Study of Hypertension in Pregnancy[2], includes arterial hypertension during pregnancy (blood pressure ≥ 140/90 mm Hg after 20 weeks of gestation) and significant proteinuria (>0.3 g/24 h).

PE affects around 3–8% of pregnancies worldwide, and is estimated to be responsible for the death of around 70,000 women annually across the world.[3] The impact of PE is reported to be more severe in developing countries.[4] In fact, PE is estimated to be the second most frequent cause of maternal mortality globally. In addition, PE is also responsible for the loss of around 300,000–500,000 newborn lives annually due to the perinatal consequences of PE.[5]

According to the National Health Portal of India, the incidence of PE in India is around 8–10% among the pregnant women.[6] According to a study reported in 2014, the prevalence of hypertensive disorders of pregnancy and PE in pregnant women in India was 7.8% and 5.4% respectively.[7] Thus, the prevalence of PE in India is on the higher side of the global average.

PE can increase both fetal and maternal mortality and morbidity. In the fetus, PE may result in adverse outcomes such as preterm birth, fetal demise/stillbirth, intrauterine growth restriction (IUGR),

neonatal thrombocytopenia, bronchopulmonary dysplasia, and neurodevelopmental disorders such as cerebral palsy.[8] Failure of early diagnosis and close monitoring of pregnancies complicated by PE may lead to potentially life-threatening complications such as eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes and low platelets), disseminated intravascular coagulation, stroke, or organ dysfunction. Further, women suffering from PE during pregnancy may have a higher risk of placental abruption.[9] Latest evidence suggests that PE can have a significant impact on the cardiovascular health of both mother and child.[10] PE may increase the risk of premature cardiovascular disease, such as chronic hypertension, ischemic heart disease, and stroke, later in life of the mother, whereas children born after pre-eclamptic pregnancies may suffer from an increased risk of coronary heart disease, stroke, and metabolic syndrome in their adult lives.[11]

Pathogenesis of Pre-eclampsia and Clinical Correlation

The basic pathological change leading to PE is a defect in placentation; specifically, it is a disorder of dysfunctional syncytiotrophoblast.[12] First proposed in 1964, this theory explains that the failure of the fetal extravillous trophoblast invasion of the maternal spiral arteries in the placenta results in an insufficient reduction in preplacental resistance. This creates placental insufficiency and ischemia.[13] The origins in defective placentation is also the reason why fetal growth restriction is more intense in early PE (<34 weeks) when compared to late PE (≥34 weeks).[14]

The classical clinical features of PE arise as a result of the placental dysfunction. They are neither specific nor precise: they only allow the obstetrician to recognize the condition. In fact, studies have shown that the classical hallmarks of PE (raised blood pressure and proteinuria) have a positive predictive value for adverse maternal and perinatal pregnancy outcomes of as low as 18–20%.[15] Consequently, the current guidelines of the American College of Obstetricians and Gynaecologists (ACOG)[16] and the International Society for the Study of Hypertension in Pregnancy (ISSHP)[17] have not included the presence of proteinuria as a diagnostic criterion for PE: the condition can now be diagnosed by documenting new onset hypertension after 20 weeks of gestation, which is associated with proteinuria or evidence of end-organ dysfunction (such as renal, hepatic, and pulmonary dysfunction, thrombocytopenia, or neurological complications). As a result of the absence of specific criteria for diagnosis of PE, and also due to the nonspecific presentation of the syndrome, it has been observed that many patients are admitted unnecessarily, while some patients who require close monitoring are missed.[14] Thus, alternative modalities for the accurate and timely diagnosis, prediction and prognosis of PE, are the need of the hour. Accurate prediction of PE will enable the obstetrician to take steps to control its adverse outcomes and to continue the pregnancy as near to term as possible.[16]

Role of Placental Growth Factor (PlGF) and Soluble FMS-like Tyrosine Kinase 1 (sFlt-1) in Pathogenesis of Pre-eclampsia

The placental ischemia arising out of inefficient placentation has been observed to result in the secretion and release into the maternal circulation of certain proinflammatory and anti-angiogenic factors such as soluble FMS-like tyrosine kinase-1 (sFlt-1)[18] and soluble endoglin (sEng, which interferes with functioning of transforming growth factor).[19]

The sFlt-1 has close structural resemblance to the membrane-bound Flt-1 receptor; the latter recognizes and binds to vascular endothelial growth factor (VEGF) (therefore, Flt-1 is also known as VEGFR-1) and placental growth factor (PlGF), and subsequently initiates actions of both of these growth factors. On the other hand, the sFlt-1 is a soluble/circulating version of Flt-1 receptor, which lacks the effect or domain of Flt-1. In fact, sFlt-1 is formed as a result of alternative splicing of Flt-1 RNA due to hypoxia.[20] Thus, sFlt-1 circulates freely in the plasma, acting as a decoy receptor to circulating VEGF and PlGF. The binding of sFlt-1 with VEGF and PlGF is thought to cause widespread endothelial dysfunction, which progresses to the clinical manifestations of pre-eclampsia.[14]

Prospective studies have found that sFlt-1 levels are increased in pregnant women who develop pre-eclampsia several weeks before the clinical detection of the condition, when compared with pregnant women with normal outcomes.[21]

PlGF is in fact a type of VEGF, and is produced by placenta (especially by syncytiotrophoblast, cytotrophoblast, and extra-filamentous trophoblast), in addition to choriocarcinoma cells and endothelium of the human umbilical vein. Alteration of the circulating

levels of PlGF due to excess binding of PlGF with sFlt-1 results in an imbalance in the placental vessel angiogenesis. Reduced PlGF levels reflect abnormalities in placental development, and are often associated with the occurrence of PE.[22] Further, similar to increased sFlt-1 levels, the reduction in PlGF levels begins 11 to 9 weeks before the onset of clinical features of PE with substantial reductions only during the 5 weeks before the onset of clinical features.[20]

Thus, failed trophoblastic invasion of the maternal spiral arteries and the resultant non-lowering of resistance and reduced blood flow of placenta stimulate the secretion of sFlt-1; the sFlt-1 acts as a decoy receptor for PlGF, resulting in the lowering of the latter's levels. An increase and fall respectively in the levels of sFlt-1 and PlGF leads to an increase in the sFlt-1/PlGF ratio. All these occur weeks before PE manifests clinically.

Role of sFlt-1 and PlGF in the Management of Pre-eclampsia

Alterations in both the markers—sFlt-1 and PlGF– are observed as early as in the 2nd trimester of pregnancy. This allows for the utilization of the sFlt-1/PlGF ratio for the diagnosis and prediction of PE. In fact, elevated sFlt-1/PlGF ratio has been detected in the second half of pregnancy in women diagnosed with PE, and limited evidence shows it to be elevated in women who develop other placenta-related disorders such as IUGR and stillbirth. Further, these alterations are more pronounced in early-onset disease, and correlates well with the severity of the condition.[23] The ratio may also be helpful to differentiate PE/HELLP from gestational hypertension or chronic hypertension.[24] Finally, these alterations predate the clinical symptoms of the conditions, thereby are invaluable in the early stratification of women at high risk of developing PE (and other placenta-related disorders) from the other low risk pregnant women.[25] Specifically speaking, sFlt-1/PlGF ratio cut-offs of > 85 (20 + 0 to 33 + 6 weeks) and > 110 (34 + 0 weeks to delivery) are shown to be strongly suggestive of PE.[26]

Thus, the increased sFlt-1/PlGF ratio is found to closely reflect the basic pathology of inefficient placentation and placental ischemia, and is considered to be a promising biomarker for prediction, diagnosis and prognosis of the disease.[27] More importantly, sFlt-1/PlGF ratio assay is currently available for clinical use, and has also been recommended recently (in 2016) by the National Institute for Clinical Excellence (NICE) to rule out PE in patients presenting with suspicion of the disease.[9]

The sFlt-1/PlGF ratio may be used for the diagnosis of PE in pregnant women from 20 weeks' gestation upto the time of delivery. In addition, the ratio can also be used to help predict PE, eclampsia and HELLP syndrome in the short term. A dual cut-off values for sFlt-1/PlGF ratio have been recommended based on the gestational age for the diagnosis of PE. The cut-off values are summarized in the **Table 1**.[26,9]

The NICE guidelines released in May 2016 recommend that the assay of sFlt-1/PlGF ratio, along with standard clinical assessment and subsequent clinical follow-up, may be used to rule out PE in women presenting with suspected PE between 20 weeks and 34 weeks plus 6 days of gestation.[9]

Table 1

Cut-off values for sFlt-1/PlGF ratio[26, 9]

Purpose	Age of gestation	Rule-out or Rule-in	Cut-off values of sFlt-1/PlGF ratio
Aid in diagnosis of pre-eclampsia	From 20 weeks to 33 weeks + 6 days	Rule-out	33
		Rule-in	85
	From 34 weeks to delivery	Rule-out	33
		Rule-in	110
Short-term prediction of pre-eclampsia	From 24 weeks to 36 weeks + 6 days	Rule-out*	<38
		Rule-in**	>38
*Rule-out pre-eclampsia for 1 week			
**Rule-in pre-eclampsia within 4 weeks			
[sFlt-1: Soluble FMS-like tyrosine kinase-1; PlGF: Placental growth factor]			

Global Evidence in Support of Use of sFlt-1/ PlGF ratio in Early and Late Pre-eclampsia

Numerous studies done worldwide have established the value of sFlt-1/PlGF ratio in the diagnosis, prediction as well as prognosis of PE. A case-control study reported in 2014 devised the dual cut-off values for the sFlt-1/ PlGF ratio for the diagnosis and prediction of PE and HELLP in early and late pregnancy. The sensitivity and specificity values for the cut-off values at <33 and >85, between 20+0 and 33+6 weeks, were 95%/94% and 88%/99.5%, respectively; similar values for the cut-offs of ≤33 and ≥110 after 34+0 weeks were 89.6%/73.1% and 58.2%/95.5%, respectively. The use of dual cut-offs, as mentioned in **Table 1** have been found to enhance the diagnostic accuracy of the sFlt-1/PlGF ratio as a diagnostic tool for PE.[26]

A 2012 study on 630 singleton pregnancies revealed that the sFlt-1/PlGF ratio was significantly higher in patients with PE as compared with controls and with patients having chronic and gestational hypertension in both <34 weeks and ≥ 34 weeks (P<0.001). The ratio can thus reliably discriminate between different types of pregnancy-related hypertensive disorders.[24]

The PROGNOSIS study reported in 2016 was a prospective, multicentric observational study performed on 1050 pregnant women of 24– 36 weeks 6 days gestation. It concluded that a cut-off of sFlt-1/ PlGF ratio of 38 has a significant predictive value in the diagnosis of PE and related conditions. The main findings of the study are represented in **Table 2**.[28]

The study also showed that a ratio of ≤ 38 was predictive of the absence of fetal adverse outcomes (perinatal or fetal death, delivery at a gestational age of less than 34 weeks, intrauterine growth restriction, placental abruption, the respiratory distress syndrome,

necrotizing enterocolitis, and intraventricular hamorrhage) within 1 week (negative predictive value 99.3% [95% CI, 97.9 to 99.9]) while a ratio> 38 was predictive of the presence of these outcomes at 4 weeks (positive predictive value 47.5% [95% CI, 38.4 to 56.8]).[28]

A secondary analysis of the above-mentioned study was performed to explore if a higher sFlt-1/PlGF has any association with time to delivery and preterm birth. It was observed that women with sFlt-1/PlGF ratio greater than 38 had a 2.9 times greater likelihood of imminent delivery (that is, delivery on the day of the test), Shorter remaining time to delivery of 17 vs 51 days (median; interquartile range [IQR] 10–26 days) and a 71.2% versus 17.8% likelihood of developing preterm birth in women with the ratio below 38, regardless of whether or not they developed PE. Thus, a higher sFlt-1/PlGF ratio indicates the potential for a shorter pregnancy and preterm delivery.[29]

In a 2017 study from the UK involving 318 pregnant women with PE, screened from 12,305 singleton pregnancies, it was observed the sFlt-1/PlGF ratio is helpful in the routine screening of singleton pregnancies for the detection of PE for upto 4 weeks of the assay. A sFlt-1/PlGF ratio of > 38 resulted in the detection of 78.6% and 76.6% cases of PE within 1 week and within 4 weeks of assay respectively, with a false positive rate of 4.5% and 4.1% respectively. Thus, the incidence of unnecessary hospitalization if using sFlt-1/ PlGF ratio cut-off of 38 is 4.5%., but it will result in the early detection of PE in over 76% of cases.[30]

In a prospective study published in 2016, pre-eclampsia Open Study (PreOS), the influence of sFlt-1/ PlGF ratio on the clinical decision-making by physicians in women with suspected PE was reported. Physicians documented their decision of hospitalization and

Table 2

Main findings of PROGNOSIS study[28]

sFlt-1/PlGF ratio value	Predictive value	Sensitivity (95% CI)	Specificity (95% CI)
≤ 38	Negative predictive value of 99.3% for the subsequent week (99.3% chance of not developing pre-eclampsia in the subsequent week)	80.0% (51.0–95.7)	78.3% (74.6–81.7)
> 38	Positive predictive value of 36.7% in the subsequent 4 weeks (36.7% chance of developing pre-eclampsia in the subsequent 4 weeks)	66.2% (54.0–77.0)	83.1% (79.4–86.3)

no hospitalization based on clinical features alone, following which the sFlt-1/PlGF ratio was disclosed. Subsequent to the knowing of the sFlt-1/PlGF ratio result, a revised decision was documented in 20/118 (17.0%) women: 13 women who were supposed to be hospitalized were now not hospitalized, and 7 women who were supposed to be not hospitalized were now hospitalized. The incidence of PE was highest, i.e. 57.1% in the group where the decision hospitalisation decision was changed from no to yes following availability of sFlt-1/PlGF results. The incidence of PE in women in whom the decision of hospitalization changed from yes to no was similar (~15.5%) to women in whom the decision of no hospitalization remained unchanged.[31]

A 2017 meta-analysis examined the dual cut-off strategy of sFlt-1/PlGF ratio for risk stratification in the detection of PE, as mentioned in the **Table 1** previously. The meta-analysis found out that using the dual cut-off strategy resulted in a sensitivity of 95.3% (95% CI 90.6-98.1%) and 88.6% (95% CI 82.9-92.9%) respectively for early and late onset PE, and a specificity of 97.6% (95% CI 95.2-98.9%) and 94.2% (95% CI 91.4-96.3%) for early and late onset PE respectively. The study concluded that the dual cut-off system optimizes the predictive performance of the single cut-off system.[32]

In a meta-analysis of 20 studies enrolling 838 PE patients and 6138 controls reported in 2015, it was found that the pooled diagnostic sensitivity and specificity of sFlt-1/PlGF were 0.78 and 0.84 with the area under the SROC curve(AUC) of 0.88. In subgroup analyses, the diagnostic value of sFlt-1/PlGF for early-onset PE is highest with a pooled diagnostic odds ratio (DOR) of 241 and AUC of 0.98. The meta-analysis concluded that the accuracy of sFlt-1/PlGF ratio for screening PE was moderate and was high for early-onsetPE.[33]

A 2014 prospective study from Germany involving 150 patients with a high risk for PE found out that the sFlt-1/PlGF ratio was significantly higher in pregnancies complicated by PE upto 4 weeks before clinical diagnosis compared to controls. Further, in women who developed IUGR, the levels of the sFlt-1/PlGF ratio were found to be consistently and significantly higher throughout pregnancy, when compared to PE/control patients. The study concluded that repeated measures of the sFlt-1/PlGF ratio can reliably identify complications of pregnancy such as IUGR and PE, well before clinical diagnosis and thus has a valuable role in the diagnosis of both of these conditions.[34]

Real World Evidence Experience from an Indian Setting

In an ongoing real-world study in a tertiary care center located in India, the sFlt-1/PlGF ratio is being used for guiding timing of delivery in singleton pregnancies with chronic or gestational hypertension. Subjects between 28–37 weeks of gestation are tested serially using the cut-offs for diagnosis mentioned in **Table 1**. In an interim analysis, the outcomes in 21 subjects (59 samples) were compared with 21 contemporaneous pregnancies with hypertension from previous years before the use of sFlt1/PlGF ratio.[35]

Use of sFlt1/PlGF ratio for monitoring resulted in reduction of deliveries at or below 30 weeks (4.7% versus 19%), increase in deliveries beyond 37 weeks (33.3% vs 0), delayed delivery in subjects with fetal growth restriction (50% versus 0) and reduction in neonatal intensive care unit stay (19% versus 47.6%). Most importantly, there were no cases of perinatal death, eclampsia or maternal death in the study group as against 2 in the historical controls.[35] Further randomized studies in India using the sFlt-1/PlGF ratio cut-off of 38 validated in global studies could be helpful.

Conclusion and Way Forward

The diagnostic and predictive value of the sFlt 1/PlGF ratio in patients at risk of placenta-related disorders such as PE and HELLP syndrome, is being increasingly reported in the contemporary literature. The estimation of the sFlt-1/PlGF ratio has the potential to be an invaluable additional tool in the detection and prediction of PE. Repeat measurements of the sFlt-1/PlGF ratio are suggested to improve individual risk assessment in these patients. The suggested cut-offs for diagnosis of PE between 20+0 and 33+6 weeks are ≤33 and ≥85 for rule-out and rule-in of PE respectively, and the values for 34+0 weeks and beyond are ≤33 and ≥110 respectively. A single cut-off of 38 is suggested for prediction of PE. The NICE in its recent recommendations has included the use of sFlt-1/PlGF ratio for the detection of PE. Pregnant women from India may benefit from this new diagnostic tool, especially because the reported prevalence of PE is on the higher side in India. Though cost may be a consideration in the Indian scenario, this test would help stratify at risk patients who require close surveillance and add value to clinical decision making. Further studies are required in

the Indian set-up to validate the results obtained from predominantly global studies.

ACKNOWLEDGMENTS

SOURCES OF SUPPORT

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