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Biomarkers

Utility of Biomarkers in Obstetric Patients With Preeclampsia

Preeclampsia is a complex syndrome whose complications bear an impact on perinatal morbidity and mortality. Angiogenic biomarkers may significantly impact both the decision to admit patients and risk stratification and may also help guide patient management and level of care.

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Preeclampsia is one of the main causes of maternal and foetal morbimortality, with a global incidence of 3-5%, and is a frequent reason for admission to the Intensive Care Unit (ICU) (Drogüe 2015). Preeclampsia is the result of deficient placentation due to maladaptation of the uterine spiral arteries with restricted trophoblast invasion (8-18 weeks). These alterations can lead to poor placental perfusion, which is associated with a complex interaction between a "stressed" syncytiotrophoblast and a "susceptible" maternal cardiovascular system, potentially leading to inflammatory, immunological and haemodynamic effects which may or may not have maternal and foetal organ consequences (Cerderia et al. 2018).

For more than a century, the most common form to diagnose preeclampsia has been through documentation of elevated blood pressure; nonetheless, there are many patients with neurological (eclampsia), hepatic (HELLP syndrome: haemolysis, elevated liver enzymes and thrombocytopenia) or other manifestations which do not critically elevate the blood pressure. International guidelines usually recommend suspecting and making the diagnosis by means of clinical parameters and past medical history, arguing that it is a low-cost screening approach, although at the expense of poor detection (MacDonald et al. 2022). Currently, however, the biomarkers related to syncytiotrophoblastic stress play an important role for the differential diagnosis in difficult cases, as well as in prediction of its development and prognosis (Cerderia et al. 2018).

Prediction of Preeclampsia

Classically, guidelines recommended to make the diagnosis of preeclampsia through assessment of risk factors and mere clinical manifestations; however, this simple approach is at the expense of a low detection rate (sensitivity) for preterm preeclampsia (40%) and term preeclampsia (35%) (Magee et al. 2022). Definitive prediction of this syndrome still remains unclear; the proposed tools that are considered effective are also considered complex and expensive. Nevertheless, an early detection should prompt the clinician to make efforts of further preventing this disease. It should also prompt the clinician to consider the potential costs of short and long-term adverse perinatal outcomes resulting from preeclampsia (Magee et al. 2021) (**Table 1**).

1. Timely work-up: before 28 weeks' gestation for early preeclampsia and before 36 weeks' gestation for late preeclampsia.
2. Clinicians should understand that many of these biomarkers are present in pregnancies with preeclampsia, but some of them have not been studied in pregnant patients without preeclampsia. This validation is necessary.
3. Generating new evidence in this area is essential.
4. In practice, the use of biomarkers (e.g., sFlt-1/PlGF) has the ability of ruling out disease in suspected patients.
5. Despite the growing literature, availability of most biomarkers is low in resource-constraint settings.

Table 1. Considerations of preeclampsia biomarkers

Multiple tools have been proposed for the prediction of preeclampsia development, including clinical measurements, ultrasonographic and laboratory parameters. Laboratory biomarkers that have been evaluated in relation to this disease include proinflammatory agents, derivatives of lipid metabolism and oxidative stress, molecules of maternal organ dysfunction and molecules of fetoplacental function (Magee et al. 2021) (**Table 2**).

Biomarker	Trend	Sensitivity (%)	Specificity (%)	AUC
PlGF	↓	62	60	ND
PP13	↓	44	80	0.83
Endothelin-1	↑	96.8	51	ND
PAPP-A	↓	11-23	ND	ND
NGAL	↑	ND	ND	0.75
S-Eng	↑	63	57	ND
Activin A	↑	20	ND	0.59
Inhibin A	↑	16-35	ND	ND
sFlt-1/PlGF	↑	38-58.2	95	ND

Table 2. Biomarkers of the first and second trimesters of pregnancy (MacDonald et al. 2022; Griffin and Shennan 2014). ND: Not determined.

Placental Proteins

Pregnancy–associated plasma protein-A (PAPP-A) and alpha-fetoprotein (AFP) have both been associated with adverse perinatal outcomes, including preeclampsia. When combined, an AFP/PAPP-A ratio of >10 resulted in an increased relative risk for preeclampsia, although with poor statistical power (MacDonald et al. 2022).

Placental and endothelial RNA

RNAs derived from placental microvilli (mRNAs, miRNA, Gata2, mir-574-5p, mir1972 and mir-4793) associated with preeclampsia have been identified in maternal circulation; however, a systematic review concluded that it is difficult to draw firm conclusions regarding their usefulness in preeclampsia prediction, given some limitations in adjustments for clinically relevant variables (MacDonald et al. 2022). Some substances derived from endothelial dysfunction, such as those derived from nitric acid metabolism (asymmetric dimethylarginine) and pro-endothelin 1, have been shown to bear alterations in pregnancies with preeclampsia, although with a modest predictive effect; therefore, their routine use is not currently recommended (MacDonald et al. 2022).

Circulating angiogenic proteins

Currently, these are considered the most promising biomarkers for the prediction and diagnosis of preeclampsia. They can be used as screening tools in the first trimester of pregnancy, even in twin pregnancies (Drogüe et al. 2015). In subsequent stages of pregnancy (>20 weeks' gestation), angiogenic factors have been associated with prediction of early preeclampsia, which is in turn associated with a higher risk of complications (Cerdeira et al. 2018). Placental dysfunction in preeclampsia causes altered expression of placental proteins with potential endothelial damage (Drogüe et al. 2015). The FLT-1 protein-encoding gene produces a complete transmembrane receptor (rFlt-1) that binds to vascular endothelial growth factor (VEGF) and to placental growth factor (PlGF). Under certain conditions, a soluble form of this transmembrane receptor (sFlt-1) is released, which lacks cytoplasmic domains and acts as a decoy receptor for VEGF and PlGF in the circulation, preventing their angiogenic function (Cerdeira et al. 2018) (**Figure 1**).

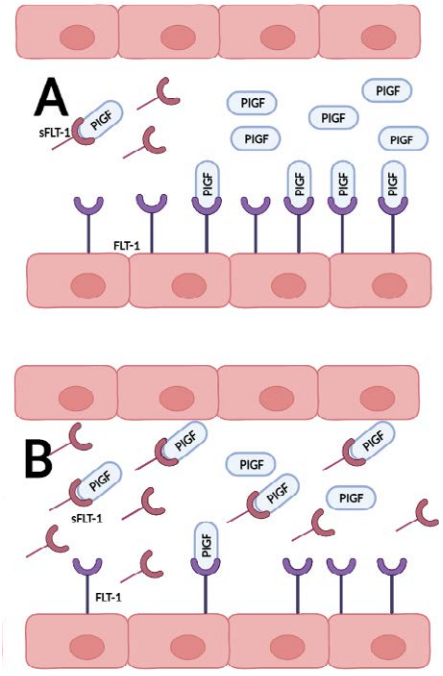

Figure 1. sFlt-1/PlGF ratio in preeclampsia. A) Normal sFlt-1/PlGF ratio: transmembrane FLT-1 receptors (purple) allow signalling of second messengers when stimulated by PlGF (pro-angiogenesis); a ratio of low sFlt-1 to high PlGF is maintained. B) Abnormal sFlt-1/PlGF ratio: high concentrations of sFlt-1 (pink) block second messenger signalling by binding to circulating PlGF (anti-angiogenesis); a ratio of high sFlt-1 to low PlGF is maintained.

Preeclampsia Diagnosis

With classical clinical diagnosis (elevated blood pressure after 20 weeks' gestation, plus proteinuria), positive predictive value is deemed at 20% (Cerdeira et al. 2018). Reference ranges and cut-off points for the diagnosis of preeclampsia using the sFlt-1/PlGF ratio have been documented: ≥85 for early preeclampsia (20–33.6 weeks gestation) and ≥110 for late preeclampsia (34–36.6 weeks gestation). In addition, a sFlt-1/PlGF ratio of ≤33 has been observed to perform well for exclusion of preeclampsia diagnosis (Cerdeira et al. 2018).

Regarding PlGF, cut-off levels for the diagnosis of preeclampsia have been defined as positive when they are below the fifth percentile adjusted for gestational age (<36 pg/ml), with sensitivity of 100% (95% CI 86-100) and specificity of 96% (95% CI 85-99) for early onset preeclampsia (Cerdeira et al. 2018). These biomarkers are important to accurately rule out preeclampsia, given their high negative predictive values. This feature allows for reduction in the number of admissions and/or unnecessary interventions, thus permitting a better allocation of resources (Cerdeira et al. 2018).

The determination of these biomarkers is useful for making differential diagnoses of patients with clinical presentations similar to preeclampsia (Cerdeira et al. 2018), some of which are frequent causes of admission to the ICU, such as chronic or acute kidney disease, hypertension, gestational thrombocytopenia, thrombocytopenic purpura, hyperaldosteronism, hyperparathyroidism, pheochromocytoma or paraganglioma, Cushing's syndrome, or obstructive sleep apnoea (Phinder-Puente et al. 2022).

Prediction of Complications

In a retrospective study that included 1,379 patients, it was shown that the levels of lactic dehydrogenase, liver enzymes, and creatinine were directly related to an increase in protein levels in a 24-hour urine collection above 5g. This relationship also includes other data such as HELLP syndrome, preterm birth, and oligohydramnios (Yildiz and Yilmaz 2022); nevertheless, international guidelines have discarded their usefulness in the prediction of adverse perinatal outcomes (Ukah et al. 2017). Furthermore, liver function tests (such as AST, ALT and LDH) have been reported to be moderate predictors of maternal and foetal complications (Ukah et al. 2017).

Corominas and colleagues (2022) demonstrated that a serum uric acid concentration less than 1.5 mg/dl is a useful, accessible, and inexpensive tool for the exclusion of preeclampsia diagnosis during the first trimester of pregnancy, with a high sensitivity. Uric acid levels should be monitored during pregnancy to assist in the identification and prediction of preeclampsia.

During the second half of pregnancy, angiogenic markers appear to be particularly useful in the short-term prediction of potential development of severe forms of the disease such as HELLP syndrome and eclampsia. The PROGNOSIS study (Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study) found that a sFlt-1/PlGF ratio of <38 could rule out preeclampsia in the following 7 days, with a negative predictive value of 99.3% (95% CI 97.9– 99.9), sensitivity of 80% (95% CI 51.9–95.7) and specificity of 78.3% (95% CI 74.8–81.7). This high negative predictive value indicates that women with suspected preeclampsia are unlikely to develop this disease, allowing for rationalisation of treatment and promoting patient reassurance (Sroka and Verlohren 2021).

It has been observed that pregnant patients with an elevated sFlt-1/PlGF ratio are prone to developing adverse perinatal events: placental abruption, acute pulmonary oedema, eclampsia, small-for-gestational-age (SGA) newborns, intrauterine growth restriction, hypertransaminasaemia and haematological alterations such as thrombocytopenia. This ratio's performance as a prediction tool of complications is superior compared to elevated blood pressure (Rana et al. 2013).

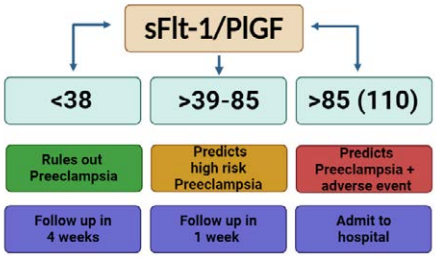

Figure 2. Utility of the sFlt-1/PlGF ratio in clinical practice.

A sFlt-1/PlGF ratio of <38 rules out preeclampsia, with a negative predictive value of 94.3% over 4 weeks. Women with suspected preeclampsia and sFlt-1/PlGF ratio ranging from 38 to 85 should be classified as at high risk for developing preeclampsia. In these patients, a one-week follow-up is suggested, depending on other clinical findings. In women with pregnancies >34 weeks' gestation, the sensitivity and specificity of a sFlt-1/PlGF ratio of ≥110 are 58.2% and 95.5%, respectively, being clearly associated with an increase in perinatal adverse events; thus, these patients must be followed up in the hospital (Cerdeira et al. 2018). The standard use of this ratio increases the risk of early delivery (with a mean of 17 days), in addition to increasing the risk of imminent delivery, although no association of altered sFlt-1/PlGF ratios with development of preterm labour has been found (Sroka and Verlohren 2021) (**Figure 2**).

Other biomarkers of maternal organ function, such as NT-proBNP, can predict complications such as preeclampsia-related preterm birth (<34 weeks gestation), with a cut-off point of >70 ng/l. If the NT-proBNP value is greater than 219 ng/L, it could surrogate a value similar to the sFlt-1/PlGF ratio for the prediction of early preeclampsia (Stepan et al. 2020; Alvarez-Fernandez et al. 2016).

Low PlGF levels were consistently associated with caesarean delivery due to foetal compromise, as well as with neonatal ICU admission, and foetal death (Alvarez-Fernandez 2016). Although attempts have been made to predict the severity of hypertensive disorders of pregnancy with haematological markers such as neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, platelet distribution width, and aspartate aminotransferase-to-platelet ratio, their clinical significance in the prediction of severe forms of preeclampsia have not been demonstrated yet (Ozkan et al. 2022).

Superimposed Preeclampsia

The sFlt-1/PlGF ratio is higher in patients with preeclampsia compared to women with normal pregnancies or women with chronic hypertension and gestational hypertension. In women with pre-existing chronic hypertension, when this ratio is higher, it accurately predicts which patients will develop preeclampsia (mainly early preeclampsia) (Stepan et al. 2020). Some authors have recognised that there is an economic impact with the use of biomarkers in preeclampsia, especially in patients at high risk for developing the disease; in this regard, there is currently no evidence for endorsement of the universal use of these biomarkers (Cerdeira et al. 2018). In women with chronic kidney disease and chronic hypertension, PlGF levels <12 pg/mL identified superimposed preeclampsia requiring delivery within the next 14 days. Importantly, PlGF levels were similar between healthy controls and women with chronic kidney disease who did not develop superimposed preeclampsia (Bramham et al. 2016).

Potential Interventions

In a pilot study, Thadhani and colleagues (2016) used an extracorporeal apheresis system to remove sFlt-1 from the maternal circulation of women with preeclampsia, which was safe and prolonged pregnancy up to 15 days.

Conclusions

Preeclampsia is a complex syndrome whose complications bear an impact on perina-

tal morbidity and mortality. Angiogenic biomarkers may significantly impact both the decision to admit patients and risk stratification and may also help guide patient management and level of care. From the study of these biomarkers, it can be concluded that the classic definition of preeclampsia (de novo hypertension plus proteinuria after 20 weeks' gestation) is outdated and is mainly based on historically described clinical conditions that precede eclamptic seizures. This vision has a low predictive value for defining such a heterogeneous pregnancy disorder with potential for multi-organ damage (**Table 3**).

Angiogenic Factors	Clinical Parameter	Adverse Pregnancy Outcome
>sFlt-1/PlGF or <PlGF alone	Hypertension	Preeclampsia**
>sFlt-1/PlGF	Seizure	Eclampsia
	Liver enzymes/platelets/ LDH/epigastric pain	HELLP syndrome
	Chronic hypertension / chronic kidney disease	Superimposed preeclampsia
	Ultrasonography	Foetal growth restriction

Table 3. Redefinition of preeclampsia syndrome, including angiogenic biomarkers. ** It has been suggested to update the definition of preeclampsia as follows: Heterogeneous maternal syndrome characterised by hypertension + de novo imbalance in angiogenic biomarkers (Stepan et al. 2020).

Conflict of Interest

None. ■

Abbreviations

sFlt-1:	Soluble fms-like tyrosine kinase-1
sEng:	Soluble endoglin
TGF-β:	Transforming growth factor beta
PAAP-A:	Pregnancy–associated plasma protein-A
AFP:	Alpha-fetoprotein

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