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# IMPORTANCE OF THE sFlt-1/PlGF RATIO IN THE EARLY IDENTIFICATION OF PREECLAMPSIA

***Ayla Gabriella Silva Ribeiro***
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/8251096578944264

***Rafael da Silva Lemos***
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/2972344057553679

***Bruno José Santos Lima***
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/6158584238563073

***Delza Correia Lima***
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/6544183380707057

***Isadora Vieira Carozo***
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/2463319410132812

***Marcela Violeta Barreto Pinto***
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/2553451558129711

***Mariana Dantas Mota***
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/7775377285699905

***Jully Cristina Vilar Barboza***
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/5672955137637024

***Ana Carolina Oliveira Santos Gonçalves***
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/3827034693453836

***Marina Prado Santos Sobral***
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/0828994482408264

***Mariana Sprakel dos Santos***
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/0081095387268674

***Michelle Fontes Sobral de Oliveira Costa***
Universidade Tiradentes, Aracaju
http://lattes.cnpq.br/3748381718649113

**Abstract: Introduction:** Preeclampsia is a multisystem disorder that occurs during pregnancy, mainly characterized by the onset of hypertension and proteinuria after 20 weeks of gestation. This condition affects 3 to 7% of pregnant women and involves changes that lead to high morbidity and mortality in the mother and newborn. For this reason, science has focused attention on the ratio between the placental biomarkers soluble Fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) in their ability to predict preeclampsia - objective of the current study. **Methods:** The work in focus is a literature review. The extraction of information was performed through articles from the VHL and PubMed databases. The research obtained 916 articles during the period from 2001 to 2020, of which 7 were selected. **Results:** Numerous experimental and clinical results, according to the researched articles, suggest that an imbalance in factors, increasing sFlt-1 and reducing PlGF, are associated with a higher risk of developing the disease. In addition, sFlt-1/PlGF tests have substantially reduced the time to clinical confirmation of preeclampsia and subsequent adverse maternal and perinatal outcomes. To predict the development of PE in the 1st trimester of pregnancy, both sFlt1 and PlGF have shown low specificity and sensitivity if used as predictors of PE in the 1st trimester, in isolation. Following the success of aneuploidy screening, several authors have sought to improve the predictive value in the 1st trimester through the development of combined models. In the following semesters, a large part of the evidence has focused on the usefulness of PlGF and the sFlt1/PlGF ratio in the 2nd and 3rd trimester of pregnancy, with promising results regarding its predictive capacity, particularly in cases of early PE. **Conclusion:** The sFlt-1/PlGF ratio is undoubtedly a good predictive marker for PE and other conditions associated with

this disease. However, in the context of implementation for *screening*, it is valid to have new scientific studies that specify the real impact of this modification on the current protocol.

**Keywords:** SFLT-1, PIGF, Diagnosis, Preeclampsia.

## INTRODUCTION

During pregnancy, blood pressure monitoring becomes even more cautious due to the maternal-fetal impacts of hypertension. This clinical condition can occur in several scenarios, such as a previous chronic condition (usually diagnosed before or up to 20 weeks of pregnancy), a gestational hypertensive syndrome (hypertension triggered after 20 weeks of gestational age), preeclampsia (hypertension and, usually, proteinuria after 20 weeks of gestational age) or, even, superimposed preeclampsia (when in addition to chronic hypertension, there is also preeclampsia).

Preeclampsia (PE) is a multisystem disorder that occurs during pregnancy, characterized primarily by the onset of hypertension (blood pressure ≥ 140x90 mmHg) and proteinuria (≥ 300 mg/day or ≥ 1+ on the urine summary tape or ratio urinary protein/creatinine ≥ 0.3) after 20 weeks of gestational age (GA). However, although this presentation is the main one, not all cases of PE present with proteinuria. Severe cases of hypertension with more than 20 weeks of GA associated with thrombocytopenia (< 100,000), creatinine > 1.1; Acute pulmonary edema, a two-fold increase in transaminases, and the presence of cerebral or visual symptoms also configure PE even in the absence of proteinuria.

This clinical condition can be classified as mild, if there are no signs of severity, or severe, in the presence of systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110, acute pulmonary edema, oliguria or signs of HELLP Syndrome, characterized by lactic dehydrogenase > 600, schizocytes, total bilirubin ≥ 1.2; AST ≥ 70 and/or platelets < 100.00. Among the signs of eclampsia, which is the main maternal-fetal risk complication of the disease manifested by maternal seizures, headache, scotomas, epigastralgia and hyperreflexia stand out.

PE affects 3 to 7% of pregnant women and involves changes that lead to high morbidity and mortality in the mother and newborn. The etiology of this comorbidity is still unknown. In 1916, Zweifel already characterized it as "the disease of theories". Numerous theories and factors have been suggested to explain its cause, but most have not been confirmed. More than 60 years ago, Page proposed the concept that in preeclampsia, placental perfusion was decreased. Currently, immunological, genetic aspects and failure of placental invasion are unanimously accepted. The demonstration of endothelial injury, associated with an exacerbated inflammatory response and the involvement of stress are the most recent theories for its occurrence.

Physiologically, in non-pregnant women, the uterine arteries are spiral and of small caliber to avoid excessive bleeding in uterine desquamation through this conformation. During pregnancy, however, trophoblastic invasions are necessary to readjust this irrigation. Thus, during gestational development, the trophoblast invades the muscular layer of the arteries that carry blood to the endometrium and promotes greater balance in the pregnant woman's blood pressure - which is naturally hypervolemic. These invading trophoblastic waves are instrumental in reducing peripheral vascular resistance and increasing blood volume to the placenta that will nourish the fetus. Naturally, the first invasion occurs in the first trimester and the second must occur by the 20th week of the GI.

Pathologically, however, some women lack the second wave of trophoblastic invasion, maintaining high peripheral vascular resistance and failing to reduce maternal blood pressure. Among other consequences, endothelial injury is characterized by increased thromboxane, reduced prostacyclin and increased platelet aggregation, in addition to kidney injury by glomerular capillary endotheliosis.

The success of physiological placentation depends on the regulation of angiogenic (PIGF) and antiangiogenic (sFlt-1) factors. The most recent studies associate the decrease in PIGF and the increase in sFlt-1, as well as the increase in the sFlt-1/PLGF ratio with the prediction, diagnosis and prognosis of pregnant women with preeclampsia.

The search for predictive tests that can identify patients at risk for the development of preeclampsia and institute prophylactic interventions have been the major focus of all researchers interested in the topic over the past forty years. Several studies have analyzed the value of Dopplerflowmetry for predicting preeclampsia, however, the sensitivity and predictive value were low and do not encourage its use in the general population. In the case of this exam, signs of vascular resistance are identified through the presence of protodiastolic notches bilaterally in the uterine artery around the end of the first trimester of pregnancy. The same results were obtained with biochemical tests applied to identify patients who would later develop preeclampsia. More recently, based on the imbalance in the control of angiogenesis, the results of the angiogenic factor PIGF (placental growth factor) and the antiangiogenic factor, the soluble form of the Flt-1 receptor (sFlt-1) known as "fms-like tyrosine kinase-1" alone or the increase in its sFlt-1/PLGF ratio) in the diagnosis or prediction of preeclampsia, however, these results require validation with a greater number of cases.

With good prediction, a better indicated and more effective prophylaxis for PE can be performed through low-dose aspirin and calcium supplementation. Most randomized trials for the prevention of preeclampsia, including more than 37,000 patients, used low-dose aspirin. Recognition of the imbalance in the prostacyclin/thromboxane ratio as a key in the pathophysiology of the disease resulted in the application of low doses of aspirin, which selectively inhibit thromboxane synthesis in the platelet, without affecting the production of prostacyclin in the vessels. As for calcium, there was a reduction in the incidence of PE in pregnant women whose intake of this mineral was greater than 1.5 grams per day, which can be obtained through diet or supplementation. Other options, such as antioxidants and vitamin E, do not yet have enough robust evidence.

For this reason, science has focused attention on the proportion between sFlt-1 and PlGF biomarkers in their ability to predict preeclampsia – the aim of the current study.

## METHODOLOGY

The work in focus is a literature review whose information extraction was performed through articles from Google Scholar and PubMed databases. The descriptors were defined by the Decs BVS and 916 articles from the national and international literature were identified during the period from 2001 to 2020. For inclusion, 9 articles addressing preeclampsia and biochemical predictive markers for the disease were chosen.

## RESULTS

The diagnosis of preeclampsia is suspected from the twentieth week of pregnancy and is based on the development of arterial hypertension and proteinuria, in most cases. However, given the severity

that preeclampsia brings to the fetus and the mother and the delay in confirming the traditional diagnosis, the use of biomarkers such as the ratio between sFlt-1 and PlGF in the prediction of this condition has been the subject of scientific discussion. Placental growth factor (PIGF) and soluble vascular endothelial growth factor receptor (sFlt-1) are respectively two pro- and anti-angiogenic molecules released by the placenta during pregnancy. Numerous experimental and clinical results, according to the researched articles, suggest that an imbalance in factors, increasing sFlt-1 and reducing PlGF, are associated with a higher risk of developing the disease. In addition, sFlt-1/PlGF tests have substantially reduced the time to clinical confirmation of preeclampsia and subsequent adverse maternal and perinatal outcomes.

Among the results obtained, a degree of change in angiogenic factors seems to be directly related to the severity of the cases of PE and inversely to the time interval from the dose to the need for delivery due to the disease. A ratio < 38 has a high negative predictive value for the need for PE delivery within one week. In addition, angiogenic imbalance appears to be associated with increased preterm birth, fetal growth restriction, light-for-gestational-age newborns and longer hospital stays in the Neonatal Intensive Care Unit.

This reason was also positive in establishing differential diagnoses. Pathologies with manifestations similar to those observed in PE (eg, chronic hypertension, gestational hypertension, chronic kidney disease, thrombocytopenia, lupus) have shown an angiogenic profile distinct from that observed in cases of PE, allowing their differentiation.

To predict the development of PE in the 1st trimester of pregnancy, both sFlt1 and PlGF have shown low specificity and sensitivity if used as predictors of PE in the 1st trimester, in isolation. Following the success of aneuploidy screening, several authors have sought to improve the predictive value in the 1st trimester through the development of combined models. Most of these take into account various parameters of maternal characteristics, biophysical markers (often mean arterial pressure (MAP) and uterine artery Doppler flowmetry (UAD)) and biochemical markers (among which PlGF). In the following semesters, a large part of the evidence has focused on the usefulness of PlGF and the sFlt1/PlGF ratio in the 2nd and 3rd trimester of pregnancy, with promising results regarding its predictive capacity, particularly in cases of early PE.

The measurement of the sFlt1/PlGF ratio in the 2nd and 3rd trimesters has shown, in most studies, a better predictive capacity of PE than each marker alone. Even so, the isolated assay of PlGF has also been shown to be very useful. As pregnancy progresses, the serum levels of the ratio in cases of PE tend to approach those recorded in uncomplicated pregnancies, impairing its value as a predictor of late PE.

It is worth mentioning that the sFlt-1/PlGF ratio presents a wide field for discussion and, although there are studies favorable to this *screening*, administrative and public health factors must be considered in determining its application. Currently, it is not yet a mandatory diagnostic method in the investigation of preeclampsia.

## CONCLUSION

In summary, the sFlt-1/PlGF ratio can both improve the prediction of early-onset PE for women at risk, and offer efficient results for the prevention of serious or even fatal complications associated with preeclampsia. Furthermore, this relationship plays an important role in the stratification of severity and exclusion of differential diagnoses.

The counterpoint, however, must consider administrative and public health biases. For

example, both markers have low specificity and sensitivity for predicting PE in the 1st trimester if performed alone (as is already the case with PIGF). If combined, this scenario changes. However, other parameters are already recommended for predicting PE at this stage, such as maternal characteristics and biophysical markers (often mean arterial pressure (MAP) and uterine artery Doppler flowmetry (UAD)), for which further comparative studies of cost-effective and of good quality of screening to the point of indicating a new implementation (the sFlt-1 dosage to relate to PIGF routinely).

In the case of the following trimesters, although the sFlt-1/PlGF ratio becomes more promising, it must be considered that the prediction after the 1st trimester of PE may be very late and ineffective in its prophylaxis, since ASA must be started up to 16 weeks GI. In addition, it is assumed that from 20 weeks onwards, some signs and symptoms of PE must already propose the diagnosis of the disease to the attending physician. Nevertheless, the isolated dosage of PIGF also presents, in the late phase, a good specificity for the disease.

Finally, it is concluded that the sFlt-1/PlGF ratio is undoubtedly a good predictive marker for PE and other conditions associated with this disease. However, in the context of implementation for *screening*, it is valid to have new scientific studies that specify the real impact of this modification on the current protocol.

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