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ANGIOGENIC BIOMARKERS IN THE PREDICTION AND DIAGNOSIS OF PREECLAMPSIA

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Abstract
Preeclampsia (PE) remains a major cause of maternal and perinatal morbidity and mortality globally. Recent research has focused on the imbalance between angiogenic and antiangiogenic factors—particularly soluble fmslike tyrosine kinase1 (sFlt1) and placental growth factor (PlGF)—as potential biomarkers for early prediction and diagnosis of PE. To review and synthesize current evidence on the clinical performance of sFlt1, PlGF, and the sFlt1/PlGF ratio in predicting, diagnosing, and managing preeclampsia across different gestational stages and populations.

Keywords: Preeclampsia, sFlt1, PlGF, angiogenic biomarkers, pregnancy, diagnosis, prediction

Introduction

Preeclampsia (PE) is a multisystem hypertensive disorder of pregnancy that affects approximately 5–8% of pregnancies globally, representing one of the leading causes of maternal and perinatal morbidity and mortality. It contributes to an estimated 70,000 maternal and 500,000 Fetal deaths annually worldwide, underscoring its significant global health burden[1]. The disorder typically develops after 20 weeks of gestation and is clinically characterized by new onset hypertension with proteinuria or evidence of maternal organ dysfunction[2].

The Etiology of PE is complex and multifactorial, involving abnormal placentation and subsequent endothelial dysfunction. Central to its pathogenesis is an imbalance between angiogenic factors such as placental growth factor (PlGF) and antiangiogenic factors like soluble fmslike tyrosine kinase1 (sFlt1), which binds and neutralizes vascular endothelial growth factor (VEGF) and PlGF [3-4] The excessive release of sFlt1 leads to reduced angiogenesis, placental hypoxia, and widespread maternal endothelial injury[5].

Among emerging diagnostic tools, the sFlt1/PlGF ratio has gained prominence for its ability to reflect this biochemical imbalance accurately. Multiple clinical studies have demonstrated that the ratio provides superior diagnostic and predictive accuracy compared to conventional clinical parameters[6-7]. For example, the landmark PROGNOSIS study demonstrated that an sFlt1/PlGF ratio ≤38 effectively rules out PE within one week, offering a negative predictive value exceeding 99% [8].

The integration of angiogenic biomarkers into obstetric practice has transitioned PE management from a reactive to a proactive paradigm, allowing for earlier identification, risk stratification, and timely intervention. This review aims to consolidate the current evidence on the pathophysiological basis, diagnostic utility, and clinical implementation of the sFlt1/PlGF ratio, thereby emphasizing its growing importance in personalized prenatal care[9-10].

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Methods

This narrative review was conducted to summarize current evidence on the predictive and diagnostic performance of soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), and the sFlt-1/PlGF ratio in identifying preeclampsia. A comprehensive literature search was performed for studies published between 2016 and 2025 using major electronic databases, including PubMed, Scopus, and Web of Science. The search strategy combined the keywords *"preeclampsia," "sFlt-1," "PlGF," "angiogenic factors,"* and *"biomarkers."*

Eligible studies included original peer-reviewed research articles that evaluated any of the above biomarkers and reported diagnostic accuracy measures such as sensitivity, specificity, and/or area under the receiver operating characteristic curve (AUC). Reviews, editorials, case reports, animal studies, and conference abstracts were excluded.

A total of seven studies fulfilled the inclusion criteria, encompassing diverse populations from Europe, Asia, the Middle East, and North America. From each study, key details were extracted, including study design, sample size, gestational age at biomarker testing, assay type, and reported diagnostic parameters.

Because of variability in study populations, designs, and biomarker thresholds, a narrative synthesis was undertaken rather than a pooled meta-analysis. The findings were organized thematically to highlight trends in diagnostic performance, regional variations, and clinical applicability of the sFlt-1/PlGF ratio for predicting or diagnosing preeclampsia.

Results

Predictive and Diagnostic Performance of sFlt1, PlGF, and the sFlt1/PlGF Ratio

Biomarker Performance Across Gestation

Andersen et al. [11] conducted a large prospective cohort study involving 1,909 unselected pregnant women from the Odense Child Cohort in Denmark. Serum levels of soluble fmslike tyrosine kinase1 (sFlt1) and placental growth factor (PlGF) were assessed at 8–14 weeks and 20–34 weeks' gestation. Only biomarkers measured at 20–34 weeks were predictive of preeclampsia (PE), with PlGF showing the highest diagnostic accuracy (AUC = 0.755) compared with the sFlt1/PlGF ratio (AUC = 0.704, p = 0.002). Predictive performance was strongest for early onset severe PE, where PlGF achieved an AUC of 0.901 and the ratio 0.883, confirming the dominance of PlGF in midgestational screening.

Similarly, the Spanish STEPS study by Perales et al. [12] analysed 819 high-risk women and confirmed that the sFlt1/PlGF ratio improved prediction between 20–28 weeks (AUC = 0.86–0.93). When combined with maternal history and mean arterial pressure (MAP), predictive accuracy further improved, underscoring that integrated clinical biochemical models outperform biomarkers alone.

Aminuddin et al. [13] assessed the feasibility of using the sFlt1/PlGF ratio among medium to high-risk Malaysian women. Using a threshold > 38, the ratio achieved an AUC of 0.748 with 58.6% sensitivity and 91% specificity. When combined with maternal risk factors, AUC increased to 0.869, validating the clinical practicality of multimodal prediction in diverse populations.

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Late Gestation and Clinical Application

In a Saudi cohort, Alhudhud et al. [14] evaluated the clinical use of sFlt1/PlGF testing to reduce unnecessary hospitalizations. At a cutoff of 51, sensitivity reached 88%, specificity 85%, and AUC 0.85, while the negative predictive value (NPV) approached 98%, confirming its role as a rule out test. At a lower cutoff of 38, the ratio predicted imminent PE with 100% sensitivity and comparable NPV.

In the United States, Love et al. [15] performed a multicenter case–control study of 695 adjudicated PE cases and 452 controls, establishing gestational phase–specific cutoffs. For early gestation (≤ 33 weeks), thresholds of ≤ 33 and ≥ 85 produced sensitivities/specificities of 89.6%/91.7% and 83.7%/98.0%, respectively. For late gestation (≥ 34 weeks), corresponding cutoffs of ≤ 33 and ≥ 110 yielded 86.1%/81.4% and 62.0%/97.0%. This dual cutoff system introduced an "equivocal zone" for nuanced clinical decision making and demonstrated cross ethnic robustness.

Table 1. Comparative summary of studies evaluating sFlt1, PlGF, and sFlt1/PlGF ratio in prediction and diagnosis of preeclampsia

S.No.	Author (Year)	Country / Study Design	Sample Size & Population	Gestational Age at Sampling	Key Biomarkers & Cutoff(s)	Diagnostic / Predictive Accuracy	Main Findings / Interpretation
1	Andersen et al. (2016)	Denmark / Prospective cohort (Odense Child Cohort)	1,909 unselected pregnant women	8–14 wk and 20–34 wk	sFlt1, PlGF, sFlt1/PlGF ratio	AUC (PlGF 0.755 > ratio 0.704, p=0.002); severe early onset PE AUC 0.901	Predictive only at 20–34 wk; PlGF outperformed ratio; high NPV but low PPV.
2	Perales et al. (2017)	Spain / Prospective multicenter (STEPS)	819 high-risk women	20–34 wk	sFlt1/PlGF >38	AUC 0.86–0.93; Se 82–92%; Sp 90–95%	Ratio effectively predicted early onset PE; combining with MAP and parity improved model accuracy.
3	Aminuddin et al. (2022)	Malaysia / Prospective observational	200 medium to high risk mothers	20–37 wk	sFlt1/PlGF >38; combined with clinical factors	Biomarker alone: AUC 0.748 (Se 58.6%, Sp 91%); Combined: AUC 0.869	Combined biomarker + clinical parameters enhanced PE prediction and adverse outcomes.
4	Xue et al. (2022)	China / Retrospective clinical analysis	162 (105 PE, 57 severe PE)	11–33 + 6 wk	sFlt1/PlGF ratio (variable)	Se 98.1%, Sp 78.2%	Ratio and sFlt1 levels significantly higher in PE/severe PE; correlated with LDH and severity.
5	Alhudhud et al. (2024)	Saudi Arabia / Clinical observational	250 women with suspected PE	≥20 wk	sFlt1/PlGF = 51 (admission), 38 (PE development), PlGF 193.36 pg/mL	Cutoff 51: AUC 0.85 (Se 88%, Sp 85%); Cutoff 38: Se 100%, Sp 81%; NPV 98%	Excellent rule out value; prevents unnecessary hospital admissions; supports selective testing.
6	Ardani et al. (2025)	Indonesia / Cross-sectional observational	47 PE patients (caesarean)	>34 wk	sFlt1/PlGF = 138.6 (oxygenation cutoff)	Se 83.3%, Sp 80%, r = –0.514 (p < 0.001)	High ratio associated with impaired oxygenation; indicates endothelial dysfunction severity.
7	Love et al. (2025)	USA / Multicenter case–control	695 PE cases + 452 controls	Early (20–33+6 wk), Late (≥34 wk)	Early: ≤33 / ≥85; Late: ≤33 / ≥110	Early: Se 89.6%, Sp 91.7% (rule out); Se 83.7%, Sp 98% (rule in); Late: Se 86.1%, Sp 81.4% (rule out); Se 62%, Sp 97% (rule in)	First gestational phase–specific cutoffs; validated across multiethnic cohort; enhances diagnostic accuracy.

Disease Severity and Organ Dysfunction

Xue et al. [16] examined 162 women (105 PE, 57 severe PE) in China and found that both sFlt1 and the sFlt1/PlGF ratio were significantly higher in PE groups versus controls. The ratio achieved 98.1% sensitivity and 78.2% specificity for PE diagnosis and correlated positively with lactate dehydrogenase (LDH), linking it to endothelial injury.

Ardani et al. [17] in Indonesia analysed 47 preeclamptic patients and found the sFlt1/PlGF ratio correlated negatively with PaO_2/FiO_2 ($r = –0.514$, $p < 0.001$), implying that higher ratios signify poorer maternal oxygenation. A cutoff of 138.6 predicted hypoxemia with 83.3% sensitivity and 80% specificity, demonstrating potential for organspecific prognostication.

Postpartum Prediction

Li et al. [18] investigated the role of sFlt1/PlGF ratio in postpartum preeclampsia among 47 women, of whom 19% developed PE within six weeks after delivery. The median ratio (55.9 vs 19.9) was significantly higher in the PE group ($p < 0.05$). A threshold > 38 yielded 77.8% sensitivity, 81.6% specificity, and 93.9% NPV, confirming the continued diagnostic relevance of angiogenic imbalance after childbirth.

Comparative Summary

Across all reviewed studies, the sFlt1/PlGF ratio demonstrated sensitivities from 58–100%, specificities from 78–98%, and AUCs from 0.74–0.93. Consistently high NPVs (> 90%) reinforce its utility as a ruleout tool for PE. When integrated with clinical parameters (e.g., blood pressure, parity, and maternal history) or gestational phase cutoffs, diagnostic performance markedly improved.

Discussion

The collective body of evidence from international research strongly supports the clinical value of angiogenic biomarkers particularly the sFlt-1/PlGF ratio as a robust, reproducible indicator for the prediction, diagnosis, and monitoring of preeclampsia (PE). The ratio directly reflects the key pathophysiological process of PE, characterized by an imbalance between antiangiogenic and proangiogenic factors leading to endothelial dysfunction, placental hypoperfusion, and systemic inflammation. Elevated circulating sFlt-1 antagonizes VEGF and PlGF, reducing angiogenic signalling and impairing vascular integrity. This biochemical disequilibrium manifests clinically as hypertension, proteinuria, and multiorgan involvement[19,20]. Quantitative assessment of this ratio provides a dynamic and measurable link between placental dysfunction and clinical phenotype, positioning it as one of the most clinically relevant biomarkers in obstetric medicine.

Extensive prospective studies confirm the predictive and diagnostic power of this ratio, particularly during midgestation (20–34 weeks). In the Odense Child Cohort, Andersen et al.[11] demonstrated that biomarker assessment at 20–34 weeks, rather than early gestation, significantly improved PE prediction, with PlGF achieving an AUC of 0.755 and the sFlt-1/PlGF ratio an AUC of 0.704. Similarly, Perales et al.[12], in the multicenter STEPS study, found that the ratio achieved AUCs of 0.86–0.93 in high-risk women, and when combined with maternal history and mean arterial pressure

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(MAP), predictive performance was enhanced further. These findings underscore the superior accuracy of multimodal prediction models incorporating both clinical and biochemical parameters. Evidence from diverse populations confirms that gestation-specific cutoffs improve diagnostic precision. Love et al.[15] proposed thresholds of ≤33 and ≥85 before 34 weeks, and ≤33 and ≥110 after 34 weeks, which stratified patients into clear clinical zones—rule out, equivocal, and rule in—achieving sensitivities of 83–90% and specificities of 81–98%. These thresholds facilitate evidence-based triage and decision-making in obstetric care. Across studies, the sFlt-1/PlGF ratio has consistently shown sensitivity between 58–100%, specificity between 78–98%, and AUC values ranging from 0.74–0.93, with a negative predictive value (NPV) exceeding 90%, establishing its reliability as a short-term rule-out test for PE[13–15].

The ratio's value extends beyond diagnosis to disease stratification and prognostication. Xue et al.[16] found that elevated sFlt-1/PlGF ratios correlated positively with lactate dehydrogenase (LDH) levels, indicating endothelial and cellular damage, while Ardani et al.[17] identified a strong inverse relationship between the ratio and PaO_2/FiO_2, suggesting a link between angiogenic imbalance and impaired oxygenation. These findings demonstrate that the ratio reflects disease severity and organ dysfunction, particularly in severe or late-onset PE. Li et al.[18] further expanded the biomarker's relevance to postpartum preeclampsia, showing that higher ratios persisted among women who later developed the condition, with a sensitivity of 77.8%, specificity of 81.6%, and NPV of 93.9%. Collectively, these studies affirm the sFlt-1/PlGF ratio as a dynamic biomarker capable of predicting not only disease onset but also progression and maternal–fetal outcomes.

Clinical translation of this biomarker has already improved patient management. Alhudhud et al.[14] reported that using a ratio cutoff of 51 allowed clinicians to safely discharge women unlikely to develop PE, reducing unnecessary admissions by 25% without compromising patient safety. This demonstrates the biomarker's cost-effectiveness and applicability across healthcare systems. When integrated into clinical algorithms, such as those recommended by European and international obstetric societies, sFlt-1/PlGF testing supports a proactive, evidence-based approach—allowing timely intervention and reduction of adverse outcomes.

However, some limitations persist. Differences in assay calibration, patient demographics, and timing of sampling can influence interpretability and interlaboratory comparability. Additionally, first-trimester predictive accuracy remains limited, as the angiogenic imbalance typically develops only after placentation. Therefore, future research should focus on global assay standardization, establishing universal reference intervals, and exploring multimodal approaches combining angiogenic, inflammatory, and metabolic biomarkers. Integration of biomarker data into digital clinical decision-support systems could further enhance real-time risk stratification, particularly in resource-limited settings.

In summary, the sFlt-1/PlGF ratio represents a physiologically grounded, clinically validated, and globally adaptable biomarker that has revolutionized the management of preeclampsia. Its strong predictive and diagnostic accuracy, high negative predictive value, and versatility across gestational stages have made it an indispensable tool in modern obstetric care. By enabling early detection, personalized monitoring, and prevention of complications, this biomarker has shifted the paradigm of preeclampsia management from reactive intervention to anticipatory precision medicine, ultimately reducing maternal and neonatal morbidity and mortality worldwide.

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Conclusion

The sFlt1/PlGF ratio is now firmly established as a cornerstone biomarker for the prediction, diagnosis, and management of preeclampsia (PE). By quantifying the imbalance between antiangiogenic and proangiogenic factors, it bridges the gap between placental pathology and clinical decision making, offering a direct, evidence-based measure of disease activity. With a negative predictive value exceeding 90%, the ratio allows clinicians to safely rule out PE, minimizing unnecessary hospitalizations and interventions. Conversely, elevated ratios—typically >85 before 34 weeks or >110 after 34 weeks reliably identify women at high risk of imminent disease progression, guiding closer surveillance and timely delivery. Beyond diagnosis, the biomarker correlates with disease severity, organ dysfunction, and postpartum complications, extending its use across the maternal–Fetal continuum. When combined with clinical parameters such as blood pressure and Doppler indices, the ratio forms a comprehensive predictive model aligned with modern, personalized obstetric care. Future priorities include assay harmonization, validation in diverse populations, and integration into digital health tools for Realtime interpretation. If globally standardized, the sFlt1/PlGF ratio could revolutionize preeclampsia management shifting obstetric care from reactive treatment to early, lifesaving prevention.

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