

Biomarkers and their Alterations in Early-Stage Preeclampsia: Recent Advances in Prediction and Clinical Application (2021–2025)

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Abstract: Preeclampsia (PE) remains one of the most serious complications of pregnancy, contributing to significant maternal and perinatal morbidity and mortality. It is increasingly evident that angiogenic / anti-angiogenic imbalance and other molecular biomarkers offer early predictive potential beyond conventional clinical parameters. Aim: This article synthesises current evidence (2021-2025) on biomarkers (notably placental growth factor [PlGF], soluble fms-like tyrosine kinase-1 [sFlt-1], the sFlt-1/PlGF ratio, natriuretic peptides, D-dimer, non-coding RNAs) in early-stage preeclampsia detection and prognostication. Materials & Methods: We conducted a narrative review of recent research including prospective cohort studies, meta-analyses and dynamic prediction models that assessed biomarker levels, cut-offs, diagnostic accuracy (AUC, sensitivity, specificity) and integration into clinical algorithms. Results: Strong evidence places the sFlt-1/PlGF ratio as the most validated biomarker for PE: multiple studies report AUCs above 0.90 for early-onset PE, high negative predictive value for PE onset within 7-28 days when ratio ≤ 38 and elevated risk when > 85 . Emerging biomarkers such as NT-proBNP, D-dimer, and non-coding RNAs show promise but lack standardized cut-offs and large-scale validation. Discussion: Biomarker measurement in early gestation (first/second trimester) enhances risk stratification and may guide surveillance and intervention. However, heterogeneity in assays, cut-offs, gestational age, ethnic background and resource settings remains a challenge. Conclusion: Incorporation of validated biomarker panels (especially sFlt-1/PlGF) into early pregnancy care can improve prediction and management of preeclampsia, yet further research is needed on cost-effectiveness, standardisation and global implementation.

Keywords: Preeclampsia; biomarker; sFlt-1; PlGF; sFlt-1/PlGF ratio; early pregnancy; prediction; non-coding RNA

Introduction

Preeclampsia (PE) is a complex, multisystem hypertensive disorder unique to human pregnancy, typically defined by the onset of hypertension ($\geq 140/90$ mmHg) and proteinuria (≥ 300 mg/24 h) or end-organ dysfunction after 20 weeks of gestation [1]. Despite improvements in obstetric care, PE continues to be a major cause of maternal and perinatal morbidity and mortality worldwide, accounting for nearly 15–20% of maternal deaths in low- and middle-income countries [2]. The global prevalence of preeclampsia ranges between 2% and 8% of pregnancies, with significant variation across populations [3].

The pathophysiology of preeclampsia is not fully elucidated but is believed to involve abnormal placentation, endothelial dysfunction, immune maladaptation, and an imbalance between angiogenic and anti-angiogenic factors [4, 5]. During normal pregnancy, cytotrophoblasts invade the maternal spiral arteries, transforming them into high-capacity, low-resistance vessels to ensure adequate perfusion of the placenta. In preeclampsia, this process is defective, leading to placental ischemia and oxidative stress [6]. The ischemic placenta releases excessive amounts of anti-angiogenic factors, notably soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), while angiogenic factors such as placental growth factor (PlGF) and vascular endothelial growth factor (VEGF) are markedly decreased [7].

This imbalance results in systemic endothelial dysfunction, vasoconstriction, and multiorgan injury affecting the kidneys, liver, brain, and placenta itself [8]. Clinically, preeclampsia manifests as

hypertension, proteinuria, edema, and in severe cases, seizures (eclampsia), HELLP syndrome, or fetal growth restriction [9]. Traditionally, diagnosis has relied on these clinical and laboratory features, which typically appear in the late second or third trimester — when disease progression is already well advanced. Thus, early detection and prediction before symptom onset remain the cornerstone of improving outcomes for both mother and child [10].

In recent years, the focus of research has shifted toward identifying biomarkers that can detect preeclampsia at a subclinical stage, ideally in the first or early second trimester, before the onset of clinical manifestations [11, 12]. Biomarkers are objectively measurable indicators of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic interventions. For preeclampsia, the most promising biomarkers reflect the angiogenic/anti-angiogenic balance (e.g., PlGF, sFlt-1, sFlt-1/PlGF ratio), cardiac stress markers (NT-proBNP, BNP), inflammatory markers (CRP, D-dimer), and novel molecular indicators such as microRNAs and other non-coding RNAs [13–15].

Among them, the sFlt-1/PlGF ratio has emerged as the most reliable and clinically validated biomarker for early detection of preeclampsia. A ratio > 38 has been shown to accurately predict the development of preeclampsia within 7–14 days in high-risk pregnancies, with an area under the ROC curve (AUC) exceeding 0.90 [16, 17]. Furthermore, studies indicate that the ratio correlates with disease severity and can guide clinical management, including timing of delivery [18].

However, significant challenges remain before these biomarkers can be universally applied. Variability in assay techniques, cut-off values, gestational timing, and population characteristics limits generalizability [19]. Additionally, most studies are conducted in high-resource settings, whereas the greatest burden of preeclampsia lies in low-income countries where laboratory infrastructure may be limited [20].

In light of these challenges, a comprehensive analysis of recent literature (2021–2025) is warranted to clarify the current understanding of biomarker dynamics, their diagnostic accuracy, and clinical applicability in predicting preeclampsia at early stages of pregnancy. Understanding how these biomarkers change throughout gestation can facilitate risk stratification, enable targeted surveillance, and inform early intervention strategies such as low-dose aspirin therapy, antioxidant supplementation, or close maternal–fetal monitoring [21, 22].

Therefore, this review focuses on summarizing and evaluating recent findings on biomarkers and their alterations in early-stage preeclampsia, highlighting their potential role in transforming prenatal screening and precision obstetric care.

The aim of this review is to critically synthesise evidence from 2021 to 2025 on biomarkers used in early-stage preeclampsia — their levels in pregnant women, alterations compared with normotensive pregnancies, diagnostic/prognostic accuracy (cut-offs, AUC, sensitivity/ specificity) and potential integration into clinical prediction models.

Materials & Methods

We performed a narrative review of English-language literature published between January 2021 and June 2025. Databases searched included PubMed/MEDLINE, Scopus, Web of Science. Search terms included “preeclampsia”, “biomarker”, “PlGF”, “sFlt-1”, “sFlt-1/PlGF ratio”, “prediction”, “early pregnancy”, “non-coding RNA”, “NT-proBNP”, “D-dimer”. We selected original cohort or case-control studies, systematic reviews or meta-analyses that reported quantitative data on biomarker levels, diagnostic accuracy metrics or prediction models. Exclusion criteria were animal studies, pre-2021 publications, non-English, and studies lacking quantitative biomarker data. Data extracted included study design, sample size, gestational age at measurement, biomarker(s) measured, cut-offs, AUC, sensitivity/specificity, and key findings.

Results

Angiogenic/Anti-Angiogenic Biomarkers (PlGF, sFlt-1, sFlt-1/PlGF ratio) Multiple recent studies validate the sFlt-1/PlGF ratio as the most robust biomarker for PE prediction. One large study found a cut-off >38 yielded diagnostic accuracy of $\sim 90.8\%$ (95% CI 85.8–95.7%), NPV of 96.4% for rule-out within 7 days, PPV of 84.8% for prediction within 28 days. [1] Another systematic review reported AUC values of 0.92 for early-onset PE and 0.87 for late-onset when using sFlt-1/PlGF ratio. [2] In a cohort of 4,212 women, the maternal serum sFlt-1/PlGF ratio strongly correlated with placental sFlt-1 but not placental PlGF in PE cases, indicating elevated sFlt-1 drives the ratio change. [3] Emerging prediction models combining ratio with clinical factors (age, BMI, blood pressure) and other biomarkers (NT-proBNP, uric acid) improved accuracy further (AUC up to ~ 0.95). [4]

Other Biomarkers: NT-proBNP/BNP, D-dimer, non-coding RNAs

Studies in 2023 found elevated NT-proBNP levels in PE, particularly severe/early onset, though cut-offs varied. [5] A meta-analysis of kinases and phosphatases found higher CK, lower sTIE2, lower sMET among PE patients versus normal, suggesting novel biomarker classes. [6] Non-coding RNAs (miRNA-27a-5p, miRNA-193b-5p) have been identified in recent single-cell and plasma studies as hypoxia-response markers in trophoblasts and PE, but clinical translation is still early. [7] D-dimer and CRP show elevated values in PE but lower independent predictive power compared to angiogenic biomarkers.

Timing of Measurement and Prediction Window

Studies highlight that measuring PlGF and sFlt-1 (and the ratio) in first or early second trimester yields optimum lead-time before clinical PE manifests. For example, a first-trimester model combining PlGF and immune-related markers achieved AUC 0.983 (sensitivity 100%, specificity 94.1%) for PE prediction. [8]

Implementation and Real-World Performance

Real-world data show the sFlt-1/PlGF ratio improves clinical decision-making in triage units: for example, cutoff ≤ 38 strongly ruled out PE within 7 days (LR- ~ 0.15), cutoff >85 provided strong rule-in (LR+ ~ 5.75) even in resource-limited settings. [9]

Discussions

The evidence strongly supports the use of sFlt-1/PlGF ratio as a key biomarker for early detection and risk stratification of preeclampsia. Its superiority over traditional clinical markers (blood pressure, proteinuria) is demonstrated in multiple studies. The early measurement (first-/second-trimester) provides a window for intervention or closer monitoring, which may improve maternal-fetal outcomes. Nevertheless, there are several considerations and limitations:

- **Assay heterogeneity and cut-offs:** Studies vary in assay platforms, gestational age of measurement, and threshold values (e.g., >38 , >85). This variation limits universal adoption.
- **Population and setting variability:** Many studies are high-resource, single-centre settings; performance in low-resource or diverse ethnic populations may differ. [9]
- **Integration into prediction models:** Biomarker alone is helpful, but combining with clinical factors, Doppler ultrasound and emerging markers (non-coding RNA, natriuretic peptides) yields better discrimination. Implementation of such integrated models needs validation.
- **Emerging biomarkers:** While promising (e.g., non-coding RNAs, D-dimer, kinases), these biomarkers are not yet standardized, cost-effectiveness unknown and require large prospective trials. [6,7]
- **Clinical pathways and outcome impact:** Knowing a high risk is beneficial only if actionable protocols (e.g., aspirin prophylaxis, intensified monitoring, early delivery) are in place; studies linking biomarker-guided interventions to improved outcomes are fewer.

- Cost and accessibility: For widespread use, biomarker tests must be affordable, reproducible and integrated into routine prenatal care, especially in settings with resource constraints.

Conclusion

In summary, angiogenic biomarkers — especially the sFlt-1/PlGF ratio — represent the most validated tools for early prediction of preeclampsia. Emerging biomarkers may add incremental value, but require further standardization and validation. To optimise clinical utility, biomarker measurement should be integrated with clinical risk factors and validated prediction models, and linked to actionable management strategies. Future research should focus on large-scale, diverse population studies, cost-effectiveness analyses and implementation pathways for biomarker-guided care in preeclampsia prevention.

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