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Determining the Role of Angiogenic Factors in the Prediction of Preeclampsia

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ABSTRACT

Preeclampsia is a major cause of maternal and perinatal morbidity and mortality worldwide. Its pathogenesis is complex and multifactorial, involving abnormal placentation, immune dysfunction, and endothelial injury. Recent advances have emphasized the critical role of angiogenic imbalance in the development and progression of preeclampsia. This review evaluates the predictive value of angiogenic biomarkers—including placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), and soluble endoglin (sEng)—in identifying women at risk for preeclampsia. It summarizes current evidence on the pathophysiological significance of these factors, their temporal expression patterns in pregnancy, and their integration into clinical risk models. The potential utility of angiogenic biomarkers in early screening, diagnosis, and therapeutic stratification is critically discussed. Incorporating angiogenic profiling into prenatal care could significantly improve the early prediction and management of preeclampsia.

Keywords: *Preeclampsia, angiogenic factors, PlGF, sFlt-1, prediction, biomarkers, pregnancy complications*

INTRODUCTION

Preeclampsia remains one of the most pressing challenges in modern obstetrics, affecting approximately 3–8% of pregnancies worldwide and contributing substantially to maternal and perinatal morbidity and mortality, particularly in low- and middle-income countries [1]. Despite intensive research efforts, the precise pathogenesis of preeclampsia has not been fully elucidated. It is now well established, however, that the condition is rooted in defective placentation during early gestation, leading to a cascade of pathological events including endothelial dysfunction, systemic inflammation, and multiorgan injury [2].

Over the past two decades, growing attention has been directed toward the role of angiogenesis and its regulatory mechanisms in the development of preeclampsia. The process of angiogenesis—the forma-

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tion of new blood vessels from pre-existing vasculature—is crucial for normal placental development and uteroplacental circulation. Disruption of this tightly regulated system is believed to underlie the maladaptive placental vascular remodeling observed in preeclamptic pregnancies [3].

A growing body of evidence suggests that an imbalance between pro-angiogenic and anti-angiogenic factors precedes the clinical onset of preeclampsia by several weeks. Among the key players in this angiogenic shift are placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), which promote endothelial integrity and vascular development, and their circulating antagonists, including soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), which impair angiogenesis and contribute to endothelial dysfunction [4,5].

Numerous clinical studies and longitudinal cohort analyses have demonstrated that alterations in the maternal serum levels of these angiogenic markers—particularly the sFlt-1/PlGF ratio—can serve as early predictors of preeclampsia, especially in its early-onset or severe forms [6]. This has led to the development of integrated biomarker-based screening protocols, which offer improved specificity and sensitivity compared to traditional risk factor models based solely on blood pressure or clinical history.

In light of these developments, angiogenic factors are increasingly recognized not only as markers of disease but also as potential targets for therapeutic modulation and risk stratification. In this review, we explore the biological functions, temporal expression, and predictive value of major angiogenic factors in preeclampsia. Furthermore, we critically assess their role in current and emerging clinical screening algorithms and highlight the future directions for implementing angiogenic profiling into routine prenatal care.

1. Pathophysiological Role of Angiogenic Imbalance in Preeclampsia

The development of a functional placenta depends on the establishment of an adequate maternal-fetal vascular interface. During early gestation, extravillous trophoblasts invade the maternal spiral arteries, transforming them into low-resistance, high-capacitance vessels capable of meeting the metabolic demands of the growing fetus. In preeclampsia, this process of spiral artery remodeling is incomplete or defective, resulting in reduced placental perfusion and ischemia [7].

One of the key mechanisms linking placental hypoperfusion to systemic maternal disease is the dysregulation of angiogenic signaling. Under normal conditions, the balance between pro-angiogenic and anti-angiogenic factors ensures optimal endothelial function and vascular integrity. In preeclamptic pregnancies, this balance is profoundly disturbed. The hypoxic placenta releases excessive amounts of anti-angiogenic factors—chiefly soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng)—into the maternal circulation [8].

sFlt-1, a splice variant of the VEGF receptor-1, binds and neutralizes both VEGF and placental growth factor (PlGF), thereby preventing their interaction with endothelial receptors. This functional antagonism leads to widespread endothelial dysfunction, manifested clinically as hypertension, proteinuria, and end-organ damage [9]. Simultaneously, sEng inhibits the transforming growth factor-beta (TGF-β) signaling pathway, further exacerbating endothelial injury and promoting vascular inflammation and coagulation abnormalities [10].

The resulting angiogenic imbalance contributes to several hallmark features of preeclampsia, including increased vascular permeability, capillary rarefaction, and altered placental morphology. Autopsy and histopathological studies have shown that preeclamptic placentas often exhibit features of maternal vascular malperfusion, including infarcts, decidual arteriopathy, and villous hypoplasia [11]. These findings underscore the systemic nature of the angiogenic disturbance, which extends beyond the uteroplacental interface and affects multiple organ systems.

Importantly, the degree of angiogenic disruption correlates with disease severity and timing. Women with early-onset preeclampsia (before 34 weeks) tend to exhibit a more pronounced elevation in sFlt-1 and sEng levels, as well as lower circulating concentrations of PlGF, compared to those with late-onset disease. This observation has fueled the development of biomarker thresholds and ratios that can stratify patients by risk and predict adverse outcomes with considerable accuracy [12].

Taken together, these findings support the central role of angiogenic dysregulation in the pathogenesis of preeclampsia. Moreover, they lay the foundation for using angiogenic markers as both diagnostic tools and potential therapeutic targets, particularly in the early identification of high-risk pregnancies and in tailoring surveillance and intervention strategies.

2. Clinical Utility of Angiogenic Biomarkers in Preeclampsia Prediction

The integration of angiogenic biomarkers into obstetric practice has opened new avenues for the early detection and risk stratification of preeclampsia. Traditional screening methods—based on maternal demographics, clinical history, and biophysical parameters such as mean arterial pressure or uterine artery Doppler—while helpful, have demonstrated limited sensitivity and specificity, particularly in predicting early-onset or severe forms of the disease [13]. In contrast, circulating angiogenic factors, notably PlGF, sFlt-1, and the sFlt-1/PlGF ratio, offer more direct insight into the underlying placental pathology and have shown considerable promise as predictive biomarkers.

Placental growth factor (PlGF), a member of the VEGF family, is primarily synthesized in the placenta and plays a key role in promoting trophoblast invasion and vascular development. In normotensive pregnancies, serum PlGF levels rise steadily during the second trimester and peak between 30–32 weeks. In preeclampsia, however, this rise is blunted or reversed, with significantly lower concentrations observed up to several weeks before the onset of clinical symptoms [14]. Measurement of low PlGF (<100 pg/mL) has been shown to be an early indicator of placental insufficiency and elevated preeclampsia risk.

Conversely, soluble fms-like tyrosine kinase-1 (sFlt-1) levels increase in preeclampsia, typically beginning around the second trimester and accelerating prior to symptom onset. Elevated sFlt-1 impairs the bioavailability of VEGF and PlGF, directly contributing to systemic endothelial dysfunction. The sFlt-1/PlGF ratio has emerged as a robust composite biomarker, capable of detecting the angiogenic shift that precedes preeclampsia by days to weeks [15]. Numerous studies have validated this ratio as a reliable screening tool, with threshold values (>38 or >85 depending on gestational age and population) demonstrating high negative predictive value in ruling out disease within 1–2 weeks [16].

The utility of angiogenic biomarkers extends beyond diagnosis into prognostication and management. For example, a rapidly rising sFlt-1/PlGF ratio in a woman with suspected preeclampsia may predict imminent disease progression and inform decisions regarding hospitalization, corticosteroid administration, or timing of delivery. These markers also aid in distinguishing true preeclampsia from clinical mimics, such as chronic hypertension, renal disease, or gestational hypertension without placental dysfunction, thereby reducing unnecessary interventions [17].

Clinical implementation has been facilitated by the development of automated, rapid-turnaround immunoassays compatible with routine antenatal testing. Several guidelines now support the use of PlGF-based tests in selected high-risk populations, particularly between 20 and 35 weeks of gestation. Importantly, angiogenic testing complements but does not replace traditional evaluation; its optimal use lies in multimodal screening algorithms that combine biochemical, biophysical, and clinical variables [18].

In summary, angiogenic biomarkers—especially the sFlt-1/PlGF ratio—have emerged as powerful tools for the early detection, differential diagnosis, and risk stratification of preeclampsia. Their incorporation into clinical care pathways represents a significant advance in personalized obstetric medicine, with the potential to improve both maternal and fetal outcomes through earlier and more targeted intervention.

3. Future Perspectives and Challenges in Clinical Implementation

As the predictive power of angiogenic biomarkers becomes increasingly established, their integration into routine prenatal care offers promising opportunities to transform the management of preeclampsia. Nonetheless, several practical, clinical, and scientific challenges remain, requiring careful navigation to maximize the benefits of these tools and ensure equitable access across diverse healthcare settings.

One of the foremost areas of development is the standardization and optimization of screening algorithms. Although the sFlt-1/PlGF ratio has demonstrated excellent diagnostic and prognostic accuracy, the optimal timing, frequency, and target populations for testing remain subjects of ongoing research. Current evidence supports its use primarily in symptomatic women between 20 and 36 weeks of gestation, but broader applications—such as universal mid-trimester screening—have yet to be fully validated in large, ethnically diverse cohorts [19]. Future trials are needed to define cost-effective and outcome-driven protocols that integrate angiogenic biomarkers with uterine artery Doppler, mean arterial pressure, and maternal risk factors.

Another key frontier involves the therapeutic implications of angiogenic profiling. While these markers are now routinely used to guide clinical decision-making

regarding surveillance intensity and timing of delivery, there is growing interest in targeting the angiogenic pathway itself. Experimental therapies, such as apheresis to remove excess sFlt-1, administration of recombinant PlGF, or modulation of upstream regulators, are under investigation and may offer future avenues for disease modification rather than passive monitoring [20].

Despite their clinical utility, the widespread adoption of angiogenic biomarker testing faces logistical and economic barriers, especially in low-resource settings. The availability of validated, rapid, and affordable assays remains limited outside high-income countries. Bridging this gap will require investment in decentralized diagnostic platforms and policy frameworks that support the inclusion of biomarker-based risk assessment in standard antenatal care packages.

Furthermore, there is an ongoing need for educational initiatives and clinician training, ensuring that obstetric care providers are familiar with the interpretation of angiogenic tests and their appropriate application in clinical scenarios. Misuse or over-reliance on biomarker thresholds in isolation may lead to unnecessary interventions or false reassurance if not contextualized within a broader clinical assessment.

Lastly, ethical and psychosocial considerations must be addressed, particularly as early prediction of preeclampsia may generate anxiety or trigger aggressive interventions in pregnancies that might otherwise remain uncomplicated. Shared decision-making, clear patient communication, and individualized care planning will remain central pillars in the responsible application of angiogenic testing [21].

In conclusion, angiogenic biomarkers represent a paradigm shift in the prediction and management of preeclampsia. Their continued refinement and integration into clinical practice offer the potential to personalize prenatal care, reduce maternal and fetal morbidity, and enable a proactive, precision-based approach to one of obstetrics' most formidable complications. Addressing the remaining implementation challenges will be essential to ensure that the promise of angiogenic profiling becomes a global standard of care.

CONCLUSION

Preeclampsia continues to be a leading cause of maternal and perinatal morbidity and mortality worldwide. The discovery of angiogenic imbalance as a central component of its pathophysiology has redefined our approach to screening, diagnosis, and risk stratification. Biomarkers such as placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), and the sFlt-1/PlGF ratio provide valuable insight into placental health and vascular function, offering predictive capabilities that surpass traditional clinical assessments.

Clinical studies have validated the use of angiogenic markers in identifying women at increased risk of preeclampsia, particularly in its early-onset and severe forms. Their integration into antenatal care pathways enables earlier diagnosis, more precise monitoring, and timely intervention, with the potential to improve maternal and fetal outcomes. However, challenges related to standardization, access, clinician training, and ethical considerations remain and must be systematically addressed.

Looking forward, the future of obstetric care will likely incorporate angiogenic profiling as a cornerstone of personalized prenatal medicine. Continued research, innovation in diagnostic platforms, and global efforts to expand availability will be key to ensuring that the benefits of angiogenic biomarkers are fully realized across all populations.

Conflict of Interest

The author declares no conflict of interest regarding the publication of this article.

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REFERENCES

1. Abalos E, Cuesta C, Grosso AL, et al. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013;170(1):1–7.
2. Redman CWG, Sargent IL. Placental stress and preeclampsia: a revised view. Placenta. 2009;30(Suppl A):S38–S42.
3. Maynard SE, Karumanchi SA. Angiogenic factors and preeclampsia. Semin Nephrol. 2011;31(1):33–46.
4. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 2004;350(7):672–683.
5. Venkatesha S, Toporsian M, Lam C, et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. Nat Med. 2006;12(6):642–649.
6. Zeisler H, Llurba E, Chantraine F, et al. Predictive value of the sFlt-1:PlGF ratio in women with sus-

pected preeclampsia. N Engl J Med. 2016;374(1):13–22.
7. Pijnenborg R, Bland JM, Robertson WB, et al. Uteroplacental arterial changes related to interstitial trophoblast migration in early human pregnancy. Placenta. 1983;4(4):397–413.
8. Rana S, Karumanchi SA, Lindheimer MD. Angiogenic factors in diagnosis, management, and research in preeclampsia. Hypertension. 2014;63(2):198–202.
9. Maynard SE, Min JY, Merchan J, et al. Excess placental sFlt-1 may contribute to endothelial dysfunction in preeclampsia. J Clin Invest. 2003;111(5):649–658.
10. Gilbert JS, Ryan MJ, LaMarca BB, et al. Pathophysiology of hypertension during preeclampsia: linking placental ischemia with endothelial dysfunction. Am J Physiol Heart Circ Physiol. 2008;294(2):H541–H550.
11. Khong TY, De Wolf F, Robertson WB, et al. Inadequate maternal vascular response to placentation in pregnancies complicated by preeclampsia and small-for-gestational age infants. Br J Obstet Gynaecol. 1986;93(10):1049–1059.
12. Chappell LC, Duckworth S, Seed PT, et al. Diagnostic accuracy of PlGF in women with suspected preeclampsia. BMJ. 2013;347:f3836.
13. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med. 2017;377(7):613–622.
14. Levine RJ, Lam C, Qian C, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. N Engl J Med. 2006;355(10):992–1005.
15. Dröge LA, Herraìz I, Zeisler H, et al. Maternal serum sFlt-1/PlGF ratio in prediction of preeclampsia-related adverse outcomes. J Perinat Med. 2021;49(6):677–685.
16. Rana S, Powe CE, Salahuddin S, et al. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. Circulation. 2012;125(7):911–919.
17. Duhig KE, Myers JE, Seed PT, et al. Placental growth factor and preeclampsia: a review. J Matern Fetal Neonatal Med. 2016;29(10):1639–1645.
18. Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: ISSHP classification and management. Pregnancy Hypertens. 2018;13:291–310.
19. Stepan H, Hund M, Andraczek T. Combining biomarkers to predict pregnancy complications and redefine preeclampsia. Hypertension. 2020;75(4):918–926.
20. Karumanchi SA, Thadhani R. Research in preeclampsia—the end of the beginning. N Engl J Med. 2016;374(8):780–782.
21. Souza JP, Tuncalp O, Vogel JP, et al. Obstetric transition: the pathway toward ending preventable maternal deaths. BJOG. 2014;121(Suppl 1):1–4.

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PREEKLAMPSIYANI BASHORAT QILISHDA ANGIOGEN OMILLARNING ROLINI ANIQLASH

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ANNOTATSIYA

Preeklampsiya butun dunyoda ona va bola salomatligiga tahdid soluvchi asosiy homiladorlik asoratlaridan biri hisoblanadi. Kasallikning murakkab patogenezi g‘ayritabiiy platsentatsiya, immun disbalans va endotelial shikastlanish bilan bog‘liq. So‘nggi yillarda angiogen muvozanatsizlik preeklampsiyaning rivojlanishida muhim omil sifatida ko‘rilmoqda. Ushbu maqolada angiogen biomarkerlardan — platsentar o‘sish omili (PlGF), erituvchi fms-similar tirozin kinaza-1 (sFlt-1) va erituvchi endoglin (sEng) — preeklampsiyani erta aniqlashdagi prognostik ahamiyati yoritilgan. Bu omillarning biologik ahamiyati, homiladorlik davomida dinamikasi va klinik risk baholash modellari bilan integratsiyasi tahlil qilinadi. Angiogen profillash orqali erta aniqlash va kasallikni nazorat qilish homiladorlik parvarishini yangi bosqichga olib chiqishi mumkin.

Kalit so‘zlar: Preeklampsiya, angiogen omillar, PlGF, sFlt-1, biomarkerlar, homiladorlik asoratlari

ОПРЕДЕЛЕНИЕ РОЛИ АНГИОГЕННЫХ ФАКТОРОВ В ПРОГНОЗИРОВАНИИ ПРЕЭКЛАМПСИИ

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АННОТАЦИЯ

Преэклампсия является одной из основных причин материнской и перинатальной заболеваемости и смертности в мире. Её патогенез сложен и многофакторен, включая нарушение плацентации, иммунную дисфункцию и эндотелиальное повреждение. В последние годы особое внимание уделяется роли ангиогенного дисбаланса в развитии и прогрессировании преэклампсии. В настоящем обзоре рассматривается прогностическая ценность ангиогенных биомаркеров — плацентарного фактора роста (PlGF), растворимой тирозинкиназы-1 (sFlt-1) и растворимого эндоглина (sEng) — в выявлении женщин с высоким риском преэклампсии. Обобщены данные о биологической значимости этих факторов, динамике их концентраций в течение беременности и их роли в клинических моделях оценки риска. Подчёркивается потенциал ангиогенной профилизации как инструмента для раннего скрининга, диагностики и выбора тактики ведения беременности.

Ключевые слова: Преэклампсия, ангиогенные факторы, PlGF, sFlt-1, биомаркеры, осложнения беременности