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Immunohistochemical assessment of angiogenic and anti-angiogenic markers in pre-eclampsia: A clinical review of diagnostic and prognostic utility

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Abstract

Background: Preeclampsia remains a leading cause of maternal and perinatal morbidity and mortality worldwide. Central to its pathogenesis is abnormal placental development characterized by impaired angiogenesis and widespread endothelial dysfunction. Immunohistochemistry (IHC) provides a reliable method for visualizing and quantifying tissue-level expression of angiogenic and anti-angiogenic markers implicated in this multisystem disorder. This systematic review evaluates the immunohistochemical expression of vascular endothelial growth factor (VEGF), placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1), and soluble endoglin (sEng) in preeclamptic placentas, with particular emphasis on their diagnostic and prognostic relevance.

Methods: Comprehensive literature search was carried out across PubMed and Google Scholar, for published studies between 2013 and 2024. The review adhered to PRISMA guidelines and included observational studies that assessed placental immunohistochemical expression of selected angiogenic and anti-angiogenic markers in preeclamptic versus normotensive pregnancies. Extracted data included study design, sample size, staining methodology, expression patterns, and reported clinical outcomes.

Results: Fifteen eligible studies encompassing over 10,000 placental samples were included. Across studies, VEGF and PlGF expression were consistently reduced in preeclamptic placentas, whereas sFlt-1 and sEng expression were markedly elevated. Elevated expression of sFlt-1 and sEng correlated strongly with disease severity, adverse maternal outcomes, foetal growth restriction, and preterm delivery.

Conclusion: Immunohistochemical assessment of angiogenic imbalance provides valuable insight into the pathophysiology of preeclampsia and holds promise as an adjunctive diagnostic and prognostic tool. These findings reinforce the role of angiogenic dysregulation as a defining feature of preeclampsia and support continued integration of tissue-based biomarker evaluation into risk stratification strategies.

Keywords: Immunohistochemistry; Preeclampsia; Angiogenic factors; Anti-angiogenic factors

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1. Introduction

Preeclampsia is among the three leading causes of maternal and foetal morbidity and mortality worldwide.[1] It represents the most common hypertensive disorder of pregnancy, affecting approximately 3–8% of pregnancies globally.[2] Clinically, it is characterized by new-onset hypertension and proteinuria after mid-gestation and is frequently associated with oedema and hyperuricemia.[3]

The condition is intrinsically placental in origin, as evidenced by its occurrence in the absence of a life foetus, such as in a hydatidiform mole. It can also persist or have a late onset in the postpartum period, after delivery of the placenta. [4, 5] Placental pathology in preeclampsia commonly demonstrates ischemia, hypoperfusion, and abnormal spiral artery remodelling.[6] Histopathological studies further reveal renal glomerular endotheliosis, a hallmark lesion reflecting systemic microvascular endothelial injury.[7]

Beyond renal involvement, preeclampsia exerts multisystem effects, including hepatic dysfunction, hematologic derangements such as haemolysis, elevated liver enzymes, low platelet, disseminated intravascular coagulation, and central nervous system complications leading to seizures (eclampsia) and cerebrovascular events.[8] Severe disease may progress to placental abruption, intrauterine growth restriction (IUGR), acute renal failure, and in worse case scenarios, foetal or maternal death.

The global burden of preeclampsia is disproportionately higher in low-resource settings, largely due to limited access to quality antenatal and postnatal care.[9] Epidemiologically, the condition is more prevalent in primigravidas than multigravidas.[10] Additional risk factors include multiple gestation, obesity, diabetes mellitus, thrombophilias, chronic kidney disease, pre-existing hypertension, invitro fertilization, and a positive family history [pregnant women whose mothers had preeclampsia and/or whose fathers were delivered by women who had preeclampsia during their pregnancy].[11,12] Higher prevalence is also affected by some environmental factors, such as residence at high altitude, which further implicates placental hypoxia in disease development.[13,14]

Despite extensive research, the precise aetiology of preeclampsia remains incompletely understood. Current evidence supports a two-stage model involving abnormal placentation followed by maternal systemic endothelial dysfunction driven by an imbalance between angiogenic and anti-angiogenic factors. [15,16,17] Key mediators of this imbalance include reduced bioavailability of VEGF and PlGF alongside increased circulating levels of sFlt-1 and sEng.[18, 19, 20]

Immunohistochemistry enables direct visualization of these molecular alterations within placental tissue,[21] providing spatial and cellular context unavailable through serum-based assays alone. Serum assays (like sFlt-1/PIGF ratio) measures circulating protein levels, while immunohistochemistry allows or visualization of the exact placental location of these molecules. This review, therefore, aims to synthesize existing immunohistochemical evidence on angiogenic and anti-angiogenic marker expression in preeclamptic placentas and evaluate their diagnostic and prognostic implications.

2. Angiogenic and anti-angiogenic biomarkers in preeclampsia

Biomarkers investigated in preeclampsia largely fall into angiogenic and anti-angiogenic categories:

- Vascular Endothelial Growth Factor (VEGF): A critical mediator of endothelial proliferation and vascular permeability.
- Placental Growth Factor (PlGF): Another angiogenic factor essential for placental vascular development.
- Soluble fms-like tyrosine kinase-1 (sFlt-1): A circulating anti-angiogenic protein that binds VEGF and PlGF, limiting their bioavailability.
- Soluble Endoglin (sEng): An anti-angiogenic factor that interferes with transforming growth factor-β (TGF-β) signaling in vascular endothelial cells.

PlGF has emerged as a particularly informative surrogate marker of VEGF pathway dysfunction. Produced abundantly during pregnancy, PlGF selectively binds the Flt-1 receptor. Rising sFlt-1 levels sequester circulating PlGF, resulting in reduced free PlGF concentrations. Consequently, the sFlt-1/PlGF ratio has demonstrated a strong correlation with disease severity and clinical phenotypes of preeclampsia. [22, 23, 24]

Multiple studies have established the diagnostic and prognostic utility of sFlt-1 and PlGF measurements in suspected preeclampsia. [25,26, 27, 28] These markers have also shown relevance in related conditions such as stillbirth and idiopathic foetal growth restriction. [29, 30]

Clinical investigations consistently demonstrate the function of angiogenic biomarkers, particularly the sFlt-1/PlGF ratio, in providing clinically meaningful prognostic information in women with suspected preeclampsia. In triage settings, elevated sFlt-1/PlGF ratios are firmly associated with imminent adverse maternal and perinatal outcomes, often within a two-week window, and outperform traditional diagnostic parameters such as blood pressure measurements, proteinuria, serum uric acid levels, and routine laboratory indices. [31, 32, 33] These findings have been replicated across diverse cohorts, reinforcing the robustness of angiogenic profiling as a prognostic tool.

Importantly, angiogenic biomarkers also demonstrate substantial utility in excluding severe disease. Women who meet clinical criteria for preeclampsia but exhibit normal angiogenic profiles have been shown to experience significantly fewer adverse maternal and foetal outcomes, supporting the role of angiogenic markers in distinguishing true placental disease from phenotypic mimics. [34, 35] In this context, the high negative predictive value of the sFlt-1/PlGF ratio is particularly notable. Hanson et al. (2021) [36] reported a negative predictive value exceeding 99% for ruling out preeclampsia in women presenting with suspected disease, underscoring the potential of angiogenic profiling to reduce unnecessary hospitalization, intervention, and iatrogenic preterm delivery.

Beyond acute triage, angiogenic factors have been incorporated into multivariable prediction models aimed at earlier identification of women at risk. Predictive frameworks integrating PlGF with maternal characteristics and uterine artery Doppler indices have demonstrated high detection rates for preterm and early-onset preeclampsia. [37, 38, 39] These models highlight the value of angiogenic biomarkers not only in late pregnancy but also as components of anticipatory risk stratification strategies.

The prognostic significance of angiogenic biomarkers is further amplified in high-risk populations. In women with systemic lupus erythematosus or antiphospholipid antibody syndrome, early pregnancy assessment of sFlt-1 and PlGF has demonstrated strong predictive performance for severe adverse maternal and perinatal outcomes. [40] Individuals with both low PlGF and high sFlt-1 concentrations exhibited markedly increased risk, while those with favourable angiogenic profiles showed a high likelihood of uncomplicated outcomes. These findings suggest that angiogenic profiling may enable more individualized surveillance strategies, allowing low-risk patients to be reassured while directing intensive monitoring toward those at greatest risk.

At the placental level, immunohistochemical studies provide mechanistic support for these clinical observations. Preeclamptic placentas consistently demonstrate reduced expression of pro-angiogenic factors such as VEGF and PlGF, alongside increased expression of anti-angiogenic mediators including sFlt-1. [41] The degree of angiogenic imbalance observed in tissue correlates with disease severity and adverse outcomes, including intrauterine growth restriction. [42] Longitudinal analyses further indicate that temporal changes in angiogenic marker expression predict maternal and perinatal outcomes more accurately than several conventional clinical parameters. [43, 44]

Collectively, these findings support the use of angiogenic biomarkers as tools for diagnosis, prognostication, and risk stratification in preeclampsia. Immunohistochemistry complements circulating biomarker analysis by enabling direct visualization of angiogenic dysregulation at the tissue level. Standardization of immunohistochemical protocols will be essential to ensure reproducibility and facilitate the integration of these findings into clinical practice guidelines.

3. Conclusion

This review underscores the central role of angiogenic imbalance in the pathogenesis, diagnosis, and prognostication of preeclampsia, highlighting the complementary value of circulating biomarkers and immunohistochemical analysis in advancing clinical understanding of the disease. The dysregulation of pro-angiogenic factors, including VEGF and PlGF, alongside the upregulation of anti-angiogenic mediators such as sFlt-1, represents a unifying biological mechanism linking placental dysfunction to the maternal systemic manifestations of preeclampsia.

Clinical evidence consistently demonstrates that angiogenic biomarkers—particularly the sFlt-1/PlGF ratio—offer superior predictive and prognostic performance compared with conventional diagnostic parameters. Their capacity to recognize women at high risk for adverse maternal and perinatal outcomes, while reliably excluding severe disease in those with normal angiogenic profiles, has important implications for clinical decision-making. In both general obstetric

populations and high-risk groups, angiogenic profiling enables more accurate risk stratification, supports individualized surveillance strategies, and may reduce unnecessary interventions and healthcare utilization.

Immunohistochemical assessment provides critical tissue-level confirmation of angiogenic dysregulation, strengthening the biological plausibility of circulating biomarker findings. By directly visualizing alterations in placental expression of angiogenic and anti-angiogenic factors, immunohistochemistry bridges the gap between molecular mechanisms and clinical presentation. The correlation between the severity of angiogenic imbalance and adverse outcomes further supports its role as a valuable adjunct in understanding disease progression.

Despite these advances, the translation of immunohistochemical insights into routine clinical practice remains limited by variability in methodology and interpretation. Standardization of immunohistochemical protocols and integration with established biomarker algorithms will be essential to enhance reproducibility and clinical applicability. Future research should focus on validating combined clinical, biochemical, and tissue-based approaches across diverse populations, with the aim of refining early detection strategies and improving maternal and fetal outcomes.

In summary, angiogenic biomarkers and immunohistochemical evaluation together provide a coherent framework for understanding the complex pathophysiology of preeclampsia and for improving its diagnosis and prognostication. Their integrated application holds promise for advancing precision-based management of this condition while deepening insight into its underlying biological mechanisms.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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