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EARLY BIOMARKERS IN THE DIAGNOSIS OF PREECLAMPSIA

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ABSTRACT
Preeclampsia is a multisystem hypertensive illness of pregnancy and a major reason of maternal and neonatal morbidity and mortality worldwide. Because clinical manifestations often appear after significant placental dysfunction has occurred, reliable early biomarkers are essential for timely diagnosis and risk assessment. This review aims to summarize current evidence on early biomarkers for the diagnosis of preeclampsia, focusing on their biological mechanisms, diagnostic performance, clinical applications, emerging molecular technologies, and future prospects for precision medicine. The review evaluates established and emerging biomarkers, including angiogenic factors, placental proteins, inflammatory and oxidative stress markers, genetic and epigenetic biomarkers, extracellular vesicles, cell-free nucleic acids, and multi-omics approaches. Current evidence indicates that soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), and the sFlt-1/PlGF ratio are among the most reliable biomarkers for early prediction. Emerging biomarkers such as microRNAs, long non-coding RNAs, circular RNAs, proteomic, metabolomic, lipidomic, and exosome-based signatures further enhance diagnostic accuracy. Integration of these biomarkers with maternal clinical characteristics, Doppler ultrasound, and artificial intelligence-based prediction models improves individualized risk assessment and clinical decision-making. Continued multicenter validation, standardized analytical methods, and accessible point-of-care technologies are essential for translating these advances into routine clinical practice and improving maternal or neonatal results.

KEYWORDS: Preeclampsia; Early biomarkers; Angiogenic biomarkers; Placental growth factor; Precision medicine.

1. INTRODUCTION

Preeclampsia is among the most severe cases of hypertensive disorders that have serious repercussions on pregnancy and are an vital basis of morbidity and mortality among pregnant women. Preeclampsia occurs due to the hypertension onset along with dysfunction of maternal organs and/or placenta insufficiency post 20 weeks of pregnancy. Though there have been many developments in obstetrics, preeclampsia still causes a large number of problems during pregnancy such as maternal deaths, prematurity, intrauterine growth retardation, and neonatal morbidity. The prevalence of the disease is high in developing nations due to lack of antenatal screening services and special care in obstetrics. Various maternal risk factors, which include maternal hypertension, obesity, diabetes, chronic kidney disease, auto-immune conditions, advanced maternal age, multifetal pregnancies, and past history of preeclampsia have been noted as key risks for this condition (Bartsch et al., 2016), highlighting the multifactored nature of the condition and the importance of early identification of risks during pregnancy. The signs and symptoms associated with preeclampsia tend to occur when the woman's placenta is severely damaged and the mother's blood vessels are extensively damaged. Diagnosing preeclampsia from symptoms alone often restricts the chance of prevention. The late onset of diagnosis leads to an increase in risks of complications in the mother including eclampsia, stroke, renal failure, liver problems, disseminated intravascular coagulation, and maternal death while posing risks to fetal health due to poor placental function, low birth weight, death, premature labour, and intrauterine growth retardation. Thus, the identification of high-risk patients during early pregnancy is currently one of the objectives in obstetrics. Early prediction assists in putting into place precautionary events, such as taking low dose aspirin for prevention, increased monitoring of both mother and baby, and personalized approach to managing pregnancy. Prediction models that include information about maternal features along with biochemical and biophysical predictors in modern medicine have performed better and helped to diagnose pregnancies at higher risks even before the development of any clinical manifestation (Cerdeira et al., 2019). The present-day analysis of preeclampsia is founded mostly on the occurrence of hypertension in combination with proteinuria or dysfunction of maternal organs after 20 weeks of gestation. Even though these criteria are still considered to be a backbone of diagnostic practices for this condition, their reactive nature lies in the fact that the diagnosis is established at the moment when the pathology becomes clinically significant. Clinical indicators demonstrate low sensitivity in the preclinical stage and do not allow distinguishing between women who will suffer from preeclampsia and healthy pregnant women. Additionally, great biological variability between early and late onset of the illness affects the efficiency of diagnostics. The recent biological methods using protein expression profiling and metabolomics analysis have shown that there are significant changes at molecular level even before the onset of clinical symptoms, implying that multidimensional biomarkers would be far more effective than the current diagnostic measures (Bahado-Singh et al., 2017). Recent developments in the field of placental biology and molecular medicine have enabled researchers to develop more accurate biomarkers for predicting the early diagnosis of preeclampsia. Placentation

disorders, insufficient trophoblastic invasion, vascular imbalance, oxidative stress, immune system disorders, dysfunction of the endothelium, and impaired maternal-fetal communication led to a number of molecular abnormalities before the development of the disease occurs. Oxidative stress has been shown to be among the major factors involved in placental damage, and recent research data confirm that there is significant diagnostic potential of oxidative stress biomarkers for early detection of the risk of preeclampsia (Afrose et al., 2022). In the same vein, placental extracellular vesicles enriched with pregnancy-specific microRNAs have been found to show alterations in their expression patterns in pregnancies affected by the condition, highlighting early dysfunction in placenta and a good resource for developing non-invasive biomarkers for predicting the disease (Awoyemi et al., 2024). Moreover, technological innovations have also made possible the examination of cell-free RNA in maternal plasma, which acts as a mirror of placental gene expression over the entire course of pregnancy and has proven highly predictive of both early- and late-onset preeclampsia, thus paving new ways for accurate prenatal diagnosis (Castillo-Marco et al., 2025). Furthermore, recent findings related to the pathogenesis of preeclampsia have strengthened the physiological significance of angiogenic imbalance through proving that soluble fms-like tyrosine kinase-1 is capable of reducing trophoblastic invasiveness and placental growth (Chen et al., 2025).

Considering the rapidly changing environment in biomarker studies, it is essential to carry out an extensive assessment of existing literature on the potential of existing and novel biomarkers for early diagnosis of preeclampsia. In this review, the molecular pathways underlying biomarker secretion in the context of disease progression are critically assessed, and the major categories of biomarkers, such as angiogenic biomarkers, placental biomarkers, oxidative stress biomarkers, microRNAs associated with extracellular vesicles, and nucleic acid-based biomarkers, are discussed. At the same time, an analysis of their diagnostic accuracy, predictive power, clinical applicability, and limitations is provided along with future perspectives in biomarker validation and multi-biomarker approaches.

2. Pathophysiology of Preeclampsia Relevant to Biomarker Discovery

2.1 Normal Placental Development and Spiral Artery Remodeling

Development of the placenta occurs shortly after implantation and requires proper coordinated processes of proliferation, Trophoblast cell differentiation and invasion of the mother's decidua. Trophoblast cells gradually remodel maternal spiral arteries by replacement of the layers of endothelium and smooth muscles in order to create vessels that have a great capacity for carrying blood without much resistance to flow and which provide the developing fetus with enough blood from the mother. Proper physiological remodeling of maternal blood vessels creates the physiological conditions for the continuation of pregnancy and development of the fetus.

2.2 Abnormal Placentation in Preeclampsia

The development of preeclampsia occurs because of faulty placentation which is marked by poor trophoblastic infiltration or insufficient transformation of the spiral arteries. In consequence, the utero-placental circulation stays narrow and highly resistant, and this results in recurrent episodes of hypoperfusion, ischemia and reperfusion in the placenta. Such pathophysiological changes cause cell stress in the placenta, and this led to the announcement of several bioactive compounds in the maternal circulation even prior to the onset of symptoms of the disease. Modern studies of proteomics performed in a longitudinal manner have shown that there appear some characteristic protein profiles long before pregnancy in connection with faulty placentation (Degnes et al., 2024).

2.3 Angiogenic Imbalance

Angiogenic imbalance is one of the characteristic features in the pathogenesis of preeclampsia. The normal growth of placental vasculature requires a precise balance of agents that are both pro- and anti-angiogenic. Excessive production of anti-angiogenic agents and a deficiency of pro-angiogenic agents affect the development of placental vasculature and lead to endothelial impairment. PlGF has been proven to be one of the most valuable biomarkers due to the decreased concentrations in the blood of pregnant women previous to developing the disease and being proportional to the severity of the disease. PlGF has become a constituent of modern predictive algorithms (Das et al., 2025).

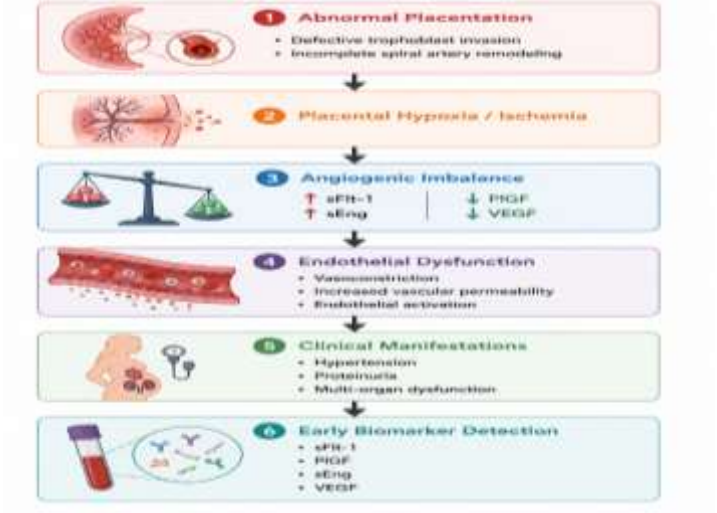

Figure 1. Angiogenic imbalance in the pathogenesis of preeclampsia

The inequity in angiogenesis that is demonstrated in Figure 1 leads to generalized injury of maternal endothelium, which serves as the main systemic feature of preeclampsia. These vascular abnormalities are responsible for various manifestations of this condition and constitute the basis for endothelial biomarkers reviewed in the subsequent section.

2.4 Endothelial Dysfunction

Endothelial dysfunction is the major systemic effect of placental damage in preeclampsia. Endothelial function is affected by placental derived factors circulating in the body, which lead to vasoconstriction, vascular permeability, activation of coagulation cascade and inflammatory response. These changes lead to the development of proteinuria and hypertension in addition to organ involvement, which are typical features of the syndrome. Since endothelial damage is related to the process of the disease, but not placenta alone, biomarkers that show endothelial activation are useful for prediction of the condition. Angiogenic biomarkers, especially when both angiogenic and anti-angiogenic factors are measured, are very useful for prediction of maternal outcome (Docheva et al., 2022).

2.5 Oxidative Stress and Inflammation

Oxidative stress or inflammation exhibit a complementary relationship in enhancing the pathophysiology of placenta involvement in preeclampsia. Poor placental perfusion outcomes in the overproduction of reactive oxygen species, which exceed the protective action of intrinsic antioxidants, thus leading to oxidative damages like lipid peroxidation, mitochondrial dysfunction, DNA damage, and apoptosis. At the same time, inflammatory reactions are triggered by high cytokine levels and leukocytes' mobilization, conducive to the worsening of endothelial dysfunction. Oxidative stress also contributes to the secretion of placental-derived biomarkers in the mother's bloodstream, resulting in biochemical changes that precede clinical signs. Scientific studies continue to show the key role of reactive oxygen species in the link between placental hypoxia and adverse pregnancy outcomes (Cheng et al., 2026).

2.6 Immunological Alterations

A carefully controlled maternal immunological environment, which favors fetal tolerance but at the same time keeps up the necessary defenses, is necessary for successful conception. In preeclampsia, the balance between the immune response becomes disturbed owing to improper activity of innate and adaptive immunity, changes in cytokines, problems with regulatory T-cells, and heightened activity of the immune response of inflammation. This affects trophoblastic invasion, activation of endothelium, and chronic inflammation of the placenta. Interaction between this immune disturbance and angiogenesis impairment and oxidative stress leads to rapid development of the damage. It gives good information about the biological foundation of some biomarkers.

2.7 Molecular Mechanisms Underlying Biomarker Release

The damage to the placenta triggers a series of biochemical processes that outcome in the emission of several biomarkers into the maternal blood. Stress, apoptosis, necrosis, extracellular vesicles release, and gene modifications work together to result in the secretion of different proteins, nucleic acids, angiogenesis regulators, cytokines, and metabolites from the mother’s blood. The biomarkers serve as a sign of the dysfunctional placenta and usually appear even a couple of weeks before clinical symptoms begin to manifest. Furthermore, economic and clinical analysis shows that the use of the biomarker evaluation increases diagnostic efficacy, aids in decision making, and makes the management of pregnant women with preeclampsia more cost-effective (Duhig et al., 2019).

3. Classification and Characteristics of Early Biomarkers

3.1 Characteristics of an Ideal Biomarker

The perfect biomarker for predicting the occurrence of preeclampsia must be able to predict the onset of the disease prior to the manifestation of symptoms. The biomarker must have a strong link to the disease physiology, reproducibility across different populations, and its quantification must involve the use of easily accessible, affordable and standardized laboratory techniques. High sensitivity in the identification of cases and high specificity in minimizing false positive cases is important in a good biomarker for preeclampsia. It must be capable of distinguishing between Early and late disease onset, predict severity and assist in decision making.

3.2 Maternal Serum Biomarkers

Biomarkers in maternal serum have proven to be one of the most extensively studied techniques for early diagnosis of preeclampsia owing to the ease, simplicity, and invasiveness of blood collection, which can be easily included in routine prenatal care. The list of these biomarkers includes angiogenic biomarkers, inflammatory biomarkers, placental biomarkers, oxidative stress biomarkers, RNA biomarkers, and biomarkers associated with extracellular vesicles. Of these, the sFLT1/PlGF ratio has demonstrated high predictability of preeclampsia with great accuracy and has been validated in Asians as well (Gao et al., 2021).

3.3 Placental Biomarkers

Placental biomarkers accurately capture the pathology of the underlying cause of preeclampsia because the condition is related with Trophoblast invasion and inadequate placental development, vascular dysfunction, and placental ischemia. Placental biomarkers could include placental proteins, angiogenic factors, metabolites, mRNAs, miRNAs, and extracellular vesicles produced by stressed placental cells and delivered through the maternal blood stream. Metabolomics and transcriptomic analyses have uncovered changes in metabolic pathways and gene expression in the placenta that can be used as biomarkers for the early detection of disease onset (Feng et al., 2022).

3.4 Genetic Biomarkers

Genetic biomarkers can shed light on genetically determined predisposition to preeclampsia and can aid in detecting high-risk women even prior to conception or at an early stage of pregnancy. Such biomarkers are related to maternal and fetal polymorphisms in genes that affect the development of vascular system and placenta, immune regulation, oxidative stress, and the process of thrombogenesis. However, although these markers can hardly be used in isolation for prediction of preeclampsia due to its complex nature, they could become more effective once coupled with other factors such as clinical history and biochemical characteristics of patients.

3.5 Epigenetic Biomarkers

Epigenetics markers are increasingly significant in preeclampsia studies owing to their representation of the dynamic regulatory gene processes which are affected by the stress of the placenta, maternal environment, inflammation, and vascular dysfunctions. Examples of epigenetic markers are DNA methylation, histones modifications, RNA profiles, circular RNA, long non-coding RNA, and miRNA within extracellular vesicles. Circulating extracellular vesicular miRNAs found in Early pregnancy has been linked to later clinical manifestations of preeclampsia, implying the possibility of using them as non-invasive markers. Epigenetics alterations often occur before clinical manifestation of a disease and therefore can aid in early diagnosis (Ghosh et al., 2024).

3.6 Urinary Biomarkers

Urinary biomarkers provide an easy method for studying renal involvement, endothelial activation, and injury in preeclampsia patients. The role of urinary biomarkers becomes especially important in view of the fact that proteinuria is considered to be a hallmark of preeclampsia. Possible urinary biomarkers may include albumin, podocyte proteins, angiogenic substances, reactive oxygen species, pro-inflammatory cytokines, and circulating free nucleic acids. Urine collection has several advantages when compared to blood sampling, since it is easy, cheap, and well tolerated by pregnant women. However, the results of urinary biomarker analysis depend on the level of hydration, renal diseases, gestational age, and severity of preeclampsia.

3.7 Multi-Marker Biomarker Panels

Multi-panel biomarkers use clinical, biochemical, biophysical, and molecular markers to provide increased predictive power than a single marker. Due to the multi-facet nature of the preeclampsia disease pathophysiology including placental malfunctioning, angiogenic imbalance, inflammation, oxidative stress, endothelial damage, and immunological dysregulation, multi-panel biomarkers are better positioned to account for the heterogeneous nature of the disease. As an illustration, PlGF tests have been assessed using threshold cut-offs for ruling in preeclampsia cases, indicating the significance of assay and clinical setting specificity in biomarker interpretation (Giblin et al., 2020). Multi-biomarkers can also encompass maternal cardiovascular risk factors, especially due to vascular issues and inflammation during pregnancy (Franczuk et al., 2022).

Table 1. Classification and characteristics of early biomarkers for preeclampsia

Biomarker category	Representative biomarkers	Sample source	Clinical significance	Reference
Maternal serum biomarkers	sFlt-1, PlGF, sEng	Maternal serum	Early diagnosis and risk stratification	Gao et al. (2021)
Placental biomarkers	PP13, PLAP, placental proteins	Placenta/Maternal blood	Reflect placental dysfunction	Feng et al. (2022)
Genetic biomarkers	Gene polymorphisms, susceptibility genes	Maternal/Fetal DNA	Assess inherited disease susceptibility	Franczuk et al. (2022)
Epigenetic biomarkers	miRNAs, lncRNAs, circRNAs	Maternal plasma/Placenta	Detect early gene-regulatory changes	Ghosh et al. (2024)
Urinary biomarkers	Proteinuria, podocyte proteins, oxidative stress markers	Urine	Monitor renal injury and disease progression	Giblin et al. (2020)
Multi-marker biomarker panels	sFlt-1/PlGF ratio, combined biomarker models	Multiple sources	Improve predictive accuracy	Gao et al. (2021)

The various categories of biomarkers presented in Table 1 constitute the building blocks for identifying the molecular mechanisms behind preeclampsia. Out of all of these, the angiogenic biomarkers have shown the greatest clinical value and have thus become integral to the diagnostic process. Hence, the subsequent part of this paper will address the biological importance and clinical inferences of angiogenic biomarkers related to preeclampsia.

4. Angiogenic Biomarkers

4.1 Soluble fms-like Tyrosine Kinase-1 (sFlt-1)

SFLT-1 (soluble fms-like tyrosine kinase-1) is one of the most studied angiogenic markers in preeclampsia and forms an important part of disease pathology. SFLT-1 is a splice form of vascular endothelial growth factor receptor, which binds to

circulating PlGF and VEGF. The excess manufacture of sFLT-1 from the placenta results in poor angiogenesis, endothelial dysfunction, hypertension, or proteinuria. High levels of sFLT-1 in the mother's blood can be identified several weeks before the disease becomes apparent clinically, thus serving as a good marker for diagnosis and disease prognosis.

4.2 Placental Growth Factor (PlGF)

PlGF is a pro-angiogenic glycoprotein that facilitates angiogenesis during placental development through proliferation, migration, and survival of endothelial cells. In a typical pregnancy, circulating levels of PlGF steadily rise throughout gestation to facilitate placental perfusion and fetal development. However, in preeclampsia cases, the placenta dysfunction causes a significant decrease in the levels of PlGF, which is known to occur even before the symptoms develop. Hence, PlGF has emerged as an important biomarker for the discovery and risk valuation of preeclampsia. Recent research utilizing single-cell and spatial omics approaches has provided insights into the mechanisms behind the production of angiogenic factors in the preeclamptic placenta (Hartmann et al., 2023).

4.3 Vascular Endothelial Growth Factor (VEGF)

Vascular endothelial growth factor (VEGF) is a crucial factor in angiogenesis, which maintains the integrity of the endothelium, vascular permeability, and creation of blood vessels in the placenta during pregnancy. Optimal VEGF signaling will promote normal trophoblastic invasion and proper adaptation of the maternal-fetal vascular systems. Excessive levels of soluble Flt-1 in preeclampsia will result in sequestration of free VEGF in plasma, leading to inhibition of its biologic function. The inhibition of biologically active VEGF affects vascular homeostasis and results in placental ischemia and endothelial damage. Studies have shown that the inhibition of the PI3K/Akt pathway also affects VEGF angiogenesis function (Kamrani et al., 2026).

4.4 Soluble Endoglin (sEng)

An anti-angiogenic protein called soluble endoglin (sEng) is secreted from the placental syncytiotrophoblast and inhibits transforming growth factor-β signaling and endothelial nitric oxide synthesis. High levels of maternal plasma sEng cause endothelial dysfunction, vasoconstriction, and poor vascular remodeling, which exacerbate the symptoms of preeclampsia. Elevated levels of sEng often correlate with elevated sFlt-1, indicating extensive placental damage. Since soluble endoglin is a product of placental injury, the measurement of soluble endoglin can help better understand the disease along with the measurement of other angiogenic markers. Recent studies have shown that there is close interaction between oxidative stress and angiogenesis pathways in the release of soluble endoglin and endothelial injury (Liu et al., 2025).

4.5 Clinical Significance of the sFlt-1/PlGF Ratio

The sFlt-1/PlGF ratio is now one of the most clinically useful biomarker indices in anticipating, identifying, and tracking preeclampsia, given that it combines the Pro-angiogenic and anti-angiogenic actions. The high ratio denotes increasing impairment of the function of the placenta and endothelial damage, which has always provided high accuracy for identifying women at risk before the emergence of the clinical disease. In addition, the ratio helps healthcare professionals differentiate preeclampsia from other pregnancy-related hypertensive disorders, assess the severity of the disease, and inform decisions on surveillance and timing of delivery. While microRNA biomarkers are being increasingly studied for complementary predictions, the placental microRNA expression profiles have remained closely associated with angiogenic imbalance and may be even more helpful in developing biomarker tests in the future (Gunel et al., 2017). Similarly, early first-trimester studies of placenta-specific C19MC microRNAs have proven their effectiveness as complementary biomarkers along with the sFlt-1/PlGF ratio (Hromadnikova et al., 2017).

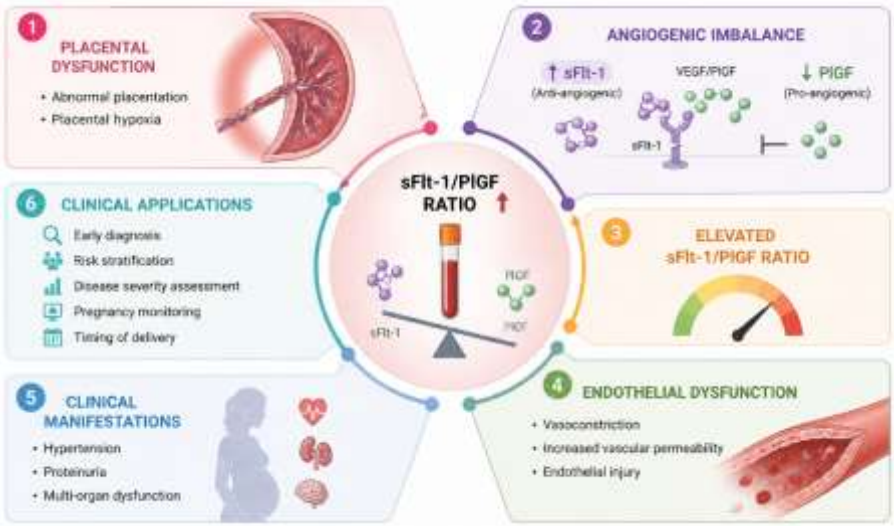

Figure 2. Clinical significance of the sFlt-1/PlGF ratio in preeclampsia

The diagnostic usefulness of the ratio of sFlt-1/PlGF in the analysis, prognostication, and organization of preeclampsia is depicted in Figure 2. While angiogenic biomarkers have made huge changes in the early analysis and organization of

preeclampsia, there are other placental and pregnancy biomarkers that provide additional insight about placental malfunctioning. The role of these biomarkers is highlighted in the next section.

5. Placental and Pregnancy-Associated Protein Biomarkers

5.1 Pregnancy-Associated Plasma Protein-A (PAPP-A)

The placenta produces the glycoprotein known as pregnancy-associated plasma protein-A (PAPP-A) mainly from the syncytiotrophoblast and is routinely used to assess the presence of aneuploidy in the fetus during Pregnancy's first trimester. The major biological role played by PAPP-A is to increase the bioactivity of insulin-like growth factors by cleaving binding proteins, thus stimulating trophoblast cell proliferation and foetal and placental growth. Low levels of maternal PAPP-A during pregnancy have been shown to be a marker for defective placentation and the later development of preeclampsia. PAPP-A has limited predictive power on its own but becomes much better with the addition of other factors (MacDonald et al., 2022).

5.2 Placental Protein 13 (PP13)

One such biomarker is placental protein 13 (PP13), which is part of the galectin family and is mainly secreted by the placental syncytiotrophoblast. It is involved in several functions such as trophoblast invasion, implantation, early pregnancy vascular remodelling and immunological tolerance. Deficiency of maternal serum concentration of PP13 levels in early pregnancy has been linked to poor placental formation and the risk of developing preeclampsia. Since this biomarker is abnormal right from the very beginning of placental formation, it makes the use of this biomarker especially valuable for early screening tests. Its efficacy is also increased by using it as a component of multimodal algorithms along with other risk factors.

5.3 Placental Alkaline Phosphatase

PLAP, or placental alkaline phosphatase, is a membrane-bound protein secreted mainly by syncytiotrophoblasts and entering maternal circulation during gestation. It serves in the processes of placental metabolism, nutrition, differentiation, and functioning. Abnormal maternal levels of PLAP indicate placental malfunctioning, endothelial damage, and developmental disorders of the fetus in preeclampsia-affected pregnancies. In recent systematic studies, it was found that several different placental kinases and phosphatases other than already known angiogenic markers can play a role in preeclamptic diseases' pathogenesis through regulation of intracellular signaling pathways associated with survival, adaptation, and inflammation in trophoblasts (Marrufo-Gallegos et al., 2023).

5.4 Placental Exosomes

Placental exosomes are nano-sized vesicles secreted from trophoblastic cells into the maternal bloodstream to facilitate communications between the placenta and maternal tissue. Placental exosomes carry a range of biomolecular contents such as proteins, mRNA, miRNAs, lipids, and metabolites representing physiological condition of placental tissue. Preeclampsia leads to abnormal placental stress, which affects the quantity and type of molecules carried by placental exosomes; therefore, placental exosomes can be considered as biomarkers for early detection of preeclampsia. New developments in the field of liquid biopsies allow characterizing placental exosomes; thus, the use of placental exosomes is becoming more relevant for detecting placental dysfunction by non-invasive maternal blood test (Ma et al., 2026).

5.5 Cell-Free Fetal DNA and Cell-Free RNA

The majority of the cffDNA and cfRNA molecules present in the circulation derive from apoptotic, necrotic, and active secretion processes occurring at the placental level. Elevated levels of the circulating nucleic acids have shown an association with placental damage and can also be detected even prior to the appearance of symptoms related to the development of preeclampsia, thus making them excellent candidates for prenatal testing. In contrast to other biomarkers, cfRNA offers dynamic insight into the process of placental gene expression and disease progression. The use of these molecular biomarkers along with artificial intelligence and machine learning algorithms has shown an improvement in prediction accuracy and therefore allows a personalized approach for predicting cases of preeclampsia at the early stages of pregnancy (Melinte-Popescu et al., 2023). Additionally, current international guidelines emphasize the significance of using molecular biomarkers together with clinical evaluation in risk stratification of hypertension during pregnancy (Magee et al., 2022).

Table 2. Placental biomarkers in preeclampsia

Biomarker	Clinical significance	Reference
Pregnancy-associated plasma protein-A (PAPP-A)	Early marker of impaired placentation	MacDonald et al. (2022)
Placental protein 13 (PP13)	First-trimester risk prediction	Magee et al. (2022)
Placental alkaline phosphatase (PLAP)	Marker of placental dysfunction	Marrufo-Gallegos et al. (2023)
Placental exosomes	Non-invasive marker of placental status	Ma et al. (2026)
Cell-free fetal DNA (cffDNA)	Early indicator of placental injury	Ma et al. (2026)

Cell-free RNA (cfRNA)	Reflects placental gene expression	Melinte-Popescu et al. (2023)

Table 2 contains the major biomarkers related to the placenta and pregnancy and their clinical relevance. Besides the biomarkers from the placenta, the other factors such as immune activation, inflammation, and oxidative stress that cause preeclampsia have been described in detail in the next section.

6. Immunological, Inflammatory, and Oxidative Stress Biomarkers

6.1 Cytokines and Chemokines

Immune communication during pregnancy is orchestrated by cytokines and chemokines through their influence on trophoblast invasion, placental vascular remodeling, and the establishment of immunological tolerance in mothers. During the development of preeclampsia, there is an overproduction of pro-inflammatory cytokines and chemokine signaling changes that lead to recruitment of leukocytes, endothelial damage, and impaired placentation. Cytokines and chemokines are mediators of chronic systemic inflammation and have become valuable biomarkers in early detection of the condition, along with maternal clinical parameters (O'Gorman et al., 2017).

6.2 Tumor Necrosis Factor-α (TNF-α)

The pro-inflammatory cytokine tumour necrosis factor alpha (TNF-α) is crucial in the pathology of preeclampsia through its many biological functions. It reduces trophoblast invasiveness and increases oxidative stress, endothelial cell activation, and vasoconstriction. It also leads to the placenta's hypoxia and damage to maternal blood vessels through persistent activation of the TNF-α signaling pathway. Because of these actions, TNF-α continues to be an important inflammatory biomarker for future studies on preeclampsia.

6.3 Interleukins (IL-6, IL-10, IL-17)

Interleukins have an vital part in maintaining maternal immune acceptance throughout pregnancy. The low levels of anti-inflammatory factors and high levels of IL-6, IL-17, and IL-10 cause immune tolerance to be lost and trigger placental inflammation, endothelial cell activation, and vascular dysfunction. Such conditions occur prior to clinical symptoms and are strongly correlated with dysregulation of placental genes. In the study conducted on noncoding RNAs, it was found that such molecules can help regulate inflammatory signaling pathways, making them valuable together with interleukin analysis in predicting preeclampsia (Munjas et al., 2021).

6.4 C-Reactive Protein (CRP)

The As part of the body's inflammatory reaction, the liver produces C-reactive protein (CRP), an inflammatory acute phase protein. High levels of maternal C-reactive proteins are linked to endothelial dysfunction, placental damage, and severe disease in preeclampsia. While C-reactive protein is not specific for the disease when used alone, it is helpful in assessing the inflammatory state of the mother. The simplicity of its use and its availability in many laboratories justify further clinical testing.

6.5 Oxidative Stress Markers

Oxidative stress biomarkers are indicative of increased manufacture of reactive oxygen species or impaired antioxidant answer in the ischemic placenta. Oxidative stress leads to injury to lipids, mitochondria, DNA, and trophoblast cells resulting in disease progression. New point-of-care techniques have made it possible to measure oxidative stress in addition to angiogenic and inflammatory markers, which helps in early diagnosis and better management of patients with preeclampsia (Ng et al., 2024).

6.6 Endothelial Activation Markers

Endothelial activation indicates the systemic consequence of placental malfunction and is marked by vascular inflammation, vasodilatation impairment, and hyper-permeability. Endothelial damage indicators appear prior to the development of any clinical signs, and they offer important insights into the course of the illness and risk for pregnant women. With the development of circulating free RNA analysis, it has been shown that the molecular markers of endothelial dysfunction originating from the placenta can be used for predicting preeclampsia several months ahead of its development (Moufarrej et al., 2022; Ogoyama et al., 2022).

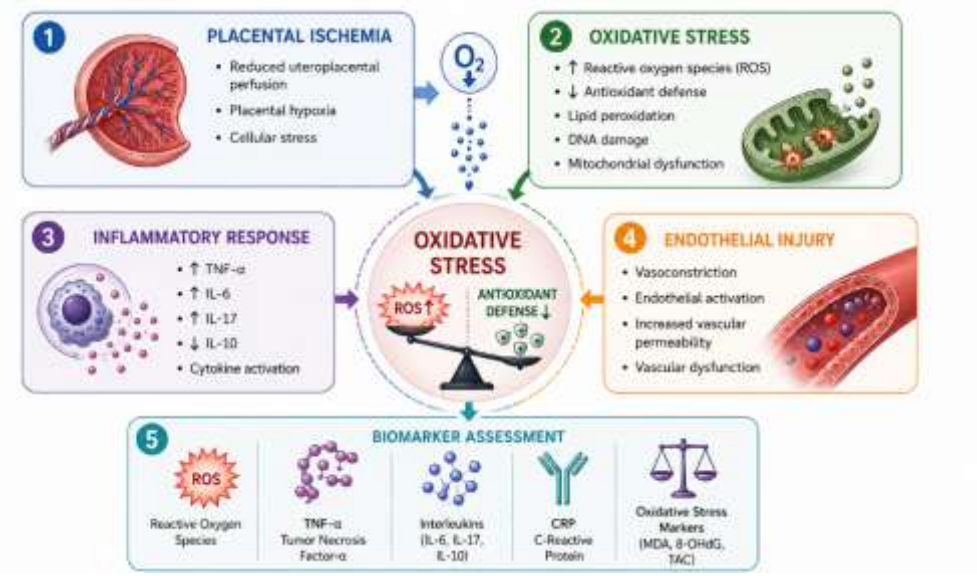

Figure 3. Role of oxidative stress in the pathogenesis of preeclampsia

The relationship between placental ischemia, oxidative stress, inflammation, endothelial dysfunction, and the relevant biomarkers in the development of preeclampsia is shown in Figure 3. The recent developments in transcriptomics, noncoding RNA, proteomics, metabolomics, lipidomics, and extracellular vesicles have increased the scope of early diagnosis and precision medicine for preeclampsia, as described in the next section.

7. Emerging Molecular Biomarkers

7.1 MicroRNAs (miRNAs)

The microRNAs (miRNAs) are tiny non-coding RNA molecules that regulate the expression of genes post transcription and are responsible for trophoblast growth, angiogenesis, immune regulation, and placentation. Abnormal expression of miRNAs leads to Endothelial malfunction and aberrant placentation in cases of preeclampsia. Since many of these placental miRNAs enter the mother's bloodstream even before any symptoms appear, they have become potential non-invasive markers for preeclampsia. The results of a thorough meta-analysis indicated the usefulness of these circulating miRNAs in diagnosing preeclampsia (Qin et al., 2022).

7.2 Long Non-Coding RNAs (lncRNAs)

lncRNAs function in modulating chromatin architecture, transcription, and post-transcriptional gene expression, which affect the development of the placenta and vascular adaptations in the mother. Mal-regulation of the LncRNA expression levels have been connected to altered trophoblast invasion, immune imbalance, oxidative stress, and angiogenesis in preeclampsia. lncRNAs are increasingly considered biomarker candidates owing to their specific expression levels in certain tissues and stability in maternal plasma. Recent research linking the dysfunction of the placenta, immune dysregulation, and miRNA epigenetics has further validated their biological importance (Procopciuc et al., 2026).

7.3 Circular RNAs (circRNAs)

CircRNAs are circular and highly stable RNA molecules due to their covalently closed structure. They serve as regulatory RNA molecules by binding to microRNAs and RNA-binding proteins and modulating placental angiogenesis, trophoblast differentiation, and inflammation signaling. The altered circRNA expression has been noted at the early stage of preeclampsia, making circRNAs a promising option for biomarker development. Their resistance to the action of exonucleases contributes to the prospects of circRNA use in diagnostics in the future.

7.4 Metabolomics

Metabolomics studies metabolites that are produced during cell metabolism and gives information about functional status of the placenta. Metabolic changes related to amino acids, lipids, carbohydrates, and oxidative metabolites prior to clinical manifestation of preeclampsia have been identified. The metabolomic profile indicates impaired energy metabolism, mitochondrial dysfunction, and hypoxic condition of the placenta. Being detected in the initial stage of disease formation, the metabolomic profile can be used for risk stratification.

7.5 Proteomics

Proteomics is used for complete evaluation of proteins associated with placental development, vasculature remodeling, inflammation, and endothelial function. Many differentially expressed proteins have been discovered using high-throughput proteomics methods which are linked with preeclampsia before its clinical presentation. Such signatures allow better elucidation of the mechanisms of the disease and aid in discovering novel biomarkers for use in diagnostics and prognosis. Modern prognostic models utilize angiogenic and protein biomarkers for predicting poor maternal outcomes in hypertensive pregnancy (Perry et al., 2020).

7.6 Lipidomics

The field of lipidomics entails the study of the global lipid content and metabolism in the body. This is an important approach towards understanding the state of the membrane, oxidative stress, inflammation, and cellular signaling. Pregnancies that have been affected by preeclampsia often display abnormal phospholipids, sphingolipids, and fatty acids due to dysfunctional placenta and endothelium. The changes in the lipids play an vital part in causing inflammation and oxidative stress and are indicators of the severity of the disease.

7.7 Extracellular Vesicles and Exosomes

Both extracellular vesicles and exosomes play vital roles in mother-to-fetus communication by delivering proteins, lipids, messenger RNA, microRNA, and various other molecules to maternal blood from the placenta. Placental stress greatly affects the levels and contents of these vesicles when the mother suffers from preeclampsia. Their resistance to degradation in biofluids, along with their strong association with placental pathology, makes them ideal non-invasive biomarkers for disease tracking and early diagnosis. The introduction of placental growth factor testing at the point-of-care in women suffering from preeclampsia further enhances the role of biomarkers for this purpose (Rogers et al., 2025).

7.8 Multi-Omics Approaches

A multi-omics approach involves the use of transcriptomics, proteomics, metabolomics, lipidomics, epigenomics, and genomics to give a complete vision into the mechanisms of preeclampsia and facilitate biomarker discovery. The combination of multiple molecular techniques allows capturing the complexity of interactions in the development of placental abnormalities. This method is in accordance with international recommendations for first trimester multimodal testing for the risk of preeclampsia (Poon et al., 2019). In addition, clinical utility of the sFlt-1/PlGF ratio in Asian populations has been validated as a part of integrated models of prediction (Ohkuchi et al., 2021).

Table 3. Multi-omics approaches for early biomarker discovery in preeclampsia

Omics approach	Major analytes	Clinical application	Reference
MicroRNA (miRNA)	Circulating miRNAs	Early prediction and diagnosis	Qin et al. (2022)
Long non-coding RNA (lncRNA)	lncRNAs	Gene regulation and risk assessment	Procopciuc et al. (2026)
Circular RNA (circRNA)	circRNAs	Non-invasive biomarker discovery	Procopciuc et al. (2026)
Metabolomics	Small-molecule metabolites	Metabolic profiling	Poon et al. (2019)
Proteomics	Differentially expressed proteins	Biomarker identification	Perry et al. (2020)
Lipidomics	Lipid metabolites	Assessment of placental dysfunction	Ohkuchi et al. (2021)
Extracellular vesicles/Exosomes	Proteins, RNAs, lipids	Liquid biopsy and disease monitoring	Rogers et al. (2025)
Multi-omics	Integrated genomic, transcriptomic, proteomic and metabolomic data	Precision diagnosis and risk prediction	Poon et al. (2019)

Table 3 presents an overview of omics techniques and their use in identifying biomarkers for preeclampsia. The combination of these molecular tools has helped expedite the transfer of biomarker research into clinical applications. Their use in first-trimester screening and individualized management of pregnant women is described in the next section.

8. Clinical Application of Early Biomarkers

8.1 First-Trimester Screening Strategies

Finding pregnant women who have a higher likelihood of having preeclampsia, even before any clinical signs appear. The current methods of first-trimester screening include blood pressure, uterine artery, and maternal history Doppler analysis and circulating biomarkers. Early detection will allow closer monitoring of patients and appropriate preventive measures to be taken without maternal and fetal complications. The recent systematic evidence suggests including placental biomarkers in the algorithm of first-trimester screening to increase the sensitivity of detecting both early-onset and late-onset preeclampsia (Salimbayeva et al., 2025).

8.2 Risk Prediction Models

The risk prediction models utilize various parameters, such as clinical, biochemical, and biophysical factors, to predict the probability of a patient developing preeclampsia. Such models perform better than single biomarkers since they account for various disease mechanisms, like placental abnormalities, angiogenic dysregulation, inflammation, and endothelial damage. The continuous development of these models based on molecular findings has led to increased model performance and practical application. Research shows that utilizing both traditional biomarkers and novel molecular biomarkers increases the predictive capacity of the risk prediction models (Rybak-Krzyszkowska et al., 2023).

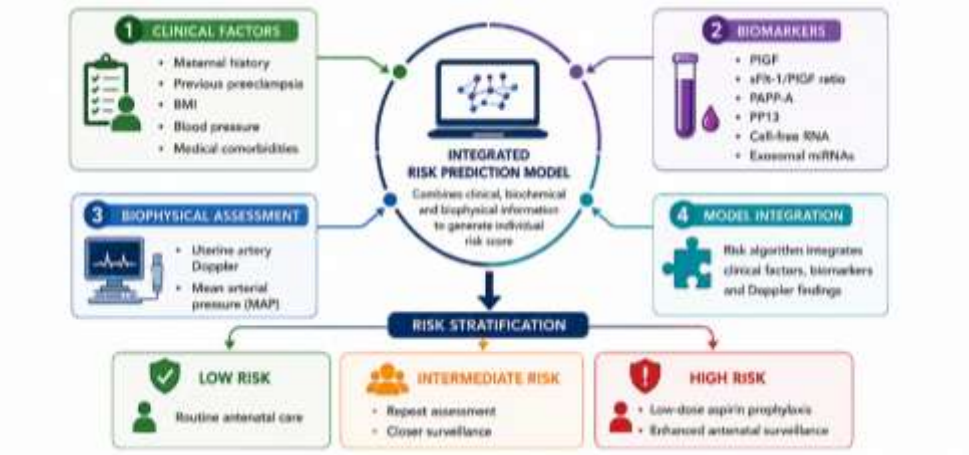

Figure 4. Integrated risk prediction model for preeclampsia

An overview of the general framework for the integrated risk prediction model during the first trimester is shown in Figure 4. With stratification of patients according to risk level, preventive measures using biomarkers can be put into place to prevent preeclampsia. Identification of high-risk pregnancies leads to preventive measures, as further elaborated upon in the next section.

8.3 Biomarker-Guided Prevention

Identifying women who are likely to develop such complications beforehand makes it possible to undertake preventative measures without causing any damage to the placenta. Stratification of patients based on biomarkers has been especially helpful in identifying those who will require the preventative management of low dose aspirin, which can decrease cases of preeclampsia at an early stage of pregnancy. Randomized clinical studies have proved that preventive therapy using aspirin, based on early screening, is effective (Rolnik et al., 2017).

8.4 Integration with Maternal Clinical Characteristics

The evaluation of biomarkers would be greatly enhanced by considering clinical attributes in women such as their chronic hypertension, diabetes mellitus, autoimmune disorders, age, BMI, parity, ethnicity, and obstetric history. The integration of biomarkers with the risk factors in clinical practice would facilitate the proper identification of pregnant women that would need intensive monitoring. The immunological status of the mother before and during the pregnancy period also affects the development of the placenta and the predisposition to disease (Sisti et al., 2016).

8.5 Combination with Doppler Ultrasound

The integration of molecular markers into the uterine artery Doppler ultrasound offers supplementary data on the perfusion of the placenta and vascular changes. The Doppler indices indicate abnormal uteroplacental blood flow, while the molecular markers provide information about placental damage and dysfunction. New biomarkers, especially exosomal microRNAs, add additional value to the performance of combined screening tests through the detection of early changes in the placenta that have not yet led to any structural changes in the vasculature (Shan et al., 2024).

8.6 Biomarker Performance in Early- and Late-Onset Preeclampsia

The predictive capability of biomarkers varies in preeclampsia with early and late onset since the two subtypes have different pathological processes. The early onset subtype is more linked to the plain malfunction of the placenta, and thus it exhibits higher biomarker changes compared to the late-onset subtype. Exosomal circulating microRNAs have been found to have an excellent capability in predicting preeclampsia among women without any symptoms in early gestation periods (Srinivasan et al., 2020).

9. Challenges, Limitations, and Future Perspectives

9.1 Variability Among Biomarker Studies

Significant variations are present in the biomarker studies because of differences in study design, gestational ages at which samples were taken, diagnostic criteria used, laboratory equipment, and patients' characteristics. Such variations make comparisons across the studies difficult and limit the applicability of results generated from different studies. Additionally, variations in sample preparation, storage, and analysis procedures cause heterogeneity in biomarkers' performances. In recent systematic reviews of proteome-based biomarkers in maternal plasma and serum, importance is attached to standardized study procedures (Starodubtseva et al., 2025).

9.2 Standardization and Validation Challenges

In spite of the encouraging results obtained from the research, very few biomarkers have been sufficiently validated using multi-center studies to apply them clinically. Assay procedures, consensus thresholds, and multi-center validation are some of the challenges faced in using biomarkers. Laboratory variation and cut-off levels play an vital role in defining the predictive value. New research shows that a combination of the sFlt-1/PlGF ratio and other biomarkers such as endocan-1 improves prediction; however, this needs to be validated clinically (Tian et al., 2025).

9.3 Cost-Effectiveness and Accessibility

However, the widespread adoption of biomarker screening not only relies on accurate diagnosis but is influenced by cost-effectiveness, laboratory equipment, and availability within various health-care systems. The use of complex molecular tests might prove to be hard to achieve in underdeveloped countries due to their high price and complexity. Thus, it is important to have cost-effective and accessible biomarkers for equal health-care delivery. Such biomarker panels, which are able to predict disease progression and help to make informed clinical decisions, can save money spent on severe complications in the future (Zeisler et al., 2016).

9.4 Population-Specific Differences

The performance of biomarkers in various ethnic and geographical groups could differ based on factors such as genetic variation, environment, comorbid conditions of the mother, nutrition levels, and access to healthcare services. In this regard, biomarkers which might be effective in one group cannot show the same level of predictive accuracy in another population group. This is due to the fact that metabolomic studies have found that metabolic markers for preeclampsia can be different in different populations (Yao et al., 2022).

9.5 Artificial Intelligence and Precision Medicine in Biomarker Interpretation

The use of machine learning and artificial intelligence techniques has proven to be a useful approach in the analysis of biomarker data through incorporation of clinical features alongside molecular and imaging data. The application of precision medicine approaches based on competing-risk algorithms is more accurate in estimating disease probability compared to traditional screening methods since it incorporates multiple variables related to the mother and the pregnancy at the same time (Wright et al., 2020).

9.6 Future Directions for Clinical Implementation

The future research needs to focus on conducting large-scale prospective multicenter studies, standardization of laboratory methodologies, and inclusion of multimodal biomarkers in the prenatal screening programs. The use of multimodal biomarkers along with advanced computing techniques could make a substantial improvement in the early diagnosis and personalized management of pregnancies. Moreover, cost-effective diagnostic tools and point-of-care assays will be very useful in making these techniques clinically available worldwide. Further analysis of serum levels of sFlt-1, PlGF, and their ratios will help refine the prognostic approach (Zhu et al., 2020).

10. CONCLUSION

Preeclampsia still constitutes among the most common reasons of morbidity or mortality both for mothers and their newborns, hence, indicating the necessity to develop reliable methods allowing diagnosing the condition before the growth of clinical symptoms. The progress made in the field of molecular biology and placenta research allowed gaining significant insight into the complicated mechanisms of preeclampsia development and identified a lot of early biomarkers related to aberrant placentation, angiogenesis oxidative stress, inflammation, endothelial dysfunction, and imbalance, immune dysfunction, and changed gene expression. Well-known biomarkers, namely, PlGF, sFlt-1, and the ratio of sFlt-1 to PlGF are already clinically effective, whereas new biomarkers like extracellular vesicles, circular RNAs, long non-coding RNAs, and microRNAs, cell-free nucleic acids, and multi-omics profiles hold a great promise. However, the inclusion of these biomarkers together with other variables such as maternal clinical features, measurement of uterine artery Doppler and sophisticated computational analysis has resulted in even better prediction and a possible precision medicine approach to the management of these patients. However, there are still several barriers that need to be addressed, including heterogeneity between studies, a lack of standardization in assays, insufficient validation in different populations, and lack of availability in under-resourced areas. Further investigations should therefore be done on the establishment of multicenter validations, standardization in laboratory methods, low-cost technologies for point-of-care testing, and artificial intelligence for biomarker evaluation.

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