REVIEW

10.2478/AMB-2025-0082

PREDICTIVE POWER OF BIOMARKERS IN PREECLAMPSIA IN SINGLETON PREGNANCIES: A COMPREHENSIVE REVIEW OF CURRENT EVIDENCE AND FUTURE DIRECTIONS

Z. Kirovakov[1,3], B. Stoilov[2], A. Anzaar[3]

[1]Department of Health care, Faculty of Public Health and Health Care,
Burgas State University "Prof. Dr Asen Zlatarov" – Burgas, Bulgaria
[2]Department of Obstetrics and Gynecology, Medical University – Plovdiv, Bulgaria
[3]Faculty of Medicine, Medical University – Pleven, Bulgaria

Abstract. *Preeclampsia is a significant cause of maternal and fetal morbidity and mortality worldwide, characterized by hypertension and proteinuria after 20 weeks of gestation. Early identification and management are critical to improving outcomes. Biomarkers have emerged as promising tools for predicting the onset and progression of preeclampsia, offering the potential for earlier intervention. This comprehensive review examines the current landscape of biomarkers in predicting preeclampsia, evaluating their predictive values, clinical applicability, and limitations, specifically in singleton pregnancies. Readers explore a range of biomarkers, including angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), which have shown high sensitivity and specificity in predicting preeclampsia. The roles of inflammatory markers, such as C-reactive protein (CRP) and cytokines, are also assessed for their predictive capabilities. In addition, the research discusses the emerging significance of metabolomic and proteomic profiles in enhancing predictive accuracy. Despite advancements, the clinical integration of these biomarkers is hindered by challenges such as variability in predictive performance across different populations and gestational stages. Moreover, the cost-effectiveness and accessibility of biomarker testing in routine prenatal care remain areas of concern. Future research should focus on validating biomarker panels in diverse populations and developing standardized guidelines for clinical implementation. In conclusion, while biomarkers hold substantial promise in the predictive landscape of preeclampsia, ongoing research is crucial to overcome existing barriers and translate these findings into improved clinical outcomes. This review aims to provide a comprehensive overview of the current evidence and future directions in the predictive use of biomarkers for preeclampsia.*

Key words: *preeclampsia, biomarkers, prediction, sFlt-1, PlGF, angiogenesis, pregnancy, maternal health, Fetal Medicine Foundation*

Corresponding author: *Dr Zlatko Kirovakov, UMHAT – Burgas, 73 Stefan Stambolov Blvd., tel: +359899922752, email: kirovakov@yahoo.com*

ORCID: *0009-0003-7643-5879 – Zlatko Kirovakov*

ORCID: *0000-0001-5221-3815 – Boris Stoilov*

ORCID: *0009-0004-3196-0044 – Ahamed Akkeel Anzaar*

Received: *05 March 2025;* ***Revised/Accepted:*** *20 May 2025*

INTRODUCTION

Women with a history of preeclampsia face a 2-4-fold increased risk of cardiovascular disease (CVD) after childbirth compared to those with normal blood pressure during pregnancy [1]. Preeclampsia is a hypertensive disorder of pregnancy, defined by new-onset hypertension (≥140/90 mm Hg) and either proteinuria (>300 mg/24h urine collection) or end-organ dysfunction developing after 20 weeks of gestation [2]. Preeclampsia, a significant contributor to maternal and fetal complications globally, is characterized by the onset of hypertension and renal issues in previously healthy women after 20 weeks of gestation. This multifaceted disorder can result in severe outcomes, including convulsions, organ dysfunction, maternal mortality, and fetal complications such as growth restriction, preterm delivery, and stillbirth. While the exact etiology of preeclampsia remains elusive, it is believed to stem from inadequate placental development, leading to fetal hypoperfusion and the release of factors that induce vascular damage and inflammation. Early and precise diagnosis of preeclampsia is vital for prompt intervention, prompting ongoing research into predictive biomarkers that can detect the condition before clinical manifestation. This review seeks to examine current biomarker candidates, including those associated with angiogenesis, inflammatory processes, and metabolic alterations in singleton pregnancies. The analysis will evaluate their efficacy, clinical feasibility, constraints, and the challenges of integrating them into standard antenatal care, as well as identify potential avenues for future investigation. The overarching objective is to present the advancement of enhanced preeclampsia prediction and management strategies, ultimately mitigating its impact on maternal health [3].

PATHOPHYSIOLOGY OF PREECLAMPSIA: RATIONALE FOR BIOMARKER USE

Understanding the underlying pathophysiology is crucial to comprehending the significance of biomarkers in preeclampsia prediction. Numerous interrelated variables contribute to preeclampsia, which ultimately results in systemic inflammation and extensive endothelial dysfunction [4]. It is thought that aberrant placentation, which results in an imbalance between angiogenic and anti-angiogenic factors, is the beginning event [4].

Aberrant Placentation and Angiogenesis

Establishing proper maternal-fetal circulation depends on the placentation process, especially in the first trimester of pregnancy [5]. Shallow placentation and decreased blood supply to the placenta result from preeclampsia's impairment of the usual process of trophoblast invasion into the mother's spiral arteries. Endothelial dysfunction is exacerbated by placental ischemia, which causes components to be released into the mother's blood [5].

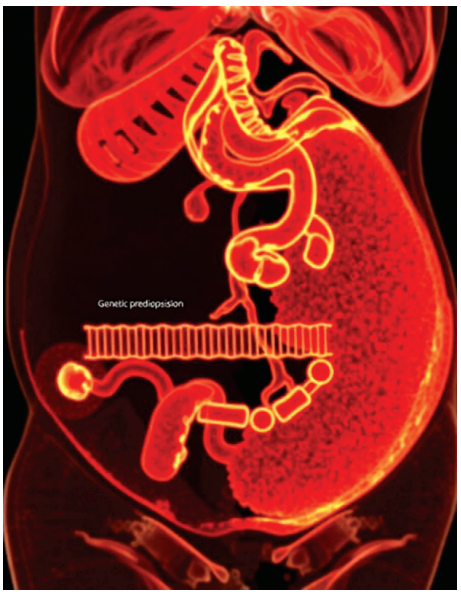

Fig. 1. Scan image of pathophysiology of preeclampsia: genetic predisposition, depicting specific gene polymorphisms associated with increased risk of preeclampsia, scanned with DNA sequencing technology for a research paper. The figure was created for the purpose of this article by artificial intelligence

Producing new blood vessels, or angiogenesis, is essential to placental growth. Vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) are two examples of angiogenic factors that support the development and stability of the placental vasculature [6]. The equilibrium between angiogenic and anti-angiogenic factors is upset in preeclampsia, and there is an overabundance of anti-angiogenic factors in the mother's bloodstream, such as soluble fms-like tyrosine kinase-1 (sFlt-1) [6].

Endothelial Dysfunction and Systemic Inflammation

Preeclampsia is typified by endothelial dysfunction, which manifests as increased vascular permeability, poor vasodilation, and coagulation cascade activation [7]. When VEGF and PlGF are bound by excess sFlt-1, their bioavailability is decreased and their angiogenic effects on endothelial cells are inhibited. Inflammatory mediators are released as a result, and endothelial damage occurs [7].

Another important characteristic of preeclampsia is systemic inflammation since affected women have higher levels of inflammatory cytokines like C-reac-

tive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [8]. These inflammatory mediators worsen endothelial dysfunction and vasoconstriction while also promoting endothelial activation [8].

Mathematical Representation of Angiogenic Imbalance

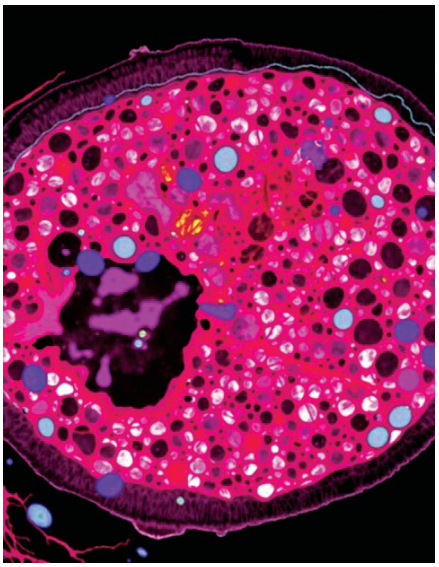

Fig. 2. Microscopic scan of angiogenic imbalance in a human tissue sample, stained with immunohistochemical markers, showing disrupted blood vessel formation in a tumor microenvironment. The figure was created for the purpose of this article by artificial intelligence

The balance between angiogenic and anti-angiogenic factors can be mathematically represented. Let:

[PlGF] = Concentration of Placental Growth Factor

[sFlt-1] = Concentration of soluble fms-like tyrosine kinase-1

The *angiogenic ratio* (AR) was defined as

AR = [PlGF] / [sFlt-1] (Equation 1)

A lower AR indicates a higher risk of preeclampsia, reflecting an increased antiangiogenic state [9].

The change in the angiogenic ratio over time can provide further insights.

ΔAR/Δt = (AR(t+Δt) – AR(t)) / Δt (Equation 2)

A negative ΔAR/Δt ratio suggests a worsening angiogenic imbalance, potentially indicating progression towards preeclampsia [9].

Implications for Biomarker Development

The use of biomarkers to forecast the development and course of preeclampsia is well supported by an understanding of its pathogenesis. Women at high risk of preeclampsia may be identified before clinical symptoms appear by assessing circulation levels of inflammatory markers, angiogenic agents, and other substances. Biomarkers can also be used to track the course of a disease and direct treatment [10].

ANGIOGENIC AND ANTI-ANGIOGENIC FACTORS

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

An anti-angiogenic protein called sFlt-1 attaches itself to VEGF and PlGF and stops their receptors on endothelial cells from activating [7]. In women with preeclampsia, the placenta produces more of it, which is then discharged into the mother's circulation. Numerous studies have shown that elevated levels of sFlt-1 are useful prognostic biomarkers, and they have been reliably linked to the onset of preeclampsia. sFlt-1 is a useful tool for early risk assessment because studies have revealed that its levels start to rise weeks before clinical symptoms appear [7, 11].

Placental Growth Factor (PlGF)

Endothelial cells are encouraged to develop and survive by PlGF, an angiogenic protein that is a member of the VEGF family [6]. PlGF levels steadily rise until the third trimester of a typical pregnancy. Excess sFlt-1 binding usually results in decreased PlGF levels in preeclampsia. Preeclampsia is predicted by low PlGF levels, especially when paired with sFlt-1 readings [6].

The sFlt-1/PlGF Ratio

One of the best biomarkers for predicting preeclampsia is the ratio of sFlt-1 to PlGF [12]. The sFlt-1/PlGF ratio offers a more thorough evaluation of angiogenic balance than either marker alone because it takes into account both angiogenic and anti-angiogenic components [12]. Numerous studies have shown that the sFlt-1/PlGF ratio has a higher predictive ability than individual markers, with good sensitivity and specificity for short-term preeclampsia prediction.

Meta-Analysis of sFlt-1/PlGF Ratio Studies

A meta-analysis of several studies assessing the sFlt-1/PlGF ratio's ability to predict preeclampsia within a week after testing revealed a pooled sensitivity of 86% and specificity of 83%. Over 5,000 pregnant women's data were included in the analysis, which demonstrated the sFlt-1/PlGF ratio's reliable and consistent prognostic ability across a range of contexts and demographics [13, 14].

Clinical Application and Guidelines

Several nations have included the sFlt-1/PlGF ratio in their clinical guidelines for the treatment of suspected preeclampsia. In Europe, for instance, the ratio is

Table 1. Summary of Studies Evaluating sFlt-1/PlGF Ratio in Preeclampsia Prediction

Study	Population	Gestational Age at Testing	Sensitivity	Specificity	Outcome Predicted
Rana et al. (2012)	Women with suspected preeclampsia	20-36 weeks	88%	83%	Preeclampsia within 4 weeks
Khalil et al. (2019)	Women with suspected preeclampsia	20-34 weeks	93%	77%	Preeclampsia within 1 week
Verlohren et al. (2010)	Women with singleton pregnancies	24-36 weeks	95%	85%	Preeclampsia within 1 week
Akolekar et al. (2013)	First-trimester screening	11-13 weeks	50-70%	90-95%	Early-onset preeclampsia

(The table above illustrates the sensitivity and specificity of the sFlt-1/PlGF ratio at various gestational ages based on data from the studies that were cited.)

used to categorize women into high- and low-risk categories for focused surveillance and intervention, as well as to rule out preeclampsia in women who exhibit suspected symptoms. Within a week, preeclampsia is usually ruled out with a sFlt-1/PlGF ratio of ≤38; a ratio of >38 suggests a higher risk and calls for additional research and closer observation [12, 14-17].

Mathematical Modeling of sFlt-1/PlGF Dynamics

A more sophisticated mathematical model could incorporate the production and clearance rates of sFlt-1 and PlGF.

dsFlt1/dt = k_sFlt1 – γ_sFlt1 * [sFlt-1] (t) (Equation 3)

dPlGF/dt = k_PlGF – γ_PlGF * [PlGF](t) (Equation 4)

Where:

k_sFlt1 and k_PlGF are the production rates of sFlt-1 and PlGF, respectively.

γ_sFlt1 and γ_PlGF are the clearance rates for sFlt-1 and PlGF, respectively.

Changes in these parameters, particularly an increase in *k_sFlt1* and a decrease in *k_PlGF* can predict the trajectory of preeclampsia [12].

INFLAMMATORY MARKERS

Preeclampsia (PE) is associated with a strong maternal inflammatory response, which plays a crucial role in its pathogenesis [18]. The pathogenesis of preeclampsia is significantly influenced by systemic inflammation, which also leads to endothelial dysfunction and hypertension. Numerous inflammatory markers have been studied as possible biomarkers for preeclampsia prediction, including cytokines, C-reactive protein (CRP), and other inflammatory mediators [19].

C-Reactive Protein

The liver produces CRP, an acute-phase protein, in reaction to inflammation. Women with preeclampsia have been found to have elevated CRP levels, which may indicate that CRP serves as a predictive biomarker. However, because CRP levels can be affected by several variables unrelated to preeclampsia, such as infection or other inflammatory disorders, their prognostic accuracy is limited [20, 21].

Cytokines

Signaling molecules called cytokines, which include TNF-α, IL-6, and IL-10, control inflammation and immunological responses. The pathophysiology of preeclampsia has been linked to dysregulation of cytokine production; women with the condition had lower levels of anti-inflammatory cytokines (like IL-10) and higher levels of proinflammatory cytokines (such TNF-α and IL-6) [22, 23].

Preeclampsia later in gestation is linked to higher levels of TNF-α and IL-6 in the early stages of pregnancy, according to studies. However, using cytokine panels may increase the forecast accuracy because individual cytokines frequently have poor predictive ability [24].

Other Inflammatory Mediators

Other inflammatory mediators have also been studied as possible preeclampsia biomarkers, including uric acid, neutrophil gelatinase-associated lipocalin (NGAL), and placental protein 13 (PP13). Preeclampsia has been linked to elevated levels of PP13, a placental protein involved in immunological regulation. Patients with preeclampsia may have high NGAL, a marker of kidney impairment, as a result of renal failure. Increased cell turnover and oxidative stress in preeclampsia can raise uric acid, a byproduct of purine metabolism [25-27].

Combining Inflammatory Markers

When compared to using individual inflammatory indicators alone, combining many markers into a panel may increase the prognostic accuracy for preeclampsia. For instance, a panel comprising TNF-α, IL-6,

and CRP may offer a more thorough evaluation of the inflammatory state and enhance the detection of women who are at a high risk of preeclampsia.

Mathematical Model for Inflammatory Response

The dynamics of cytokine production can be modeled using a system of differential equations.

d[IL-6]/dt = k_IL6 * [Stimulus] – γ_IL6 * [IL-6] (t) (Equation 5)

d[TNFα]/dt = k_TNFα * [Stimulus] – γ_TNFα * [TNFα] (t) (Equation 6)

d[IL-10]/dt = k_IL10 * [Stimulus] – γ_IL10 * [IL-10] (t) (Equation 7)

Where:

[IL-6], [TNFα], and [IL-10] are the concentrations of their respective cytokines.

k_IL6, k_TNFα, and k_IL10 are production rate constants.

γ_IL6, γ_TNFα, and γ_IL10 are the decay rate constants.

[Stimulus] represents an inflammatory trigger.

Changes in these parameters particularly increased in *k_IL6* and *k_TNFα* relative to *k_IL10*, indicating an inflammatory state predictive of preeclampsia [28].

Table 2. Summary of Studies Evaluating Inflammatory Markers in Preeclampsia Prediction

Study	Marker(s)	Gestational Age at Testing	Sensitivity	Specificity	Outcome Predicted
Duggan et al. (2003)	CRP	Second trimester	60%	70%	Preeclampsia
Chaiworapongsa et al. (2002)	CRP, IL-6, TNF-α	Second trimester	75%	80%	Preterm preeclampsia
Gagnon et al. (2010)	PP13	First trimester	55%	85%	Preeclampsia
D'Ascenzo et al. (2017)	PTX3	Second trimester	65%	75%	Preeclampsia

METABOLOMICS AND PROTEOMICS

Fig. 3. Metabolomics data visualization, displaying a 3D scatter plot of metabolite concentrations, with vibrant color coding to differentiate compound classes. The figure was created for the purpose of this article by artificial intelligence

Metabolomics and proteomics are emerging fields that offer the potential to identify novel biomarkers for preeclampsia by providing a comprehensive assessment of metabolic and protein profiles in biological samples. Metabolomics involves the identification and quantification of small molecules (metabolites) in biological fluids, while proteomics focuses on the identification and quantification of proteins [29-32].

Metabolomic Profiling

Particularly in pathways linked to oxidative stress, lipid metabolism, and amino acid metabolism, metabolomic profiling offers important insights into the metabolic changes linked to preeclampsia. Research has revealed notable variations in metabolite levels between women with preeclampsia and those with healthy pregnancies. Significantly, changes in the amounts of amino acids like citrulline and arginine indicate problems with the metabolism of nitric oxide, which is essential for endothelial function. Furthermore, there is a notable impact on lipid metabolism, as evidenced by elevated triglyceride levels and lower HDL cholesterol levels, both of which are linked to the cardiovascular issues associated with preeclampsia. The disease's course is further exacerbated by higher oxidative stress markers, such as malondialdehyde (MDA) and isoprostanes, which signal heightened oxidative damage [33, 34].

Proteomic Profiling

Finding proteins that are differently expressed in preeclampsia using proteomic profiling is essential for illuminating the underlying pathophysiology

of the condition. Key pathophysiological alterations are reflected in the upregulation or downregulation of many proteins in preeclamptic women. For example, there is a change in the expression of placental proteins such as human placental lactogen (hPL) and placental growth factor (PlGF), which could lead to a decline in placental function. Furthermore, dysregulation of inflammatory biomarkers, such as serum amyloid A (SAA) and CRP, suggests an excessive inflammatory response. The hypercoagulable state linked to preeclampsia is further highlighted by alterations in coagulation proteins, such as von Willebrand factor (vWF) and fibrinogen, which raise the risk of vascular problems. These proteomic alterations provide a deeper understanding of the molecular mechanisms driving the disease and may serve as potential biomarkers for early diagnosis and therapeutic intervention [35-39].

Integration of Metabolomics and Proteomics

Combining metabolomic and proteomic data may provide a more comprehensive and accurate prediction of preeclampsia than the use of either approach alone. By integrating information on metabolic pathways and protein expression, it is possible to identify the complex interactions and regulatory networks that contribute to the development of preeclampsia [40, 41].

Mathematical Modeling of Metabolic Pathways

Metabolic pathways can be modeled mathematically to understand their dynamics and predict their behavior under different conditions. For example, the arginine-nitric oxide pathway, which is dysregulated in preeclampsia, can be modeled using a system of differential equations:

$$d[Arginine]/dt = k\_Arg – (Vmax * [Arginine]) / (Km + [Arginine]) – \gamma\_Arg * [Arginine](t) \quad \text{(Equation 8)}$$

$$d[NO]/dt = (Vmax * [Arginine]) / (Km + [Arginine]) – \gamma\_NO * [NO](t) \quad \text{(Equation 9)}$$

Where:

[Arginine] and [NO] are the concentrations of arginine and nitric oxide, respectively.

k_Arg is the rate of arginine production

Vmax is the maximum reaction rate of NO synthase.

Km is the Michaelis-Menten constant.

γ_Arg and *γ_NO* are decay rate constants.

Changes in these parameters, particularly a decrease in Vmax or increase in Km, can indicate dysregulation of the arginine-nitric oxide pathway and predict endothelial dysfunction in preeclampsia [42].

OTHER POTENTIAL BIOMARKERS

In addition to the previously discussed biomarkers, researchers have investigated several other molecules as potential indicators of preeclampsia. Increased uric acid levels, commonly observed in preeclampsia cases, are thought to be associated with enhanced cellular turnover and reduced renal function [4]. Early pregnancy levels of inhibin A, a hormone produced by the placenta, are lower in women who subsequently develop preeclampsia [4]. Similarly, decreased first-trimester concentrations of pregnancy-associated plasma protein-A (PAPP-A) have been linked to an elevated risk of preeclampsia and other gestational complications. Moreover, reduced levels of placental protein 13 (PP13), also referred to as galectin-13, have been detected in individuals who later develop preeclampsia, indicating a possible disruption in immune tolerance at the maternal-fetal interface [44]. Additionally, elevated levels of soluble endoglin (sEng), an anti-angiogenic protein that disrupts TGF-β signaling, have been associated with preeclampsia. Although no single biomarker can conclusively predict preeclampsia, a combination of these markers may improve diagnostic precision [44].

Table 3. Summary of Studies Evaluating Metabolomic and Proteomic Profiling in Preeclampsia Prediction

Study	Approach	Samples	Key Findings	Outcome Predicted
Bahado-Singh et al. (2012)	Metabolomics	Maternal serum	Altered lipid metabolism, increased triglycerides	Preeclampsia
Laino et al. (2014)	Metabolomics & Proteomics	Maternal plasma	Combination improved prediction of preterm preeclampsia	Preterm preeclampsia
Hauguel-de Mouzon et al. (2011)	Proteomics	Maternal serum	Increased acute-phase proteins (SAA, haptoglobin)	Preeclampsia
Johnson et al. (2005)	Metabolomics	Maternal plasma	Altered amino acid metabolism, decreased arginine, increased SDMA	Preeclampsia

PSEUDO CODE FOR PREECLAMPSIA RISK ASSESSMENT USING BIOMARKERS

```
Algorithm Preeclampsia Risk Assessment
Input:
PatientDemographics: Patient›s age, BMI, parity, medical history, singleton pregnancy
  AngiogenicFactors: sFlt-1 level, PlGF level
  InflammatoryMarkers: CRP level
  UterineDoppler: Uterine Artery PI
Output:
  RiskScore: Preeclampsia risk score (Low, Moderate, High)
Constants:
  sFlt1_ThresholdHigh = 5000 // Example threshold for sFlt-1 (pg/mL)
  PlGF_ThresholdLow = 100 // Example threshold for PlGF (pg/mL)
  CRP_ThresholdHigh = 10  // Example threshold for CRP (mg/L)
  UterinePI_ThresholdHigh = 1.0 // Example threshold for uterine artery PI
Variables:
  RiskScore: Integer = 0
Begin
  // Step 1: Assess Baseline Risk based on Demographics and History
  If PatientDemographics.Age > 35 Then
    RiskScore = RiskScore + 1
  EndIf
  If PatientDemographics.BMI > 30 Then
    RiskScore = RiskScore + 1
  EndIf
  If PatientDemographics.Parity = 0 Then //Nulliparous
    RiskScore = RiskScore + 1
  EndIf
  If  PatientDemographics.MedicalHistory.Hypertension = True Or
    PatientDemographics.MedicalHistory.Diabetes = True Then
    RiskScore = RiskScore + 2 // Higher risk for pre-existing conditions
  EndIf
  / Step 2: Incorporate Biomarker Data
  If AngiogenicFactors.sFlt1 > sFlt1_ThresholdHigh Then
    RiskScore = RiskScore + 3
  EndIf
  If AngiogenicFactors.PlGF < PlGF_ThresholdLow Then
    RiskScore = RiskScore + 3
  EndIf
  If InflammatoryMarkers.CRP > CRP_Threshold-High Then
    RiskScore = RiskScore + 1
  EndIf
  // Step 3: Incorporate Uterine Doppler Data
  If UterineDoppler.UterineArteryPI > UterinePI_ThresholdHigh Then
    RiskScore = RiskScore + 2
  EndIf
  // Step 4: Risk Stratification
  If RiskScore <= 3 Then
    Return "Low Risk"
  ElseIf RiskScore > 3 And RiskScore <= 6 Then
   Return "Moderate Risk"
  Else
    Return "High Risk"
  EndIf
End [45].
```

CHALLENGES IN CLINICAL IMPLEMENTATION

Despite the promising potential of biomarkers for predicting preeclampsia, several challenges hinder their widespread clinical implementation. These challenges include variability in predictive performance across different populations and gestational stages, lack of standardization in biomarker assays and measurement protocols, cost-effectiveness and accessibility issues, and ethical considerations. The variability in biomarker performance necessitates the development of population-specific reference ranges, while the lack of standardization limits data comparability across studies. Cost and accessibility barriers may restrict implementation, particularly in resource-limited settings [46]. More studies are needed to evaluate the biomarkers in multiple pregnancies and if their potential is similar. Ethical concerns surrounding informed consent, potential anxiety from false positives, and the risk of discrimination based on test results must also be carefully addressed. Overcoming

these challenges is crucial for the effective integration of biomarker testing in clinical practice for preeclampsia prediction and management [47].

Future Directions

Future research in preeclampsia biomarkers should focus on addressing clinical implementation challenges, improving predictive accuracy, and enhancing clinical utility [48]. Key areas for advancement include validating biomarker panels in diverse populations to ensure generalizability and establish population-specific reference ranges, developing standardized guidelines for biomarker testing to improve reliability and reproducibility, integrating biomarker data with clinical information using machine learning algorithms for personalized risk assessments, and discovering novel biomarkers through high-throughput technologies like metabolomics, proteomics, and genomics [49]. These efforts will contribute to a deeper understanding of preeclampsia pathophysiology and ultimately improve patient outcomes through more accurate prediction and management of the disease.

CONCLUSION

Biomarkers show promise for early preeclampsia detection and management in singleton pregnancies. The sFlt-1/PlGF ratio, inflammatory markers, and omics profiles have predictive potential, but challenges persist in population variability, standardization, and cost-effectiveness. Future research should validate multi-marker panels, optimize assessment timing, and integrate biomarkers with clinical risk factors. Standardized guidelines and cost-benefit analyses are crucial for implementation. Integrating biomarkers into prenatal care could personalize risk assessment, enable early intervention, and reduce adverse outcomes.

Conflicts of Interest Statement: *The authors have declared that no competing interests exist.*

Ethical statements: *The authors declared that no clinical trials were used in the present study.*

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans in this study.

The authors declared that no commercially available immortalized human and animal cell lines were used in the present study.

Funding Statement: *No funding was reported*

Author contributions: *All authors have contributed equally.*

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