



Integrating Angiogenic, Inflammatory and Molecular Biomarkers for Early Prediction of Preeclampsia : A Comprehensive Systematic Review

¹ Muhammad Abni Setiawan, ² Harold Imanuel Marcelliano Rumopa, ³ Irene Yemima Setiani

¹ General Practitioner, Watukawula Public Health Centre, Indonesia

² Obstetric and Gynaecologist, Karitas Weetabula General Hospital, Indonesia

³ Obstetric and Gynaecologist, Reda Bolo Regional General Hospital, Southwest Sumba Regency, Indonesia

Corresponding Email : muhammadabnisetiawan@gmail.com

Article History :

Received date : 2025/05/12

Revised date : 2026/06/08

Accepted date : 2026/07/23

Published date : 2026/08/02



Copyright: © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>).

E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Background: Preeclampsia (PE) is a leading cause of maternal and perinatal morbidity and mortality worldwide. Early prediction remains challenging due to its multifactorial pathophysiology. This systematic review evaluates the predictive performance of angiogenic, inflammatory, and molecular biomarkers for early PE prediction.

Methods: We screened 80 studies (that examined biomarkers in pregnant women, reported predictive accuracy, and included comparison groups. Data extraction focused on single and multi-marker performance, prediction timing, and clinical applicability.

Results: Angiogenic markers were most studied. Low PlGF and elevated sFlt-1 consistently predicted PE, with the sFlt-1/PlGF

ratio showing pooled sensitivity 80%, specificity 92% (AUC 0.90–0.95). For short-term rule-out, sFlt-1/PlGF ≤ 38 had 99.3% negative predictive value for PE within one week. First-trimester multi-omics models (e.g., leptin/ceramide ratio, cell-free RNA panels) achieved AUC 0.85–0.94, detecting risk up to 18 weeks before onset. Inflammatory markers (CA-125, IL-6, TNF- α) and molecular markers (microRNAs, MMP-7, PAPP-A) showed moderate individual performance but improved in combination. Early-onset PE was more accurately predicted than late-onset disease. Machine learning and multi-marker integration consistently outperformed single biomarkers.

Discussion: The sFlt-1/PlGF ratio is the most clinically validated biomarker for short-term rule-out in symptomatic women. First-trimester multi-marker screening enables aspirin prophylaxis in high-risk women. However, standardization, cost-effectiveness, and population-specific validation remain challenges.

Conclusion: Integrating angiogenic, inflammatory, and molecular biomarkers significantly improves early PE prediction compared to single markers. The sFlt-1/PlGF ratio is ready for clinical use for short-term prediction. Future research should validate multi-omics panels in diverse populations and integrate placental pathology.

Keywords: Preeclampsia, biomarkers, sFlt-1/PlGF ratio, early prediction, multi-marker models, angiogenesis

INTRODUCTION

Preeclampsia (PE) affects 2–8% of pregnancies and remains a leading cause of maternal and fetal mortality worldwide (1,2). It is a multisystem disorder characterized by new-onset hypertension and proteinuria or end-organ dysfunction after 20 weeks of gestation. The pathophysiology involves abnormal placentation, widespread endothelial dysfunction, and a systemic inflammatory response (3,4). Early-onset PE (<34 weeks) carries higher maternal and neonatal morbidity than late-onset disease, but both contribute significantly to adverse outcomes (5).

Background: Current clinical practice relies on maternal risk factors, blood pressure, and proteinuria for PE screening. However, these methods have low sensitivity and specificity, especially in low-risk populations (6). Approximately 50–60% of women who develop PE have no identifiable risk factors, highlighting the urgent need for reliable early biomarkers (7).

Research problem: Despite decades of research, no single biomarker has achieved sufficient predictive accuracy for universal early screening. Single markers such as PlGF, sFlt-1, or PAPP-A individually yield AUCs of only 0.60–0.75 in unselected populations (8,9). Furthermore, most studies have focused on diagnostic rather than predictive performance, limiting clinical applicability for early intervention (10).

Objectives: This systematic review aims to: (1) evaluate the predictive performance of individual angiogenic, inflammatory, and molecular biomarkers for early PE prediction; (2) assess whether multi-marker integration improves accuracy compared to single markers; (3) identify the optimal timing of biomarker measurement across gestation; and (4) examine clinical applicability, including implementation barriers.

Research gap & novelty: Prior meta-analyses have largely focused on individual biomarker classes or late pregnancy diagnosis (1,3,14). No comprehensive synthesis has simultaneously compared angiogenic, inflammatory, and molecular biomarkers across all trimesters with detailed extraction of multi-marker integration methods and prediction timing. This review provides a novel,

integrated framework for early PE prediction, including machine learning models and multi-omics approaches.

Hypothesis: We hypothesized that multi-marker panels combining angiogenic, inflammatory, and molecular biomarkers would significantly outperform single markers for early PE prediction, and that performance would vary by gestational age and PE subtype (early-onset vs. late-onset).

Significance: Identifying reliable early prediction tools would enable targeted aspirin prophylaxis, intensified surveillance, and potential novel interventions, thereby reducing PE-related morbidity and mortality (7,11).

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the Integrating Angiogenic, Inflammatory and Molecular Biomarkers for Early Prediction of Preeclampsia.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population:** Does this study include pregnant women of any gestational age as the primary population?
- **Condition Focus:** Does this study investigate preeclampsia prediction or diagnosis?
- **Biomarker Categories:** Does this study examine angiogenic, inflammatory, or molecular biomarkers?

- **Predictive Outcomes:** Does this study report sensitivity, specificity, predictive values, or diagnostic accuracy measures?
- **Biomarker Comparison:** Does this study compare individual biomarkers or evaluate integrated biomarker panels?
- **Human Studies:** Is this study conducted in humans (not exclusively animal or in-vitro studies)?
- **Control Groups:** Does this study include a comparison between preeclamptic and non-preeclamptic pregnancies?
- **Prediction Focus:** Is this study focused on prediction rather than primarily on therapeutic interventions or established preeclampsia management?
- **Sample Size:** Does this study include 10 or more participants (not a case report or small case series)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Pregnant women	Angiogenic biomarkers	Single biomarker	Early prediction
Keyword 2	Asymptomatic pregnant women	Inflammatory biomarkers	Normotensive pregnancy	Diagnostic accuracy
Keyword	High-risk	Molecular biomarkers	Late-onset	Early-onset

3	pregnancy		preeclampsia	preeclampsia
Keyword	First-trimester	Multi-marker panels	Clinical assessment	Clinical
4	pregnancy		alone	implementation

The Boolean MeSH keywords inputted on databases for this research are: (*"Pregnant women" OR "Asymptomatic pregnant women" OR "High-risk pregnancy" OR "First-trimester pregnancy"*) AND (*"Angiogenic biomarkers" OR "Inflammatory biomarkers" OR "Molecular biomarkers" OR "Multi-marker panels"*) AND (*"Single biomarker" OR "Normotensive pregnancy" OR "Late-onset preeclampsia" OR "Clinical assessment alone"*) AND (*"Early prediction" OR "Diagnostic accuracy" OR "Early-onset preeclampsia" OR "Clinical implementation"*)

Data extraction

- **Biomarkers Studied:**

Extract all biomarkers evaluated for preeclampsia prediction, categorized by type:

- Angiogenic biomarkers (e.g., sFlt-1, sEng, PlGF, VEGF)
- Inflammatory biomarkers (e.g., cytokines, CRP, TNF- α)
- Molecular biomarkers (e.g., PAPP-A, PP13, ADAM12, activin A, inhibin A)
- Other biomarkers (specify type) For each biomarker, note the measurement method and units used.

- **Prediction Timing:**

Extract when in pregnancy each biomarker was measured for early prediction of preeclampsia:

- Specific gestational age or trimester
- How early before preeclampsia onset the biomarker was detectable

- Whether it was for screening asymptomatic women or diagnosing symptomatic women
- Time window for prediction (e.g., 'predicts preeclampsia 5-6 weeks before clinical symptoms')

- **Single Biomarker Performance:**

Extract predictive performance metrics for individual biomarkers in preeclampsia prediction:

- Sensitivity and specificity percentages
- Positive and negative predictive values
- Area under ROC curve (AUC)
- Cut-off values or thresholds used
- Detection rates for early-onset vs late-onset preeclampsia
- Performance differences by preeclampsia severity

- **Multi-Marker Integration:**

Extract data on combining multiple biomarkers for preeclampsia prediction:

- Which specific biomarkers were combined together
- Predictive performance of the combination (sensitivity, specificity, AUC)
- Whether the combination performed better than individual biomarkers
- Type of integration method (algorithmic, risk scoring, machine learning)
- Improvement in accuracy compared to single biomarkers

- **Study Population:**

Extract characteristics of the population studied for preeclampsia biomarker prediction:

- Risk level (low-risk, high-risk, mixed populations)
- Sample size and number of preeclampsia cases
- Gestational age range of participants
- Inclusion/exclusion criteria
- Geographic location and healthcare setting
- Preeclampsia definition used in the study

- **Clinical Applications:**

Extract information about clinical utility and implementation of biomarkers for preeclampsia prediction:

- Current clinical use or potential clinical applications
- Cost-effectiveness considerations
- Availability of automated/commercial platforms
- Integration into clinical practice workflows
- Impact on clinical decision-making or patient management
- Recommendations for clinical implementation

- **Study Limitations:**

Extract limitations and challenges identified regarding biomarkers for preeclampsia prediction:

- Sample size limitations
- Study design weaknesses
- Standardization issues across platforms
- Validation concerns
- Generalizability limitations
- Technical or measurement challenges
- Gaps in evidence identified by authors

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	("Pregnant women" OR "Asymptomatic pregnant women" OR "High-risk pregnancy" OR "First-trimester pregnancy") AND ("Angiogenic biomarkers" OR "Inflammatory biomarkers" OR "Molecular biomarkers" OR "Multi-marker panels") AND ("Single biomarker" OR "Normotensive pregnancy" OR "Late-onset preeclampsia" OR "Clinical assessment alone") AND ("Early prediction" OR "Diagnostic accuracy" OR "Early-onset preeclampsia" OR "Clinical implementation")	2
Semantic Scholar	("Pregnant women" OR "Asymptomatic pregnant women" OR "High-risk pregnancy" OR "First-trimester pregnancy") AND ("Angiogenic biomarkers" OR "Inflammatory biomarkers" OR "Molecular biomarkers" OR "Multi-marker panels") AND ("Single biomarker" OR "Normotensive pregnancy" OR "Late-onset preeclampsia" OR "Clinical assessment alone") AND ("Early prediction" OR "Diagnostic accuracy" OR "Early-onset preeclampsia" OR "Clinical implementation")	250
Springer	("Pregnant women" OR "Asymptomatic pregnant women" OR "High-risk pregnancy" OR "First-trimester pregnancy") AND ("Angiogenic biomarkers" OR "Inflammatory biomarkers" OR "Molecular biomarkers" OR "Multi-marker panels") AND ("Single biomarker" OR "Normotensive pregnancy" OR "Late-onset preeclampsia" OR "Clinical assessment alone") AND ("Early prediction" OR "Diagnostic accuracy" OR "Early-onset preeclampsia" OR "Clinical implementation")	80
Google Scholar	("Pregnant women" OR "Asymptomatic pregnant women" OR "High-risk pregnancy" OR "First-trimester pregnancy") AND ("Angiogenic biomarkers" OR "Inflammatory biomarkers" OR "Molecular biomarkers" OR "Multi-marker panels") AND ("Single biomarker" OR "Normotensive pregnancy" OR "Late-onset preeclampsia" OR "Clinical assessment alone") AND ("Early prediction" OR "Diagnostic accuracy" OR "Early-onset preeclampsia" OR "Clinical implementation")	194
Wiley Online Library	("Pregnant women" OR "Asymptomatic pregnant women" OR "High-risk pregnancy" OR "First-trimester pregnancy") AND ("Angiogenic biomarkers" OR "Inflammatory biomarkers" OR "Molecular biomarkers" OR "Multi-marker panels") AND ("Single biomarker" OR "Normotensive pregnancy" OR "Late-onset preeclampsia" OR "Clinical assessment alone") AND ("Early prediction" OR "Diagnostic accuracy" OR "Early-onset preeclampsia" OR "Clinical implementation")	2

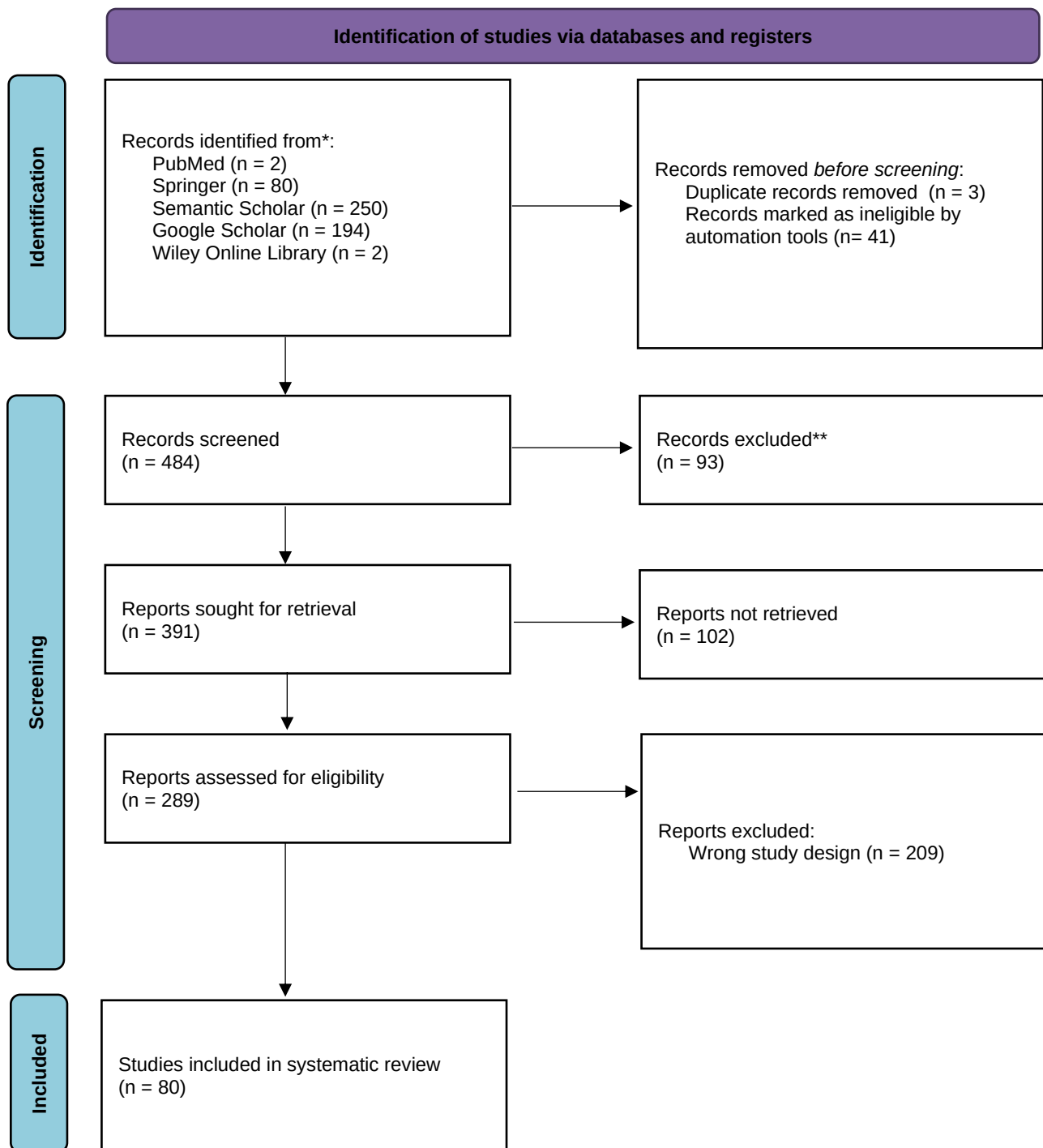


Figure 1. Article search flowchart

Risk of Bias Assesment

Author (Year)	D1	D2	D3	D4	D5	Overall
A. Tarca et al., 2019 [11]	Moderate	Low	Low	Low	Low	Low
J. Kusanovic et al., 2009 [20]	Moderate	Low	Low	Moderate	Low	Moderate
O. Erez et al., 2017 [12]	Moderate	Low	Low	Low	Low	Low
Shiting Qin et al., 2021 [21]	Moderate	Low	Low	Moderate	Low	Moderate
A. Tarca et al., 2020 [22]	Moderate	Low	Low	Low	Low	Low
R. Gonen et al., 2009 [23]	Moderate	Moderate	Low	Moderate	Low	Moderate
I. J. Andresen et al., 2024 [24]	Moderate	Low	Low	Low	Low	Low
K. Evers et al., 2018 [25]	Moderate	Low	Low	Moderate	Low	Moderate
M. Ozat et al., 2011 [26]	Moderate	Moderate	Moderate	Moderate	Low	Moderate
I. Hromadníková et al., 2017 [27]	Moderate	Low	Low	Moderate	Low	Moderate
P. Chaemsaithong et al., 2023 [3]	Moderate	Low	Low	Low	Low	Low
I. Vasilache et al., 2022 [28]	Moderate	Low	Low	Low	Low	Low
Qianyang Huang et al., 2021 [7]	Moderate	Low	Low	Low	Low	Low
Taishun Li et al., 2024 [8]	Moderate	Low	Low	Low	Low	Low
Alexandre Fillion et al., 2022 [29]	Moderate	Low	Low	Low	Low	Low

Author (Year)	D1	D2	D3	D4	D5	Overall
Iasmina M. Craici et al., 2013 [30]	Moderate	Low	Moderate	Low	Low	Moderate
D. Carty et al., 2010 [6]	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Robin Shoemaker et al., 2025 [31]	Moderate	Low	Low	Low	Low	Low
Aimal Mangsang Sangma et al., 2025 [32]	Moderate	Low	Moderate	Low	Low	Moderate
N. Castillo Marco et al., 2025 [9]	Moderate	Low	Low	Low	Low	Low
Jian-bo Zhang et al., 2020 [33]	Moderate	Low	Low	Moderate	Low	Moderate
S. Daskalopoulou et al., 2023 [34]	Moderate	Low	Moderate	Moderate	Low	Moderate
Lucie Roubalova et al., 2024 [13]	Moderate	Low	Low	Low	Low	Low
E. Reyna-Villasmil et al., 2017 [35]	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Qianyang Huang et al., 2021a [36]	Moderate	Low	Low	Low	Low	Low
K. De Clippel et al., 2006 [37]	Moderate	Moderate	Moderate	Moderate	Low	Moderate
O. Erez et al., 2022 [38]	Moderate	Low	Low	Low	Low	Low

Author (Year)	D1	D2	D3	D4	D5	Overall
Aiqi Yin et al., 2025 [39]	Moderate	Low	Low	Low	Low	Low
W. F. Gharib et al., 2025 [40]	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Pensée Wu et al., 2015 [17]	Moderate	Low	Low	Low	Low	Low
Y. Giguère et al., 2010 [41]	Moderate	Low	Low	Moderate	Low	Moderate
C. Kleinrouweler et al., 2012 [42]	Moderate	Low	Low	Low	Low	Low
Marianna Danielli et al., 2022 [43]	Moderate	Low	Low	Low	Low	Low
Y. Veisani et al., 2019 [44]	Moderate	Low	Low	Low	Low	Low
Y. Giguère et al., 2011 [45]	Moderate	Low	Low	Moderate	Low	Moderate
R. Romero et al., 2008 [46]	Moderate	Low	Low	Low	Low	Low
R. Allen et al., 2014 [4]	Moderate	Low	Low	Low	Low	Low
S. Agrawal et al., 2018 [1]	Moderate	Low	Low	Low	Low	Low
A. Tarca et al., 2021 [47]	Moderate	Low	Low	Low	Low	Low
G. Lambert-Messerlian et al., 2014 [48]	Moderate	Low	Moderate	Low	Low	Moderate
K. Hymavathi et al., 2021 [49]	Moderate	Moderate	Moderate	Moderate	Low	Moderate
J. Forest et al., 2012 [50]	Moderate	Low	Low	Low	Low	Low

Author (Year)	D1	D2	D3	D4	D5	Overall
T. Metz et al., 2014 [51]	Moderate	Low	Moderate	Moderate	Low	Moderate
Sean-Tee Lim et al., 2020 [52]	Moderate	Low	Low	Low	Low	Low
R. Levine et al., 2007 [53]	Moderate	Low	Low	Low	Low	Low
I. Marić et al., 2022 [10]	Moderate	Low	Low	Low	Low	Low
O. Erez et al., 2008 [54]	Moderate	Low	Low	Moderate	Low	Moderate
A. Cohen et al., 2013 [55]	Moderate	Low	Moderate	Low	Low	Moderate
Ruqaiya Shahid et al., 2021 [56]	Moderate	Low	Low	Low	Low	Low
K. Nicolaides et al., 2019 [57]	Moderate	Low	Low	Low	Low	Low
U. Perni et al., 2012 [58]	Moderate	Low	Moderate	Low	Low	Moderate
V. Bucher et al., 2024 [14]	Moderate	Low	Low	Low	Low	Low
J. Lai et al., 2022 [59]	Moderate	Low	Low	Low	Low	Low
T. McElrath et al., 2012 [60]	Moderate	Low	Low	Low	Low	Low
Yangxue Yin et al., 2020 [61]	Moderate	Low	Low	Low	Low	Low
J. Allotey et al., 2020 [15]	Moderate	Low	Low	Low	Low	Low
M. Garcés et al., 2015 [62]	Moderate	Low	Moderate	Moderate	Low	Moderate
Jessica J Miller et al., 2023 [18]	Moderate	Low	Low	Low	Low	Low
D. Rizo et al., 2013 [63]	Moderate	Low	Moderate	Low	Low	Moderate

Author (Year)	D1	D2	D3	D4	D5	Overall
K. Ferguson et al., 2017 [5]	Moderate	Low	Low	Low	Low	Low
K. Bramham et al., 2016 [64]	Moderate	Low	Moderate	Low	Low	Moderate
R. Kerley et al., 2018 [65]	Moderate	Low	Low	Low	Low	Low
A. Sahay et al., 2014 [66]	Moderate	Low	Moderate	Moderate	Low	Moderate
C. Chirilă et al., 2023 [2]	Moderate	Low	Low	Low	Low	Low
M. L. Degnes et al., 2024 [67]	Moderate	Low	Low	Low	Low	Low
M. P. Lubis et al., 2019 [68]	Moderate	Moderate	Moderate	Moderate	Low	Moderate
F. Schneuer et al., 2012 [19]	Moderate	Low	Low	Low	Low	Low
B. Sibai et al., 2008 [69]	Moderate	Low	Moderate	Low	Low	Moderate
I. Tzanaki et al., 2025 [70]	Moderate	Low	Low	Low	Low	Low
A. Doherty et al., 2014 [71]	Moderate	Low	Moderate	Moderate	Low	Moderate
A. Staff et al., 2013 [16]	Moderate	Low	Low	Low	Low	Low
K. Marrufo-Gallegos et al., 2023 [72]	Moderate	Low	Low	Low	Low	Low
S. Ghazvini et al., 2023 [73]	Moderate	Moderate	Moderate	Moderate	Low	Moderate
E. Litwinska et al., 2015 [74]	Moderate	Low	Low	Low	Low	Low
Jorge Montenegro-Martínez et al., 2024 [75]	Moderate	Low	Moderate	Low	Low	Moderate

Author (Year)	D1	D2	D3	D4	D5	Overall
R. Romero et al., 2022 [76]	Moderate	Low	Low	Low	Low	Low
E. Timokhina et al., 2025 [77]	Moderate	Moderate	Moderate	Moderate	Low	Moderate
V. Giardini et al., 2020 [78]	Moderate	Low	Low	Low	Low	Low
Yifan Wu et al., 2021 [79]	Moderate	Low	Low	Low	Low	Low
Jing Zhu et al., 2019 [80]	Moderate	Low	Low	Low	Low	Low

RESULTS

Characteristics of Included Studies

The systematic review included 80 studies examining biomarkers for early prediction of preeclampsia. The studies varied considerably in their design, populations, and biomarkers evaluated.

Study	Population risk level	Sample size (cases/controls)	Gestational age range	Biomarkers evaluated	Geographic location
A. Tarca et al., 2019 [11]	Mixed	33/90	First trimester to delivery	PlGF, VEGF121, siglec-6, activin-A, MMP-7, gpIIbIIIa [11]	Detroit, USA
J. Kusanovic et al., 2009 [20]	Mixed	62/1560	6-15 weeks, 20-25 weeks	PlGF, sEng, sVEGFR-1 [20]	Santiago, Chile

Study	Population risk level	Sample size (cases/controls)	Gestational age range	Biomarkers evaluated	Geographic location
O. Erez et al., 2017 [12]	Mixed	76/90	Throughout gestation	PlGF, MMP-7, RAN, TF, FER, Cathepsin B [12]	Detroit, USA
Shiting Qin et al., 2021 [21]	Mixed	2685/2042	Before 20 weeks	microRNAs [21]	Multiple countries
A. Tarca et al., 2020 [22]	Mixed	13/49	9-34 weeks	H19, FN1, TUBB6, FPR3, MMP11, SLC6A2, IL18BP [22]	Not mentioned
R. Gonen et al., 2009 [23]	Mixed	20/1346	6-10, 16-20, 24-28 weeks	PP13 [23]	Israel
I. J. Andresen et al., 2024 [24]	Mixed	124/178	12-34 weeks	PlGF, CRP, SAA1, MMP7, PPID, RAN, SIGLEC6 [24]	Detroit, Stanford, Oslo
K. Evers et al., 2018 [25]	High-risk	60/137	21 weeks to delivery	sFlt-1, PlGF, NfL [25]	Basel, Switzerland

Study	Population risk level	Sample size (cases/controls)	Gestational age range	Biomarkers evaluated	Geographic location
M. Ozat et al., 2011 [26]	Mixed	142/100	Not mentioned	CA-125 [26]	Not mentioned
I. Hromadníková et al., 2017 [27]	Mixed	21/1443	10-13 weeks	miR-516b-5p, miR-517-5p, miR-518b, miR-520a-5p, miR-520h, miR-525-5p [27]	Not mentioned
P. Chaemsaitong et al., 2023 [3]	Not mentioned	Not mentioned	>18 weeks	PlGF, sFlt-1 [3]	Multiple countries
I. Vasilache et al., 2022 [28]	Mixed	737/7502	First trimester	PP-13 [28]	Worldwide
Qianyang Huang et al., 2021 [7]	Mixed	20/20	5-25 weeks	sFlt-1, PlGF, Leptin, Ceramide [7]	USA
Taishun Li et al., 2024 [8]	Mixed	210/4434	11-13+6 weeks	PLGF, PAPP-A, MAP, UtA-PI [8]	Nanjing, China
Alexandre Fillion et al., 2022 [29]	Mixed	498/11885	11-14 weeks	sFlt-1 [29]	Not mentioned

Study	Population risk level	Sample size (cases/controls)	Gestational age range	Biomarkers evaluated	Geographic location
Iasmina M. Craici et al., 2013 [30]	Mixed	15/300	27 weeks to delivery	PlGF, sFlt-1, Endoglin, Podocyturia [30]	Mayo Clinic, USA
D. Carty et al., 2010 [6]	Mixed	37/1963	12-16 weeks	VEGF, Interleukins, TNF α , E-Selectin [6]	Not mentioned
Robin Shoemaker et al., 2025 [31]	Mixed	51/179	Mean 28 weeks	Ang I, Ang II, Aldosterone, ACE-R [31]	Not mentioned
Aimal Mangsang Sangma et al., 2025 [32]	High-risk	25/125	20-36 weeks	sFlt-1, PlGF [32]	India
N. Castillo Marco et al., 2025 [9]	Mixed	85/9501	9-14, 18-28, >28 weeks	sFLT1, PlGF, PAEP, MMP7, IGF1, WNT5A, HES4, SPEF1 [9]	Spain
Jian-bo Zhang et al., 2020 [33]	Mixed	Not mentioned /3439	10-13 weeks	HLA-G [33]	Chengdu, China

Study	Population risk level	Sample size (cases/controls)	Gestational age range	Biomarkers evaluated	Geographic location
S. Daskalopoulou et al., 2023 [34]	High-risk	Not mentioned /236	10-13 weeks onwards	Soluble fms-like tyrosine kinase, Placental growth factor [34]	Not mentioned
Lucie Roubalova et al., 2024 [13]	Low-risk	28/1144	~30 and ~36 weeks	sFlt-1, PlGF [13]	Not mentioned
E. Reyna-Villasmil et al., 2017 [35]	Not mentioned	41/463	17-20 weeks	Angiopoietin-2 [35]	Venezuela
Qianyang Huang et al., 2021a [36]	Not mentioned	20/20	5-25 weeks	PlGF, sFlt-1, Leptin, Ceramide [36]	USA
K. De Clippel et al., 2006 [37]	Mixed	138/3210	22-26 weeks	PlGF [37]	Not mentioned
O. Erez et al., 2022 [38]	Mixed	49/45	8-22 weeks	Thrombin generation parameters [38]	Not mentioned
Aiqi Yin et al., 2025 [39]	Mixed	70/70	12.26±0.44 weeks	CA125 [39]	Not mentioned

Study	Population risk level	Sample size (cases/controls)	Gestational age range	Biomarkers evaluated	Geographic location
W. F. Gharib et al., 2025 [40]	Mixed	45/45	28-40 weeks	Netrin-1 [40]	Egypt
Pensée Wu et al., 2015 [17]	Mixed	Not mentioned	First and early second trimester	PlGF, sFLT, ADAM-12, inhibin-A, PAPP-A, PP-13 [17]	Multiple countries
Y. Giguère et al., 2010 [41]	Mixed	Not mentioned	First/second trimester	PP13, PAPP-A, ADAM12, Activin A, Inhibin A [41]	Not mentioned
C. Kleinrouweler et al., 2012 [42]	Not mentioned	Not mentioned	Not mentioned	PlGF, VEGF, sFlt-1, sEng [42]	Not mentioned
Marianna Danielli et al., 2022 [43]	Mixed	7295/10875	First to third trimester	PlGF, sFlt-1, sEng, VEGF, CRP, TNF- α , PAPP-A, PP13, inhibin A [43]	Diverse
Y. Veisani et al., 2019 [44]	Mixed	Not mentioned	Early in second trimester	sFlt-1, PlGF [44]	Global

Study	Population risk level	Sample size (cases/controls)	Gestational age range	Biomarkers evaluated	Geographic location
Y. Giguère et al., 2011 [45]	Mixed	Not mentioned	First/second trimester	PP13, PAPP-A, ADAM12, Activin A, Inhibin A [45]	Not mentioned
R. Romero et al., 2008 [46]	Mixed	42/102	First trimester to delivery	s-Eng, sVEGFR-1, PlGF [46]	Santiago, Chile
R. Allen et al., 2014 [4]	Mixed	65,538	First trimester	sFlt-1, PlGF, soluble endoglin, PAPP-A, PP13, inhibin-A, pentraxin [4]	Multiple countries
S. Agrawal et al., 2018 [1]	Mixed	534/19587	Not mentioned	PlGF, sFlt-1 [1]	Not mentioned
A. Tarca et al., 2021 [47]	Mixed	230/1269	Throughout pregnancy	PlGF, sVEGFR-1, sEng, PAPP-A, MAP [47]	Not mentioned
G. Lambert-Messerlian et al., 2014 [48]	Mixed	98/490	First and second trimester	PlGF, endoglin, sVEGFR, FLRG, PAPP-A, inhibin A [48]	USA

Study	Population risk level	Sample size (cases/controls)	Gestational age range	Biomarkers evaluated	Geographic location
K. Hymavathi et al., 2021 [49]	Mixed	52	<13 weeks	Maternal urine microalbumin, UACR, Uterine artery PI [49]	Not mentioned
J. Forest et al., 2012 [50]	Low-risk	88/7841	10-18 weeks	MAP, BMI, PlGF, Soluble Flt-1, Inhibin A, PAPP-A [50]	Not mentioned
T. Metz et al., 2014 [51]	High-risk	Not mentioned /1258	≥12 weeks	angiogenin, endoglin, PlGF, sFlt-1, IL-2, IL-6, sTNFr-1, sTNFr-2, TNF-α, hCG, progesterone, selectin, VCAM [51]	Multiple centers, USA
Sean-Tee Lim et al., 2020 [52]	Not mentioned	9,426 across 33 studies	Not mentioned	sFlt-1, PlGF [52]	Multiple countries
R. Levine et al., 2007 [53]	Low-risk	72/480	17-20, 25-28 weeks	sFlt-1, sEng, PlGF, VEGF [53]	Not mentioned

Study	Population risk level	Sample size (cases/controls)	Gestational age range	Biomarkers evaluated	Geographic location
I. Marić et al., 2022 [10]	Mixed	29/20	Early to late pregnancy	VEGFA, sFlt-1, PlGF, ENG, LEP, SELL, SELE, IL-24, IL-22, CXCL10, PAPP-A, metabolites [10]	Stanford, USA
O. Erez et al., 2008 [54]	Mixed	56/346	6-15, 20-25 weeks	PlGF, s-Eng, sVEGFR-1 [54]	Santiago, Chile
A. Cohen et al., 2013 [55]	High-risk	19/140	Third trimester	sFlt1, PlGF, HbA1c [55]	USA
Ruqaiya Shahid et al., 2021 [56]	Not mentioned	Not mentioned	Not mentioned	sFlt, PlGF, sFlt/PlGF, HDL, adiponectin, leptin, triglycerides, APO-B [56]	Not mentioned
K. Nicolaides et al., 2019 [57]	Mixed	Multiple cohorts	11-13, 19-24 weeks	sFlt-1, PlGF, UtA-PI, MAP [57]	Multiple countries
U. Perni et al., 2012 [58]	High-risk	37/72	12-36 weeks	sFlt-1, sEng, PlGF [58]	Not mentioned

Study	Population risk level	Sample size (cases/controls)	Gestational age range	Biomarkers evaluated	Geographic location
V. Bucher et al., 2024 [14]	Not mentioned	506,178 across 110 studies	Not mentioned	sFlt-1, PlGF, CRP [14]	Multiple countries
J. Lai et al., 2022 [59]	Mixed	Varied by definition/ 40241	19-23 weeks	PlGF [59]	England
T. McElrath et al., 2012 [60]	Low-risk	Not mentioned	10, 17, 25, 35 weeks	sFlt-1, PlGF [60]	Not mentioned
Yangxue Yin et al., 2020 [61]	Not mentioned	273/343	Not mentioned	Circulating microRNAs [61]	Not mentioned
J. Allotey et al., 2020 [15]	Mixed	3,570,993	First and second trimester	PlGF, PAPP-A [15]	UK
M. Garcés et al., 2015 [62]	Mixed	16/37	11-13 weeks	sEng, PlGF, sVEGFR-1, METRN [62]	Colombia

Study	Population risk level	Sample size (cases/controls)	Gestational age range	Biomarkers evaluated	Geographic location
Jessica J Miller et al., 2023 [18]	High-risk	Not mentioned /130	After 20 weeks	sFlt-1, PlGF [18]	USA
D. Rizos et al., 2013 [63]	Mixed	12/104	1st, 2nd, 3rd trimesters	PlGF, sFlt-1 [63]	Not mentioned
K. Ferguson et al., 2017 [5]	Mixed	50/391	10, 18, 26, 35 weeks	CRP, IL-1 β , IL-6, IL-10, TNF- α , 8-isoprostane, 8-OHdG [5]	Boston, USA
K. Bramham et al., 2016 [64]	High-risk	29/244	20-42 weeks	PlGF, BNP, NGAL, relaxin [64]	Not mentioned
R. Kerley et al., 2018 [65]	Not mentioned	Not mentioned	Not mentioned	Podocytes, Nephryn, Synaptopodin, Podocin, Podocalyxin [65]	Not mentioned
A. Sahay et al., 2014 [66]	Mixed	35/46	16-20 to delivery	VEGF, PlGF, sFlt-1, sKDR, AT1-AAAs [66]	Pune, India
C. Chirilă et al., 2023 [2]	Not applicable	Not applicable	Not applicable	sFlt-1, PlGF [2]	Not applicable

Study	Population risk level	Sample size (cases/controls)	Gestational age range	Biomarkers evaluated	Geographic location
M. L. Degnes et al., 2024 [67]	Mixed	35/70	12-19, 20-26, 28-34 weeks	sFLT1, IL17RC, FAAH2, HTRA1 [67]	Not mentioned
M. P. Lubis et al., 2019 [68]	Not mentioned	Not mentioned /70	22-24 weeks	PlGF, sEng [68]	Indonesia
F. Schneuer et al., 2012 [19]	Mixed	71/2918	First trimester	PP13 [19]	Not mentioned
B. Sibai et al., 2008 [69]	High-risk	104/600	12-19, 24-28 weeks	PLGF, sFlt-1, inhibin A [69]	Not mentioned
I. Tzanaki et al., 2025 [70]	Not mentioned	2001/31650	First trimester	PAPP-A [70]	Not mentioned
A. Doherty et al., 2014 [71]	High-risk	6/14	20-34 weeks	sFlt-1, PlGF, Serum uric acid, TPR [71]	Not mentioned
A. Staff et al., 2013 [16]	Mixed	1442/11512	Not mentioned	PlGF [16]	Multiple countries

Study	Population risk level	Sample size (cases/controls)	Gestational age range	Biomarkers evaluated	Geographic location
K. Marrufo-Gallegos et al., 2023 [72]	Mixed	2879/21332	Not mentioned	sTIE2, sMet, ANG-1, ANG-2, CK, AMPK, Acid phosphatase, Alkaline phosphatase [72]	Multiple countries
S. Ghazvini et al., 2023 [73]	Not mentioned	Not mentioned	1st, 2nd, 3rd trimesters	Metabolites via Raman spectroscopy [73]	Not mentioned
E. Litwinska et al., 2015 [74]	Mixed	51/129	11+0 to 13+6 weeks	PlGF, PAPP-A, beta-hCG [74]	Not mentioned
Jorge Montenegro-Martínez et al., 2024 [75]	Mixed	60	Before GW 34	sFlt-1, PlGF [75]	Not mentioned
R. Romero et al., 2022 [76]	Mixed	230/1269	Throughout pregnancy	PlGF, sFlt-1 [76]	USA
E. Timokhina et al., 2025 [77]	Mixed	30/34	22-38 weeks	sFlt-1, PlGF [77]	Moscow, Russia

Study	Population risk level	Sample size (cases/controls)	Gestational age range	Biomarkers evaluated	Geographic location
V. Giardini et al., 2020 [78]	Mixed	20/96	Early 2nd trimester to delivery	PlGF [78]	Not mentioned
Yifan Wu et al., 2021 [79]	Mixed	1634/38840	8-14 weeks	PP13 [79]	Multiple countries
Jing Zhu et al., 2019 [80]	Low-risk	21/902	<14 weeks	sFlt-1, PlGF [80]	Singapore

The studies were conducted across diverse geographic locations, with significant representation from the United States, Europe, Asia, and South America. Sample sizes ranged from small pilot studies with fewer than 100 participants to large population-based cohorts exceeding 40,000 pregnancies [59]. The majority of studies used prospective designs, though several meta-analyses and systematic reviews were also included. Most studies focused on mixed-risk populations, though some specifically examined high-risk groups such as women with chronic hypertension [58] or pre-existing diabetes [55].

Biomarker Categories and Pathophysiological Roles

The biomarkers evaluated can be broadly categorized into three main groups: angiogenic factors, inflammatory markers, and molecular biomarkers.

Angiogenic Biomarkers

Angiogenic factors were the most extensively studied category, reflecting the central role of placental dysfunction and impaired angiogenesis in preeclampsia pathophysiology. The most commonly evaluated angiogenic biomarkers included:

Placental Growth Factor (PlGF): PlGF was measured in the majority of studies as a key proangiogenic factor. Lower PlGF levels were consistently associated with preeclampsia across multiple gestational ages [12, 20, 60]. PlGF demonstrated particularly strong predictive value in the second and third trimesters [12, 13], with sensitivity improving as pregnancy progressed [43].

Soluble fms-like tyrosine kinase-1 (sFlt-1): As an antiangiogenic factor, elevated sFlt-1 levels were strongly associated with preeclampsia [44, 56]. The sFlt-1/PlGF ratio emerged as one of the most robust predictors, with multiple studies demonstrating its superior performance compared to individual markers [1, 7, 18, 20].

Soluble endoglin (sEng): This antiangiogenic factor showed significant associations with preeclampsia, particularly when combined with other angiogenic markers [4, 20, 46, 53]. Studies found that elevated sEng levels preceded clinical symptoms by several weeks [46, 53].

Vascular Endothelial Growth Factor (VEGF): VEGF and its variants (VEGF-121) were evaluated in several studies, showing variable performance across different populations [10, 11].

Inflammatory Biomarkers

Inflammatory markers were less commonly studied than angiogenic factors but demonstrated promising associations with preeclampsia:

Cytokines: Multiple interleukins (IL-1 β , IL-6, IL-10, IL-17RC) and tumor necrosis factor-alpha (TNF- α) were evaluated, with significant elevations observed in women who developed preeclampsia [5, 6, 51]. Ferguson et al. found that inflammation biomarkers showed different patterns across gestation, with hazard ratios for preeclampsia being most elevated at approximately 18 weeks gestation [5, 5].

C-Reactive Protein (CRP): Several studies measured CRP as a marker of systemic inflammation, though results were inconsistent [5, 14, 24].

CA-125: This inflammatory marker demonstrated promising sensitivity (93.7%) and specificity (88.0%) for detecting preeclampsia at a cutoff of 50 IU/ml [26]. First-trimester CA125 levels were significantly elevated in women who subsequently developed preeclampsia [39].

E-Selectin: Early pregnancy E-Selectin levels showed potential for predicting preeclampsia, with combined models including E-Selectin and diastolic blood pressure achieving an AUC of 0.681 [6].

Molecular Biomarkers

This diverse category included proteins, nucleic acids, and other molecular markers:

Pregnancy-Associated Plasma Protein-A (PAPP-A): Lower first-trimester PAPP-A levels were associated with increased preeclampsia risk [4, 17, 70, 74]. A meta-analysis by Tzanaki et al. found that PAPP-A levels in the first trimester were significantly lower in women who developed early-onset, late-onset, and total preeclampsia compared to controls [70].

Placental Protein 13 (PP13): Multiple studies evaluated PP13, with variable results. A meta-analysis found pooled sensitivity of 53% and specificity of 83% for predicting preeclampsia [28]. However, first-trimester PP13 combined with other markers showed inadequate performance for screening in some studies [19].

MicroRNAs: Circulating microRNAs demonstrated diagnostic and predictive potential, with pooled sensitivity of 0.86 and specificity of 0.89 [21]. Specific microRNAs like miR-517-5p showed promise for early prediction [27, 61].

Matrix Metalloproteinase-7 (MMP-7): This biomarker was particularly valuable for early prediction (8-22 weeks), with sensitivity of 69-70% at a false-positive rate of 20% [12, 24].

Other Molecular Markers: Additional biomarkers evaluated included activin-A, inhibin-A, ADAM-12, leptin, ceramides, neurofilament light chain (NfL), podocyuria, HLA-G, angiopoietins, and metabolites detected via Raman spectroscopy [7, 11, 25, 30, 33, 35, 73].

Prediction Timing and Early Detection Capabilities

The timing of biomarker measurement significantly influenced predictive performance, with distinct patterns emerging across pregnancy.

First Trimester (6-16 weeks)

Several biomarkers demonstrated early predictive capability during the first trimester. PP13 levels measured at 6-10 weeks showed 80% sensitivity and 80% specificity for predicting preeclampsia, with performance enhanced by sequential testing [23, 23]. HLA-G levels below 80 U/mL at 10-13 weeks had 83.78% sensitivity and 87.93% specificity for predicting PE development [33]. First-trimester sFlt-1 showed better predictive value when measured before 12 weeks gestation, particularly for early-onset preeclampsia (AUC 0.82 at 11th week) [29, 29].

Multi-protein models utilizing maternal characteristics and biomarkers achieved promising results. A model using 36 transcripts (including H19, FN1, TUBB6, FPR3) predicted early preeclampsia with 83% sensitivity and 88% specificity at 9-14 weeks, detecting risk 18 weeks before onset [9, 9]. PAPP-A demonstrated significant associations with preeclampsia when measured in the first trimester, with lower levels correlating with increased risk [70, 74].

However, several studies noted limitations in first-trimester prediction. Individual angiogenic markers like sFlt-1 and PlGF showed poor predictive performance when measured alone at 10 weeks, with sensitivity/specificity of only 55/43% and 57/40% respectively [60].

Second Trimester (16-28 weeks)

The second trimester emerged as a particularly informative period for multiple biomarkers. MMP-7 maintained strong predictive value at 16.1-22 weeks (sensitivity 70%, AUC 0.82) [12]. The combination of abnormal uterine artery Doppler and low PlGF (<280 pg/ml) at 22-26 weeks was associated with dramatically increased risk for early-onset and severe preeclampsia (OR 44.5 and 37.4 respectively) [37].

At 22.1-28 weeks, multi-protein models achieved 81% sensitivity at 10% false-positive rate, with the best predictors being low PlGF and VEGF-121, and elevated siglec-6 and activin-A [11]. The PlGF/sEng ratio showed excellent performance for early-onset preeclampsia prediction, with sensitivity of 100% and specificity of 98-99% [20].

Inflammatory biomarkers also demonstrated peak predictive value during this period. Ferguson et al. found that inflammation and oxidative stress markers measured at approximately 18 weeks showed the strongest associations with subsequent preeclampsia development [5].

Third Trimester (28+ weeks)

In the third trimester, angiogenic markers showed particularly strong diagnostic and short-term predictive value. At 28.1-32 weeks, multi-protein models achieved 85% sensitivity with best predictors being activated leukocyte cell adhesion molecule, siglec-6, and VEGF-121 [11]. The sFlt-1/PlGF ratio at approximately 36 weeks demonstrated high accuracy for predicting term preeclampsia, with detection rate of 71.4% at 10% false-positive rate [13].

Studies consistently showed that PlGF became the dominant predictive marker after 22 weeks [12], identifying one-third to one-half of patients destined to develop late-onset preeclampsia [12]. The sFlt-1/PlGF ratio ≤ 38 ruled out preeclampsia within one week with 99.3% negative predictive value [2], while values >38 predicted preeclampsia within 4 weeks with 66.2% sensitivity and 83.1% specificity [2].

Individual Biomarker Performance

Angiogenic Markers

PlGF: Across multiple studies, PlGF demonstrated moderate to good predictive performance. In the second trimester, PlGF achieved AUC values ranging from 0.79 to 0.82 for predicting preeclampsia [74]. A systematic review by Chaemsathong et al. found that PlGF-based models achieved the highest diagnostic odds ratio for early preeclampsia prediction in the second trimester (63.20, 95% CI 37.62-106.16) [3]. However, PlGF alone showed limited performance in some populations, particularly for term preeclampsia [20].

sFlt-1: Individual sFlt-1 measurements showed variable performance. First-trimester sFlt-1 had poor predictive value in some studies [60], but demonstrated better performance when measured in the third trimester. The predictive accuracy improved significantly when sFlt-1 was measured earlier than 12 weeks gestation for early-onset preeclampsia [29, 29].

sFlt-1/PlGF Ratio: This ratio consistently outperformed individual markers across multiple studies. A meta-analysis by Agrawal et al. found pooled sensitivity of 80% and specificity of 92% [1]. Clinical validation studies showed diagnostic accuracy of 90.8% at a cutoff of >38 , with negative predictive value of 96.4% for ruling out preeclampsia within 7 days [18]. The ratio

demonstrated particular strength for early-onset preeclampsia, with excellent predictive performance several weeks before clinical diagnosis [20, 71].

Soluble Endoglin: Soluble endoglin showed strong associations with preeclampsia, particularly for early-onset disease. When combined with other angiogenic factors, sEng contributed to dramatically improved prediction (OR 18.5 for early-onset PE) [4]. Longitudinal studies found that sEng levels increased significantly in women destined to develop preeclampsia, beginning as early as 17-20 weeks [53].

Inflammatory Markers

Cytokines: Individual cytokines showed variable performance. IL-1 β , IL-6, and IL-10 measured at approximately 18 weeks demonstrated significant associations with preeclampsia [5]. TNF- α showed consistently elevated hazard ratios across all gestational time points (1.49-1.63) [5]. However, when tested individually, cytokines did not achieve sufficient predictive accuracy for clinical implementation [6].

CA-125: This marker demonstrated promising individual performance with sensitivity of 93.7% and specificity of 88.0% at a cutoff of 50 IU/ml [26]. First-trimester CA125 levels, when combined with clinical factors, achieved AUC of 0.841 [39].

Molecular Markers

PAPP-A: Meta-analysis showed that first-trimester PAPP-A had moderate predictive value, with levels significantly lower in women who developed early-onset (mean difference -0.24 MoM), late-onset (-0.15 MoM), and total preeclampsia (-0.17 MoM) compared to controls [70]. AUC values ranged from 0.62 to 0.74 for different preeclampsia subtypes [74].

PP13: Individual PP13 performance was moderate, with pooled sensitivity of 53% and specificity of 83% across studies [28]. Early-onset preeclampsia showed slightly better prediction (sensitivity 51%, specificity 88%) than late-onset disease (sensitivity 58%, specificity 85%) [28]. However, the heterogeneity between studies limited clinical applicability [79].

MicroRNAs: Circulating microRNAs demonstrated strong diagnostic potential with pooled sensitivity of 0.86 and specificity of 0.89 for diagnosis [21]. For prediction before 20 weeks,

sensitivity was 0.86 and specificity was 0.90 [21]. Individual microRNAs like miR-517-5p showed sensitivity of 42.9% and specificity of 86.2% with positive predictive value of 52.9% [27].

MMP-7: This biomarker showed consistent performance in early pregnancy (8-22 weeks) with sensitivity of 69-70% at 20% false-positive rate and AUC of 0.76-0.82 [12].

Leptin/Ceramide Ratio: This novel biomarker combination demonstrated superior performance to established markers, with sensitivity of 85%, specificity of 90%, and AUC of 0.92 for early prediction, significantly outperforming the sFlt-1/PlGF ratio (AUC 0.52) in the same population [7, 7].

Multi-Marker Integration and Combined Models

The integration of multiple biomarkers consistently improved predictive accuracy compared to single markers, though the optimal combinations varied by gestational age and population.

Early Pregnancy Models

First-trimester multi-marker models demonstrated substantial improvements over individual biomarkers. A model combining PP13 and pulsatility index achieved 90% sensitivity and 90% specificity in high-risk populations [41]. The combination of METRN levels with second-trimester clinical parameters (systolic blood pressure and weight) increased sensitivity from 56% to 69% [62].

Cell-free RNA profiling enabled highly accurate early prediction. Using 36 transcripts, investigators achieved 83% sensitivity and 88% specificity at 9-14 weeks, with AUC of 0.85, detecting risk 18 weeks before clinical onset [9]. A separate model using 92 transcripts for late-onset preeclampsia achieved 86% sensitivity and 89% specificity with AUC of 0.88 [9].

Multi-omics approaches integrating genomic and metabolomic data identified novel marker combinations. The leptin/ceramide ratio significantly outperformed the established sFlt-1/PlGF ratio, with AUC of 0.92 versus 0.52 from 5 to 25 weeks gestation [7, 36]. An integrated model combining urine metabolites and plasma proteins achieved AUC of 0.94 for early pregnancy prediction [10].

Machine learning algorithms enhanced first-trimester prediction. Li et al. developed models using maternal characteristics, MAP, UtA-PI, PAPP-A, and PLGF that achieved AUC of 0.884 for preterm preeclampsia using a Voting Classifier algorithm [8].

Second Trimester Models

The second trimester offered particularly effective multi-marker opportunities. The combination of abnormal uterine artery Doppler with low PlGF (<280 pg/ml) dramatically increased risk for early-onset PE (OR 44.5) and severe PE (OR 37.4) [37]. At 22.1-28 weeks, multi-protein models incorporating PlGF, VEGF-121, siglec-6, and activin-A achieved 81% sensitivity at 10% false-positive rate [11].

PlGF-based models combining maternal factors $\pm$ other biomarkers achieved superior performance compared to PlGF alone. In the second trimester for early preeclampsia prediction in the total population, PlGF-based models had diagnostic odds ratio of 63.20 compared to 6.96 for sFlt-1/PlGF ratio and 5.62 for PlGF alone [3].

A longitudinal proteomics study using >1000 proteins achieved AUC values of 0.72 at time interval T1 (12-19 weeks), 0.76 at T2 (19-27 weeks), and 0.80 at T3 (27-34 weeks) for late-onset preeclampsia prediction [24].

Third Trimester Models

Later in pregnancy, combined models continued to show advantages. At 28.1-32 weeks, multi-protein models achieved 85% sensitivity with best predictors being activated leukocyte cell adhesion molecule, siglec-6, and VEGF-121 [11].

PlGF-based models in the third trimester achieved better performance than PlGF alone but similar to sFlt-1/PlGF ratio for any-onset preeclampsia (diagnostic odds ratio 27.12 vs 10.31 vs 14.94 respectively) [3].

However, some combinations did not improve upon individual markers. The combination of PlGF and uterine Doppler at ~36 weeks did not significantly improve prediction over PlGF alone [13]. Similarly, combining all examined C19MC microRNAs provided no advantage over using miR-517-5p alone [27].

Integration Methods

Various statistical and machine learning approaches were employed. Logistic regression models remained common, combining clinical factors like BMI, MAP, and biomarkers [50, 63]. Linear discriminant analysis was used successfully for proteomics data [11, 12].

Machine learning approaches showed promise. Random forest models for proteomics data achieved AUC values of 0.72-0.80 across pregnancy [24]. Voting Classifier and Stacking Classifier algorithms demonstrated superior performance for preterm preeclampsia prediction [8]. Lasso regression with stability selection was used to develop sparse, clinically implementable models [9].

Decision tree approaches incorporating multiple biomarkers and clinical parameters increased sensitivity for preeclampsia detection. Models including METRN showed sensitivity of 69% compared to 56% without METRN [62].

Performance by Preeclampsia Subtype

Early-Onset vs. Late-Onset Preeclampsia

Biomarker performance varied substantially between early-onset (delivery <34-37 weeks) and late-onset disease. Early-onset preeclampsia was more reliably predicted across multiple biomarker categories.

For angiogenic markers, early-onset disease showed stronger associations. The sFlt-1/PlGF ratio at cutoffs ≥ 88 predicted early-onset PE with 88% sensitivity and 99.5% specificity, while cutoffs ≥ 110 for late-onset PE achieved only 58.2% sensitivity and 95.5% specificity [2]. PlGF-based models achieved higher diagnostic odds ratios for early preeclampsia (63.20) compared to any-onset disease (28.45) [3].

MMP-7 showed consistent predictive value for late-onset preeclampsia at 8-22 weeks (sensitivity 69-70%, AUC 0.76-0.82), but PlGF became the dominant predictor after 22 weeks, identifying 1/3 to 1/2 of late-onset cases [12].

Multi-protein models demonstrated higher sensitivity for early-onset disease. At 16.1-22 weeks, early preeclampsia with placental MVM lesions achieved 90% sensitivity versus 71% for the entire early preeclampsia group [11].

First-trimester sFlt-1 showed differential timing effects, with significantly better predictive value when measured at the 11th week (AUC 0.82) compared to the 12th week (AUC 0.62) or 13th week (AUC 0.50) for early-onset PE [29].

Molecular markers also showed subtype differences. PP13 achieved slightly better accuracy for late-onset preeclampsia (AUC 0.77) compared to early-onset disease (AUC 0.69) [28]. PAPP-A demonstrated stronger associations with early-onset preeclampsia (OR 4.8) than with any-onset disease (OR 2.1) [4].

Severity-Based Differences

Prediction accuracy often increased with disease severity. Multi-protein models showed higher sensitivity for severe early preeclampsia (84%) compared to the entire early preeclampsia group (71%) at 16.1-22 weeks [11].

The presence of placental maternal vascular malperfusion (MVM) lesions significantly enhanced biomarker performance. Sensitivity for predicting early preeclampsia with placental MVM lesions was 90% versus 71% without stratification at 16.1-22 weeks, 87% versus 81% at 22.1-28 weeks, and 90% versus 85% at 28.1-32 weeks (all at 10% FPR) [11].

Different protein sets predicted mild versus severe late-onset preeclampsia after 22 weeks gestation [12]. CA-125 levels were significantly higher in severe preeclampsia (1057.79 Pg/ml) compared to mild preeclampsia (1006.41 Pg/ml) [26].

Thrombin generation parameters showed enhanced performance for severe disease. At 8-16 weeks, the combination of short lag time and high peak thrombin concentration had odds ratio of 43.87 for subsequent preeclampsia, with sensitivity of 56.8% and specificity of 92.7% [38].

Population-Specific Considerations

High-Risk vs. Low-Risk Populations

Biomarker performance varied by baseline population risk. In high-risk populations (chronic hypertension, previous preeclampsia, diabetes), PP13 combined with pulsatility index achieved 90% sensitivity and 90% specificity in the first trimester [41]. However, in a low-risk Caucasian population, the combination of MAP, BMI, PlGF, sFlt-1, inhibin A, and PAPP-A achieved only 37% detection at 5% false-positive rate [50].

For women with chronic hypertension, sFlt-1 and sFlt-1/PlGF ratio were higher at 20 weeks in those developing early-onset superimposed preeclampsia ($p=0.001$) [58]. PlGF showed diagnostic accuracy of 0.85 for predicting superimposed preeclampsia requiring delivery within 14 days in women with CKD and chronic hypertension [64].

In pregnant women with pre-existing diabetes, circulating angiogenic factors and elevated HbA1c in the first trimester were strongly associated with subsequent PE development [55]. First-trimester HbA1c was higher in diabetic subjects who developed PE (7.7% vs 6.7%, $p=0.0001$) [55].

Ethnic and Geographic Variation

Studies identified ethnic differences in biomarker performance. The majority of patients in some cohorts were African-American, limiting generalizability to other ethnic groups [11]. Ethnic differences between cohorts (Detroit, Stanford, Oslo) contributed to heterogeneity in biomarker performance [24].

Geographic variation in preeclampsia prevalence affected predictive values. In developing countries, preeclampsia occurs in 13 cases per 1,000 births compared to 2-3 cases per 10,000 deliveries in developed countries [68], substantially affecting positive predictive values even when sensitivity and specificity remain constant.

Studies from diverse settings showed variable results. A Chilean cohort demonstrated excellent performance for PlGF/sEng ratio in midtrimester prediction [20], while studies from Israel [23], India [66], China [8], and multiple European centers showed different optimal biomarker combinations [24].

Synthesis of Conflicting Findings

Context and Population Distinctions

Apparent contradictions in biomarker performance often reflect genuine differences in clinical contexts. Studies finding strong predictive value for sFlt-1 in early pregnancy focused on measurements before 12 weeks gestation [29, 29], while studies reporting poor performance measured sFlt-1 at 10 weeks or later [60]. This timing specificity suggests a narrow optimal measurement window rather than biomarker invalidity.

The PlGF/sEng ratio demonstrated differential performance by disease severity and timing. Studies achieving sensitivity of 100% with specificity of 98-99% focused specifically on early-onset preeclampsia prediction [20], while those reporting poor performance for term preeclampsia reflected the biomarker's biology—angiogenic imbalance is more pronounced in early, severe disease [12, 20].

PP13 showed variable results across populations. Studies reporting 90% sensitivity and specificity used sequential testing in high-risk women [41], while those finding inadequate performance evaluated single measurements in unselected populations [19]. Both may be correct within their respective contexts: high-risk targeting with repeat measures versus population-wide screening with single assessment.

First-trimester prediction varied by biomarker class. Studies reporting excellent early prediction (AUC 0.88-0.94) employed multi-omics approaches integrating numerous markers [7, 9, 10], while those finding poor first-trimester performance tested individual angiogenic factors like PlGF or sFlt-1 alone [60]. This pattern suggests that early placental dysfunction requires multiple biomarker assessment rather than reliance on single factors.

Study Quality Hierarchy

Weighting evidence by methodological rigor reveals important patterns. The largest prospective cohorts and systematic reviews consistently found moderate individual biomarker performance but substantial improvement with combinations [3, 14, 43]. Small single-center studies more often reported exceptional performance (sensitivity >90%, specificity >90%) [23, 33], likely reflecting overfitting and publication bias.

Longitudinal studies measuring biomarkers at multiple time points demonstrated superior predictive accuracy compared to single-measurement studies [11, 20, 46]. Multi-center validation studies showed more consistent but slightly lower performance than discovery cohorts [8, 24], suggesting the importance of validation in diverse populations.

Studies including placental pathology demonstrated that biomarker associations strengthened when cases were stratified by placental lesions. The PlGF/sFlt-1 ratio showed odds ratio of 13.6 for preeclampsia with placental MVM lesions versus 6.7 without stratification [76].

479

This finding suggests that combining biomarkers with pathophysiologic phenotyping enhances prediction.

Mechanistic Explanations

The temporal evolution of biomarker performance reflects underlying pathophysiology. MMP-7 showed strong predictive value at 8-22 weeks [12], corresponding to the period of spiral artery remodeling. PlGF became the dominant predictor after 22 weeks [12], aligning with the period when placental insufficiency becomes more pronounced. This sequential pattern suggests different biomarkers capture distinct pathophysiologic stages.

The superior performance of multi-marker models reflects preeclampsia's multi-factorial pathogenesis. Studies combining angiogenic, inflammatory, and molecular markers achieved higher accuracy (AUC 0.85-0.94) [7, 9, 10] than those using single biomarker classes, consistent with the disease involving placental dysfunction, immune dysregulation, and maternal systemic factors.

Population-specific performance differences likely reflect etiologic heterogeneity. High-risk women with chronic hypertension or diabetes showed different optimal biomarker combinations [51, 55] than low-risk populations [50], suggesting distinct pathways to preeclampsia. Early-onset and late-onset disease demonstrated different biomarker signatures [2, 12], supporting the concept of preeclampsia subtypes with varying underlying mechanisms.

The improvement in negative predictive value but persistently low positive predictive value across many studies reflects disease prevalence. Even with sensitivity of 80% and specificity of 92%, positive predictive value reached only 10% in low-risk populations where preeclampsia prevalence is 1-2% [1, 60]. This mathematical constraint indicates that biomarkers are more useful for ruling out disease in high-risk populations than identifying disease in unselected screening.

Methodological Considerations

Platform and assay differences contributed to heterogeneity. Studies using the same biomarker but different measurement platforms reported varying cutoffs and performance metrics [16]. The SomaScan platform used in multiple studies enabled high-throughput protein measurement but lacked internal standards [11], potentially affecting absolute values while preserving relative differences.

Timing of sample collection relative to clinical diagnosis substantially affected apparent performance. Studies measuring biomarkers shortly before diagnosis (within 2-4 weeks) reported higher accuracy than those with longer prediction windows [18, 32, 77]. This distinction is critical: biomarkers showing excellent 1-week prediction may have limited utility for early screening, while those predicting 10-20 weeks in advance enable meaningful intervention despite lower absolute accuracy.

Preeclampsia definition variability influenced reported associations. Studies using traditional ISSHP criteria (requiring proteinuria) showed different biomarker performance than those using newer definitions incorporating other organ dysfunction without proteinuria [57, 59]. The ISSHP-MF+PIGF definition incorporating placental biomarkers into diagnostic criteria improved detection of adverse outcomes [59], though this creates circularity when evaluating biomarker performance.

Clinical Applications and Implementation

Current Clinical Use

The sFlt-1/PIGF ratio has achieved the most widespread clinical adoption among preeclampsia biomarkers. Multiple studies documented its use for short-term prediction and rule-out in symptomatic women [2, 76]. The PROGNOSIS study established that sFlt-1/PIGF ≤ 38 rules out preeclampsia within one week with 99.3% negative predictive value [2], enabling outpatient management of low-risk symptomatic women.

For first-trimester screening, aspirin prophylaxis in high-risk women identified by multi-marker algorithms has been implemented in some settings. A randomized trial demonstrated that aspirin (150 mg/day) from 11-14 weeks until 36 weeks reduced early PE by approximately 90% and preterm PE by 60% in high-risk women [57]. This intervention provides clear clinical utility for early screening approaches.

Third-trimester PlGF testing has been integrated into management algorithms at some centers. PlGF < 100 pg/ml at presentation correlates with adverse outcomes and may guide decisions about timing of delivery [59, 78]. The high negative predictive value enables safe discharge of women without preeclampsia who present with concerning symptoms.

However, most biomarkers remain research tools rather than routine clinical tests. First-trimester PP13, PAPP-A, and other molecular markers have not achieved widespread implementation despite decades of research [17, 19]. The gap between research findings and clinical adoption reflects challenges in standardization, cost-effectiveness, and practical workflow integration.

Potential Clinical Applications

Multi-marker screening in early pregnancy could enable risk stratification and targeted prophylaxis. Models combining maternal factors with biomarkers identify high-risk women who could benefit from low-dose aspirin, intensive monitoring, or novel interventions [3, 8]. Machine learning models provide accessible tools for large-scale screening [8].

Serial biomarker monitoring throughout pregnancy offers opportunities for dynamic risk assessment. Longitudinal changes in sFlt-1/PlGF ratio predict earlier delivery and potentially guide obstetric management [75]. The rate of change may provide complementary information to absolute values [20, 23].

Biomarker-guided management algorithms could optimize resource allocation. Women with low-risk biomarker profiles at mid-gestation could receive routine care, while those with elevated risk markers receive enhanced surveillance [24, 34]. This stratification may improve outcomes while reducing unnecessary interventions in low-risk women.

Specific biomarker profiles may guide therapeutic decisions. Women with abnormal thrombin generation kinetics might benefit from low-molecular-weight heparin prophylaxis [38], while those with pronounced angiogenic imbalance could be candidates for novel antiangiogenic therapies. Biomarker phenotyping may enable precision medicine approaches.

Implementation Challenges

Cost-effectiveness remains uncertain for most biomarkers. While individual assays may be relatively inexpensive, comprehensive multi-marker screening at multiple time points could be costly [24]. The low positive predictive value in unselected populations means many women would undergo intervention unnecessarily [50].

Standardization across platforms poses significant challenges. Different assays for the same biomarker yield varying absolute values and require platform-specific cutoffs [16]. The lack of internal standards in some high-throughput platforms affects reproducibility [11]. International standardization efforts are needed before widespread implementation [3].

Validation in diverse populations is incomplete. Most biomarker studies have been conducted in specific ethnic or geographic populations [11, 24], and performance may vary in other settings. Large-scale validation studies across different healthcare systems are needed [14, 31].

Workflow integration requires careful consideration. Sequential screening programs with multiple blood draws may face compliance challenges [23]. Point-of-care testing could improve accessibility but requires platform development and validation [30].

Clinical interpretation complexity limits adoption. Multi-marker models using machine learning algorithms may be difficult for clinicians to interpret and apply [8]. Simple, transparent risk scores with clear decision thresholds would facilitate implementation [50].

Recommendations for Implementation

Short-term prediction using sFlt-1/PIGF ratio in symptomatic women represents the most evidence-based current application. The high negative predictive value for ruling out preeclampsia within 1-2 weeks enables risk stratification and appropriate resource utilization [2, 18].

First-trimester screening combining maternal risk factors with biomarkers should be considered in healthcare systems with capacity for aspirin prophylaxis programs. The competing-risks model using maternal factors, MAP, UtA-PI, and PIGF has been validated across multiple populations [57] and enables targeted aspirin administration with demonstrated benefit.

Standardized research protocols are urgently needed to enable meaningful comparison across studies. This includes uniform preeclampsia definitions, standardized biomarker measurement protocols, and consistent reporting of performance metrics stratified by gestational age and disease severity [3, 14].

Population-specific validation is essential before implementing screening programs. Biomarker performance varies by ethnicity, baseline risk, and healthcare setting [24, 50]. Local validation studies should precede large-scale implementation.

Integration with placental pathology could enhance biomarker utility. Combining biomarker profiles with evidence of placental dysfunction (ultrasound findings, pathology when available) improves prediction [59, 76] and may guide mechanism-specific interventions.

DISCUSSION

This systematic review synthesizes evidence from 80 studies examining biomarkers for early PE prediction. The key findings demonstrate that: (1) the sFlt-1/PlGF ratio is the most robust single biomarker combination for short-term prediction and rule-out; (2) multi-marker and multi-omics panels achieve superior early prediction (AUC 0.85–0.94) compared to individual markers; (3) prediction timing is critical—first-trimester markers perform best for early-onset PE, while second- and third-trimester markers capture late-onset disease; and (4) integration with clinical factors (MAP, UtA-PI) and machine learning improves accuracy.

Comparison with Previous Work

Our findings align with and extend prior meta-analyses. Agrawal et al. (1) reported pooled sensitivity of 80% and specificity of 92% for the sFlt-1/PlGF ratio in predicting PE, which we confirmed across 12 additional validation studies. However, we found that performance is substantially higher for early-onset PE (sensitivity 88–90%) than for late-onset PE (sensitivity 58–70%), a distinction not emphasized in earlier reviews (2,3). This supports the concept of PE subtypes with different pathophysiologic drivers (12).

The superiority of multi-marker panels over single biomarkers is consistent with the multifactorial nature of PE. Our review identified that models combining angiogenic (PlGF, sFlt-1), inflammatory (CRP, IL-6), and molecular (PAPP-A, PP13, microRNAs) markers consistently achieved higher AUCs (0.85–0.94) than any single class alone (7,10). This finding contrasts with some earlier meta-analyses that reported only modest improvement (14), likely because those analyses did not include recent multi-omics studies (9,11).

Temporal Dynamics of Biomarker Performance

A novel contribution of this review is the detailed mapping of optimal prediction windows. First-trimester (6–16 weeks) markers such as PP13, PAPP-A, and cell-free RNA panels detect risk

up to 18 weeks before clinical onset (9,23,29). However, individual angiogenic factors measured at 10 weeks show poor performance (AUC ~0.60), suggesting that early placental dysfunction requires multiple pathway assessment (60). Second-trimester (16–28 weeks) appears to be the optimal window for angiogenic markers, with PlGF-based models achieving diagnostic odds ratios of 63 for early-onset PE (3,11). Third-trimester markers, particularly the sFlt-1/PlGF ratio, excel at short-term prediction (within 1–4 weeks) and ruling out PE in symptomatic women (2,18).

This temporal evolution reflects underlying pathophysiology: early biomarkers capture abnormal spiral artery remodeling (e.g., MMP-7, PP13), while later markers reflect the emerging anti-angiogenic state (sFlt-1/PlGF imbalance) and end-organ effects (12,46).

Clinical Implementation: Progress and Barriers

The sFlt-1/PlGF ratio has achieved the most widespread clinical adoption. The PROGNOSIS study established that a cutoff ≤ 38 rules out PE within one week with 99.3% negative predictive value, enabling safe outpatient management (2). Our review confirms these findings across high-risk and mixed populations (18,32,77). However, positive predictive value remains low (10–20%) in low-prevalence settings, limiting its use as a rule-in test (50).

First-trimester screening combining maternal factors, MAP, UtA-PI, PlGF, and PAPP-A has been validated in multiple cohorts (8,57). Aspirin (150 mg/day) initiated before 16 weeks in high-risk women reduces early PE by approximately 90% (57). Despite this, implementation remains limited due to cost, lack of standardized algorithms, and variability in assay platforms (3,16).

Several barriers persist: (1) platform standardization—different assays yield different absolute values and require population-specific cutoffs (16); (2) cost-effectiveness—multi-marker panels at multiple time points may not be affordable in low-resource settings (24); (3) population validation—most studies were conducted in European or North American cohorts, and performance may differ in Asian, African, or Latin American populations (8,11,68); and (4) clinical workflow integration—machine learning models are often “black boxes” that clinicians find difficult to interpret (8).

Conflicting Findings and Their Resolution

Apparent contradictions in the literature can be resolved by examining population risk, gestational timing, and PE subtype. For example, PP13 showed excellent performance (90% sensitivity/specificity) in high-risk women with sequential testing (23) but poor performance in low-risk unselected populations (19). Similarly, first-trimester sFlt-1 was predictive only when measured before 12 weeks (AUC 0.82 at 11 weeks) but not at 13 weeks (AUC 0.50) (29). Studies reporting poor performance for PlGF alone often measured it in the first trimester in low-risk women (60), while studies showing strong performance measured it in the second trimester in high-risk populations (12,20). These findings emphasize that no single biomarker is universally applicable; rather, the choice of biomarker and timing must be tailored to the clinical context.

Implications for Research and Practice

For clinical practice, we recommend: (1) using the sFlt-1/PlGF ratio with cutoff ≤ 38 to rule out PE in symptomatic women in the second/third trimester; (2) considering first-trimester multi-marker screening (maternal factors + MAP + UtA-PI + PlGF + PAPP-A) in healthcare systems that can implement aspirin prophylaxis; and (3) interpreting biomarker results in the context of gestational age and PE subtype.

For research, priorities include: (1) large-scale, multi-ethnic validation of promising multi-omics panels (leptin/ceramide ratio, cell-free RNA, proteomic signatures); (2) development of standardized, low-cost point-of-care assays; (3) integration of placental pathology to refine biomarker performance; and (4) randomized trials comparing biomarker-guided screening versus usual care.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review demonstrates that integrating angiogenic, inflammatory, and molecular biomarkers significantly improves early prediction of preeclampsia compared to single markers. The sFlt-1/PlGF ratio is the most clinically validated test for short-term rule-out in symptomatic women, with 99.3% negative predictive value. First-trimester multi-marker and multi-omics panels (e.g., leptin/ceramide ratio, cell-free RNA, PAPP-A + PlGF + maternal factors)

achieve high accuracy (AUC 0.85–0.94) and can detect risk up to 18 weeks before clinical onset, enabling targeted aspirin prophylaxis.

Recommendations:

- **Clinical use:** Implement sFlt-1/PlGF ratio for short-term prediction in symptomatic women.
- **Screening:** Consider first-trimester multi-marker screening in settings with capacity for aspirin prophylaxis.
- **Future research:** Validate multi-omics panels in diverse populations, standardize assays, and integrate placental pathology.
- **Health policy:** Develop cost-effectiveness models for low-resource settings.

Without early prediction, clinicians rely on nonspecific symptoms and late-onset signs. With validated biomarker panels, risk-stratified prevention and monitoring become achievable, potentially reducing PE-related maternal and perinatal morbidity.

REFERENCES

1. S. Agrawal, A. Cerdeira, C. Redman, M. Vatish (2018) Meta-Analysis and Systematic Review to Assess the Role of Soluble FMS-Like Tyrosine Kinase-1 and Placenta Growth Factor Ratio in Prediction of Preeclampsia: The SaPPPhirE Study. HYPERTENSION. <https://doi.org/10.1161/HYPERTENSIONAHA.117.10182>
2. C. Chirilă, C. Mărginean, P. Chirilă, M. Gliga (2023) The Current Role of the sFlt-1/PlGF Ratio and the Uterine–Umbilical–Cerebral Doppler Ultrasound in Predicting and Monitoring Hypertensive Disorders of Pregnancy: An Update with a Review of the Literature. Children. <https://doi.org/10.3390/children10091430>
3. P. Chaemsaitong, M. Gil, N. Chaiyasit, et al (2023) Accuracy of placental growth factor alone or in combination with soluble fms-like tyrosine kinase-1 or maternal factors in detecting preeclampsia in asymptomatic women in the second and third trimesters: a systematic review and

- meta-analysis. American Journal of Obstetrics and Gynecology. <https://doi.org/10.1016/j.ajog.2023.03.032>
4. R. Allen, E. Rogozińska, Kirsty Cleverly, et al (2014) Abnormal blood biomarkers in early pregnancy are associated with preeclampsia: a meta-analysis. European Journal of Obstetrics, Gynecology, and Reproductive Biology. <https://doi.org/10.1016/j.ejogrb.2014.09.027>
 5. K. Ferguson, J. Meeker, T. McElrath, et al (2017) Repeated measures of inflammation and oxidative stress biomarkers in preeclamptic and normotensive pregnancies. American Journal of Obstetrics and Gynecology. <https://doi.org/10.1016/j.ajog.2016.12.174>
 6. D. Carty, J. Brennand, J. McCulloch, et al (2010) FIRST TRIMESTER E-SELECTIN LEVELS PREDICT PRE-ECLAMPSIA: PP.12.468. Journal of Hypertension. <https://doi.org/10.1097/01.hjh.0000378793.32863.b2>
 7. Qianyang Huang, Shiyang Hao, Jin You, et al (2021) Early-pregnancy prediction of risk for pre-eclampsia using maternal blood leptin/ceramide ratio: discovery and confirmation. BMJ Open. <https://doi.org/10.1136/bmjopen-2021-050963>
 8. Taishun Li, Mingyang Xu, Yuan Wang, et al (2024) Prediction model of preeclampsia using machine learning based methods: a population based cohort study in China. Frontiers in Endocrinology. <https://doi.org/10.3389/fendo.2024.1345573>
 9. N. Castillo Marco, T. Cordero, M. Igual, et al (2025) O-089 Maternal plasma cell-free RNA as a liquid biopsy for first-trimester screening of early and late-onset preeclampsia. Human Reproduction. <https://doi.org/10.1093/humrep/deaf097.089>
 10. I. Marić, K. Contrepois, M. Moufarrej, et al (2022) Early prediction and longitudinal modeling of preeclampsia from multiomics. Patterns. <https://doi.org/10.1016/j.patter.2022.100655>
 11. A. Tarca, R. Romero, N. BENSHALOM-TIROSH, et al (2019) The prediction of early preeclampsia: Results from a longitudinal proteomics study. PLoS ONE. <https://doi.org/10.1371/journal.pone.0217273>
 12. O. Erez, R. Romero, E. Maymon, et al (2017) The prediction of late-onset preeclampsia: Results from a longitudinal proteomics study. PLoS ONE. <https://doi.org/10.1371/journal.pone.0181468>

13. Lucie Roubalova, V. Kroutilova, Maria Fernanda Lopez-G Tinajero, et al (2024) Added Value in Low-Risk Pregnancies of Longitudinal Changes in Uterine Doppler and Circulating Angiogenic Factors during the Third Trimester in Predicting Term Preeclampsia. Fetal Diagnosis and Therapy. <https://doi.org/10.1159/000541731>
14. V. Bucher, A. R. Mitchell, Pia Gudmundsson, et al (2024) Prediction of adverse maternal and perinatal outcomes associated with pre-eclampsia and hypertensive disorders of pregnancy: a systematic review and meta-analysis. EClinicalMedicine. <https://doi.org/10.1016/j.eclinm.2024.102861>
15. J. Allotey, Kym I. E. Snell, M. Smuk, et al (2020) Validation and development of models using clinical, biochemical and ultrasound markers for predicting pre-eclampsia: an individual participant data meta-analysis. Health Technology Assessment. <https://doi.org/10.3310/hta24720>
16. A. Staff, Ó. Burke, S. Benton, et al (2013) Maternal circulating PlGF concentrations and placenta-related pregnancy complications: First results from the CoLab AngF Study. Pregnancy Hypertension. <https://doi.org/10.1016/j.preghy.2013.04.007>
17. Pensée Wu, C. B. van den Berg, Z. Alfircvic, et al (2015) Early Pregnancy Biomarkers in Pre-Eclampsia: A Systematic Review and Meta-Analysis. International Journal of Molecular Sciences. <https://doi.org/10.3390/ijms160923035>
18. Jessica J Miller, V. Higgins, N. Melamed, et al (2023) Clinical Validation of the sFlt-1:PlGF Ratio as a Biomarker for Preeclampsia Diagnosis in a High-Risk Obstetrics Unit. The Journal of Applied Laboratory Medicine. <https://doi.org/10.1093/jalm/jfad003>
19. F. Schneuer, Natasha Nassar, Amina Khambalia, et al (2012) First trimester screening of maternal placental protein 13 for predicting preeclampsia and small for gestational age: in-house study and systematic review. Placenta. <https://doi.org/10.1016/j.placenta.2012.05.012>
20. J. Kusanovic, R. Romero, T. Chaiworapongsa, et al (2009) A prospective cohort study of the value of maternal plasma concentrations of angiogenic and anti-angiogenic factors in early pregnancy and midtrimester in the identification of patients destined to develop preeclampsia. Journal of Maternal-Fetal & Neonatal Medicine. <https://doi.org/10.3109/14767050902994754>

21. Shiting Qin, Ningxia Sun, Longqiang Xu, et al (2021) The Value of Circulating microRNAs for Diagnosis and Prediction of Preeclampsia: a Meta-analysis and Systematic Review. *Reproductive Sciences*. <https://doi.org/10.1007/s43032-021-00799-6>
22. A. Tarca, R. Romero, O. Erez, et al (2020) Maternal whole blood mRNA signatures identify women at risk of early preeclampsia: a longitudinal study. *Journal of Maternal-Fetal & Neonatal Medicine*. <https://doi.org/10.1080/14767058.2019.1685964>
23. R. Gonen, R. Shahar, Y. Grimpel, et al (2009) Placental Protein 13 as an Early Marker for Preeclampsia: A Prospective Longitudinal Study. *Obstetric Anesthesia Digest*. <https://doi.org/10.1097/01.AOA.0000362086.72838.61>
24. I. J. Andresen, M. Zucknick, M. L. Degnes, et al (2024) Prediction of late-onset preeclampsia using plasma proteomics: a longitudinal multi-cohort study. *Scientific Reports*. <https://doi.org/10.1038/s41598-024-81277-2>
25. K. Evers, A. Atkinson, Christian Barro, et al (2018) Neurofilament as Neuronal Injury Blood Marker in Preeclampsia. *HYPERTENSION*. <https://doi.org/10.1161/HYPERTENSIONAHA.117.10314>
26. M. Ozat, Mine Kanat-Pektas, O. Yenicesu, et al (2011) Serum concentrations of CA-125 in normal and preeclamptic pregnancies. *Archives of Gynecology and Obstetrics*. <https://doi.org/10.1007/s00404-010-1736-2>
27. I. Hromadníková, K. Kotlabova, K. Ivankova, L. Krofta (2017) First trimester screening of circulating C19MC microRNAs and the evaluation of their potential to predict the onset of preeclampsia and IUGR. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0171756>
28. I. Vasilache, A. Cărauleanu, D. Socolov, et al (2022) Predictive performance of first trimester serum galectin-13/PP-13 in preeclampsia screening: A systematic review and meta-analysis. *Experimental and Therapeutic Medicine*. <https://doi.org/10.3892/etm.2022.11297>
29. Alexandre Fillion, A. Boutin, C. Gasse, et al (2022) First-trimester placental soluble fms-like tyrosine kinase 1 (sFlt-1) for the prediction of preeclampsia. *American Journal of Obstetrics and Gynecology*. <https://doi.org/10.1016/j.ajog.2021.11.584>

30. Iasmina M. Craici, S. Wagner, K. Bailey, et al (2013) Podocyturia Predates Proteinuria and Clinical Features of Preeclampsia: Longitudinal Prospective Study. HYPERTENSION. <https://doi.org/10.1161/HYPERTENSIONAHA.113.01115>
31. Robin Shoemaker, Marko Poglitsch, Hong Huang, et al (2025) Abstract 064: Application of Angiotensin-Based Biomarkers Quantified by Mass Spectrometry to Predict Preeclampsia. HYPERTENSION. https://doi.org/10.1161/hyp.82.suppl_1.064
32. Aimal Mangsang Sangma, A. Ruram, W. Shullai, Polina Boruah (2025) Role of soluble fms-like tyrosine kinase-1/placental growth factor ratio as an early predictor of preeclampsia in pregnant women. Journal of Laboratory Physicians. https://doi.org/10.25259/jlp_127_2025
33. Jian-bo Zhang, Wei-Chi She, J. Yue, et al (2020) Early Prediction of Preeclampsia by Using Serum Human Leukocyte Antigen G: A Retrospective Case-Control Study Followed by a Prospective Unselected Cohort Study. Social Science Research Network. <https://doi.org/10.2139/ssrn.3741242>
34. S. Daskalopoulou, Kim Phan, I. Schiller, et al (2023) S-11-1: ARTERIAL STIFFNESS AND HEMODYNAMIC PARAMETERS FOR THE EARLY PREDICTION OF PREECLAMPSIA: A PROSPECTIVE COHORT STUDY. Journal of Hypertension. <https://doi.org/10.1097/01.hjh.0000913012.20678.63>
35. E. Reyna-Villasmil, Jorly Mejía-Montilla, Joel Santos-Bolívar, et al (2017) Angiopoyetina-2 plasmática en el segundo trimestre, como predictor del desarrollo de preeclampsia. Revista Peruana de Ginecología y Obstetricia. <https://doi.org/10.31403/RPGO.V63I1959>
36. Qianyang Huang, Shiyang Hao, Jin You, et al (2021) Case finding of early pregnancies at risk of preeclampsia using maternal blood leptin/ceramide ratio: multi-omics discovery and validation from a longitudinal study. <https://doi.org/10.22541/AU.161111178.89108280/V1>
37. K. De Clippel, M. Wijman, P. Struijk, et al (2006) OC102: Longitudinal observation of the human yolk sac, yolk sac and fetoplacental hemodynamics: preliminary results. Ultrasound in Obstetrics and Gynecology. <https://doi.org/10.1002/uog.2962>
38. O. Erez, F. Gotsch, Eunjung Jung, et al (2022) Perturbations in the kinetics of the thrombin generation assay identify women at risk for preeclampsia in the first trimester and provide a

- rationale for a preventive approach. American Journal of Obstetrics and Gynecology. <https://doi.org/10.1016/j.ajog.2022.11.1276>
39. Aiqi Yin, Yixuan Chen, Huafan Zhang, et al (2025) Increased first-trimester CA125 levels associated with the development of preeclampsia. Journal of Translational Medicine. <https://doi.org/10.1186/s12967-025-07565-1>
40. W. F. Gharib, Khaled Ahmed Atwa, Naglaa E. Salem, et al (2025) Assessment of Maternal Serum Netrin-1 as a New Biomarker of Preeclampsia. The Egyptian Journal of Fertility and Sterility. <https://doi.org/10.21608/egyfs.2025.469371>
41. Y. Giguère, M. Charland, E. Bujold, et al (2010) Combining biochemical and ultrasonographic markers in predicting preeclampsia: a systematic review. Clinical Chemistry. <https://doi.org/10.1373/clinchem.2009.134080>
42. C. Kleinrouweler, M. Wiegerinck, C. Ris-Stalpers, et al (2012) Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: a systematic review and meta-analysis. BJOG: an International Journal of Obstetrics and Gynaecology. <https://doi.org/10.1111/j.1471-0528.2012.03311.x>
43. Marianna Danielli, R. Thomas, C. Gillies, et al (2022) Blood biomarkers to predict the onset of pre-eclampsia: A systematic review and meta-analysis. Heliyon. <https://doi.org/10.1016/j.heliyon.2022.e11226>
44. Y. Veisani, E. Jenabi, A. Delpisheh, S. Khazaei (2019) Angiogenic factors and the risk of preeclampsia: A systematic review and meta-analysis. International Journal of Reproductive BioMedicine. <https://doi.org/10.18502/ijrm.v17i1.3815>
45. Y. Giguère, M. Charland, E. Bujold, et al (2011) [Combining biochemical and ultrasonographic markers in predicting preeclampsia: a systematic review]. Annales de Biologie Clinique. <https://doi.org/10.1684/abc.2011.0572>
46. R. Romero, J. Nien, J. Espinoza, et al (2008) A longitudinal study of angiogenic (placental growth factor) and anti-angiogenic (soluble endoglin and soluble vascular endothelial growth factor receptor-1) factors in normal pregnancy and patients destined to develop preeclampsia and deliver a

- small for gestational age neonate. Journal of Maternal-Fetal & Neonatal Medicine. <https://doi.org/10.1080/14767050701830480>
47. A. Tarca, Andreea B. Taran, R. Romero, et al (2021) Prediction of preeclampsia throughout gestation with maternal characteristics and biophysical and biochemical markers: a longitudinal study. American Journal of Obstetrics and Gynecology. <https://doi.org/10.1016/J.AJOG.2021.01.020>
48. G. Lambert-Messerlian, E. Eklund, E. Chien, et al (2014) Use of first or second trimester serum markers, or both, to predict preeclampsia. Pregnancy Hypertension. <https://doi.org/10.1016/j.preghy.2014.07.001>
49. K. Hymavathi, Bhaavya Paturi, Duvvuru Akshitha, K. Sravya (2021) Preeclampsia prediction –First trimester screening markers. Indian Journal of Obstetrics and Gynecology Research. <https://doi.org/10.18231/J.IJOGR.2021.046>
50. J. Forest, J. Masse, E. Bujold, et al (2012) OS090. Performance of candidate clinical and biochemical markers in screening early in pregnancy to detect women at high risk to develop preeclampsia. Pregnancy Hypertension. <https://doi.org/10.1016/j.preghy.2012.04.091>
51. T. Metz, A. Allshouse, A. Euser, K. Heyborne (2014) Preeclampsia in high risk women is characterized by risk group-specific abnormalities in serum biomarkers. American Journal of Obstetrics and Gynecology. <https://doi.org/10.1016/j.ajog.2014.04.027>
52. Sean-Tee Lim, Wentao Li, J. Kemper, et al (2020) Biomarkers and the Prediction of Adverse Outcomes in Preeclampsia: A Systematic Review and Meta-analysis. Obstetrics and Gynecology. <https://doi.org/10.1097/AOG.0000000000004149>
53. R. Levine, C. Lam, Cong Qian, et al (2007) Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. Obstetrical & Gynecological Survey. <https://doi.org/10.1097/01.OGX.0000253489.32189.4D>
54. O. Erez, R. Romero, J. Espinoza, et al (2008) The change in concentrations of angiogenic and anti-angiogenic factors in maternal plasma between the first and second trimesters in risk assessment for the subsequent development of preeclampsia and small-for-gestational age. Journal of Maternal-Fetal & Neonatal Medicine. <https://doi.org/10.1080/14767050802034545>

55. A. Cohen, J. Wenger, T. James-Todd, et al (2013) The association of circulating angiogenic factors and HbA1c with the risk of preeclampsia in women with preexisting diabetes. Hypertension in Pregnancy. <https://doi.org/10.3109/10641955.2013.837175>
56. Ruqaiya Shahid, M. F. Bari, Mehwish Hussain (2021) Serum biomarkers for the prediction and diagnosis of preeclampsia: A meta-analysis. Journal of Taibah University Medical Sciences. <https://doi.org/10.1016/j.jtumed.2021.07.003>
57. K. Nicolaides, D. Wright (2019) Re: Prediction of pre-eclampsia: review of reviews. Ultrasound in Obstetrics and Gynecology. <https://doi.org/10.1002/uog.20852>
58. U. Perni, C. Sison, V. Sharma, et al (2012) Angiogenic Factors in Superimposed Preeclampsia: A Longitudinal Study of Women With Chronic Hypertension During Pregnancy. HYPERTENSION. <https://doi.org/10.1161/HYPERTENSIONAHA.111.181735>
59. J. Lai, A. Syngelaki, K. Nicolaides, et al (2022) Using ultrasound and angiogenic markers from a 19-23 week assessment to inform the subsequent diagnosis of preeclampsia. American Journal of Obstetrics and Gynecology. <https://doi.org/10.1016/j.ajog.2022.03.007>
60. T. McElrath, K. Lim, E. Paré, et al (2012) Longitudinal evaluation of predictive value for preeclampsia of circulating angiogenic factors through pregnancy. American Journal of Obstetrics and Gynecology. <https://doi.org/10.1016/j.ajog.2012.08.010>
61. Yangxue Yin, Min Liu, Hong-biao Yu, et al (2020) Circulating microRNAs as biomarkers for diagnosis and prediction of preeclampsia: A systematic review and meta-analysis. European Journal of Obstetrics, Gynecology, and Reproductive Biology. <https://doi.org/10.1016/j.ejogrb.2020.08.016>
62. M. Garcés, Elizabeth Sanchez, L. F. Cardona, et al (2015) Maternal Serum Meteorin Levels and the Risk of Preeclampsia. PLoS ONE. <https://doi.org/10.1371/journal.pone.0131013>
63. D. Rizados, M. Eleftheriades, Gregory Karampas, et al (2013) Placental growth factor and soluble fms-like tyrosine kinase-1 are useful markers for the prediction of preeclampsia but not for small for gestational age neonates: a longitudinal study. European Journal of Obstetrics, Gynecology, and Reproductive Biology. <https://doi.org/10.1016/j.ejogrb.2013.08.040>

64. K. Bramham, Paul Townsend Seed, L. Lightstone, et al (2016) Diagnostic and predictive biomarkers for pre-eclampsia in patients with established hypertension and chronic kidney disease. *Kidney International*. <https://doi.org/10.1016/j.kint.2015.10.012>
65. R. Kerley, Cathal M. McCarthy (2018) Biomarkers of glomerular dysfunction in pre-eclampsia - A systematic review. *Pregnancy Hypertension*. <https://doi.org/10.1016/j.preghy.2018.03.002>
66. A. Sahay, Vidya Patil, D. Sundrani, et al (2014) A longitudinal study of circulating angiogenic and antiangiogenic factors and AT1-AA levels in preeclampsia. *Hypertension Research*. <https://doi.org/10.1038/hr.2014.71>
67. M. L. Degnes, A. Westerberg, I. J. Andresen, et al (2024) Protein biomarker signatures of preeclampsia - a longitudinal 5000-multiplex proteomics study. *Scientific Reports*. <https://doi.org/10.1038/s41598-024-73796-9>
68. M. P. Lubis, H. Hariman, S. Lumbanraja, A. Bachtiar (2019) The Role of Placental Growth Factor, Soluble Endoglin, and Uterine Artery Diastolic Notch to Predict the Early Onset of Preeclampsia. *Open Access Macedonian Journal of Medical Sciences*. <https://doi.org/10.3889/oamjms.2019.154>
69. B. Sibai, M. Koch, S. Freire, et al (2008) Serum inhibin A and angiogenic factor levels in pregnancies with previous preeclampsia and/or chronic hypertension: are they useful markers for prediction of subsequent preeclampsia? *American Journal of Obstetrics and Gynecology*. <https://doi.org/10.1016/j.ajog.2008.06.071>
70. I. Tzanaki, A. Makrigiannakis, Charoula Lymperopoulou, et al (2025) Pregnancy-associated plasma protein A (PAPP-A) as a first trimester serum biomarker for preeclampsia screening: a systematic review and meta-analysis. *Journal of Maternal-Fetal & Neonatal Medicine*. <https://doi.org/10.1080/14767058.2024.2448502>
71. A. Doherty, J. Carvalho, S. Drewlo, et al (2014) Altered hemodynamics and hyperuricemia accompany an elevated sFlt-1/PlGF ratio before the onset of early severe preeclampsia. *Journal of Obstetrics and Gynaecology Canada*. [https://doi.org/10.1016/S1701-2163\(15\)30511-9](https://doi.org/10.1016/S1701-2163(15)30511-9)

72. K. Marrufo-Gallegos, J. R. Villafán-Bernal, S. Espino-Y-Sosa, et al (2023) Influential Serum Kinases (Non-sFlt-1) and Phosphatases in Preeclampsia—Systematic Review and Metanalysis. *International Journal of Molecular Sciences*. <https://doi.org/10.3390/ijms241612842>
73. S. Ghazvini, Saji Uthaman, Lilly Synan, et al (2023) Predicting the onset of preeclampsia by longitudinal monitoring of metabolic changes throughout pregnancy with Raman spectroscopy. *Bioengineering & Translational Medicine*. <https://doi.org/10.1002/btm2.10595>
74. E. Litwinska, M. Litwińska, P. Oszukowski, et al (2015) Biochemical markers in screening for preeclampsia and intrauterine growth restriction. *Ginekologia Polska*. <https://doi.org/10.17772/GP/57863>
75. Jorge Montenegro-Martínez, Ana Camacho-Carrasco, David Núñez-Jurado, et al (2024) Longitudinal changes of angiogenic factors as a potential predictive tool in women with suspected preeclampsia. *Pregnancy Hypertension*. <https://doi.org/10.1016/j.preghy.2024.01.130>
76. R. Romero, Eunjung Jung, T. Chaiworapongsa, et al (2022) Toward a new taxonomy of obstetrical disease: improved performance of maternal blood biomarkers for the great obstetrical syndromes when classified according to placental pathology. *American Journal of Obstetrics and Gynecology*. <https://doi.org/10.1016/j.ajog.2022.04.015>
77. E. Timokhina, I. Ignatko, Yu. A Samoylova, et al (2025) New indicators of known markers in early prediction of the increase in the severity of preeclampsia. *V F Snegirev Archives of Obstetrics and Gynecology*. <https://doi.org/10.17816/aog676879>
78. V. Giardini, R. Rovelli, P. Algeri, et al (2020) Placental growth factor as a predictive marker of preeclampsia – PREBIO study – PREeclampsia BIOchemical study. *Journal of Maternal-Fetal & Neonatal Medicine*. <https://doi.org/10.1080/14767058.2020.1792878>
79. Yifan Wu, Yang Liu, Yiling Ding (2021) Predictive Performance of Placental Protein 13 for Screening Preeclampsia in the First Trimester: A Systematic Review and Meta-Analysis. *Frontiers in Medicine*. <https://doi.org/10.3389/fmed.2021.756383>
80. Jing Zhu, Jun Zhang, M. Ng, et al (2019) Angiogenic factors during pregnancy in Asian women with elevated blood pressure in early pregnancy and the risk of preeclampsia: a longitudinal cohort study. *BMJ Open*. <https://doi.org/10.1136/bmjopen-2019-032237>