Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 16s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Biomarkers For Predicting Preeclampsia : An Updated Review

Mrs. Varna E M[1], Dr. R Sripradha[*2], Dr. Prejisha B[3], Dr. Sneha Henry[4]

[1]Phd scholar, Tutor, Department of Biochemistry, Malabar Medical College and Research Centre, Kerala-673323, India.

Email ID: varna0402@gmail.com

[*2]Associate Professor, Department of Biochemistry, Shri Sathya Sai Medical College and Research Institute, SBV Chennai Campus, Sri Balaji Vidyapeeth University, Chennai-603108, India.

Email ID: rspradha12@gmail.com

[3]Professor, Department of Obstetrics and Gynecology, Malabar Medical College & Research Centre, Calicut. Kerala-673323, India.

[4]Associate Professor, Department of Biochemistry, Malabar Medical College & Research Centre, Calicut. Kerala- 673323, India.

***Corresponding Author:**

Dr. R Sripradha,

Email ID: rspradha12@gmail.com

Cite this paper as: Mrs. Varna E M, Dr. R Sripradha, Dr. Prejisha B, Dr. Sneha Henry, (2025) Biomarkers For Predicting Preeclampsia: An Updated Review. *Journal of Neonatal Surgery*, 14 (16s), 156-163.

ABSTRACT

Preeclampsia is a hypertensive condition that affects both the fetus and the mother during pregnancy. It affects 3.8% of the pregnant women worldwide. Raised mean arterial blood pressure, increased blood levels of Placental Growth Factor (PlGF) and Doppler ultrasonography aid in the early diagnosis of preeclampsia.

This review focuses on the use of various biomarkers in the prediction and diagnosis of preeclampsia. The main biomarkers include Placental Growth Factor (PlGF), Pregnancy-associated Plasma Protein 1 (PAPP-A) and soluble Fms-Like Tyrosine Kinase-1 (sFlt1).

PlGF has been shown to serve as a marker of abnormal placentation, with lower levels observed in the first trimester. Studies have found that angiogenic biomarkers, including PlGF, can predict the risk of developing preeclampsia at 20 weeks of gestation. Studies have also found that sFlt-1 (soluble fms-like tyrosine kinase-1) can be used to predict preeclampsia. Pregnancy-associated plasma protein A (PAPP-A) helps to identify primigravid women at high risk for preterm preeclampsia. It is also valuable in assessing their likelihood of developing other major obstetrical syndromes. Reduced PAPP-A levels during the first trimester have been found to positively correlate with pregnancy - associated complications.

In conclusion, these biomarkers have shown a promising role in predicting and diagnosing preeclampsia, thus providing valuable insights into the disease progression and potential complications.

Keywords: *Biomarkers, Pregnancy, Pre-eclampsia, Hypertension*

1. INTRODUCTION

Preeclampsia (PE) is a hypertensive condition that affects the health of the fetus and the mother during pregnancy. It is described as newly developed hypertension that appears after 20 weeks of pregnancy and is linked to the mother's organ failure or proteinuria (1). Preeclampsia impacts 3.8% of pregnant women worldwide, and it causes more than 70,000 maternal and 500,000 fetal deaths annually (2) (3). Pregnancy-related hypertensive disorders contribute to 7–8% of maternal deaths both in India and globally (4).

Although preventive measures can slightly reduce the risk of preeclampsia, the condition remains prevalent. Moreover, the exciting biomarkers for predicting PE are not highly effective. Preeclampsia is one of the major causes of maternal morbidity and is linked to various adverse fetal outcomes, such as intrauterine growth restriction, premature delivery, placental abruption, fetal distress, and fetal death in utero. Mounting evidence suggests that preeclampsia has been linked to long-term negative consequences on the progeny, in addition to the hazards to the fetus during pregnancy; preeclampsia has been specifically linked to cardiovascular complications in offspring, leading to hypertension and impaired vascular function (1).

Earlier prediction and diagnosis of preeclampsia is of utmost importance to prevent the occurrence of deleterious consequences. Preeclampsia can be categorized as early-onset (first clinical manifestation before 34 gestational weeks) or late-onset (disease develops at or after 34 weeks of gestation) based on the clinical onset of symptoms (5). Biomarkers for preeclampsia could improve treatment and prevention measures in susceptible pregnant women by acting as predictive indicators and possible therapeutic targets. Preeclampsia, classified under ICD-10 code O14, is a pregnancy-related disorder characterized by high blood pressure and proteinuria, sometimes accompanied by pathological swelling. It poses significant risks, including placental dysfunction, premature separation of the placenta, and even intrauterine fetal demise. Given its severity, medical professionals prioritize early detection, risk assessment, and tailored interventions to safeguard maternal and fetal health (6).

Several biomarkers for early diagnosis and screening of pre eclampsia have been investigated. These markers include those for inflammation, oxidative stress, endothelial damage, endocrine functions, lipid metabolism, fetal distress, angiogenic and antiangiogenic variables (7). Doppler ultrasonography, mean arterial blood pressure, and placental growth factor (PlGF) levels in blood have been developed as more reliable screening for the early (first trimester) identification of pre-eclampsia; however, because of associated costs, they have not been integrated into routine clinical practice (3). The National Institute for Health and Clinical Excellence (NICE) Guidelines recommend ruling out a diagnosis of pre-eclampsia when the condition is suspected by combining PlGF and sFlt-1 during the third trimester (but before 37 gestational weeks) (8).The most recent definition of PE now includes organ dysfunction in addition to the traditional trio of symptoms—hypertension, proteinuria, and edema. The American College of Obstetricians and Gynecologists (ACOG) was the first to declare that PE may be diagnosed even in the absence of proteinuria and to relativize the significance of proteinuria (9).

The ACOG definition still does not highlight all symptoms that can be a consequence of PE. ACOG does not take intrauterine fetal growth restriction or the effects of an inefficient placenta into account. The International Society for the Study of Hypertension in Pregnancy (ISSHP) revised the definition of PE in 2018. This definition states that PE is defined as a recent development of hypertension during pregnancy accompanied by symptoms related to peripheral organs, such as thrombocytopenia, hemolysis, liver failure, fetal growth limitation, maternal endothelial dysfunction and chronic immune activation (3,10).

In this review, we have assessed the current research landscape and its potential implications for diagnosing preeclampsia (PE). We will examine the benefits, drawbacks, and gaps in the literature to clarify the clinical significance of the several PE biomarkers. The aim of this review is to determine which blood biomarker is most relevant for early detection and diagnosis of PE.

Pathogenesis of PE

Appropriate blood flow via the placenta is crucial for a normal and healthy pregnancy. The invasion of placental trophoblasts rebuilds the uterine spiral arteries in pregnant women by widening them and decreasing their resistance.

There is inadequate placental perfusion in PE leading to incomplete remodeling of the arteries. These alterations make the placental cells secrete various biochemical components, which lead to endothelial dysfunction, oxidative stress, activation of coagulation pathways, and also alter the mother's immunological response. These changes result in hypertension, proteinuria, and internal organ dysfunction (11, 12).

The process of extravillous cytotrophoblast invasion occurs between 13 and 18 weeks of pregnancy, resulting in the loss of endothelium and muscle-elastic fibers of the uterus. These changes increase the size of the uterus and enhance the sensitivity of the uterus to various vasoactive drugs.

This process improves blood flow through the uterus and creates a low-pressure, high-flow uteroplacental circulatory system (13-15). In preeclampsia-complicated pregnancies, cytotrophoblast invasion is limited to the intradermal part, resulting in narrower spiral arteries and reduced uteroplacental blood flow. This process is completed between weeks 18 and 22 of pregnancy (16, 17).

Diagnosis of PE

The diagnosis is usually done after 20 weeks of pregnancy by measuring the new onset of persistently high blood pressure (more than 140 mmHg systolic blood pressure or greater than 90 mmHg diastolic blood pressure). Symptoms such as headache due to insensitivity to analgesics, abnormal laboratory test results, onset of proteinuria, signs of internal organ failure, pulmonary edema, and renal dysfunction are indicative of preeclampsia (18).

PE's complications

Untreated preeclampsia can lead to adverse complications such as severe hypertension, HELLP syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelets eclampsia), pulmonary edema, myocardial infarction, stroke, acute respiratory distress syndrome, retinal impairment, and renal failure. A normally functioning placenta may detach from the fetus too soon, or fetal growth may be restricted within the womb due to the above-mentioned complications affecting the developing embryo. In severe cases, these conditions can pose life-threatening risks to both the mother and the fetus (18).

Figure 1 shows the adverse effects of preeclampsia.

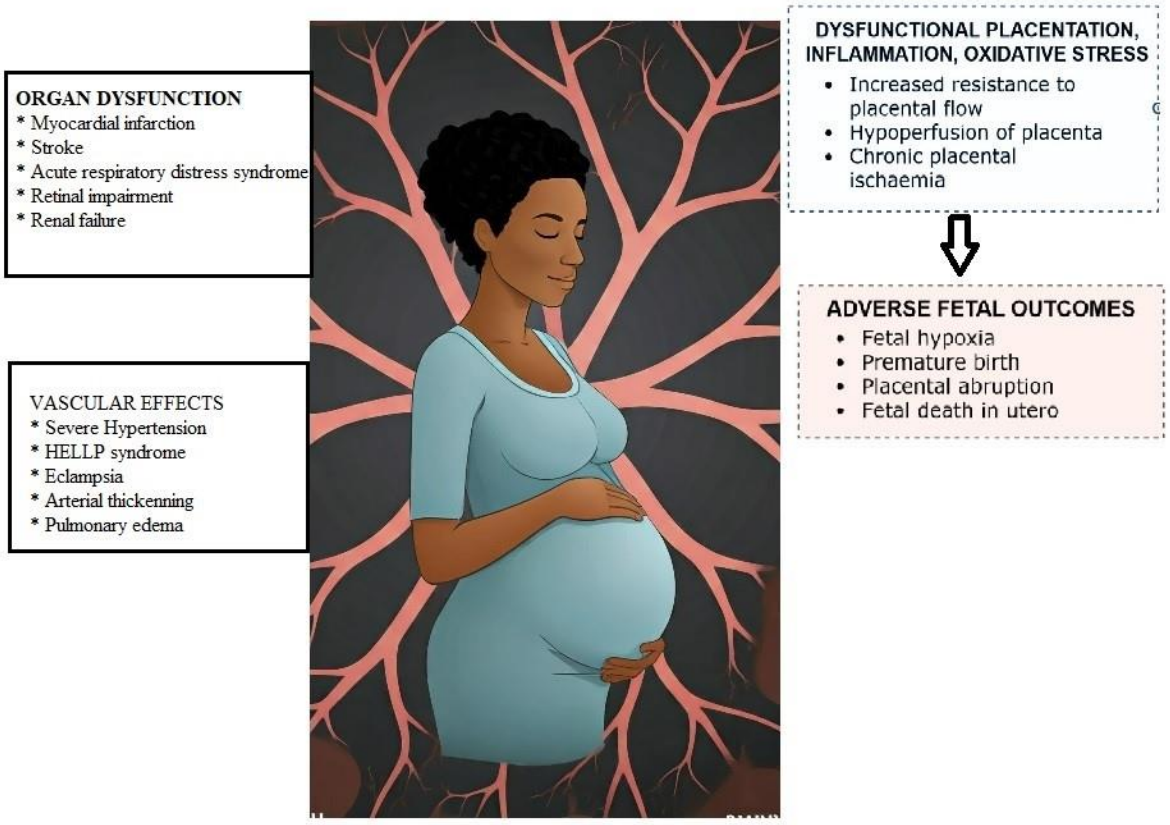

Figure1. Effects of preeclampsia on the fetus and mother

2. METHODS

Search method and data sources:

Based on pathophysiological observations that have been noted in cases of preeclampsia, such as placental dysfunction, generalized inflammatory response, endothelial dysfunction, and activation of the coagulation system, various biophysical and biochemical markers have been studied for many years.

Electronic databases such as PubMed, Medline, and Elsevier were used for the literature search regarding the role of biological markers in predicting preeclampsia from January 2014 to March 2024.

Biomarkers

With advancements in understanding the pathophysiology of preeclampsia, various tests have been designed to assess maternal levels of biochemical markers. These assays may also contribute to improving diagnostic accuracy and clinical outcomes.

This review explains the role of Placental Growth Factor (PlGF), Pregnancy-associated plasma protein 1 (PAPP-A) and soluble Fms-Like Tyrosine Kinase-1 (sFlt1) as biomarkers in predicting Preeclampsia.

Placental growth factor (PlGF):

A member of the vascular endothelial growth factor (VEGF) family, placental growth factor is primarily expressed in the placenta; however, it is also found in many other tissues, such as the heart, lung, thyroid gland, liver, skeletal muscle and bone at lower levels. Four isoforms of PlGF are encoded by the human PlGF gene, which is found on chromosome 14q14. The protein is secreted as a glycosylated homodimer, with PlGF-2 and PlGF-4 containing heparin-binding domains, while PlGF-1 and PlGF-3 function as diffusible isoforms. Among them, PlGF-1 and PlGF-2 are most abundant, and their secretion during pregnancy indicates a shared regulatory mechanism. During pregnancy, markedly increased levels of circulating PlGF are secreted by the placenta and PlGF contributes to the growth and maturation of the placental vascular system (19, 20).

Serum levels of PIGF increase at the end of the first trimester, peak at 30th week, and decrease in the third trimester. In an uncomplicated pregnancy, PlGF concentrations are low during the first trimester, rise from 11 to 12 weeks, reach high levels at 30th week and decline after that. The lower limit of the normal level (the 5th centile) ranges from a peak of around 141 pg/ml at about 30th weeks gestation to 23 pg/ml at term. Normal PlGF concentrations depend on gestational age (21).

Lower levels of serum and urine PlGF were observed in women at the time of diagnosis of preeclampsia and well before the onset of the illness. Declined PlGF level is likely due to reduced PlGF expression and a decrease in free PlGF, which causes elevated levels of sFLT-1 observed in affected women. (22). Both the anomalous early events in placentation and the ongoing abnormal growth in the second part of pregnancy are most likely caused by low circulating PlGF levels. Low PIGF levels in early pregnancy could be the reason for the underweight babies born to women without pre-eclampsia which highlights that decreased PIGF concentration is a sign of aberrant placentation (23). PlGF levels were significantly decreased in preeclampsia compared to normal pregnant women (20, 24, 25, and 26).

Pregnancy-associated plasma protein 1 (PAPP-A)

PAPP-A, also known as papalysin-1, is a 200 KDa, 1547 amino acid glycoprotein that is produced by placental trophoblasts and released into the mother's circulation (27). PAPP-A is important for placental and fetal growth and interacts with insulin-like growth factors. PAPP-A is a zinc-binding proteinase that participates in the proteolytic cleavage of the insulin-like growth factor binding protein (IGFBP). This process ultimately controls the local action of insulin-like growth factor (IGF), an enzyme that promotes growth and is crucial for the development of the fetus and the placenta. PAPP-A plays a crucial role in growth and development, folliculogenesis, wound healing, bone remodeling, and the elevated level is associated with atherosclerosis & accumulation of peak bone mass during puberty. (28-30).

Decreased plasma levels of PAPP-A have been reported in all trimesters in women with preeclampsia.

Studies have shown that PAPP-A levels have high predictive value in early pregnancy in the first trimester. Several lines of evidence report PAPP-A levels were significantly reduced in pre-eclamptic women. (31-35)

These findings suggest the usefulness of both PlGF & PAPP-A in predicting the risk of preeclampsia. Thus a combination of antiangiogenic and angiogenic biomarkers could be the most effective method for diagnosing preeclampsia.

Soluble fms-like tyrosine kinase-1 (sFlt): It is an antiangiogenic tyrosine kinase protein that binds PlGF and vascular endothelial growth factor (VEGF) and blocks their pro-angiogenic effects; it is mainly produced by placental tissue (36). By binding and preventing VEGF and placental growth factor from interacting with their receptors Flt1 and Flk1, the soluble receptor known as soluble fms-like tyrosine kinase (sFlt1) functions as an antagonist of these growth factors. Additionally, they showed that the levels of sFlt1 in the blood were noticeably higher during pregnancy and considerably higher during preeclampsia. Moreover, animals that overexpressed this receptor had a condition resembling preeclampsia (37). Later, it was discovered that sFlt1 was elevated weeks prior to clinically detectable preeclampsia, thus indicating the pathophysiological involvement of sFlt1 as a predictor of preeclampsia (38).

Researchers have stated that sFlt1 level is greater in preeclampsia (26, 41, 42) and a few other studies report that sFlt had a negative influence on preeclampsia (39, 40)

Table 1 shows the various serum biomarkers that can be used for early prediction of preeclampsia

Table 1: Serum biomarkers evaluated in the analysis for the prediction and diagnosis of preeclampsia

1. Placental growth factor (PlGF):		
Publishers and Year	MAJOR RESULTS	**Role in Preeclampsia Diagnosis**
• K. Chau et al. (2017).	PlGF may serve as a marker of abnormal placentation, although it remains uncertain whether it is a cause or consequence.	Lower levels of PlGF in the first trimester. Promising role of PlGF as a predictive marker for pre-eclampsia (20).
NICE Diagnostics Guidance [DG23], 2016	• NICE guidelines recommend PlGF-based testing for diagnosing suspected preeclampsia.	Used to rule out preeclampsia in women presenting with symptoms who do not meet the diagnostic criteria. Serum levels show a decline between 28 and 30 weeks of gestation (24).

Kumar et al. (2017).	• Used first-trimester PlGF concentrations to predict hypertensive disorders in a low-risk Asian population.	PlGF concentration, combined with biochemical markers, serves as an effective screening test for preeclampsia (PE) during the first trimester(25).
Güngör et al. (2017)	• Explored the relationship between adipocytokines and angiogenesis factors, including PlGF, in untreated preeclampsia patients.	PlGF, P-selectin, and collagen-induced platelet aggregation were lower in affected individuals compared to healthy pregnant women. In preeclampsia, decreased angiogenesis may alleviate endothelial dysfunction, but not platelet aggregation (26).
• Widmer et al. (2015)	A multicenter study found that angiogenic biomarkers, including PlGF, measured at 20 weeks gestation can help to predict the risk of preeclampsia.	Both the angiogenic and anti-angiogenic biomarkers could not predict the risk of preeclampsia development at ⩽20 weeks of gestation (43).
2. <u>Pregnancy-associated plasma protein 1 (PAPP-A)</u>		
Amélie Boutin et al. (2021)	The study found that first-trimester screening using angiogenic biomarkers, including PlGF, can effectively predict the risk of preterm preeclampsia in nulliparous women.	Low serum levels of **PAPP-A is** seen in pre-eclampsia. Pregnancy-associated plasma protein A levels correlated with pregnancy complications in the first trimester (31).
J. Hu et al. (2021)	The triple-marker model incorporating MAP (Mean Arterial Pressure), UtA-PI (Uterine Artery Pulsatility Index), and PAPP-A demonstrated detection rates of 65.0%, 72.7%, and 76.1% for preterm preeclampsia at fixed false-positive rates of 10%, 15%, and 20%, respectively.	Women screened positive for preterm PE had increased risk for other placenta-associated pregnancy complications (32).
T.J. Hanchard et al. (2020)	The mean multiples of the median (MoM) values for trophoblast volume, PAPP-A, and PlGF were significantly lower in pregnancies that later developed maternal hypertensive disorders (MHD).	Patients who develop preeclampsia tend to have lower levels of PAPP-A (33).
Karuna Sharma et al. (2018)	Low PAPP-A levels may be associated with impaired implantation, while increased proinflammatory cytokines suggest a role for underlying inflammation in the pathophysiology of hypertensive disorders in pregnancy. Combining biomarkers may enhance the prediction of pregnancy hypertension in the early stages of gestation.	Hypertensive women exhibited significantly lower maternal serum PAPP-A levels compared to normotensive mothers (34).
Manisha Kumar et al. (2017)	PlGF levels, combined with biochemical markers, provided an effective first-trimester screening test for hypertensive disorders of pregnancy (HDP)	As a biomarker for prediction of PE, PlGF fared better than pregnancy-associated plasma protein A (PAPP-A) (35)
3. Soluble fms-like tyrosine kinase-1.		
Chaiyasit et al. (2022)	Evaluated prediction models and emphasized the role of serum sFlt-1 (soluble fms-like tyrosine kinase-1) to	No significant differences were found in the maternal serum sFlt-1 levels at 11-13 weeks of gestation between women who

	PlGF ratio in predicting preeclampsia.	subsequently developed preeclampsia and those who did not (39).
I Herraizet al. (2018)	A contingent technique enables accurate prediction of PE/FGR (Fetal Growth Restriction) by measuring the sFlt-1/PlGF ratio at 24–28 weeks in women who were preselected based on clinical criteria and uterine artery Doppler imaging.	The study demonstrated that the sFlt-1/PlGF ratio is a valuable tool for identifying preeclampsia and fetal growth restriction, aiding in early risk stratification and clinical decision-making (40).
Tobinaga et al. (2014)	Investigated angiogenic factors and uterine Doppler velocimetry in early- and late-onset preeclampsia.	Serum levels of soluble endoglin and fms-like tyrosine kinase-1 are higher in preeclamptic patients, and this elevation was directly associated with uterine artery resistance, particularly in those with early-onset preeclampsia (41).
M C Honigberg et al. (2015)	Observed the changes in maternal angiogenic factors throughout pregnancy to predict the development of preeclampsia	sFlt-1 during pregnancy can be used to identify women who are more likely to develop preeclampsia (42).
Güngör et al. (2017)	Explored the relationship between adipocytokines and angiogenesis factors, including PlGF, in untreated preeclampsia patients.	Endoglin, leptin, and vWF levels were increased in preeclampsia. Endoglin also correlated with sflt-1 in preeclamptic patients. In preeclampsia, decreased angiogenesis may alleviate endothelial dysfunction, but not platelet aggregation (26).

3. CONCLUSION

Preeclampsia is a complex condition; is a multifactorial pregnancy complication characterized by high blood pressure, proteinuria, and potential damage to organs such as the liver and kidneys. It typically arises after 20 weeks of gestation and is associated with placental dysfunction, which can lead to Fetal Growth Restriction (FGR) and other complications.

According to the current research, three biomarkers—PlGF, PAPP-A, and sFlt1—were found to be sensitive enough to either detect or rule out PE, when compared a range of biomarkers used in clinical settings to diagnose the condition. To accurately assess the predictive value of these markers and ensure their routine clinical application, it is essential to conduct high-quality, large-scale multicenter trials. These studies should include patients with diverse risk profiles for developing the syndrome and represent a wide range of ethnic backgrounds to enhance the generalizability and reliability of findings.

REFERENCES

[1] Fox R, Kitt J, Leeson P, Aye CYL, Lewandowski AJ. Preeclampsia: risk factors, diagnosis, management, and the cardiovascular impact on the offspring. J Clin Med. 2019 Oct 4;8(10):1625. doi: 10.3390/jcm8101625. PMID: 31590294; PMCID: PMC6832549.

[2] Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. BMJ. 2013;347:f6564.

[3] Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension. 2018;72(1):24-43.

[4] Malik A, Jee B, Gupta SK. Preeclampsia: disease biology and burden, its management strategies with reference to India. Pregnancy Hypertens. 2019;15:23-31.

[5] Raymond D, Peterson E. A critical review of early-onset and late-onset preeclampsia. Obstet Gynecol Surv. 2011;66(8):497-506.

[6] ICD-10-CM codes: pre-eclampsia, 2018/19. Available from: https://www.icd10data.com/ICD10CM/Codes/O00-O9A/O10-O16/O14.

[7] De Kat AC, Hirst J, Woodward M, Kennedy S, Peters SA. Prediction models for preeclampsia: a systematic review. Pregnancy Hypertens. 2019;16:48-66.

[8] Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennstrom M, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med. 2016;374(1):13-22.

[9] ACOG Practice Bulletin No. 202: gestational hypertension and preeclampsia. Obstet Gynecol. 2019;133(1):1.

[10] Cornelius DC. Preeclampsia: from inflammation to immunoregulation. Clin Med Insights Blood Disord. 2018;11. doi:10.1177/1179545X17752325.

[11] Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. BMJ. 2019;366:l2381.

[12] Rybak-Krzyszkowska M, Staniczek J, Kondracka A, et al. From biomarkers to the molecular mechanism of preeclampsia – a comprehensive literature review. Int J Mol Sci. 2023;24(17):13252.

[13] Pijnenborg R. The placental bed. Hypertens Pregnancy. 1996;15(1):7-23.

[14] Pijnenborg R. Trophoblast invasion and placentation in the human: morphological aspects. In: Trophoblast invasion and endometrial receptivity. Springer US; 1990. p. 33-47.

[15] Strickland S, Richards WG. Invasion of the trophoblasts. Cell. 1992;71(3):355-357.

[16] Khong TY, Sawyer IH, Heryet AR. An immunohistologic study of endothelialization of uteroplacental vessels in human pregnancy – evidence that endothelium is focally disrupted by trophoblast in preeclampsia. Am J Obstet Gynecol. 1992;167(3):751-756.

[17] Lam C, Lim KH, Karumanchi SA. Circulating angiogenic factors in the pathogenesis and prediction of preeclampsia. Hypertension. 2005;46(5):1077-1085.

[18] Fox R, Kitt J, Leeson P, Aye CYL, Lewandowski AJ. Preeclampsia: risk factors, diagnosis, management, and the cardiovascular impact on the offspring. J Clin Med. 2019 Oct 4;8(10):1625. doi: 10.3390/jcm8101625. PMID: 31590294; PMCID: PMC6832549.

[19] LeGallo R. Placental vasculogenesis/angiogenesis. In: McManus LM, Mitchell RN, editors. Pathobiology of human disease. San Diego: Academic Press; 2014. p. 2342-2351.

[20] Chau K, Hennessy A, Makris A. Placental growth factor and pre-eclampsia. J Hum Hypertens. 2017;31(12):782-786.

[21] Saffer C, Olson G, Boggess KA, Beyerlein R, Eubank C, Sibai BM. Determination of placental growth factor (PlGF) levels in healthy pregnant women without signs or symptoms of preeclampsia. Pregnancy Hypertens. 2013;3(2):124-132.

[22] Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 2004;350(7):672-683.

[23] Poon LC, Zaragoza E, Akolekar R, Anagnostopoulos E, Nicolaides KH. Maternal serum placental growth factor (PlGF) in small for gestational age pregnancy at 11(+0) to 13(+6) weeks of gestation. Prenat Diagn. 2008;28(12):1110-1115.

[24] National Institute for Health and Care Excellence (NICE). PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 Test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGFPlusKryptor PE Ratio). Diagnostics Guidance [DG23]. 2016.

[25] Kumar M, Singh A, Sharma K, Singh R, Bhattacharjee J, Singh S. Use of first-trimester placenta growth factor concentration to predict hypertensive disorders of pregnancy in a low-risk Asian population. Int J Obstet Gynecol. 2017;139(3):301-306.

[26] Gungor ZB, Ekmekci H, Tuten A, Toprak S, Ayaz G, Caliskan O, et al. Is there any relationship between adipocytokines and angiogenesis factors to address endothelial dysfunction and platelet aggregation in untreated patients with preeclampsia? Arch Gynecol Obstet. 2017;296(3):495-502.

[27] Geno KA, Cervinski MA, Nerenz RD. Pregnancy and the fetus. In: Winter WE, Holmquist B, Sokoll LJ, Bertholf RL, editors. Handbook of Diagnostic Endocrinology. 3rd ed. Academic Press; 2021. p. 543-579.

[28] Gathiram P, Moodley J. Pre-eclampsia: its pathogenesis and pathophysiology. Cardiovasc J Afr. 2016;27:71-78.

[29] Kalousová M, Muravská A, Zima T. Pregnancy-associated plasma protein A (PAPP-A) and preeclampsia. Adv Clin Chem. 2014;63:169-209.

[30] Fruscalzo A, Cividino A, Rossetti E, Maurigh A, Londero AP, Driul L. First-trimester PAPP-A serum levels and long-term metabolic outcome of mothers and their offspring. Sci Rep. 2020;10:5131.

[31] Boutin A, Gasse C, Guerby P, Giguere Y, Tetu A, Bujold E. First-trimester preterm preeclampsia screening in nulliparous women: the great obstetrical syndrome (GOS) study. J Obstet Gynaecol Can. 2021;43(1):43-49.

[32] Hu J, Gao J, Liu J, Meng H, Hao N, Song Y, et al. Prospective evaluation of first-trimester screening strategy for preterm pre-eclampsia and its clinical applicability in China. Ultrasound Obstet Gynecol. 2021;58(4):529-539.

[33] Hanchard TJ, de Vries BS, Quinton AE, Sinosich M, Hyett JA. Ultrasound features prior to 11 weeks' gestation and first-trimester maternal factors in prediction of hypertensive disorders of pregnancy. Ultrasound Obstet Gynecol. 2020;55(5):629-636.

[34] Sharma K, Singh R, Bhattacharjee J, Kumar M, Gupta U, Rohil V. First-trimester inflammatory markers for risk evaluation of pregnancy hypertension. J Obstet Gynaecol India. 2018;68(1):27-32.

[35] Kumar M, Singh A, Sharma K, Singh R, Bhattacharjee J, Singh S. Use of first-trimester placenta growth factor concentration to predict hypertensive disorders of pregnancy in a low-risk Asian population. Int J Obstet Gynecol. 2017;139(3):301-306.

[36] Chen J, Khalil RA. Matrix metalloproteinases in normal pregnancy and preeclampsia. In: Khalil RA, editor. Prog Mol Biol Transl Sci. Academic Press; 2017. p. 87-165.

[37] Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest. 2003;111:649-658.

[38] Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 2004;350:672-683.

[39] Chaiyasit N, Sahota DS, Ma R, Choolani M, Wataganara T, Sim WS. Prospective evaluation of international prediction of pregnancy complications collaborative network models for prediction of preeclampsia: role of serum sFlt-1 at 11–13 weeks' gestation. Hypertension. 2022;79(2):314-322.

[40] Herraiz I, Simón E, Gómez-Arriaga PI, Quezada MS, García-Burguillo A, López-Jiménez EA, Galindo A. Clinical implementation of the sFlt-1/PlGF ratio to identify preeclampsia and fetal growth restriction: a prospective cohort study. Pregnancy Hypertens. 2018;13:279-285. doi: 10.1016/j.preghy.2018.06.017. PMID: 30177066.

[41] Tobinaga CM, Torloni MR, Gueuvoghlanian-Silva BY, Pendeloski KPT, Akita PA, Sass N, et al. Angiogenic factors and uterine Doppler velocimetry in early- and late-onset preeclampsia. Acta Obstet Gynecol Scand. 2014;93(5):469-476.

[42] Honigberg MC, Cantonwine DE, Thomas AM, Lim KH, Parry SI, McElrath TF. Analysis of changes in maternal circulating angiogenic factors throughout pregnancy for the prediction of preeclampsia. J Perinatol. 2016;36(3):172-177.

[43] Widmer M, Cuesta C, Khan KS, Conde-Agudelo A, Carroli G, Fusey S. Accuracy of angiogenic biomarkers at 20 weeks' gestation in predicting the risk of preeclampsia: a WHO multicentre study. Pregnancy Hypertens. 2015;5(4):330-338.