Biomarkers for Early Prediction and Management of Preeclampsia: A Comprehensive Review

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Preeclampsia is a common complication of pregnancy. It is a multi-organ disorder that remains one of the main causes of maternal morbidity and mortality. Additionally, preeclampsia leads to many complications that can occur in the fetus or newborn. Preeclampsia occurs in about 1 in 20 pregnant women. This review focuses on the prediction of preeclampsia in women, using various biomarkers, in particular, a factor combining the use of soluble FMS-like tyrosinokinase-1 (sFlt-1) and placental growth factor (PlGF). A low value of the sFlt-1/PlGF ratio rules out the occurrence of preeclampsia within 4 weeks of the test result, and its high value predicts the occurrence of preeclampsia within even 1 week. The review also highlights other factors, such as pregnancy-associated plasma protein A, placental protein 13, disintegrin and metalloprotease 12, β-human chorionic gonadotropin, inhibin-A, soluble endoglin, nitric oxide, and growth differentiation factor 15. Biomarker testing offers reliable and cost-effective screening methods for early detection, prognosis, and monitoring of preeclampsia. Early diagnosis in groups of women at high risk for preeclampsia allows for quick intervention, preventing the undesirable effects of preeclampsia. However, further research is needed to validate and optimize the use of biomarkers for more accurate prediction and diagnosis. This article aims to review the role of biomarkers, including the sFlt1/PlGF ratio, in the prognosis and management of preeclampsia.

Keywords: **Preeclampsia Eclampsia 2 • PGF Protein, Human • Biomarkers • FLT1 Protein, Human • Eclampsia**

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Introduction

Preeclampsia (PE) is a common complication in pregnancy. It is a multisystem disorder that continues to be one of the leading causes of maternal morbidity and mortality [1,2]. PE affects approximately 5% of all pregnant women. Annually, this disease causes up to 500 000 deaths among fetuses and newborns, as well as 46 000 maternal deaths, most of them in low-developed countries [3]. According to research, PE is one of the most common causes of death among pregnant women, second only to hemorrhage and sepsis, which have caused deaths in women in the early stages of pregnancy [4].

In addition to impacting morbidity and mortality in pregnant women and their babies, improving PE prediction has enormous health and financial implications. Treatment of PE generates huge costs in many highly developed countries, which is why various types of research are conducted to increase the chances of predicting, diagnosing, and treating this condition. There remains a medical need to improve the accuracy of PE prediction and diagnosis, and to increase the ability to detect adverse outcomes later in pregnancy. Centers still use diagnostic tests for PE based on doctors' observations and tests, such as laboratory parameters, biomarkers, and ultrasound results [1].

The characteristic symptoms of PE are proteinuria and hypertension appearing after week 20 of pregnancy. PE affects many organ systems, such as the respiratory, hepatic, urinary, neuroendocrine and circulatory systems, leading to fetal growth restriction, preterm birth, and other adverse effects on the fetus [5]. After many years of using standard symptoms in the diagnosis of PE, which was then the "criterion standard", it was found that this method had significant drawbacks. These diagnostic criteria had very low positive predictive value. Additionally, they predicted unfavorable outcomes related to PE in only 20% to 30% of effected pregnancies [6]. Currently, the latest definition of PE has evolved from the classic triad of symptoms, namely hypertension, proteinuria, and edema, to hypertension and organ dysfunction. As a result, many international and national guidelines have changed. The American College of Obstetricians and Gynecologists (ACOG) was the first to relativize the role of proteinuria and stated that PE can be diagnosed in the absence of proteinuria [7].

Gestational hypertension is the most common disorder occurring in hypertensive pregnancy and is defined by the first appearance of hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) at 20 weeks or later of gestation, in the absence of new signs of organ dysfunction or proteinuria [8].

However, the ACOG definition still does not highlight all symptoms that can be a consequence of PE. ACOG does not consider the consequences of an inefficiently functioning placenta, and therefore, also intrauterinal fetal growth restriction. The definition of PE was updated in 2018 by the International Society for the Study of Hypertension in Pregnancy (ISSHP). According to this definition, PE is a new onset of hypertension in association with peripheral organ symptoms, such as liver dysfunction, hemolysis, thrombocytopenia, or fetal growth restriction [9].

The poor prognosis associated with PE includes many complications in both the mother and fetus. These can include maternal and/or fetal death, as well as specific peripheral organ damage, such as acute renal failure, pulmonary edema, eclampsia, and HELLP (hemolysis, elevated liver enzyme levels, and low platelet levels) syndrome. The fetus can have prematurity and its complications, such as necrotizing enterocolitis, intraventricular hemorrhage, and growing too small for gestational age. While most are late-onset cases after 34 weeks of gestation, women with early-onset disease have a higher incidence of adverse maternal and fetal outcomes [10]. It is believed that the symptoms of PE do not appear earlier than week 20 of pregnancy; however, the molecular pathways involved in the pathogenesis of the syndrome appear quite early in pregnancy [11]. The etiology of PE is still not precisely defined. Evidence suggests that the complexity of the pathophysiology and etiology of PE differs between early- and late-onset PE. PE detected before week 34 of pregnancy, known as early PE, is believed to be caused by placental disfunction. However, in the case of late-onset PE, namely symptoms that appear after week 34 of pregnancy, cardiovascular dysfunction is considered to be the cause [12].

This article aims to review the role of biomarkers, including the soluble FMS-like tyrosine kinase 1 and placental growth factor (sFlt1/PlGF) ratio, in the prognosis and management of PE.

PE Frequency and Diagnosis

PE is a complication in 2% to 8% of pregnancies worldwide and contributes to 9% to 26% of deaths among pregnant women. Diagnosis is based on the new onset of persistent high blood pressure (greater than 140 mmHg systolic blood pressure or greater than 90 mmHg diastolic blood pressure within 4 h), which must be diagnosed after the 20th week of pregnancy. Other important factors are the appearance of proteinuria, symptoms of internal organ dysfunction, headache that does not respond to analgesic treatment, pulmonary edema, or renal dysfunction, with abnormal laboratory test values [13].

Pathogenesis of PE

An important factor in a properly developing pregnancy is properly functioning blood flow through the placenta. In pregnant

women, as a result of the invasion of placental trophoblasts, the uterine spiral arteries are rebuilt, which causes them to widen and reduce resistance. In PE, the arteries are not completely remodeled, which means there is insufficient perfusion in the placenta. As a result of these abnormalities, placental cells secrete numerous biochemical factors into the pregnant woman's bloodstream that influence endothelial dysfunction, stimulation of the mother's immune response, oxidative stress, and activation of coagulation pathways. These changes lead to hypertension, proteinuria, and dysfunction of internal organs [14,15].

The process of extravillous cytotrophoblast invasion into the spiral arteries takes place between weeks 13 and 18 of pregnancy. The consequence of this phase of trophoblast invasion into the spiral arteries is the loss of endothelium and most of the muscle-elastic fibers. The size of the spiral arteries increases and, at the same time, they become insensitive to vasoactive drugs. These modifications improve blood flow through the uterus. The endothelium, internal elastic membrane, and muscular layer are replaced by the trophoblast. These changes concern the spiral arteries in their temporal part and in their part running within two-thirds of the thickness of the uterine muscle. The diameter of the spiral arteries increases 4 to 6 times, compared with the state before pregnancy. Because the autonomic innervation is destroyed, there is a loss of

sensitivity to vasoactive substances. Then, the vascular endothelium layer is recreated. Dilated uteroplacental arteries are formed, ensuring sufficient perfusion of the intervillous space. These physiological changes create a low-pressure, high-flow uteroplacental circulatory system. This process is completed between weeks18 and 22 of pregnancy [16-18].

When it comes to a pregnancy complicated by PE, cytotrophoblast invasion of the spiral arteries is limited to their intradermal part, excluding the part running inside the uterine muscle. Spiral arteries that have not undergone the complete spectrum of changes are much narrower. Their diameter is less than half the diameter of these vessels in a normal pregnancy. The number of spiral arteries into which the trophoblast enters is reduced. These changes cause a reduction in uteroplacental blood flow in pregnancy complicated by preeclampsia [19,20]. The above changes are schematically presented in **Figure 1**, and the stages of PE pathogenesis are shown in **Figure 2**.

PE Risk Factors

A huge number of multi-center studies have been conducted including pregnant patients, in which attempts have been made to distinguish various factors contributing to the more frequent occurrence of PE.
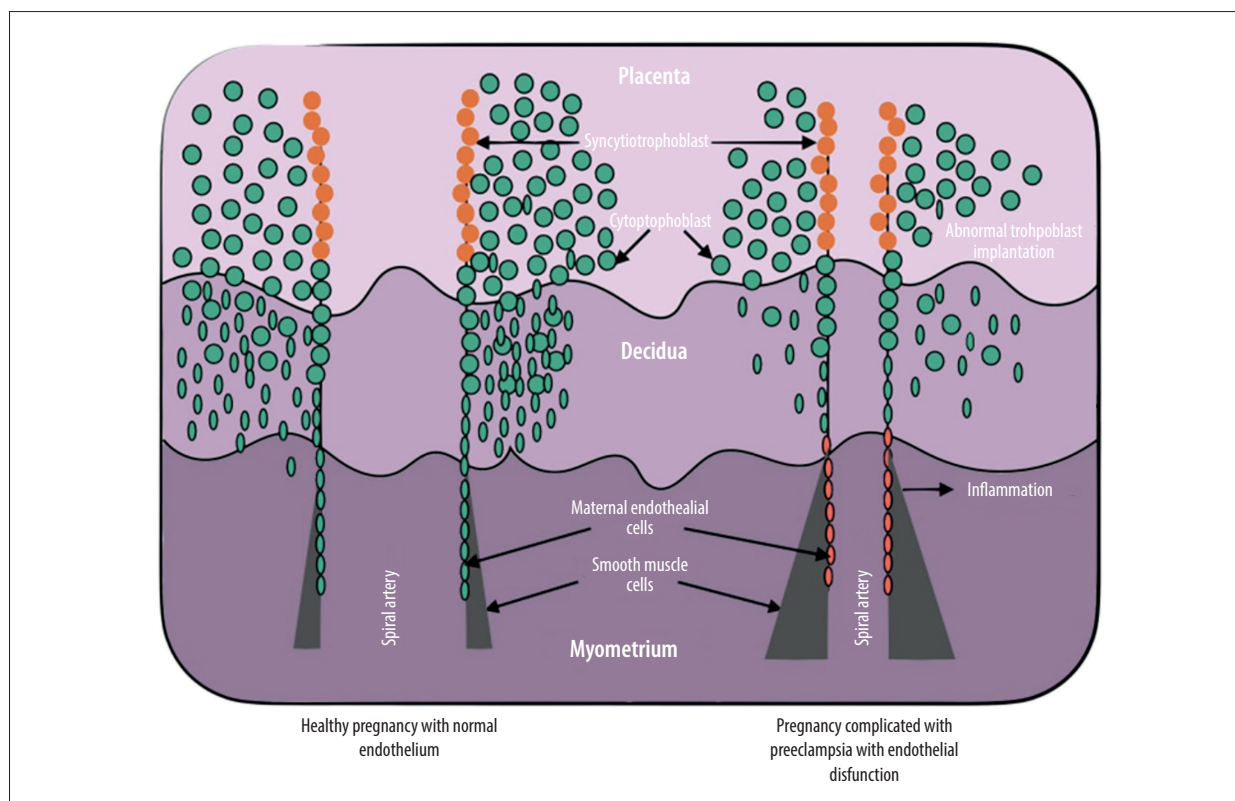

Figure 1. Comparison of changes occurring in pregnancy without preeclampsia and in pregnancy with preeclampsia.

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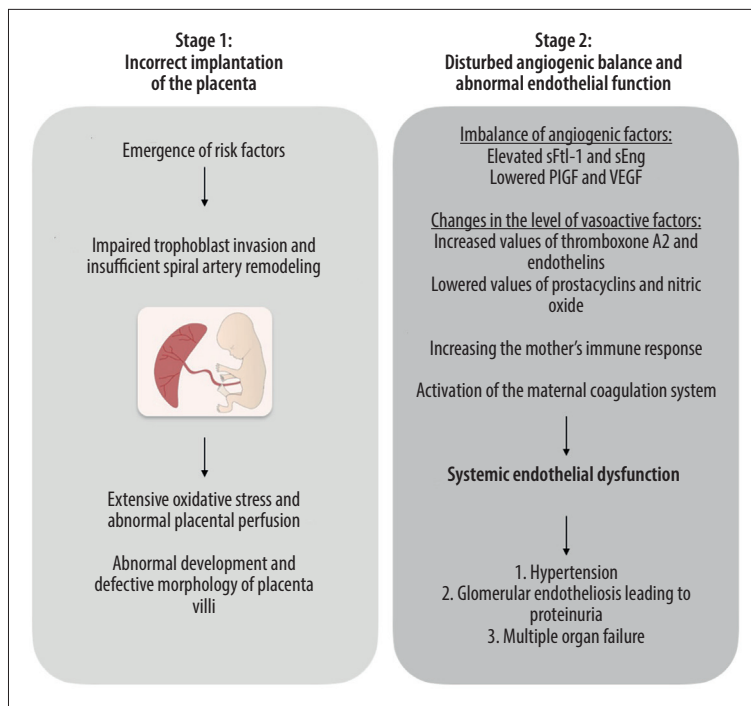
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Figure 2. Stages of preeclampsia pathogenesis [14].

PE risk factors can be divided into several groups: demographic factors and family history, medical or obstetric history, conditions occurring in the first trimester of pregnancy, and conditions occurring in the second trimester [10] (**Table 1**).

Therapeutic Management in PE

The basis of treatment when diagnosing PE is the control of blood pressure using antihypertensive drugs, which can be used in pregnant women. The condition of the fetus should be constantly monitored using ultrasound and cardiotocography. However, the only treatment for PE is to end the pregnancy as soon as possible. Absolute termination of pregnancy is recommended in patients after 37 weeks of pregnancy with moderate PE and after 34 weeks of pregnancy in patients with severe PE (after administration of fetal steroid therapy). Additionally, intravenous administration of magnesium sulfate is used to prevent eclamptic seizures [13].

Complications of PE

Failure to treat PE can result in severe hypertension, HELLP syndrome, eclampsia, pulmonary edema, myocardial infarction, stroke, acute respiratory distress syndrome, retinal damage, and renal failure. Disorders can also occur in the fetus, including the possibility of intrauterine inhibition of fetal growth or premature separation of a properly implanted placenta. There is also a risk of death for the mother and fetus [13].

Role of the sFlt-1/PlGF Ratio

Over the last 20 years, there has been an increase in the number of screening tests being performed and in the predictability of the occurrence of PE in women of high-risk groups. Angiogenic biomarkers may exclude conditions that can mimic PE and have overlapping symptoms [26,27]. Recently, screening biomarkers have been introduced into diagnostics. One of them is the sFlt-1/PlGF ratio, which is a promising contribution in the prediction and management of PE [1]. Studies have shown that the use of the sFlt-1/PlGF ratio has greater diagnostic significance than the use of each biomarker separately [26]. However, each component of the coefficient used should be mentioned.

PlGF is a glycosylated dimeric protein that is important in placental angiogenesis in early pregnancy and stimulates the growth, differentiation, and invasion of trophoblasts into the maternal decidua [28]. In addition to its location in the placenta, this biomarker can be found in skeletal muscle, heart, lung, thyroid, and endothelial cells. It increases in ischemic states, inducing the maturation and stabilization of newly formed blood vessels, and mobilizes inflammatory, vascular, and hematopoietic progenitor cells of the bone marrow participating in the formation of collateral vessels [29]. Its concentration is significantly increased during the beginning of pregnancy; the greatest increase occurs in week 30 of pregnancy, and then it slowly decreases [30]. PlGF has a strong correlation with the partial pressure of oxygen; therefore, its level is reduced in placental hypoxia. This explains why PlGF levels are depleted in women with PE [16].

Table 1. Summary of preeclampsia risk factors [20-25].

Group of factors	Factor
Demographic and family factors	Maternal age 40 years or older
	Preeclampsia (PE) in the family (mother or sister)
	Early occurrence of cardiovascular diseases in the family
Medical history	PE in previous pregnancies
	Antiphospholipid syndrome
	Hypertension before pregnancy
	Kidney disease before pregnancy or proteinuria at the first visit
	Diabetes before pregnancy
	Low maternal birth weight or premature birth
	Congenital thrombophilias
	Elevated triglyceride values
	Using cocaine and methamphetamines
	History of pregnancy loss before 10 weeks
Current pregnancy – 1st trimester	Multiple pregnancy
	New partner
	Use of assisted reproductive techniques
	Long interval between pregnancies (more than 10 years)
	Systolic blood pressure of 130 mmHg or higher and diastolic blood pressure of 80 mmHg or higher at the first visit
	Bleeding from the genital tract in early pregnancy
	Pregnancy trophoblastic disease
	Abnormal biomarker values
Current pregnancy – 2nd and 3rd trimester	Increased blood pressure
	Abnormal values of alpha fetoprotein, chorionic gonadotropin, inhibin-A, estrogens
	Excessive weight gain during pregnancy
	Infections complicating pregnancy
	Intrauterine fetal growth restriction
	Abnormal Doppler result of uterine arteries
	Abnormal biomarker values

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sFlt-1 is an anti-angiogenic protein that binds to and inhibits proteins, such as PlGF and vascular endothelial growth factor (VEGF), thereby causing endothelial dysfunction [31,32]. sFlt-1 is one of the isoforms of the glycosylated sFlt protein [33]. The main source of sFlt-1 is the placenta of the pregnant woman. Studies have found that sFlt-1 concentrations are highly elevated in the circulation of women with PE, and this elevated concentration existed before the development of other symptoms of PE, such as proteinuria and hypertension [16]. Studies indicate that increased sFlt-1 values occur even before the appearance of proteinuria and hypertension [33]. In women with PE, the concentration of this protein can reach values 5 times higher than those found in women without suspicion of PE [28].

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Attention was first paid to the sFlt-1/PlGF ratio in 2003 and 2004. It was then shown that women with PE had an increased sFlt-1 value and a decreased PlGF value. It has also been proved that the more dysregulated the placental expression and circulating concentration in peripheral blood, the more severe the disease [34,35]. The identification of the sFlt-1/PlGF ratio led to the rapid automation of tests examining the use of the ratio to improve the prediction and diagnosis of PE [36,37].

In 2016, a multicenter study was conducted to assess whether a low value of the sFlt-1/PlGF ratio could predict the absence of PE within a week of the test result and whether a high value could predict the occurrence of PE within the next 4 weeks. Five hundred pregnant women were examined, using a cut-off value of 38 [26,38]. It was found that a value of 38 and lower could be used to predict the short-term absence of PE in women in whom this syndrome was clinically suspected. According to this study, the negative predictive value of a coefficient at the cut-off point or below was 99.3%. The ability to accurately rule out PE within 1 week based on the sFlt-1/PlGF ratio can improve clinical decisions regarding hospitalization, compared with outpatient monitoring and the intensity of ambulatory monitoring [26,39]. A very high negative predictive value is crucial in the evaluation of a patient with suspected PE, because failure to detect this disease can have serious consequences for the fetus and mother [25]. Multiple clinical studies have shown that the sFlt-1/PlGF ratio demonstrated better diagnostic performance than did single biomarkers [26,37,40]. One study extends the recommendations by prospectively validating the sFlt-1/PlGF ratio cut-off of 38 by calculating it using available and fully automated immunoassays [26].

A study conducted in 2016 by Zeiser et al showed that time to delivery is significantly correlated with sFlt-1/PlGF ratio levels, regardless of the presence of features of PE defined by hypertension and proteinuria [41].

According to a study conducted in 2019, an sFlt-1/PlGF ratio higher than 85 can be a predictive marker for the early onset of PE and possible adverse outcomes in the mother and fetus. However, an sFlt-1/PlGF ratio lower than 38 in women between 24 and 37 weeks of pregnancy can be a reliable parameter to rule out PE [31].

In 2021, a study called ROBUS aimed to determine the usefulness of outpatient biomarkers in the treatment of hypertensive pregnancies in the third trimester. It was a cohort study of 50 women, 48% of whom had chronic hypertension, and 52% of patients had hypertension for the first time during pregnancy. Pregnant patients with a high sFlt-1/PlGF ratio were more likely to experience PE with severe symptoms, higher rates of maternal complications, and preterm birth, whereas women

with a low sFlt-1/PlGF ratio were able to carry the pregnancy to term, with close supervision [42].

Studies of pregnant women that focused on how to best use the sFlt-1/PlGF ratio to identify women at risk for PE who were at risk for adverse complications have focused on the interpretation of single test results. Retesting has been shown to add predictive accuracy. An analysis was performed of 550 women whose cut-off value was below 38, and the onset of PE was excluded in 1-time testing 2 and 3 weeks after the examination, with high negative predictive values of 97.9% and 95.7%, respectively. In case of retesting, onset of PE within 4 weeks was excluded, with high negative predictive values (94.3%) and high sensitivity (66.2%) and specificity (83.1%). According to this study, repeated sFlt-1/PlGF ratio testing in women suspected of having PE should increase confidence in clinicians' decision making [43].

In 2021, a study was conducted in Spain to determine whether longitudinal changes in angiogenic factors improve the prediction of adverse outcomes in women with early onset of severe PE; 63 pregnant women were examined, 26 of whom had complications. Longitudinal changes in biomarkers were shown to be more pronounced in pregnancies with complications than in pregnancies without complications. The above study demonstrated that in early-onset severe PE, longitudinal changes in sFlt-1 levels improve the prediction of adverse outcomes and the interval to delivery [44].

One study compared the sFlt-1/PlGF ratio to traffic light signaling, including 3 groups: a green light, yellow light, and red light group. The green light group consisted of women with ratio value below 38 – those in whom there was a high degree of certainty that no PE or related complications would occur within 4 weeks. The yellow light group consisted of women with suspected PE and sFlt-1/PlGF values between 38 and 85, who were at increased risk of PE and related complications within the next 4 weeks, and for whom it was recommended to repeat the test after a week. The red light group consisted of women with suspected PE and sFlt-1/PlGF ratio values above 85, in whom this phenomenon was expected to occur in the near future. For women in the green group, follow-up was recommended within the next 4 weeks of the examination; for women in the yellow group, follow-up was recommended within a week of the examination. However, for the red group, with the possibility of PE symptoms and complications, immediate hospital control was recommended, if possible, in a perinatal center, and depending on the ultrasound examination, cardiotocography, and laboratory results, hospitalization could be indicated [45] (**Figure 3**). In the case of patients with an sFlt-1/PlGF ratio 85 and higher, the standard of care is admission to hospital and reassessment of parameters. If the results remain stable, the patient should continue
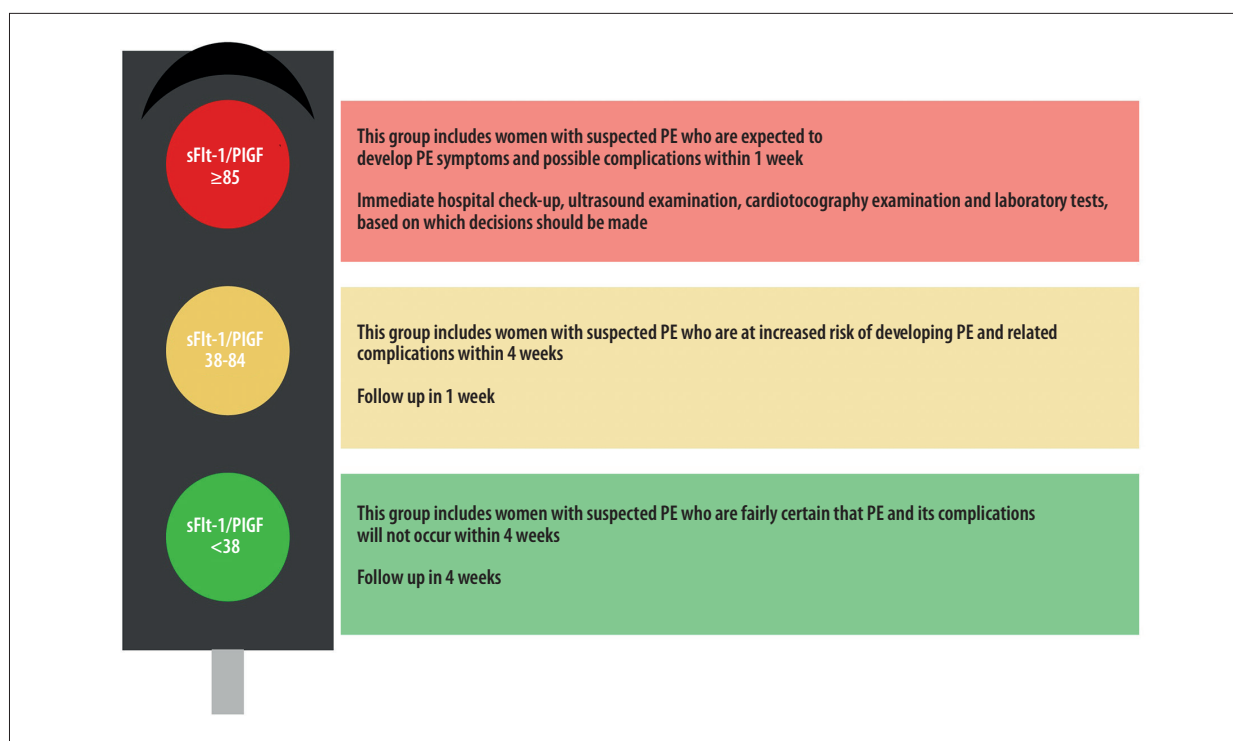
Figure 3. Interpretation of the soluble FMS-like tyrosinokinase-1/placental growth factor ratio and plan of action in case of different values of test results as a comparison to road signaling [1,45].

to be closely monitored. The vast majority of these patients develop symptoms of the disease or need to be continuously monitored. The sFlt-1/PlGF ratio is particularly useful between weeks 24 and 34 of pregnancy because it allows for better control and the ability to make decisions regarding further diagnostics and treatment [25,46].

In 2023, research was conducted on the usefulness of predicting the sFlt-1/PlGF ratio in detecting unfavorable pregnancy outcomes related to placental dysfunction in twin pregnancies. PE is twice as common in twin pregnancies. Additionally, it often occurs in more severe forms, and its onset usually occurs earlier than in singleton pregnancies. The majority of studies found an increased sFlt-1/PlGF ratio in twin pregnancies with PE or other adverse perinatal outcomes than in pregnancies without disease. This experience suggests that data from 3 prospective studies indicate that classical cut-offs used for singleton pregnancies can be transferable to twin pregnancies. One of the main goals of the studies was to define an effective cut-off value to exclude or diagnose PE in twin pregnancy patients. Most authors confirmed the existing cut-off values for singleton pregnancies of 38 and 85 from previous studies can be used in twin pregnancies. This finding should be considered as promising, because 80% of the published results show a positive predictive value [47]. Another study analyzed the results of 269 women with twin pregnancies. PE was suspected in 62 of these patients, and only 21 patients ultimately

developed PE. After analyzing the results of the sFlt-1/PlGF ratio test, it was found that up to week 29 of twin pregnancy, no differences were observed in the median, compared with that of singleton pregnancies. However, after week 29 of pregnancy, the median values of twin pregnancies were higher than those of women with singleton pregnancies [48].

The latest article on the sFlt-1/PlGF ratio proves that it is an additional and advanced diagnostic tool for PE, independent of blood pressure or laboratory markers related to HELLP syndrome, to identify pregnant patients who will develop PE or its severe form requiring premature birth. The study also confirmed the economic importance of using this coefficient, as it allows for reduced costs and shorter hospital stays for patients. According to the study, this will reduce the number of unjustified tests and even premature births, and will allow for a better focus on patients actually affected by PE [49].

Currently, there are no clear recommendations for the practical use of angiogenic biomarkers in the detection and treatment of PE in routine clinical practice. For some time now, the main international clinical guidelines have indicated the possibility of using specific biomarkers in cases of suspected PE, and most researchers follow this in their local practices. However, the guidelines do not specify the values of specific parameters [25].

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The conclusions resulting from these studies contributed to the initiation of the use of this coefficient in women with suspected PE.

Other Biomarkers Used to Predict PE in Pregnancy

Understanding the pathogenesis of PE has allowed for the development of many different biochemical tests, allowing for better and faster diagnosis [50].

One of the factors investigated when PE is suspected is the glycoprotein pregnancy-associated plasma protein-A (PAPP-A), a protein important for the development of the placenta and fetus, which is used as a predictive biomarker. PAPP-A is also involved in growth and development processes, such as bone remodeling during puberty, folliculogenesis, wound healing, and atherosclerosis. PAPP-A concentration is low in the first trimester of pregnancy and increases gradually until the third trimester of pregnancy. It is also a marker used in screening tests for chromosomal abnormalities. A 2018 study found that pregnancies with reduced PAPP-A protein levels were largely associated with an increased risk of early PE. It was also confirmed that reduced PAPP-A concentrations, with a cut-off of <10th percentile, could be used to predict PE [50]. It is now suggested that PAPP-A measurement along with other biochemical markers, maternal factors, and Doppler ultrasound can be used as an early marker for PE screening [51,52].

Another biomarker used to predict PE is placental protein 13 (PP-13), a protein synthesized by the syncytiotrophoblast. PP-13 plays a major role in the processes of maintaining pregnancy. Studies show that in the first trimester of pregnancy, PP-13 values are low, and its concentration increases with the duration of pregnancy. If PE is suspected, the value of this protein is lower than the expected norm [53,54]. According to a recent study, PP-13 has a specificity of 0.83 (95% CI) and a sensitivity of 0.53 (95% CI). The results of the study suggest that PP-13 can be considered a strong predictor of early-onset PE [55].

Research has also been conducted on the use of a-disintegrin and metalloprotease 12 (ADAM-12) in the prediction of PE, but the studies have not shown their significant importance in the prediction of PE. Moreover, even when several diagnostic methods were combined, ADAM-12 still had only a 44% detection rate [56,57].

Another molecule used in PE prediction is β-human chorionic gonadotropin (β-hCG), a hormone produced by placental trophoblasts. The serum concentration peaks around week 8 to 10 of pregnancy and then decreases [58]. Reduced β-hCG values in the early trimester of pregnancy indicate abnormal trophoblast function and are a marker of delayed implantation and impaired placental function. Its low concentration can contribute to the development of PE. There are studies indicating that low β-hCG levels <50 IU/L quadruple the risk of developing PE. However, one study also found that a single low β-hCG value may not serve as a strong biomarker for predicting the risk of PE [54]. It is said that the use of β-hCG as a biomarker to predict PE nevertheless shows a low detection rate with low sensitivity [58-60].

Tests for the prediction of PE also use the placental protein inhibin-A, a hormone involved in fetal growth and maintaining pregnancy. Its values peak twice during pregnancy, for the first time between week 8 and 10 of pregnancy, after which it stabilizes and then reaches another peak in the third trimester [15,61]. Existing research shows a relationship between high inhibin-A levels and the possibility of developing PE. Despite these suggestions, the sensitivity of inhibin-A as a strong predictive biomarker is considered to be low, so it is recommended to be used in combination with other measurements to obtain the best result [15,62].

For the prediction of PE, the test of one of the anti-angiogenic factors, soluble endoglin (sEng), was also introduced. There are reports that a high sEng value in women with PE correlates with disease severity. sEng expression was 4 times higher in women with PE than in women with a healthy pregnancy. Elevated sEng levels can be observed even before the onset of clinical symptoms. It has been proven that measuring sEng concentration can allow for early prediction and diagnosis of PE [63-65].

Additionally, research was conducted on the use of nitric oxide in the prediction of PE. Nitric oxide is a gaseous molecule that helps in the processes of angiogenesis, neovascularization, regulation of vascular tone, and regulation of systemic blood pressure. During pregnancy, nitric oxide acts as a modulator of angiogenic factors, such as VEGF, PlGF, and transforming growth factor β, which are the others biomarkers used in prediction of PE. However, there is still too little research on the use of nitric oxide in the prediction and diagnosis of PE for it to be widely used [15,66].

Finally, research has been conducted on the use of growth differentiation factor 15 (GDF-15) as a biomarker. GDF-15 is a peptide produced in the placenta that is secreted in response to stress and during cell damage and inflammation. GDF-15 has been found to have a cardioprotective function. GDF-15 values increase with the duration of pregnancy, and in the case of PE, they are dysregulated. In women with a pregnancy lasting 30 to 34 weeks, higher values were found in women with PE than in women without PE. Despite these observations, the values varied very little; therefore, the use of GDF-15 as a sole predictive marker is not recommended [67,68]. The biomarkers used in the prediction of PE are shown in **Table 2**.

Table 2. Biomarkers used in preeclampsia prediction [14,31,50-64].

Biomarker	A change from a healthy pregnancy
Soluble FMS-like tyrosinokinase-1 (sFlt-1)	Very elevated values in women with suspected preeclampsia (PE)
Placental growth factor (PlGF)	Decreased values in women with suspected PE
sFtl-1/PlGF ratio	A score higher than 85 may be a predictive marker for early onset of PE, and a score lower than 38 is highly likely to exclude PE
Pregnancy-associated plasma protein A (PAPP-A)	A decreased value indicates an increased risk of PE
Placental protein 13 (PP-13)	A value lower than the norm during certain periods of pregnancy most likely indicates PE
Disintegrin and metalloprotease 12 (ADAM-12)	Low diagnostic significance
β-human chorionic gonadotropin (β-hCG)	A reduced value may indicate the probability of PE, but its detection rate is too low
Inhibin-A	A high level of Inhibin-A can indicate the likelihood of developing PE, but the sensitivity is too low
Soluble endoglin (sEng)	An increased value can indicate PE; the value strongly correlates with the severity of the disease

Future Directions

Larger studies focusing on investigating the best biomarkers with better predictive values still need to be conducted. Due to the lack of a certain etiology of PE, research should also be conducted to fully understand the molecular mechanism of the disease and the importance of biomarkers in various processes. Thanks to further research on individual markers, these markers may in the future allow for faster detection and capture of groups at increased risk, as well as distinguishing early and late forms of PE.

Research is currently underway to predict PE in the early stages of pregnancy. One study combined patient clinical data, routine laboratory indicators, and biological markers to improve the clinical capacity for early diagnosis of PE [69].

A study from Paris investigated the use of the sFlt-1/PlGF ratio to improve perinatal care and reduce costs in patients with suspected PE before 35 weeks of pregnancy [70].

A study called PREMOM, being conducted since 2021, aims to investigate the use of molecular tests in the prediction of PE in women in the first trimester of pregnancy. Researchers assume that there is a unique molecular profile in peripheral blood specific to women who develop PE, which allows for early assessment of the risk of this pregnancy complication [71].

Many countries are conducting research on the introduction of new biomarkers. Currently, work is underway to use markers such as endocrine gland-derived VEGF and its receptors PROKR1 and PROKR2, aquaporin, fatty acids, or lncRNA, which are long, non-coding RNA molecules that negatively regulate gene expression. The above biomarkers seem to offer promising prospects in the context of PE [72-75].

It is hoped that conducting more new research will allow us to adopt certain assumptions and standards for better predicting, diagnosing, and monitoring PE.

Conclusions

The identification and treatment of patients at increased risk of PE is a rapidly changing field. Better prediction of PE and its associated adverse outcomes is still needed. Recently, many studies have been conducted on the introduction of angiogenic biomarkers into everyday clinical practice to better identify pregnant women at risk of PE and its effects and to enable faster and more reliable exclusion of the disease, despite the presence of clinical indications. Many centers have begun to use recently introduced criteria to define PE. The use of biomarkers is increasing and has the potential to improve care and reduce maternal and fetal morbidity and mortality.

Based on numerous studies, it can be safely concluded that the sFlt-1/PlGF ratio plays an important role in predicting the occurrence of PE in pregnant women. The sFlt-1/PlGF ratio showed better diagnostic performance than did single biomarkers. Literature analysis showed that the occurrence of PE significantly increased the level of sFlt-1 and significantly increased the level of the sFlt1/PlGF ratio. An sFlt-1/PlGF ratio

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≤38 has a high negative predictive value for excluding PE within 4 weeks of assessment, between 24 and 37 weeks of gestation. In turn, high sFlt-1/PlGF ratio values allow for the prediction of symptoms and possibly adverse effects of PE with high certainty.

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All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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