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Risk assessment of preeclampsia

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Abstract

Introduction and purpose:

Preeclampsia (PE) is a complication during pregnancy characterized by high blood pressure (≥140/90 mmHg) and signs of organ involvement appearing after 20 weeks' of gestation. Various factors are known to increase the risk of this condition as well as clinical factors. The pathogenesis of the disease is complex and not fully understood.

State of Knowledge:

The main roles play two angiogenic factors: soluble fms-like tyrosine kinase 1 (sFlt-1), which is an antiangiogenic protein, and placental growth factor (PlGF), which is a pro-angiogenic protein. Elevated sFlt-1 and reduced PlGF levels in the mother's blood can predict the future development of preeclampsia during pregnancy. The imbalance between these two angiogenic biomarkers indicates de new-onset preeclampsia, distinct from chronic hypertension. Both MAP and UTA-PI are essential components of first-trimester screening protocols, which, combined with maternal history and other biochemical markers, allow for accurate preeclampsia risk assessment and early intervention to improve maternal and fetal outcomes.

Conclusions:

Preeclampsia is a major cause of maternal and perinatal morbidity and mortality. The integration of multiple biomarkers, such as PlGF and sFlt-1, along with advanced analytical techniques, enhances early detection and accurate risk stratification, improving maternal and fetal outcomes. Aspirin prophylaxis before 16 weeks' gestation has been shown to reduce the risk of preeclampsia.

Introduction and purpose

Pregnancy is a comprehensive physiological challenge for a woman's body, requiring significant adaptations across multiple systems to support fetal development. A successful pregnancy outcome depends on these adaptations to meet increased metabolic demands. PE is a hypertensive disorder during pregnancy posing significant risks to maternal and fetal health, including eclampsia, HELLP syndrome, and preterm birth. Despite extensive research, the exact pathophysiology of preeclampsia remains poorly understood, making its prediction and prevention challenging. Early identification of high-risk women is crucial for timely interventions to improve pregnancy outcomes. Biomarkers are vital for early identification process, providing insights into the disease's mechanisms and aiding accurate risk stratification. This study aims to evaluate the current knowledge and future prospects of early preeclampsia risk identification through a detailed understanding of how early diagnosis and biomarker-based approaches can revolutionize the early diagnosis and its treatement.

Description of the state of kownledge

Definition of preeclampsia

According to World Health Organization (WHO) data, the incidence of preeclampsia is currently rising globally (1). Preeclampsia is characterized by new-onset hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) after 20 weeks of gestation, along with endothelial dysfunction leading to maternal organ dysfunction. Hypertension alone is often only useful when preeclampsia has already developed (2)(3). The condition may present with proteinuria, but the current diagnostic criteria do not require it if there are other severe systemic involvement signs such as renal insufficiency indicated by serum creatinine concentration >1 mg/dL or >1.1 mg/dL; liver dysfunction by transaminase levels elevated twofold over the reference range or ≥40 IU/L; hematological disorders by blood platelet levels <100,000/μL or <150,000/μL; haemolysis; neurological symptoms or fetal growth restriction (4-7). Recent scientific studies have showed that proteinuria, or the presence of protein in urine, is no longer a reliable predictor for the diagnosis of preeclampsia, as its presence does not consistently correlate with the disease's severity or outcomes. Some patients with severe preeclampsia may have minimal or no proteinuria, while others with significant proteinuria may not exhibit severe disease symptoms. It is important that the levels of protein in urine can be influenced by various factors such as hydration status, physical activity, and timing of sample collection. It reduces the reliability of proteinuria as a standalone diagnostic marker (8).

Patophysiology of preeclampsia

The pathophysiology of preeclampsia involves several interconnected mechanisms centered around placental dysfunction and maternal endothelial damage, such as abnormal placentation. Poor trophoblast invasion of the uterine spiral arteries leads to inadequate placental perfusion, resulting in hypoxia and oxidative stress within the placenta, resulting in hypoxia and oxidative stress within the placenta. which are key drivers of the disease. Placental cells respond by releasing harmful substances into the maternal circulation, contributing to systemic endothelial dysfunction. The systemic also release of antiangiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1), as well as proinflammatory cytokines and cell-free fetal DNA. This endothelial damage impairs the normal vasodilation of blood vessels, leading to hypertension and proteinuria. A significant imbalance between proangiogenic and antiangiogenic factors are crucial in patophysiology of preeclampsia. Elevated levels of sFlt-1 antagonize vascular endothelial growth factor (VEGF) and PlGF, critical for normal blood vessel formation and maintenance. An exaggerated maternal immune response to the placenta further promotes inflammation and endothelial injury,
compounding the maternal syndrome of preeclampsia. These mechanisms highlight the multifaceted nature of preeclampsia, necessitating ongoing research to better understand its

complex etiology and to develop effective interventions (4). There are also certain risk factors that differ between two types of preeclampsia: early-onset (<34 weeks) and late-onset (≥34 weeks) pre-eclampsia(9).
Early-onset PE is associated with a higher risk of adverse maternal and fetal outcome (10). Effective screening, diagnosis, prediction, and monitoring of preeclampsia development are crucial(11). Severe studies have shown that treating high-risk women with low-dose aspirin early in pregnancy can reduce the risk of preterm preeclampsia and its adverse outcomes(12-14).

First-timester screening for PE

MAP and UtA-PI
First-trimester screening aims to identify women at high risk of developing preeclampsia later in pregnancy based on maternal risk factors, allowing preventative strategies to be put in place. The American College of Obstetricians and Gynecologists (ACOG) (3), the National Institute for Health and Care Excellence (NICE) and the International Society for the Study of Hypertension in Pregnancy (ISSHP)(15) recommend screening pregnant women with a history of pregnancy with hypertension or diagnosis of PE, or family history of PE; pregnancy diabetes mellitus; kidney diseases or chronic hipertension but also nulliparity or multiple pregnancy or pregnancy conceived by assisted reproductive technology; maternal age ≥ 35 years or prepregnancy body mass index > 30 kg/m2 and interpregnancy interval >
10 years.

Currently, many centers do not use a combined first-trimester screening approach(16) and, often, identification of women at high risk of developing PE is based on assessment of clinical risk factors only, as recommended by the ACOG 2018 and NICE 2019 guidelines. Combining clinical risk factors, maternal blood pressure, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and maternal angiogenic biomarkers into an algorithm may be a more accurate way of identifying high-risk women (16-18).

One of the most powerful PE screening algorithms, developed by The Fetal Medicine Foundation (FMF), uses a combination of clinical risk factors, maternal age, MAP and mean UtA-PI measurements and maternal PlGF to identify high-risk women in the first trimester (16, 19-21). The FMF algorithm, which includes these factors, is recommended for first-trimester screening and can be used later in pregnancy. Recommendations of The International Federation of Gynecology and Obstetrics (FIGO) suggest all pregnant women to be screened for PE early in pregnancy by including both clinical risk factors and maternal biomarkers(22).

UtA-PI is a key biomarker in assessing the risk of preeclampsia, especially in the first trimester. It measures the blood flow resistance in the uterine arteries. The pulsatility index should be the first parameter assessed in the context of pre-eclampsia screening, according to ISUOG Practice Guidelines 2018. In the first trimester, mainly during the 11–14 weeks of

gestation, UtA-PI values >90th centile predict 48% of early-onset preeclampsia cases and 26% of total preeclampsia cases. In addition to PI, uterine artery notching, an indicator of endothelial dysfunction, has also been evaluated, but it is relatively common during pregnancy (found in 43% of normal pregnancies in the first trimester).
Mean uterine artery PI continues to be the gold-standard Doppler parameter for pre-eclampsia screening(23). Elevated UtA-PI values indicate greater resistance, implying inadequate placentation and an increased risk of preeclampsia. Assessing UtA-PI with Doppler ultrasound in the first trimester can identify women at high risk by directly showing placental blood flow status. When combined with other biomarkers such as mean arterial pressure (MAP) and PlGF, UtA-PI improves the predictive accuracy for early-onset preeclampsia.

Both MAP and UtA-PI are integral to first-trimester screening protocols, often used in conjunction with maternal history and other biochemical markers. This combined approach allows for more precise stratification of preeclampsia risk and facilitates early intervention strategies to improve maternal and fetal outcomes (24).

Second-and third-timester diagnosis and prediction of PE

One of the most promising biomarkers useful in second- and third-trimester are soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF).

sFlt-1
sFlt-1 is an anti-angiogenic protein that works by binding to vascular endothelial growth factor (VEGF) and PlGF, thereby preventing their interaction with receptors on endothelial cells. It is not useful for first-trimester screening for PE since sFlt-1 levels start to rise only at 21–24 weeks of gestation in women who develop PE. Elevated sFlt-1 levels are linked to endothelial dysfunction, a key feature of preeclampsia. High sFlt-1 levels interfere with normal angiogenesis, contributing to the disease's development. Recent studies show a significant increase in sFlt-1 levels in women with preeclampsia, particularly in severe cases and early-onset instances.

PlGF
PlGF is a pro-angiogenic protein that promotes the growth and development of blood vessels in the placenta. Low PlGF levels of 80-120- pg/mL were able to diagnose PE in asymptomatic women and are indicative of poor placental development and function, which are central features of preeclampsia (25). The prospective, multicenter Pre-eclampsia Triage by Rapid Assay Trial (PETRA) trial (26) reported that low PlGF levels (≤ 100 pg/mL) in pregnant women at < 35 weeks of gestation with suspected PE had a sensitivity of 76%, a specificity of 69% and a negative predictive value (NPV) of 53% for predicting a final diagnosis of PE at any time. Another analysis of the PETRA trial showed that low PlGF levels (≤ 100 pg/mL) were linked with significantly higher risk for a composite maternal adverse outcome compared with normal PlGF levels (6.2% vs 1.9%), and had a sensitivity and specificity of 86.8% and 34.3%, respectively, for predicting the composite maternal outcome(27). Reduced

PlGF levels can also predict the development of PE requiring delivery within 14 days in women with suspected PE.

The prospective, multicenter Plasma Placental Growth Factor in the Diagnosis of Women with Pre-Eclampsia Requiring Delivery Within 14 Days (PELICAN) study (28) showed that a PlGF concentration < 5th percentile had a sensitivity of 96%, a specificity of 55% and a NPV of 98% for predicting the development of PE requiring delivery within the next 14 days. Decreased PlGF levels have been assosiated with the onset of preeclampsia. Measuring PlGF, especially in combination with sFlt-1 levels, improves the accuracy of predicting preeclampsia. PlGF alone is involved in placental angiogenesis. It's concentration increases initially, peaks in mid-gestation and then decreases gradually (29)(28). PlGF concentration decreases prematurely in women who go on to develope PE. Moreover it is often detectable before the onset of symptoms, so regular measurement of maternal circulating PlGF levels may help to diagnose preeclampsia earlier
(25, 30). Low maternal PlGF levels of 80–120 pg/mL were able to diagnose preeclampsia in asymptomatic women.

sFlt-1/PlGF ratio
The ratio of sFlt-1 to PlGF is a powerful diagnostic tool for predicting preeclampsia risk. An elevated sFlt-1/PlGF ratio indicates an imbalance between antiangiogenic and proangiogenic factors. It leads to a higher risk of developing severe complications. According to recent findings, an sFlt-1/PlGF ratio of <38 can effectively rule out preeclampsia within 4 weeks of assessment, between 24 and 37 weeks of gestation, with a negative predictive value of 99.3% (31). A ratio greater than 85 signifies a high risk for preeclampsia, requiring close monitoring and potential intervention. This ratio is particularly useful in late pregnancy, where a value of 110 or more is associated with a higher likelihood of adverse outcomes, such as placental abruption, eclampsia, and intrauterine growth restriction. In summary, sFlt-1 and PlGF are crucial biomarkers in the risk assessment of preeclampsia. The combined use of sFlt-1 and PlGF in a ratio offers a powerful predictive tool that improves early diagnosis and timely management, benefiting both mother and baby. Integrating these biomarkers into clinical practice marks a major advancement in prenatal care, providing a more accurate and effective method for managing preeclampsia risk.

The combination of these biomarkers with clinical assessments enhances the ability to diagnose and manage preeclampsia effectively. Incorporating biomarkers into routine screenings can help identify women at risk of developing preeclamspia earlier, allowing for timely interventions such as the administration of low-dose aspirin or closer monitoring to improve pregnancy outcomes.

These advances in biomarker research are essential for reducing the incidence and severity of preeclampsia, ultimately aiming to improve maternal and fetal health outcomes through more personalized and precise medical care. The benefit of identifying women at higher risk of

preeclampsia in early pregnancy (<16 weeks) has utility in preventing preterm preeclampsia through administration of low-dose prophylaxis with aspirin to reduce preterm disease (32, 33)

Integration of various biomarkers in prediction of PE

Recent research underscores that a combination of various biomarkers provides the most effective method for evaluating preeclampsia risk. This multi-biomarker approach improves predictive accuracy and allows for earlier and more reliable identification of pregnancies at high risk. Moreover, combining different biomarkers, addresses the multifacgtorial nature of preeclampsia, involving complex interactions between maternal, placental and fetal factors. Using mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and sFlt-1/PlGF ratiooffers a more accurate prediction of preeclampsia than any single marker alone.

By integrating multiple biomarkers, each representing different pathophysiological aspects of preeclampsia, clinicians can achieve a more comprehensive assessment. MAP reflects maternal cardiovascular status, UtA-PI indicates placental blood flow resistance, and PlGF levels relate to placental development and function. This multi-faceted approach not only improves early detection but also stratifies patients into appropriate risk categories, facilitating tailored monitoring and intervention strategies (8).

Therefore, according to the latest scientific evidence, combining different biomarkers in preeclampsia screening is the most effective strategy, as it utilizes the strengths of each marker to offer a comprehensive and detailed risk assessment.

Asprin as preeclampsia prevention

Low-dose aspirin (ASA) has shown significant efficacy in preventing preeclampsia, reducing the risk by about 60% (33). The ASPRE (Aspirin for Evidence-Based Preeclampsia Prevention) trial showed that low-dose ASA initiated in the first trimester minimizes preeclampsia risk in high-risk women (34). Other reaserch have also suggested that aspirin may have additional benefits such as lowering the risk of preterm birth and intrauterine growth restriction (35, 36). However supplementation must begin before week 16 week' of pregnancy, as starting later can reduce its positive effects on gestation and may even increase the risk of negative outcomes (33, 35, 37)
Despite recommendations from various gynecological and obstetrical societies to use aspirin as a preventative measure for preeclampsia, there is no consensus on the dosage. WHO suggested a minimum dosage of 75 mg per day for high-risk women, while other organizations like the International Society for the Study of Hypertension in Pregnancy (ISSHP) recommend higher doses, up to 162 mg/day. The recommended time to start treatment ranges from the 11th to the 20th week of gestation, with the optimal time being before the 16th week (38). Aspirin may not esignificantly preeclampsia rates in women with chronic hypertension(34).

Summary
Preeclampsia is a major cause of maternal and perinatal morbidity and mortality. Combining maternal factors and biomarkers provides effective first-trimester screening for preterm-preeclampsia. The future of preeclampsia risk assessment lies in the development and integration of multiple biomarkers. This approach is expected to enhance early detection and improve maternal and fetal outcomes. The combination of biomarkers such as placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1) has shown significant promise. Recent advancements, including the FDA's clearance of Thermo Fisher's PlGF and sFlt-1 assays, highlight the effectiveness of these biomarkers in predicting preeclampsia. These tests, when used alongside other clinical assessments, provide a more accurate risk stratification, particularly for women hospitalized with hypertensive disorders of pregnancy(39). Maternal PlGF, sFlt-1 and sFlt-1/PlGF ratio show good performance for screening and diagnosing PE, for predicting development of PE in the short term. The sFlt-1/PlGF ratio is clinically useful in guiding management of pregnant women with unclear symptoms of PE and can therefore rule out PE. The sFlt-1/PlGF ratio may be preferred over PlGF level alone because PlGF decreases with disease severity and, in cases of early-onset disease, PlGF concentrations may be so low as to be undetectable. In cases of early-onset PE, measurement of PlGF alone is not a useful tool and may limit monitoring of disease progression. There is a need for further integration of tests for these angiogenic factors into clinical practice. Research indicates that machine learning models can refine risk assessment by analyzing a wide array of genetic markers and cellular interactions within the placenta in the future. This computational approach can identify novel genes and pathways involved in preeclampsia, offering new insights into its pathogenesis and potential therapeutic targets (8).
Overall, the integration of multiple biomarkers, supported by advanced analytical techniques, represents a forward-looking strategy in the management of preeclampsia, potentially leading to more personalized and timely interventions (40). Aspirin prophylaxis has been shown to reduce the risk of preeclampsia. The dose between 100–150 mg should be started before 16 weeks' until 36 weeks' gestation.

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