Advancements in preeclampsia: innovative screening methods and effective prevention strategies

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Abstract

Preeclampsia, affecting 5-10% of pregnancies, is a major cause of maternal and fetal morbidity and mortality, characterized by elevated blood pressure and proteinuria after 20 weeks of gestation. The complications include intrauterine growth restriction, eclampsia, placental abruption, and HELLP syndrome. Effective first-trimester screening, recommended by international societies, considers maternal risk factors such as the PlGF (placental growth factor) value, the pulsatility index of the uterine arteries, and the mean blood pressure. Advances in soluble biomarkers, especially the sFlt-1/PlGF ratio, offer improved early diagnosis and management by predicting preeclampsia weeks before the symptoms appear. Preventive measures – notably, low-dose aspirin – have been validated by the ASPRE study, showing a 62% reduction in preterm preeclampsia risk when administered from 11-14 weeks of gestation. Implementing these screening and prevention strategies nationwide, especially in resource-limited areas, is essential to reduce the incidence and to improve the outcomes for mothers and babies.

Keywords: *preeclampsia, screening, prevention, aspirin, PlGF, sFlt1*

Rezumat

Preeclampsia, afectând 5-10% din sarcini, este o cauză majoră de morbiditate și mortalitate maternă și fetală, fiind caracterizată prin valori crescute ale tensiunii arteriale și proteinurie decelate după 20 de săptămâni de gestație. Complicațiile includ restricția de creștere intrauterină, eclampsia, dezlipirea prematură de placentă normal inserată și sindromul HELLP. Screeningul eficient în primul trimestru, recomandat de societățile internaționale, ia în considerare factori de risc materni precum valoarea PlGF (placental growth factor), indexul de pulsatilitate al arterelor uterine și tensiunea arterială medie. Progresele în utilizarea biomarkerilor solubili, în special raportul sFlt-1/PlGF, oferă un diagnostic și o gestionare îmbunătățite, prin predicția preeclampsiei cu săptămâni înainte de apariția simptomelor. Măsurile preventive, în special administrarea de aspirină în doză mică, au fost validate de studiul ASPRE, arătând o reducere cu 62% a riscului de preeclampsie cu debut precoce atunci când este administrată între 11 și 14 săptămâni de gestație. Implementarea acestor strategii de screening și prevenție la nivel național, în special în zonele cu resurse limitate, este esențială pentru a reduce incidența și a îmbunătăți prognosticul pentru mame și nou-născuți.

Cuvinte-cheie: *preeclampsie, screening, prevenție, aspirină, PlGF, sFlt1*

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Progrese în managementul preeclampsiei: metode noi de screening și strategii eficiente de prevenție

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Introduction

Preeclampsia is a condition that affects 5-10% of pregnancies, being considered a systemic vascular dysfunction that is characterized by proteinuria and increased blood pressure values. The complications of preeclampsia include intrauterine growth restriction, convulsions (eclampsia), placental abruption, and an association that includes hemolysis, elevated transaminases and thrombocytopenia (HELLP syndrome). The manifestations of preeclampsia disappear after birth, the obstetrical solving being the only effective treatment of preeclampsia. However, a history of preeclampsia is associated with an increased cardiovascular risk throughout life[(1)].

The diagnosis of preeclampsia is made when there is an increase in blood pressure above 140/90 mmHg associated with a value of proteinuria/24 hours above 300 mg/24 hours, or when the urinary protein/creatinine ratio is above 0.3, or when the urine dipstick test result is +1, manifestations that appear after 20 weeks of gestation. In the absence of proteinuria, the diagnosis can be made when there are manifestations such as pulmonary edema, thrombocytopenia, liver or kidney damage[(2)].

Preeclampsia screening

The National Institute for Health and Care Excellence (NICE)[(3)], the American College of Obstetricians and Gynecologists (ACOG)[(4)] and the International Society for the Study of Hypertension in Pregnancy (ISSHP)[(5)] advocate for screening pregnant women for preeclampsia (PE) during the first trimester. This screening is

recommended based on various maternal risk factors which include: interpregnancy interval exceeding 10 years, family history of preeclampsia, factors related to the pregnancy itself, such as nulliparity, multiple pregnancy, or conception through assisted reproductive technology, chronic hypertension or kidney disease, previous occurrence of preeclampsia or hypertension during pregnancy, maternal age of 35 years old or above, a pre-pregnancy Body Mass Index exceeding 30 kg/m^2, or pre-pregnancy conditions like diabetes mellitus or autoimmune diseases. These organizations also suggest that women at a high risk of preeclampsia be offered low-dose aspirin as a preventive measure against the onset of preeclampsia. The administration of aspirin before 16 weeks of pregnancy to women at a high risk of developing preeclampsia has been shown to be effective in reducing this risk. Therefore, the development of prediction methods for this condition represents an important area of research in the medical field[6].

Soluble fms-like tyrosine kinase 1 (sFlt-1), an antiangiogenic factor crucial for regulating angiogenic balance during pregnancy, plays a pivotal role[7]. Typically, its concentration rises steadily during the third trimester of normal pregnancy. However, in women who later develop preeclampsia (PE) or experience pregnancy complicated by fetal growth restriction (FGR), sFlt-1 levels elevate prematurely[8]. Maternal levels of circulating sFlt-1 have been observed to increase approximately five weeks before the onset of symptoms[8]. sFlt-1 binds to PlGF, and recent research indicates that the excess circulating sFlt-1 largely mediates the decreased levels of PlGF[9]. PlGF – a proangiogenic factor expressed in the placenta – aids in the action of vascular endothelial growth factor-A (VEGF-A), vital for placental vascular development[7]. Initially, maternal PlGF concentration rises, peaks around mid-gestation, and then gradually decreases towards term[8,10]. However, this decline in PlGF concentration occurs prematurely in women who later develop PE, often detectable before the symptom onset[11]. The elevation of sFlt-1 levels and the decrease in PlGF levels lead to an increased sFlt-1/PlGF ratio. Consequently, this ratio serves as a valuable tool for predicting and/or diagnosing placenta-related disorders, including preeclampsia, FGR, stillbirth, and preterm birth[12]. While other antiangiogenic factors like VEGF-A and soluble endoglin have been explored as biomarkers for diagnosing and predicting preeclampsia, they have not yet been integrated into clinical practice due to their limited additional value[8,13].

In the first trimester, the preeclampsia predictive value of sFlt1 and PlGF was extensively researched. Although no correlation was established between the sFlt1 level and the occurrence of preeclampsia in the first trimester, the value of PlGF proved to be a good predictor of the development of preeclampsia[14,15]. Compared to the conventional method of evaluating maternal risk factors for the prediction of preeclampsia, a new method consisting of an algorithm that combines maternal factors, the PlGF value, the pulsatility index of the uterine arteries and the mean blood pressure, proved to be clearly superior[16]. The ASPRE study demonstrated that the administration of aspirin in high-risk patients identified using this algorithm significantly reduced the risk of preterm preeclampsia[17].

In the second and third trimesters, for women suspected of having preeclampsia, the sFlt1/PlGF ratio demonstrates a notably high negative predictive value for excluding the onset of preeclampsia within seven days[18], adverse maternal outcomes within 14 days[19], or delivery with preeclampsia within 14 days[18]. Various thresholds for the sFlt-1/PlGF ratio have been determined through ROC-curve analysis. Verlohren et al. validated a series of gestational-age-dependent thresholds for diagnosing preeclampsia. For early-onset PE (<34 weeks of gestation), an sFlt-1/PlGF ratio ≤33 effectively ruled out preeclampsia at the time of testing, with a sensitivity of 95% and a specificity of 94.0%. Conversely, an sFlt-1/PlGF ratio ≥85 diagnosed preeclampsia with a sensitivity of 88% and a specificity of 99.5%. For late-onset PE (≥34 weeks of gestation), an sFlt-1/PlGF ratio ≤33 ruled out preeclampsia at the time of testing with a sensitivity of 89.6% and a specificity of 73.1%. Conversely, an sFlt-1/PlGF ratio ≥110 diagnosed PE with a sensitivity of 58.2% and a specificity of 95.5%[20]. Herraiz et al. reported that using an sFlt-1/PlGF ratio cutoff >95th percentile at 24-28 weeks of gestation identified 100% of women at high risk of preeclampsia, who subsequently developed the early-onset form of the disease, in a prospective observational study of 5601 pregnant women[21].

Prevention of preeclampsia

The effects of aspirin consist of an anti-inflammatory, analgesic and antipyretic effect, this drug being part of the class of nonsteroidal anti-inflammatory drugs. The mechanism of action of aspirin consists in the inhibition of cyclooxygenase COX-1 and COX-2, which causes a decrease in prostaglandins and thromboxane. The decrease in thromboxane has an antithrombotic effect by decreasing platelet aggregation[22,23]. Recently, new evidence has suggested that in the etiology of preeclampsia a deficient trophoblastic invasion would be involved, which causes a discordance between angiogenic and antiangiogenic factors, this leading to inflammation and systemic vascular damage, following an increase in platelet aggregation, with thrombotic events and placental infarcts[24]. Thus, the hypothesis was raised that aspirin, through its effects, would be a good medicinal agent to reduce the risk of preeclampsia[25].

Numerous studies have evaluated the role of aspirin in the prevention of preeclampsia, but with contradictory results, considering the various definitions of the pathology used in the studies, the different doses in which aspirin was administered, as well as the gestational age at which the treatment was started[26]. Therefore, to establish the effectiveness of aspirin in the prevention of preeclampsia, the ASPRE study was carried out. In this study, high-risk women received aspirin starting with 11-14 weeks of pregnancy, in a dose of 150 mg, until 36 weeks or until

delivery. Aspirin was administered in the evening, taking into account the results of previous studies that demonstrated better efficacy when aspirin was administered before bedtime[27]. In this study, aspirin decreased the risk of preterm preeclampsia by 62%, an effect that was later confirmed by a meta-analysis, but it had no effect on the risk of occurrence of term preeclampsia[17,28].

The ASPRE study data were used to evaluate the effects of aspirin in different subgroups of patients, in which the beneficial effects of aspirin were confirmed, with the exception of the subgroup with preexisting hypertension. This may be due to the fact that in the preexisting hypertension of the pregnancy there could already be a vascular damage with cardiovascular dysfunction[29]. Studies on a large number of patients have demonstrated the safety of aspirin during pregnancy. Aspirin does not cause congenital defects, but also does not cause the arterial canal to close, thus excluding this theoretical risk[30-33]. Aspirin was associated in one study with an increased risk of placental abruption, a risk that could be explained by the fact that aspirin treatment was initiated at an advanced gestational age[34]. Other unwanted effects of aspirin that have been reported are postpartum hemorrhages and hemorrhagic events[35,36].

Conclusions

Preeclampsia remains one of the most significant medical complications of pregnancy, with substantial consequences for maternal and fetal health. In this context, screening for preeclampsia has become an essential component of prenatal care, allowing for early identification of women at a high risk of developing this condition. The algorithm proposed by the Fetal Medicine Foundation (FMF) in the first trimester has shown efficacy in the detection of women at risk for preeclampsia, particularly for early-onset forms, with a heightened risk for severe maternal-fetal complications. Implementing this algorithm nationwide could improve the pregnancy outcomes and reduce morbidity and mortality associated with preeclampsia. However, access to preeclampsia screening remains limited at present, being available only in certain medical centers with adequate infrastructure and resources. To ensure equitable prenatal care for all pregnant women, promotion and expansion of this service to a national level are necessary. In conclusion, first-trimester screening for preeclampsia should become a standard practice nationwide, and the administration of aspirin as a preventive measure should be advocated and used by all obstetricians to reduce the risk and enhance the maternal-fetal outcomes. ■

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