CODREANU NADEJDA, BOTNARI-GUȚU MIHAELA

NEW ASPECTS IN SCREENING OF PREECLAMPSIA

Universitatea de Stat de Medicină și Farmacie "Nicolae Testemițanu"

REZUMAT

ASPECTE NOI ÎN SCREENINGUL PREECLAMPSIEI

Preeclampsia afectează 2-5% din femeile însărcinate și este una dintre principalele cauze ale morbidității și mortalității materne și perinatale, mai ales atunci când debutul bolii este timpuriu. Scopul principal al acestui articol este revizuirea literaturii privind metodele efi ciente de prezicere a preeclampsiei în primul trimestru de sarcină pentru a identifi ca femeile cu risc ridicat de a dezvolta preeclampsie, astfel încât măsurile necesare să poată fi inițiate cât mai devreme, pentru a preveni sau a reduce cel puțin frecvența apariției acestei afecțiuni. Până în prezent au fost găsiți câțiva biomarkeri promițători pentru predicția preeclampsiei, folosiți aparte sau în combinație. Aceștia includ: a) markeri biochimici, cum ar fi nivelul factorului de creștere placentar (PlGF), al tirozin-kinazei 1 solubile (sFlt-1) și al raportului sFlt-1/PlGF, precum și nivelul de proteină placentară 13 (PP13), endoglină solubilă (sEng), proteină plasmatică A (PAPP-A) asociată cu sarcina; b) markeri fi ziologici și biofi zici, cum ar fi presiunea arterială medie și indicele de pulsatilitate al arterei uterine. În concluzie, markerii biochimici s-au dovedit a fi promițători în predicția preeclampsiei încă din primul trimestru de sarcină la gravidele cu factori de risc.

Cuvinte-cheie: preeclampsie, predicție, primul trimestru de sarcină.

РЕЗЮМЕ

НОВЫЕ АСПЕКТЫ СКРИНИНГА ПРЕЭКЛАМПСИИ

Преэклампсия встречается у 2–5% беременных женщин и является одной из основных причин материнской и перинатальной заболеваемости и смертности, особенно в ранних стадиях. Основная цель этой статьи – обзор литературы об эффективных методах прогнозирования преэклампсии в первом триместре беременности, чтобы выявить женщин с высоким риском развития преэклампсии, а необходимые меры были бы приняты достаточно рано, чтобы предотвратить или уменьшить по крайней мере частоту этой болезни. До настоящего времени были найдены некоторые многообещающие биомаркеры для прогнозирования преэклампсии, отдельно или в комбинации. К ним относятся: а) биохимические маркеры, такие как уровни фактора роста плаценты (PlGF), соотношение растворимой тирозин-киназы 1 (sFlt-1) и sFlt-1/PlGF, а также уровни белка плаценты 13 (PP13), растворимого эндоглина (sEng), белка плазмы А (PAPP-A), связанного с беременностью; б) физиологические и биофизические маркеры, такие как среднее артериальное давление и индекс пульсирующей маточной артерии. Биохимические маркеры оказались многообещающими в прогнозировании преэклампсии у беременных женщин с факторами риска с первого триместра беременности.

Ключевые слова: преэклампсия, прогнозирование, первый триместр беременности.

INTRODUCTION

An important medical condition associated with a high risk of maternal and perinatal morbidity and mortality(1), preeclampsia is a unique pregnancy hypertensive disorder, characterized by poor perfusion, especially of the fetoplacental unit, and completely reversible with the end of pregnancy(2,3). Research data has shown that preeclampsia is usually identified during the second half of pregnancy, when it can complicate between 2% and 8% of pregnancies(4).

The pathophysiological mechanisms of preeclampsia show impaired placentation processes, in particular from the beginning of pregnancy and continued with a generalized inflammatory response, with progressive endothelial transformation(2). Therefore, through such a nonspecific mechanism, preeclampsia becomes a pregnancy-associated syndrome that can actually alter each organ system(5). Mainly, preeclampsia is defined through the onset of a new episode of hypertension after 20 weeks of gestation (with persistent high blood pressure ≥140/90 mmHg) and the occurence of sub-

stantial proteinuria (>0.3 g/24 h) or other pathophysiological changes (persistent epigastric pain, persistent headache or other cerebral or visual disturbance, elevated serum transaminase levels, microangiopathic hemolysis, platelets <100,000/μL, serum creatinine level >1,2 mg/dL)(5).

Extensive research have shown that the short-term prognosis is worse in relation to severe preeclampsia and in early onset demanding delivery before 34 weeks of gestation, than at term(6,7). The early detection of pregnancies at high risk of preterm preeclampsia has become a significant challenge in nowadays obstetrics follow-up. The latest studies have demonstrated that between 11 and 13 weeks of gestation an important rate of pregnancies at high risk of preterm preeclampsia can be detected, using an algorithm with significant data features regar¬ding early biopshysical and biochemical markers of altered placentation(8). These markers include maternal medical and obstetrical history, biophysical measurements such as uterine artery pulsatility index (PI) and mean arterial pressure (MAP), and biochemical markers like maternal serum pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF)(8).

MATERNAL MEDICAL AND OBSTETRICAL HISTORY

Reviewing the international literature and the latest studies on identifying the high risk pregnancies which can possible develop preterm preeclampsia, it can be seen that different maternal demographic characteristics and maternal medical features were associated with this condition. Mainly, the approaches in screening on preeclampsia using maternal history include parameters which depend on the regional guidelines. The National Institute for Health and Clinical Excellence (NICE), from UK, studied a number of maternal demographic and medical features, and considers that pregnancies with high risk of developing preeclampsia include any one high-risk factor or any two moderate-risk factors presented in Table **1**(9).

The American College of Obstetricians and Gynecologists (ACOG) recommends identifying the traditional maternal risk factors without considering specific high or moderate risk in developing preeclampsia **(Table 1)** (10). These significant internatio¬nal guidelines, NICE and ACOG, have carefully studied each risk factor, and estimated the additive detection rate (DR) and the screen positive rate for each risk factor as a separate screening test. As a result, according to NICE guidelines, in order to prevent preterm preeclampsia in women with high-risk pregnancies, low-dose of acetylsalicylic acid should be offered. In contrast with this statement, according to ACOG guidelines, only women with a history of preeclampsia (PE) in more than two previous pregnancies or preeclampsia demanding urgent delivery at <34 weeks of gestation should be offered acetylsalicylic acid(11).

Table 1 Maternal medical and obstetrical history characteristics

NICE guidlines[9]	ACOG guidlines[10]
High-risk factors ■ history of hypertensive disease in previous pregnancy ■ chronic kidney disease, autoimmune diseases ■ diabetes mellitus ■ chronic hypertension	■ nulliparity ■ age >40 years old ■ body mass index >30 kg/m² ■ conception by *in vitro* fertilization ■ history of previous pregnancy with PE ■ family history of PE ■ chronic hypertension ■ chronic renal disease ■ diabetes mellitus ■ systemic lupus erythematosus ■ thrombophilia
Moderate-risk factors ■ first pregnancy ■ age >40 years old ■ interpregnancy interval >10 years ■ body mass index (BMI) at first visit of >35 kg/m² ■ family history of PE	

Table 1. ***Maternal medical and obstetrical history characteristics***

The Fetal Medicine Foundation (FMF) presents an alternative to traditional screening on preterm preeclampsia according to NICE and ACOG guidelines, by including not only the risk factors of preterm preeclampsia after analyzing the maternal medical and obstetrical history, but also biophysical and biochemical parameters(12-14). FMF combines the a priori risk from maternal medical and obstetrical history traditional factors, with various serum biomarkers. The result is specific to each patient and derives from a multivariable logistic model using Bayes theorem. At 11-13 weeks of gestation, a significant proportion of pregnancies at high risk for preterm preeclampsia can be detected using the maternal risk factors described in NICE and ACOG guidelines and the measurement of uterine artery pulsatility index, mean arterial pressure and maternal serum pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF)(12,13).

MATERNAL BIOPHYSICAL AND BIOCHEMICAL MARKERS

Preeclampsia is a specific pregnancy disorder, where elevated levels of arterial blood pressure appear as a

result of reduced peripheral vascular compliance and vasoconstriction(16). The early detection of hypertension using automated arterial blood pressure devices and the accurate monitoring of arterial blood pressure, during antenatal care, are major clinical statements in every pregnancy standard follow-up(17). Substantial clinical evidence demonstrate that an elevated level in arterial blood pressure in women who develop preeclampsia can be detected in the first and second trimesters of pregnancy, and the mean arterial pressure is significantly more important than the values of systolic and diastolic blood pressure alone(3,18). First trimester mean arterial pressure depends on maternal factors such as age, body mass index, racial origin, previous history of preeclampsia, smoking habbits, history of chronic hypertension, as shown in previous studies(15). Therefore, the mean arterial pressure measurement should be expressed as a multiple of the median, or MoM, after the adjustment for these factors, and then included in the algorithm for the detection of preterm preeclampsia at 11-13 weeks of gestation. According to D. Wright et al. (2012), who made a study of singleton pregnancies at 11-13 weeks, including 1,426 (2.4%) cases that subsequently developed preeclampsia, the mean arterial pressure was significantly increased and there was a negative linear relation between mean arterial pressure expressed as MoM and the gestational age at delivery(15).

Another important maternal biophysical parameter observed to reflect, from the beginning, the impaired placentation in pregnancies associated with preterm preeclampsia is the pulsatility index of the uterine arteries, measured during a standard ultrasound examination between 11-13 weeks of gestation(19). During normal pregnancies, as an adjustment to the new body conditions, the blood flow in the intervillous space increases through the enlargement of the spiral arteries(20). In cases of pregnancy with possible development of preeclampsia, the maternal spiral arteries convert themselves, in the condition of impaired trophoblastic invasion, from thight muscular vassels to large non-muscular channels(21). When measured with Doppler ultrasound, these changes reflect in increased uterine artery pulsatility index(19). Doppler ultrasound estimates the uteroplacental circulation in a noninvasive transabdominal approach and the sonographers should be trained following a standard ultrasound technique, in order to rule out the possible bias(19). Similar to the mean arterial pressure, it was observed that at 11-13 weeks of gestation, the pulsatility uterine artery index is affected by maternal factors. After adjustment for these factors, D. Wright et al. (2012) observed that there was a significant negative linear relation between uterine artery pulsatility index espressed as MoM and the gestational age at delivery(15).

As a result of the pathological placentation derived from improper trophoblastic invasion of the maternal spiral arteries, the modified ischemic tissue release various biomarkers that activate the inflammatory pathways, activate platelet cascade, increase endothelial dysfunction and oxidative stress, and change the normal renal excretion(12,21). Among numerous others biomarkers, two maternal serum proteins – preg¬¬nancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) – have been closely studied and have significant results in the screening at 11-13 weeks of gestation, not only for aneuploidies, but also for preterm preeclampsia(22).

The syncytiotrophoblast generates, in normal pregnancy conditions, a specific protein, called pregnancy-associated plasma protein-A (PAPP-A), which separates the insulin-like growth factor from the binding protein. PAPP-A increases the effect of serum available insulin-like growth factor and supports the normal development of the placenta(23). In pregnancies considered chromosomally normal, but with high risk of preterm preeclampsia, it was observed that the level of maternal serum PAPP-A was low in the first and second trimester(24). Like the previous maternal biomarkers, PAPP-A should not be analyzed alone, but after maternal factors adjustment and expressed in MoM, because not every affected case has the protein serum level below the normal percentile, considered 0.4 MoM(15).

The cytotrophoblast synthesise in villous and extravillous spaces a particular glycoprotein called placental growth factor (PlGF). This protein plays an important role in the angiogenetic process, controlling the normal expansion of the capillary system. In pregnancies with high risk of developing preterm preeclampsia, as expected, due to poor placentation, the serum level of PlGF is low(25). Besides maternal factors that affect both PAPP-A and PlGF serum level, such as maternal body mass index, racial origin, smoking habbits, conception by in vitro fertilization, nulliparity and preexisting diabetes mellitus, and therefore need specific adjustments, PlGF level also depends on maternal age(26). At 11-13 weeks of gestation, both MoM values of PAPP-A and PlGF are reduced and related to the gestational age, and a significant positive linear relation was demonstrated(27).

CONCLUSIONS

According to many studies, at 11-13+6 weeks of gestation, the screening of preterm preeclampsia should mandatory consider both maternal medical and obstetrical history, and biomarkers such as uterine artery pulsatility index (PI) and mean arterial pressure (MAP), and biochemical markers like maternal serum pregnancy-associated plasma protein-A and placental grewth factor(8).

Compared to traditional screening for preterm preeclampsia using only maternal risk factors and a detection rate of about 40%(30), the combined algorithm shows a greater rate of preterm preeclampsia detection. Therefore, an important group of women with pregnancies can benefit

from a prophylactic administration of acetylsalicylic acid from the first trimester, at 11-13 weeks of gestation.
Given the recent studies regarding the screening algorithm for preterm preeclampsia in the first trimester and the significant advantage in the perinatal outcome after early acetylsalicylic acid use in every high-risk preterm preeclampsia pregnancies, the actual tendency should be followed on a greater scale.

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