New concepts in the screening of preterm preeclampsia

Alexandra Bouariu[1], Gabriela Popescu[1], Alexandru Liță[2], Nicolae Gică[1], Gheorghe Peltecu[1,2], Anca Panaitescu[1,2]

1. Filantropia Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania

2. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Corresponding author:
Anca Panaitescu
E-mail: panaitescu.anca@yahoo.com

Abstract

Preeclampsia is a unique pregnancy hypertensive disorder, being an important medical condition associated with a high risk of maternal and perinatal morbidity and mortality. 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 11-13 weeks of gestation an important rate of pregnancies at high risk of preterm preeclampsia can be detected, using an algorithm with significant data features regarding early biopshysical and biochemical markers of altered placentation.

Keywords: *preeclampsia, PLGF, first trimester, screening, mean arterial pressure, uterine artery pulsatiliy index*

Rezumat

Preeclampsia este o patologie unică asociată sarcinii, aparținând spectrului tulburărilor hipertensive, cu morbiditate și mortalitate maternă și perinatală crescute. Detectarea precoce a sarcinilor cu risc înalt de a dezvolta preeclampsie a devenit o preocupare importantă a obstetricienilor în zilele noastre. Cele mai recente studii în domeniu demonstrează posibilitatea de detecție, în primul trimestru al sarcinii, a cazurilor cu risc crescut de a dezvolta preeclampsie precoce, folosind un algoritm ce cuprinde atât antecedente medicale și obstetricale materne, cât și parametri biofizici și biochimici materni, secundari unei placentații deficitare, caracteristică preeclampsiei.

Cuvinte-cheie: *preeclampsie, PLGF, primul trimestru, screening, tensiune arterială medie, index de pulsatilitate pe arterele uterine*

Submission date:
2.10.2018
Acceptance date:
30.11.2018

Aspecte noi în screeningul pentru preeclampsia cu debut precoce

Suggested citation for this article: *Bouariu A, Popescu G, Liță A, Gică N, Peltecu G, Panaitescu A. New concepts in the screening of preterm preeclampsia. Ginecologia.ro. 2018;22(4):8-11.*

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 substantial 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 regarding 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].

On the other hand, 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 international 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].

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].

An important issue observed on a survival time model explains that the gestation at time of delivery for preeclampsia should be considered a continuous variable, not a categorical one, because if the pregnancy continued indefinitely, all women would enhance preeclampsia[14]. The mean gestational age for delivery with preeclampsia was observed to be 55 weeks, with an estimated standard deviation of 7 weeks, and can be modified by analyzing the various maternal risk factors. In low-risk pregnancies for preterm preeclampsia, women would deliver before the developement of preeclamsia, while in high-risk pregnancies, the smaller the mean gestational age, the higher the risk for preeclampsia[15]. The major maternal risk factors for developing preterm preeclampsia are the maternal age over 35 years old, an increased body mass index, particular racial origin like Afro-Caribbean and South Asian, medical history of chronic diseases such as chronic hypertension, preexisting diabetes mellitus, antiphospholipid syndrome, systemic lupus erythematosus, previous pregnancies with preeclampsia and conception by *in vitro* fertilization[3].

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

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/m^2 ■ 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/m^2 ■ family history of PE	

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 developement 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 – pregnancy-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].

Discussion and 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].

The latest prospective observational screening study, developed in 2018 in UK and other countries by Yi Tan et al., observed a large number of singleton pregnancies (61,174), with 1,770 (2.9%) that developed preeclampsia[8]. They studied each maternal history high-risk factor for preterm preeclampsia, but also the main biochemical and biophysical factors. The results encourage the screening for preterm preeclampsia, identified in 75% enrolled pregnancies with modified parameters such as maternal factors, mean arterial pressure, uterine artery pulsatility idex and PlGF, at a screen positive rate of 10%. It was also demonstrated that this result was not significantly changed by the PAPP-A results, towards racial origin, which made an important shift in the preterm preeclampsia detected percentage, up to 69% for Caucasian women with a screen positive rate of 10%, and 92% for women with Afro-Caribbean racial origin, with a screen positive rate of 34%[8].

The importance for screening and indentifying pregnancies with high-risk factors in developing preterm preeclampsia was highlighted in the ASPRE trial. After e careful screening using the previous preterm preeclampsia algorithm, all pregnancies with high-risk factors recieved acetylsalicylic acid (150 mg/day from 11-14 weeks of gestation to 36 weeks) and the rate of preterm preeclampsia with delivery at <37 weeks was significantly reduced by 60%[28]. The ASPRE trial shows that when the compliance to acetylsalicylic acid administration

exceeds 90%, the rate of preterm preeclampsia reduces at 75% and the maternal factors, excepting maternal preexisting chronic hypertension, don't interfere with this rate. The optimal administration of acetylsalicylic acid in order to reduce the risk of preterm preeclampsia with 67% is ≤16 weeks of gestation and a daily dose of ≥100 mg[29].

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.

Another survival time model, with reduced based evidence at the time, was developed analyzing maternal medical and obstetrical history and biomarkers at 30-33 weeks of gestation in order to determine the developing preeclampsia requiring immediate delivery[31]. The traditional maternal history risk factors and the measurements of mean arterial pressure and uterine artery pulsatility index maintain the role in predicting preeclampsia in the same manner at 30-33 weeks of gestation as at 11-13 weeks of gestation, indentifying approximately 90% of cases of preeclampsia that should involve delivery within the following four weeks[31]. In this cases, soluble fms-like tyrosine kinase-1 (sFlt-1) and PlGF ratio identifies with a greater accuracy the group of women with immediate delivery due to preeclampsia[32]. Even though the soluble fms-like tyrosine kinase was observed to be influenced by maternal traditional medical and obstetrical factors, more evidence-based results are required in order to consider the future significant benefits in estimating the moment of delivery and the clinical complications that can develop during the third trimester in pregnancies with high risk of preeclampsia.

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. ■

Conflict of interests: The authors declare no conflict of interests.

References

1. Basso O, Rasmussen S, Weinberg C, et al. Trends in fetal and infant survival following preeclampsia. *JAMA*. 2006; 296, 1357-1362.
2. World Health Organization. WHO recommendations for prevention and treatment of preeclampsia and eclampsia. Geneva, Switzerland: World Health Report; 2011.
3. Poon L, Nicolaides K. First-trimester maternal factors and biomarker screening for preeclampsia. *Prenatal Diagnosis*. 2014; 34, 618-627.
4. Steegers E, von Dadelszen P, Duvekot J, et al. Pre-eclampsia. *Lancet*. 2010:631-44.
5. Cunningham G, Leveno K, Bloom S, et al. Pregnancy Hypertension. In: Williams Obstetrics: McGraw-Hill Companies; 2010; 706-56.
6. Witlin G, Saade G, Mattar F, et al. Predictors of neonatal outcome in women with severe preeclampsia or eclampsia between 24 and 33 weeks' gestation. *Am J Obstet Gynecol*. 2000; 182:607-11.
7. Yu C, Khouri O, Onwudiwe N, et al. Prediction of preeclampsia by uterine artery Doppler imaging: relationship to gestational age at delivery and small-for-gestational age. *Ultrasound Obstet Gynecol*. 2008; 31:310-3.
8. Tan M, Syngelaki A, Poon L, Nicolaides K, et al. Screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Ultrasound Obstet Gynecol*. 2018; 52(2):186-195.
9. National Collaborating Centre for Women's and Children's Health. Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy. London (UK), RCOG Press; 2010.
10. ACOG. First-trimester risk assessment for early-onset preeclampsia. *Obstet Gynecol*. Committee opinion No. 638; 2015.
11. ACOG. Task Force on hypertension in pregnancy. Washington, 2013.
12. Wright D, Syngelaki A, Akolekar R, Poon L, Nicolaides K. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *Am J Obstet Gynecol*. 2015; 213(62):e1-10.
13. O'Gorman N, Wright D, Syngelaki A, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation. *Am J Obstet Gynecol*. 2016; 214:103. e1-103.e12.
14. O'Gorman N, Wright D, Poon L, et al. Multicenter screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks' gestation: comparison to NICE guidelines and ACOG recommendations. *Ultrasound Obstet Gynecol*. 2017; 49(6):756-60.
15. Wright D, Akolekar R, Syngelaki A, et al. A competing risks model in early screening for preeclampsia. *Fetal Diagn Ther*. 2012; 32:171-8.
16. Salas S. What causes preeclampsia? *Baillieres Best Pract Res Clin Obstet Gynaecol*. 1999; 13:41–57.
17. Poon L, Zymeri N, Zamprakou A, et al. Protocol for measurement of mean arterial pressure at 11-13 weeks' gestation. *Fetal Diagn Ther*. 2012; 31:42–8.
18. Moutquin J, Rainville C, Giroux L, et al. A prospective study of blood pressure in pregnancy: prediction of preeclampsia. *Am J Obstet Gynecol*. 1985; 151:191–6.
19. Plasencia W, Maiz N, Bonino S, et al. Uterine artery Doppler at 11+0 to 13+6 weeks in the prediction of preeclampsia. *Ultrasound Obstet Gynecol*. 2007; 30:742–9.
20. Brosens I, Robertson W, Dixon H. The physiological response of the vessels of the placental bed to normal pregnancy. *J Pathol Bacteriol*. 1967; 93:569–79.
21. Granger J, Alexandra B, Llinas M, et al. Pathophysiology of hypertension during preeclampsia linking placental ischemia with endothelial dysfunction. *Hypertension*. 2001; 38:718–22.
22. Wright D, Syngelaki A, Bradbury I, et al. First-trimester screening fortrisomies 21, 18 and 13 by ultrasound and biochemical testing. *Fetal Diagn Ther*. 2014; 35:118–26.
23. Dugoff L, Hobbins J, Malone F, et al. First trimester maternal serum PAPP-A and free beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (TheFASTERTrial). *Am J Obstet Gynecol*. 2004;191:1446–51.
24. Spencer K, Cowans N, Chefetz I, et al. First trimester maternal serum PP-13, PAPP-A and second trimester uterine artery Doppler pulsatility index as markers of preeclampsia. *Ultrasound Obstet Gynecol*. 2007; 29:128–34.
25. Akolekar R, Zaragoza E, Poon LC, et al. Maternal serum placental growth factor at 11+0 to 13+6weeks of gestation in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol*. 2008; 32:732–9.
26. Pandya P, Wright D, Syngelaki A, et al. Maternal serum placental growth factor in prospective screening for aneuploidies at 8-13 weeks' gestation. *Fetal Diagn Ther*. 2012; 31:87–93.
27. Akolekar R, Syngelaki A, Poon L, et al. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. *Fetal Diagn Ther*. 2013; 33:8–15.
28. Rolnik D, Wright D, Poon L, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med*. 2017; 377: 613-22.
29. Roberge S, Bujold E, Nicolaides K. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. *Am J Obstet Gynecol*. 2017; S0002-9378(17)32326-8.
30. Tan MY, Wright D, Syngelaki A, et al. Comparison of diagnostic accuracy of early screening for preeclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. *Ultrasound Obstet Gynecol*. 2018; 10.1002/uog.19039.
31. Tayyar A, Garcia-Tizon Larroca S, Poon L, et al. Competing risks model in screening for preeclampsia by mean arterial pressure and uterine artery pulsatility index at 30-33 weeks' gestation. *Fetal Diagn Ther*. 2014; 36(1):18-27.
32. Verlohren S, Herraiz I, Lapaire O, et al. The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. *Am J Obstet Gynecol*. 2012; 206:58.e1–8.