Hypertensive syndrome in pregnacy – how to predict

Hipertenzivni sindrom u trudnoći – Kako ga predvideti?

Aleksandar Grdinic[1], Aleksandra Grdinic[2]

[1] Clinic for Gynecology and Obstetrics, Clinical Centre of Montenegro, Podgorica, Montenegro

[2] Clinic for Cardiology, Military Medical Academy, Belgrade, Serbia

Aleksandar Grdinić[1], Aleksandra Grdinić[2]

[1] Clinic za ginekologiju i akušerstvo, Klinički centar Crne Gore, Podgorica, Crna Gora

[2] Klinika za kardiologiju, Vojnomedicinska akademija, Beograd, Srbija

Abstract

Preeclampsia complicates about 5% of all pregnancies worldwide. It is a major cause of maternal, fetal and neonatal morbidity and mortality. The aim of this systematic review was to study the literature on the predictive potential of screening for preeclampsia based on serum markers and uterine artery Doppler velocity waveform assessment. First-trimester uterine artery Doppler can identify over half of women who will develop preeclampsia. Detection rates may be increased by a combination with maternal serum markers. In screening for early preeclampsia, the detection rate for a 10% false-positive rate was 96.3% for a combination of maternal factors, soluble endoglin, placental growth factor and uterine artery lowest Pulsatility Index. First trimester placental protein 13 predicts preeclampsia in women at increased a priori risk and predicts early-onset better than late-onset disease. The Fetal Medicine Foundation has released in 2009 the new software to allow calculation of risks for preeclampsia and gestational hypertension. Uterine artery Doppler velocimetry in combination with some biochemical markers seems to be an effective first-trimester screening tool for preeclampsia and in particular early-onset preeclampsia.

Key words: Preeclampsia, screening, first-trimester, morbidity.

Apstrakt

Preeklampsia komplikuje oko 5% svih trudnoća i glavni je uzrok maternalnog, fetalnog i neonatalnog morbiditeta i mortaliteta. Cilj ovog revijalnog članka je da pruži pregled literature o prediktivnom potencijalu skrininga preeklampsije baziranom na serumskim markerima i Doppler ultrazvučnom procenom protoka kroz arterije uterine. Doppler pregled uterinih arterija može otkriti više od polovine trudnica koje će razviti preeklampsiju. Stope detekcije se mogu povećati kombinacijom sa serumskim maternalnim markerima. U ranom skriningu preeklampsije, stope detekcije sa 10% lažno pozitivnih rezultata iznose 96.3%, ako se koriste solubilni endoglin, placentalni faktor rasta i najniži Pulzatilni indeks arterija uterina. Placentalni protein 13 prvog trimestra ima bolju predikciju ranog u odnosu na kasni početak bolesti. Fondacija za fetalnu medicinu je 2009. godine lansirala novi softver koji na osnovu ovih kombinovanih podataka preračunava rizik preeklampsije. Doppler pregled arterija uterina u kombinaciji sa biohemijskim markerima je efikasno sredstvo skrininga preeklampsije, naročito one koja se rano ispoljava.

Ključne reči: Preeklampsija, skrining, prvi trimestar, morbiditet

Introduction

Preeclampsia (PE) complicates about 5% of all pregnancies worldwide, occurring mainly after 20th weeks of gestation. It is a major cause of maternal, fetal and neonatal morbidity and mortality. An inadequate invasion of trophoblasts with consequential placental ischemia as a result of insufficiently dilated uterine spiral arteries is the firste stage in the pathogenesis of pre-eclampsia. The second stage in pathogenessys of PE is thought to be the maternal response to abnormal placentation resulting from endothelial dysfunction and an imbalance in circulating angiogenic/vasculogenic factors such as soluble vascular endothelial growth factor receptor-1, placental growth factor and the transforming growth factor-beta receptor endoglin[1]. The prognosis is much more severe when the desease develops very early in the pregnancy. Risk factors for pre-eclampsia are: chronic hypertension, advanced maternal age at first pregnancy, nephropathy, thrombophilia, multiple gestation and prior pregnancy with preeclampsia. The sooner the disease is detected and confirmed, the better maternal and

fetal prognoses are, so the major importance is to identify patients with risk factors with pre-eclampsia though an adequate screening method[2]. Early identification of the high-risk group for the development of PE is also important for future studies investigating the potential role of pharmacological interventions starting from the first trimester to improve placentation and reduce the prevalence of the disease[3].

Material and methods

The aim of this systematic review was to study the literature on the predictive potential of screening for preeclampsia based on serum markers and uterine artery Doppler velocity waveform assessment.

Results and discussion

The criteria for definitions of PE and GH(gestational hypertension) were given by the International Society for the Study of Hypertension in Pregnancy. In GH, the diastolic blood pressure should be ≥90 mm Hg on ≥2 occasions 4 hours apart developing after 20 weeks of gestation in previously normotensive women in the absence of significant proteinuria, and in PE there should be GH with proteinuria of ≥300 mg in 24 hours or 2 readings of ≥2 pluses on dipstick analysis of midstream or catheter urine specimens if no 24-hour collection is available. In PE superimposed on chronic hypertension, significant proteinuria should develop after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks of gestation in the absence of trophoblastic disease)[4]. The early-onset preeclampsia is defined as the onset before 34 weeks of pregnancy, the intermediate-onset PE between the 34 and 37 weeks and the late-onset PE after 37 weeks. Early onset disease is more likely to be associated with abnormal villous and vascular morphology, whereas in late onset disease, the placental morphology and histology are not dissimilar to those in controls. Late onset compared with early onset disease is more likely to be related to impaired glucose metabolism and a hyperdynamic-low peripheral resistance (as opposed to a low-cardiac output-vasoconstricted) maternal cardiovascular profile. Screening can be carried out in all three trimesters of pregnancy. Of course, it is best to to implement early in pregnancy, ie in the first trimester. However, we will mention some research on screening in the second and third trimesters of pregnancy. Group of authors has conducted screening in the second trimester getting into account serum inhibin-A combined with uterine artery Doppler performed at 20 weeks' gestation for the prediction of pre-eclampsia. Inhibin-A levels measured between 15 and 19 weeks' gestation subsequently had color flow pulsed Doppler of both uterine arteries at the time of the anomaly scan (mean 20.5, range 18-22 weeks' gestation). For a false-positive rate of 7%, the sensitivity using bilateral notches/mean resistance index > or = 0.65 was 60% with a positive likelihood ratio of 8.6 (confidence interval 5.7-12.6). For the same false-positive rate, when bilateral notches/mean resistance index > or = 0.55 and unilateral notches/mean resistance index > or = 0.65 were combined with inhibin-A > or = 1.0 multiples of the median, the sensitivity improved to 71%[5].

In second trimester the authors from another study have evaluated the importance of micro-albuminuria and uterine artery Doppler resistance index as a screening test for pre-eclampsia. Test for micro-albuminuria was done at 14 weeks, 18 weeks, 28 weeks and 34 weeks of gestation. Uterine artery Doppler resistance index (0.58 taken as cut-off) was recorded at 18 weeks of gestation. Sensitivity, specificity, positive and negative predictive value of micro-albuminuria was recorded as 66.67%, 93.24%, 44.44% and 97.18% respectively. The conclusion was that uterine artery Doppler study is a better screening test amongst the two[6,7].

In third trimester some other authors evaluated relationship of maternal and umbilical cord interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-alpha) serum levels with the existence and severity of preeclampsia. They have concluded that increased concentrations of IL-6, IL-8, and TNF-alpha in the maternal and umbilical serum play a significant role in pathogenesis of preeclampsia. Alterations in maternal and umbilical serum levels of IL-6, IL-8, and TNF-alpha may also play role in preeclampsia complicated by intrauterine growth retardation[8]. In the other study, authors investigated the levels and clinical significance of high sensitive-CRP (C-reactive protein), IL-6, TNF, homocysteine, folic acid and vitamin B12 measured in the third trimester; and correlations between these markers and the severity of preeclampsia and fetal birth

weight. They concluded that elevated level of hs-CRP is a useful parameter in the severity of clinical risk of pre-eclampsia in patients with BMI < 25 kg/m(2) at third trimester[9].

As we said earlier, today the greatest attention paid to screening in the early period of pregnancy, so the topic will be given special attention in the following text. Much effort has been put into assessing potential markers and their combination with other screening methods such as Doppler sonography. First-trimester uterine artery Doppler can identify over half of women who will develop preeclampsia[10]. The traditional method of screening for PE is maternal history. The likelihood of developing PE is increased in black and in nulliparous women, in those with a high body mass index (BMI), and in those with a previous or family history of PE. However, this kind of screening would identify approximately 30% of cases destined to develop early PE, requiring delivery before 34 weeks of gestation, and 20% of late PE, for a false-positive rate of 5%. Detection rates may be increased by a combination with maternal serum markers and 7 most studied serum markers are: ADAM12 -A Desintegrin And Metalloproteinase 12, fβ-hCG- free β subunit of human chorionic gonadotropin, Inhibin A, Activin A, PP13- Placental Protein 13, PlGF- Placental Growth Factor, and PAPP-A- pregnancy associated plasma protein-A[11,12].

There is evidence that, in a high proportion of pregnancies destined to develop PE at 11 to 13 weeks of gestation, the maternal mean arterial pressure (MAP) and uterine artery pulsatility index (PI) are increased, and the maternal serum concentration of the PAPP-A and PlGF are reduced[13]. Since this reduction is already visible in the first trimester, PlGF assay helps to identify women at high risk for pre-eclampsia at an early stage of pregnancy. PAPP-A and PlGF are significantly decreased during first trimester (0.53 multiple of the median (MoM) and 0.61 MoM respectively) in women who vill develope early-onset PE, whereas they were only mildly diminished in women who developed late PE. The detection rate of preeclampsia using PlGF alone for the early-onset preeclampsia is between 41% and 59% and for late-onset preeclampsia 33%[14]. At a 5% false-positive rate, the estimated respective detection rates of early PE, late PE, and GH were 93.1%, 35.7%, and 18.3% using the algorithm for early PE; 82.8%, 44.9%, and 23.2% using the algorithm for late PE; and 41.4%, 40.8%, and 34.1% using the algorithm for GH. The patient-specific risk for the development of these complications can be derived by combining maternal racial origin, BMI, and personal or family history of PE with the measurements of MAP, uterine artery PI, PAPP-A, and PlGF[15].

PlGF is a member of the vascular endothelial growth factor subfamily. It is expressed by trophoblast cells and has proangiogenic function. PE is resulting in an increased secretion of antiangiogenic factors such as sFlt-1 (soluble Fms-like tyrosine kinase-1) and sEng (soluble endoglin) in the maternal circulation. This process leads to a course of antagonizing the angiogenic factors such as PlGF. PAPP-A is a syncytiotrophoblast-derived metalloproteinase that enhances the mitogenic function of the insulin-like growth factors. Because the insulin-like growth factor system is believed to play a very important role in trophoblast invasion, low-serum PAPP-A is associated with a higher incidence of PE. MAP is increased in all types of hypertensive disorders, with the values being higher in those developing early PE and similar between late PE and GH. So, PAPP-A and PIGF is telling us much more about placental function and Uterine artery Doppler about uteroplacental circulation[16]. PP-13 appears to be an interesting marker for risk assessment of preterm PE but a weak marker for severe PE at term, and ineffective for identifying mild PE at term. Some other data, from different studies, suggested that first trimester serum PP-13 as a single marker in a low-risk population showed poor predictive performance [17,18].

Conclusion

It is clear that a single diagnostic marker does not have the strength to safely predict subsequent preeclampsia. For this reason, it seems to be promising to use history, biophysical, and several biochemical parameters to ensure the best possible detection rate achieved. Our systematic review underscore a real need to develop experimental approaches that would allow comparison of candidate biomarker combinations. Such information would likely improve statistical power and our capability for finding a screening procedure that can better identify risk women. Studies performed during the first trimester could guide the assessment of new prophylactic interventions (such as acetylsalicylic acid) in at-risk women. The high detection rate for early PE is very

important because it is this rather than late PE or GH that is associated with increased risk of perinatal mortality and morbidity and both short-term and long-term maternal complications. Finally, we have to ask ourselves: how far it may succeed in establishing the first-trimester screening tests with the consecutive possible prevention by aspirin and/or low-molecular-weight heparin, as a screening in a large, unselected collective? Screening for preeclampsia should be for a much larger collective of pregnant women, not at least because of the higher risk to get preeclampsia as a chromosomal abnormal baby and the ease of prophylaxis. Another important reason for early preeclampsia risk calculation is the fact that women with preeclampsia have a higher life-time risk for getting cardiovascular diseases. Further studies are expected, that show which of the biochemical markers are really useful in clinical practice. The relation of costs and benefit must be explored. It would be desirable in the future to integrate preeclampsia risk calculation to the regular prenatal care in first trimester.

Literature

1. Foidart JM, Munaut C, Chantraine F, Akolekar R, Nicolaides KH. Maternal plasma soluble endoglin at 11-13 weeks' gestation in pre-eclampsia. Ultrasound Obstet Gynecol. 2010;35(6):680-7. doi: 10.1002/uog.7621.

2. Poon LC, Karagiannis G, Leal A, Romero XC, Nicolaides KH. Hypertensive disorders in pregnancy: screening by uterine artery Doppler imaging and blood pressure at 11-13 weeks. Ultrasound Obstet Gynecol. 2009;34(5):497-502. doi: 10.1002/uog.7439.

3. Scazzocchio E, Figueras F. Contemporary prediction of preeclampsia. Curr Opin Obstet Gynecol. 2011;23(2):65-71. doi: 10.1097/GCO.0b013e328344579c.

4. Poon LC, Stratieva V, Piras S, Piri S, Nicolaides KH. Hypertensive disorders in pregnancy: combined screening by uterine artery Doppler, blood pressure and serum PAPP-A at 11-13 weeks. Prenat Diagn. 2010;30(3):216-23. doi: 10.1002/pd.2440.

5. Aquilina J, Thompson O, Thilaganathan B, Harrington K. Improved early prediction of pre-eclampsia by combining second-trimester maternal serum inhibin-A and uterine artery Doppler. Ultrasound Obstet Gynecol. 2001;17(6):477-84.

6. Mukhopadhyay A, Sharma P, Dasgupta S, Dasgupta S, Sharma PP, Ghosh TK. Prediction of pre-eclampsia: comparative analysis of two screening tests. J Indian Med Assoc. 2012;110(8):546-7.

7. Kang A, Struben H. Pre-eclampsia screening in first and second trimester. Ther Umsch. 2008;65(11):663-6. doi: 10.1024/0040-5930.65.11.663.

8. Tosun M, Celik H, Avci B, Yavuz E, Alper T, Malatyalioğlu E. Maternal and umbilical serum levels of interleukin-6, interleukin-8, and tumor necrosis factor-alpha in normal pregnancies and in pregnancies complicated by preeclampsia. J Matern Fetal Neonatal Med. 2010;23(8):880-6. doi: 10.3109/14767051003774942.

9. Guven MA, Coskun A, Ertas IE, Aral M, Zencirci B, Oksuz H. Association of maternal serum CRP, IL-6, TNF-alpha, homocysteine, folic acid and vitamin B12 levels with the severity of preeclampsia and fetal birth weight. Hypertens Pregnancy. 2009;28(2):190-200. doi: 10.1080/10641950802601179.

10. Bahado-Singh RO, Jodicke C. Uterine artery Doppler in first-trimester pregnancy screening. Clin Obstet Gynecol. 2010;53(4):879-87. doi: 10.1097/GRF.0b013 e3181fbb65d.

11. Kuc S, Wortelboer EJ, van Rijn BB, Franx A, Visser GH, Schielen PC. Evaluation of 7 serum biomarkers and uterine artery Doppler ultrasound for first-trimester prediction of preeclampsia: a systematic review. Obstet Gynecol Surv. 2011;66(4):225-39. doi: 10.1097/OGX.0b013e3182227027.

12. Baumann MU, Bersinger NA, Surbek DV. Serum markers for predicting pre-eclampsia. Mol Aspects Med. 2007;28(2):227-44.

13. Di Lorenzo G, Ceccarello M, Cecotti V, Ronfani L, Monasta L, Vecchi Brumatti L, Montico M, D'Ottavio G. First trimester maternal serum PIGF, free β-hCG, PAPP-A, PP-13, uterine artery Doppler and maternal history for the prediction of preeclampsia. Placenta. 2012;33(6):495-501. doi: 10.1016/j.placenta.2012.03.003

14. Audibert F, Boucoiran I, An N, Aleksandrov N, Delvin E, Bujold E, Rey E. Screening for preeclampsia using first-trimester serum markers and uterine artery Doppler in nulliparous women. Am J Obstet Gynecol. 2010;203(4):383. e1-8. doi: 10.1016/j.ajog.2010.06.014.

15. Onwudiwe N, Yu CK, Poon LC, Spiliopoulos I, Nicolaides KH. Prediction of pre-eclampsia by a combination of maternal history, uterine artery Doppler and mean arterial pressure. Ultrasound Obstet Gynecol. 2008;32(7):877-83. doi: 10.1002/uog.6124.

16. Papageorghiou AT, Campbell S. First trimester screening for preeclampsia. Curr Opin Obstet Gynecol. 2006;18(6):594-600.

17. Spencer K, Cowans NJ, Chefetz I, Tal J, Meiri H. First-trimester maternal serum PP-13, PAPP-A and second-trimester uterine artery Doppler pulsatility index as markers of pre-eclampsia. Ultrasound Obstet Gynecol. 2007;29(2):128-34.

18. Khalil A, Cowans NJ, Spencer K, Goichman S, Meiri H, Harrington K. First trimester maternal serum placental protein 13 for the prediction of pre-eclampsia in women with a priori high risk. Prenat Diagn. 2009;29(8):781-9. doi: 10.1002/pd.2287.

Author for correspondence:
Dr Aleksandar Grdinić
Ulica Džordža Vašingtona br 6/Unistan
153-Podgorica
aleksandargrdinic@yahoo.com
branavracevic@hotmail.com

851