



Viti i XIV-të i Botimit, Nr. 2,
Dhjetor 2022

VLERA PREDIKTIVE E DOPPLERIT TË ARTERIEVE UTERINE NË TREMUIJORIN E PARË PËR PREEKLAMPSINË

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Abstrakt

Qëllimi: Ky studim ka për qëllim të evidentojë rëndësinë e indeksit të pulsilitetit (PI) të arterieve uterine në tremujorin e parë të shtatzënisë për parashikim e preeklampsisë (PE).

Përshkrimi i studimit: Ne kemi realizuar një studim prospektiv të grave shtazëna nga 11-13 javë me një fetus. UtA-Doppler’s është kryer në dy arteriet uterine e majta dhe e djathta) dhe është vlerësuar mesatarja e PI të arterieve uterine në lidhje me moshën gestacionale. Duke llogaritur mesataret e kurbave dhe sipërfaqet nën to u kalkulua performance e PI të arterieve uterine për parashikim e preeklampsisë.

Rezultatet: 300 shtatzëna që morrën pjesë në këtë studim u pa se 21 ose 7% zhvilluan PE, në term 12 ose 4% dhe preterm 9 ose 3%. Mesatarja e PI ulet në moshën gestacionale 11-13 javë ($p < 0.001$). Vlerat e ulta të PI-UtA në tremujorin e parë të kombinuara me karakteristikat amëtare mund të parashikojnë 45% të preeklampsisë preterm dhe një fals pozitivitet prej 15%.

Konkluzionet: Vlerat e ulta të PI të UtA në tremujorin e parë ndërmjet 11-13 javë shoqërohen me risk të lartë për zhvillimin e PE në preterm, por jo të preeklampsisë të zhvilluara në term.

Fjalë çelës: Doppler, Arterie Uterine, Indeksi i pulsilitetit, Pre-eklampsia

THE PREDICTION OF PREECLAMPSIA IN FIRST-TRIMESTER UTERINE ARTERY BY DOPPLER

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Abstract

Objective: This study aimed to estimate the performance of first-trimester uterine artery (UtA) pulsatility index (PI) for the prediction of preeclampsia (PE)

Study design: We conducted a prospective study of women with singleton gestation at 11 to 13 weeks. UtA-Doppler's was performed on both UtAs and the mean UtA-PI was reported in multiple of median (MoM) adjusted for gestational age. Using receiver operating characteristic curves and their area under the curves (AUC); we calculated the performance of UtA-PI for the prediction of PE.

Results: Out of 300 participants with completed follow-up, 12 (4%) developed PE, including 12 (4%) term and 6 (0.5%) preterm PE. Mean UtA-PI decreased with gestational age between 11 and 13 ^{6/7} weeks ($p < 0.001$). First-trimester UtA-PI was associated with preterm. UtA-PI combined with maternal characteristics could predict 45% of preterm PE at a false positive rate of 15%.

Conclusion: First trimester UtA-PI decreases with gestational age between 11 and 13 weeks and is associated with the risk of preterm but not term PE.

Key words: *Doppler, Uterine Artery, Pulsatility Index, Pre-eclampsia*

Introduction

Preeclampsia (PE) is a multisystem disorder of pregnancy defined by the combination of new-onset hypertension and proteinuria that contribute substantially to perinatal morbidity and mortality worldwide [1,2]. The etiology of PE remains controversial but it is now recognized that alterations in the growth and development of placental villi and their underlying vasculature play an important role in the pathogenesis of the disease [3]. The physiological transformation of uterine spiral arteries by the cytotrophoblast invading the myometrium is typically altered in the preterm forms of pre-eclampsia [4,5]. Recent evidence suggest that low-dose aspirin started before 16 weeks of gestation can prevent preterm pre-eclampsia [6–10]. Currently, low-dose aspirin is recommended in high-risk women based on previous pregnancy complications or other risk factors such as chronic hypertension. Uterine artery (UtA) pulsatility index (PI) measured by Doppler's ultrasound allows an indirect measure of placental vascular resistance which is usually increased in cases of incomplete transformation of uterine spiral arteries. Therefore, UtA-PI can be used to estimate the risk of PE [11–14]. In the second and third-trimester of pregnancy, UtA-PI is strongly related to the risk of PE and fetal growth restriction (FGR)(12). Some studies evaluated the role of UtA-Doppler's for prediction of PE in the first-trimester with controversial results(15–21). In women with previous PE, first-trimester UtA-PI was shown to discriminate those at high from those at low-risk for recurrence of PE and other adverse pregnancy outcomes, such as FGR and fetal death. We aimed to evaluate the performance of first trimester UtA-PI sampled at the level of internal cervical of,

as recommended from the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) for the prediction of PE and preterm PE in nulliparous women.

Materials and Methods

We conducted a prospective of nulliparous women (great obstetrical syndrome study) at the University Clinic of Obstetrics and Gynecology “Mbretësja Geraldine” between March 2019 and December 2020. Women with a singleton pregnancy were recruited between 11 and 13 weeks. Women with crown-rump length (CRL) below 45 mm or over 85 mm at the time of ultrasound examination were excluded. We excluded fetal demises up to 20 weeks of gestation, fetal structural anomalies, or chromosomal anomalies leading to medical termination of pregnancy. We also excluded women who reported taking daily aspirin over the course of their pregnancy. Informed consent was obtained from all women prior to study participation. Transabdominal ultrasound was conducted by experts using a Voluson S6 (GE Healthcare). CRL was measured and UtA-Doppler’s was performed on both uterine sides to measure and to calculate mean UtA-PI according to the ISUOG criteria (24)

Mean UtA-PI was log-transformed to obtain normal distribution and reported in multiple of median (MoM) adjusted for gestational age. Medical charts were reviewed for pregnancy outcomes (PE, FGR, fetal death) after delivery by research nurses blinded to first-trimester data. A maternal-fetal medicine subspecialist blinded to first-trimester data reviewed all cases of gestational hypertension, PE, preterm birth, and low birth weight to confirm all diagnoses. Family history of PE was not collected and therefore could not be included. Analyses were conducted with complete observations. The relationship between log₁₀ UtA-PI MoMs and PE-risk varied with time. The association was stronger with preterm cases of PE than term cases. In time-dependent models, the coefficient of the association between UtA-PI and PE for the time period before 37 weeks was 1.09 (standard error [SE] 0.30) against 0.22 (SE 0.11), subsequently. Using ROC curves, we observed that mean UtA-PI MoM was not associated with term PE (AUC $\frac{1}{4}$ 0.52; 95% CI: 0.48–0.56) but was associated with preterm PE (AUC $\frac{1}{4}$ 0.69; 95% CI: 0.59–0.78). At false-positive rates of 10%, UtA-PI alone could have predicted 16% of term PE and 40% of preterm PE.

Discussion

We observed that first-trimester mean UtA-PI is associated with the risk of preterm PE but not with the risk of term PE in nulliparous women. Combined with maternal characteristics, UtA-Doppler’s could predict about half of the preterm PE. Our findings suggest that UtA-PI should be included in first-trimester models for the prediction of preterm PE. American Journal of Perinatology Vol. 36 No. 9/2019 First-Trimester Uterine Artery Doppler’s to Predict We observed no difference of uterine artery pulsatility index between women who developed (red) and those who did not develop (blue) preeclampsia (A)[15-19]. On the other hand, we observed significant higher values of uterine artery pulsatility index in women who developed preterm preeclampsia compared with those who did not developed preterm preeclampsia. Our results agree with those of Melchior et al who observed that first-trimester UtA-PI is predictive of preterm but not term PE.16. However, this study was limited by its size (220 participants) and by the fact that UtA Doppler’s was sampled at the crossing of external iliac vessels in opposition with Doppler’s acquired at the level of internal cervical of in the first-trimester [20-22]. From literature and the current study, we could conclude that first-trimester UtA-PI is likely to be useful in the prediction of preterm PE in nulliparous women, when collected at the level of internal cervical os, when adjusted for gestational age, and when combined with maternal characteristics and ideally with additional biochemical markers such as pregnancy-associated plasma protein A (PAPP-A) and placental growth factor (PIGF) [23-25]. The current study has some limitations. First, UtA-Doppler’s were performed by a limited numbers of certified ultrasound technicians with strong experience in UtA-PI. It is possible that similar predictive values required a minimum of training and experience from the sonographers. It is possible that such information

could improve the predictive value of a model combining UtA-PI and maternal characteristics. With the recent publication of the ASPRE trial confirming the important reduction of preterm PE with low-dose aspirin when started at 11 to 13 weeks in high-risk women, it is very important to determine the optimal screening test in each population [26-28]. Prediction of term and preterm preeclampsia with first-trimester uterine artery pulsatility index alone or in combination with maternal characteristics

Conclusion: First-trimester UtA-PI decreases with gestational age between 11 and 13 weeks and is associated with the risk of preterm but not term PE.

References

1. World Health Organization International Collaborative Study of Hypertensive Disorders of Pregnancy. Geographic variation in the incidence of hypertension in pregnancy. *Am J Obstet Gynecol* 1988;158(01):80–83
2. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009;33(03):130–137
3. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet* 2010;376(9741):631–644
4. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The “Great Obstetrical Syndromes” are associated with disorders of deep placentation. *Am J Obstet Gynecol* 2011;204(03):193–201
5. Ogge G, Chaiworapongsa T, Romero R, et al. Placental lesions associated with maternal under-perfusion are more frequent in early-onset than in late-onset preeclampsia. *J Perinat Med* 2011; 39(06):641–652
6. Bujold E, Roberge S, Lacasse Y, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol* 2010;116(2, Pt 1):402–414
7. Roberge S, Giguère Y, Villa P, et al. Early administration of lowdose aspirin for the prevention of severe and mild preeclampsia: a systematic review and meta-analysis. *Am J Perinatol* 2012;29 (07):551–556
8. Roberge S, Villa P, Nicolaides K, et al. Early administration of lowdose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis. *Fetal Diagn Ther* 2012;31(03):141–146
9. Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. *Am J Obstet Gynecol* 2017;216(02):110–120
10. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017;377(07):613–622
11. Espinoza J, Romero R, Mee Kim Y, et al. Normal and abnormal transformation of the spiral arteries during pregnancy. *J Perinat Med* 2006;34(06):447–458
12. Cnossen JS, Morris RK, ter Riet G, et al. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. *CMAJ* 2008;178(06):701–711
13. Papageorgiou AT, Yu CK, Nicolaides KH. The role of uterine artery Doppler in predicting adverse pregnancy outcome. *Best Pract Res Clin Obstet Gynaecol* 2004;18(03):383–396
14. Poon LC, Volpe N, Muto B, Yu CK, Syngelaki A, Nicolaides KH. Second-trimester uterine artery Doppler in the prediction of stillbirths. *Fetal Diagn Ther* 2013;33(01):28–35
15. Martin AM, Bindra R, Curcio P, Cicero S, Nicolaides KH. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler at 11-14 weeks of gestation. *Ultrasound Obstet Gynecol* 2001;18(06):583–586

15. American Journal of Perinatology Vol. 36 No. 9/2019 First-Trimester Uterine Artery Doppler's to Predict Preeclampsia Demers et al.
16. Melchiorre K, Wormald B, Leslie K, Bhide A, Thilaganathan B. Firsttrimester uterine artery Doppler indices in term and preterm preeclampsia. *Ultrasound Obstet Gynecol* 2008;32(02):133–137
17. Plasencia W, Maiz N, Poon L, Yu C, Nicolaides KH. Uterine artery Doppler at 11 þ 0 to 13 þ 6 weeks and 21 þ 0 to 24 þ 6 weeks in the prediction of pre-eclampsia. *Ultrasound Obstet Gynecol* 2008; 32(02):138–146
18. Rizzo G, Capponi A, Cavicchioni O, Vendola M, Arduini D. First trimester uterine Doppler and three-dimensional ultrasound placental volume calculation in predicting pre-eclampsia. *Eur J Obstet Gynecol Reprod Biol* 2008;138(02):147–151
19. Poon LC, Staboulidou I, Maiz N, Plasencia W, Nicolaides KH. Hypertensive disorders in pregnancy: screening by uterine artery Doppler at 11-13 weeks. *Ultrasound Obstet Gynecol* 2009;34(02):142–148
20. Audibert F, Boucoiran I, An N, et al. Screening for preeclampsia using first-trimester serum markers and uterine artery Doppler in nulliparous women. *Am J Obstet Gynecol* 2010;203(04):383.e1–383.e8
21. 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(04):225–239
22. 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(05):497–502
23. Demers S, Bujold E, Arenas E, Castro A, Nicolaides KH. Prediction of recurrent preeclampsia using first-trimester uterine artery Doppler. *Am J Perinatol* 2014;31(02):99–104
24. Salomon LJ, Alfrevic Z, Bilardo CM, et al. ISUOG practice guidelines: performance of first-trimester fetal ultrasound scan. *Ultrasound Obstet Gynecol* 2013;41(01):102–113
25. Wright D, Akolekar R, Syngelaki A, Poon LC, Nicolaides KH. A competing risks model in early screening for preeclampsia. *Fetal Diagn Ther* 2012;32(03):171–178
26. O’Gorman N, Wright D, Syngelaki A, et al. Competing risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11-13 weeks gestation. *Am J Obstet Gynecol* 2016;214(01):103.e1–103.e12
27. Lefebvre J, Demers S, Bujold E, et al. Comparison of two different sites of measurement for transabdominal uterine artery Doppler velocimetry at 11-13 weeks. *Ultrasound Obstet Gynecol* 2012;40 (03):288–292
28. Velauthar L, Plana MN, Kalidindi M, et al. First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55,974 women. *Ultrasound Obstet Gynecol* 2014;43 (05):500–507