MÆDICA - a Journal of Clinical Medicine

ORIGINAL PAPER

MAEDICA – a Journal of Clinical Medicine
2023; 18(1): 50-54
https://doi.org/10.26574/maedica.2023.18.4.50

Correlation of Fetal Heart Rate, Uterine Artery Pulsatility Index, Pregnancy Associated Plasma Protein-A and Crown-Rump Length in Pre-eclampsia – a Prospective Cohort Study

Sedigheh HANTOUSHZADEH[a], Roghaye AHANGARI[b], Souzan SOUFIZADEH BALANEJI[c], Azin GHAMARI[d, e], Maryam HASHEMNEJAD[f], Solmaz PIRI[g]

[a]Maternal, Fetal and Neonatal Research Center, Tehran University of Medical Science, Tehran, Iran

[b]Qom University of Medical Science, Qom, Iran

[c]Urmia University of Medical Sciences, Urmia, Iran

[d]Growth and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran

[e]Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

[f]Department of Obstetrics and Gynecology, School of Medicine, Kamali Hospital, Alborz University of Medical Sciences, Alborz, Iran

[g]Obstetrician and Gynecologist, Perinatalogist, Director of International Affairs of National Association of Iranian Gynecologists and Obstetricians (NAIGO), Ambassador of ISUOG in Middle East and North Africa

ABSTRACT

Background: *The prevalence of pre-eclampsia (PE) as a systemic disease in pregnancy is about 3-5%, but it is still one of the most important causes of maternal and infant mortality worldwide. This study aimed to investigate the association between fetal heart rate (FHR) and uterine artery pulsatility index (UtA-PI) in Doppler.*

Methods: *The current cohort study was carried out on 317 pregnant women with a gestational age of 11 to 13 weeks and six days. Mothers were followed up from the first trimester until the delivery between*

Address for correspondence:
Maryam Hashemnejad
Postal address: Department of Obstetrics and Gynecology, School of Medicine, Kamali Hospital, Alborz University of Medical Sciences, Alborz, Iran
Tel: +989127026961; email: maryamhasheminejad98@gmail.com

Article received on the 18th of November 2022 and accepted for publication on the 9th of March 2023

March 2019 and March 2020. Uterine artery pulsatility index, FHR and ductus venosus pulsatility index (DVPI) were recorded. Finally, the Doppler index of ductus venosus, FHR and other design variables were compared between the two groups with and without preeclampsia.

Results: *Subjects' mean body mass index (BMI) was 25.31±3.98 kg/m^2. The UtA-PI was correlated with Crown rump length (CRL) (r=-0.207, p=0.001), pregnancy associated plasma protein-A (PAPP-A) (r=-0.167, p=0.003), FHR (r=0.14, p=0.011) and uterine artery multiples of the median (UA MoM) (r=0.990, p=0.001), with the last one showing a strong positive correlation with CRL; PAPP-A had a reverse correlation with UA MoM (r=-0.171, p=0.002) and UtA-PI (r=-0.167, p=0.003), while FHR had a poor correlation with UA MoM (r=0.118, p=0.035) and UtA-PI (r=0.142, p=0.011).*

Conclusion: *Uterine artery multiples of the median (UA MoM) was found to have a strong correlation with UtA-PI and, but a reverse correlation with PAPP-A. Intrauterine growth restriction (IUGR) had a significant association with FHR and UtA-PI. These findings imply the necessity of further future follow-up of offspring with a history of increased UtA-PI or maternal PE for cardiac alteration.*

Keywords: fetal heart rate, uterine artery pulsatility index, Doppler, pregnancy.

INTRODUCTION

Pre-eclampsia (PE) is a systemic disease in pregnancy that is defined as high blood pressure with proteinuria after the 20th week of pregnancy. It has a prevalence of about 3-5%, but it is still one of the most important causes of maternal and infant mortality in the world (1). Pre-eclampsia is a multifactorial clinical syndrome in which more than one pathological process plays a role in its pathogenesis (2). Inadequate activity of trophoblasts in spiral arteries reduces placental blood supply and ischemia, which causes the release of various factors, including angiogenic, inflammatory factors and angiotensin 1 antibodies. These factors enter the mother's blood stream and cause an inflammatory response, activation and endothelial dysfunction in different organs of the mother, causing clinical symptoms such as vascular contraction, increased vascular resistance and increased blood pressure. Also, fetal syndrome occurs in the fetus, which includes fetal growth restriction, amniotic fluid volume reduction, and fetal hypoxia. Fetal hypoxia may occur from very early stages of pregnancy (3). Placental hypoxia and ischemia leads to increased maternal cytokines (3), which transfer through the placenta (4) and therefore, the fetal cardiac function could also be altered as the maternal cardiovascular system is affected by PE-related cytokine increment. One of the ways to check the blood supply to the fetus is to check fetal heart rate and fetal blood vessel Doppler. Various studies (5-7) showed a relationship between the uterine artery pulsatility index (UtA-PI) in the first trimester of pregnancy and an increase in the incidence of PE in pregnant women. Several previous studies have revealed a significant association between abnormal first trimester UtA-PI and occurrence of intrauterine growth restriction (IUGR) (8, 9). The UtA-PI, combined with mean arterial pressure (MAP) and maternal baseline characteristics during the first trimester, could detect 50%-73% of upcoming IUGRs (8). Early identification of increased risk for IUGR development becomes more important for patients who need targeted long-term follow-up for neonatal complications, including cardiovascular involvement. In this regard, we aimed to assess the association between different Doppler indices and fetal heart rate (FHR). ❑

METHODS AND MATERIALS

In the present cohort study we included 317 pregnant women with a gestational age of 11 to 13 weeks and six days after obtaining their written informed consent for voluntary participation to our research. Subjects were investigated from the first trimester until the delivery to identify the association of UtA-PI, FHR and ductus venosus pulsatility index (DVPI) and occurrence of PE in a prospective study which was carried out between March 2019 and March 2020 based on the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) standard. The sample size calculation was based on the formula of estimating a mean in a group with a mean of 0.93 and standard deviation (SD) of 0.17 (5),

and with a beta of 0.02 and alpha of 0.05. The contact numbers of patients were obtained and their follow-up was done in terms of PE occurrence until delivery. Finally, the Doppler index of ductus venosus, FHR and other design variables were compared and analyzed in two groups with and without PE.

Ethical issue

The present study was conducted in accordance with the tents of the Declaration of Helsinki, and it was approved by the Ethics Committee of Tehran University of Medical Sciences, Iran. All study protocols were accepted by the institutional ethical committee of Tehran University of Medical Sciences (IR.TUMS.IKHC.REC.1398.001). Accordingly, written informed consent was taken from all participants before the commencement of the study.

Statistical analysis

At the end of the study, data analysis was performed using SPSS version 21 with related tests such as paired t-test. A p value < 0.05 was considered significant. ❑

TABLE 1. Comparison of mean PAPP-A in subjects with/without a history of cesarean section

Variable		Mean	SD	P value
History of cesarean section	Yes	1.07	0.60	0.745
	No	1.08	0.57	

TABLE 2. Comparison of mean PAPP-A in subjects based on the placenta position

Variable		Mean	SD	P value
Placenta position	Anterior	1.08	0.57	0.789
	Lateral	1.32	0.88	
	Left lateral	1.06	0.74	
	Posterior	1.07	0.56	

RESULTS

Subjects had a mean age of 25.31±3.98 years and 76 (23.7%) of them had a history of cesarean section. The PAPP-A score in mothers with and without a history of cesarean section showed no statistically significant difference (P=0.745) (Table 1).

TABLE 3. Correlation of CRL, MAP, birth weight, PAPP-A, DV-PI, BMI, UA MOM, UtA-PI and FHR

Variable		PAPP-A	DV-PI	BMI	UA MOM	UtA-PI	FHR
CRL	Correlation	0.053	-0.097	0.173	-0.101	-0.207	-0.306
	P value	0.343	0.085	0.002	0.070	0.001	0.001
PAPP-A	Correlation	1	-0.071	-0.104	-0.171	-0.167	0.029
	P value	-	0.211	0.064	0.002	0.003	0.610
DV-PI	Correlation	-0.071	1	0.038	0.082	0.085	0.052
	P value	0.211	-	0.505	0.145	0.134	0.355
BMI	Correlation	-0.104	0.038	1	-0.002	-0.076	0.005
	P value	0.064	0.505	-	0.966	0.175	0.926
UA MOM	Correlation	-0.171	0.082	-0.002	1	0.990	0.118
	P value	0.002	0.145	0.968	-	0.001	0.035
UtA-PI	Correlation	-0.167	0.085	-0.076	0.990	1	0.142
	P value	0.003	0.134	0.175	0.001	-	0.011
FHR	Correlation	0.029	0.052	0.005	0.118	0.142	1
	P value	0.610	0.355	0.926	0.035	0.011	-
MAP	Correlation	0.044	0.009	0.142	-0.105	-0.110	0.091
	P value	0.431	0.871	0.011	0.061	0.049	0.104
Birth weight	Correlation	0.022	0.010	0.012	0.026	0.016	0.041
	P value	0.692	0.859	0.836	0.644	0.777	0.471

The PAPP-A score in mothers based on the placenta position showed no statistically significant difference (P=0.789) (Table 2).

The UA-PI was correlated with Crown rump length (CRL) (r=-0.207, p=0.001), PAPP-A (r=-0.167, p=0.003), FHR (r=0.14, p=0.011) and UA MoM (r=0.990, p=0.001), with the last one showing a strong positive correlation with CRL; PAPP-A had a reverse correlation with UA MoM (r=-0.171, p=0.002) and UtA-PI (r=-0.167, p=0.003), while FHR had a poor correlation with UA MoM (r=0.118, p=0.035) and UtA-PI (r=0.142, p=0.011). In more detail, PE was developed for eight subjects, DV-PI was not different among women with and without PE (p=0.554), but the UtA-PI (p=0.024) and UA MoM (p=0.018) and the mean arterial pressure (MAP) (p=0.018) were different (Table 3).

DISCUSSION

Generally, systematic Doppler evaluations can anticipate placental dysfunction as the fetal growth restriction or PE or both. Previous studies indicated that high uterine artery impedance was associated with PE occurrence (10, 11). Uterine artery measurements can predict the development of PE, maternal and fetal complications, and IUGR (12). The findings of the current study showed a significant association between FHR and UtA-PI. This result indicates that fetal cardiac abnormality develops as the maternal abnormal placentation exists. Particularly in individuals with PE, the secretion of the inflammatory cytokines and endothelial dysfunction affects the maternal cardiovascular system; spiral artery remodeling in the first trimester, followed by increased vascular stiffness and resistance, generalized vasoconstriction, decreased cardiac output, and diastolic dysfunction left ventricular (LV) remodeling caused by increased after-load are among the most common maternal cardiac complications (13). The fetus is as well affected by an increased level of cytokines such as TNF-α produced by the decidua and placenta (14). These findings imply that cytokines affecting the maternal cardiovascular system could affect the fetal cardiovascular system likewise. Several studies showed the effects of PE on fetal and neonatal cardiac alterations early after labor; diastolic cardiac dysfunction, pulmonary edema, decreased cardiac myocardium wall thickness and cardiomyocyte proliferation in rats, as well as increased aortic intima-media thickness, have been pointed out (15).

In a study by Karampas *et al* (5), 541 pregnant women were examined. They first underwent an ultrasound screening between 11 and 13 weeks and six days in terms of major fetal anomalies, NT, UtA-PI and DV-PI. Simultaneously, biochemical markers including PAPP-A, placental growth factor (PlGF), sFlt-1 (soluble fms-like tyrosine kinase), asymmetric dimethylarginine (ADMA), neutrophil gelatinase-associated lipocalin (NGAL) and matrix metallopeptidase 9 (MMP-9) was checked for them. Among the results obtained from regression analysis, BMI and NGAL were able to predict 70% of PE cases. By adding UtA-PI and DVPI to the regression model, its sensitivity in predicting PE reached 77.8%. In a study by Karakoc *et al* (7), 174 pregnant women underwent ultrasound and DV Doppler examination. Those with a reverse wave in Doppler DV had a higher incidence of PE and diabetes mellitus than the control group (15 and 23%). In a study by Yazicioglu *et al* (16), the amount of abnormal Doppler DV in the group with PE was significantly higher than that in the control group (21% versus 4.4%). Additionally, in a study by Wright *et al* (6), 61,174 pregnant women were examined by ultrasound in the first and second trimesters. Maternal mean arterial blood pressure, UtA-PI and PlGF can predict 90% of early-PE and 75% of PE before 37 weeks. In a study by Seravalli *et al* (17), 2,267 pregnant women were examined in the first trimester of pregnancy. There was a higher rate of bilateral notching of the uterine artery, a higher mean of UtA-PI and DV-PI in pregnancies that eventually led to the birth of a small-for-gestational age (SGA) baby. These results were consistent with our findings, showing the predictive effect of Doppler finding in maternal-related outcomes. ❑

CONCLUSION

There was a strong correlation between UtA-PI and UA MoM, but a reverse correlation between PAPP-A and UA MoM. Malplacentation indicated by abnormal UtA-PI causes IUGR, as shown by the significant association with FHR and UtA-PI. These findings imply the necessity of further future follow-up of offspring with a his-

tory of increased UtA-PI or maternal PE for cardiac alteration. ❑

Conflict of interest: none declared.
Financial support: none declared.

Acknowledgement: The authors would like to express their gratitude to the "Maternal, Fetal and Neonatal Research Center" of Tehran University of Medical Science for their help.

References

1. **Cunningham FG, Leveno KJ, Bloom SL.** *Williams Obstetrics.* Mc Graw-Hill Education. 25th edition. 2018, p 713.
2. **James D, Steer PJ, Weiner CP.** *High-Risk Pregnancy: Management Options.* Cambridge University Press. 5th edition. 2017, pp 867-878.
3. **Benyo DF, Miles TM, Conrad KP.** Hypoxia stimulates cytokine production by villous explants from the human placenta. *J Clin Endocrinol Metab* 1997;82:1582-1588.
4. **Zaretsky MV, Alexander JM, Byrd W, Bawdon RE.** Transfer of inflammatory cytokines across the placenta. *Obstet Gynecol* 2004;103:546-550.
5. **Karampas GA, Eleftheriades MI, Panoulis KC, et al.** Prediction of pre-eclampsia combining NGAL and other biochemical markers with Doppler in the first and/or second trimester of pregnancy. A pilot study. *Eur J Obstet Gynecol Reprod Biol* 2016;205:153-157.
6. **Wright A, Wright D, Syngelaki A, et al.** Two-stage screening for preterm preeclampsia at 11-13 weeks' gestation. *Am J Obstet Gynecol* 2019;220:197.e1-.e11.
7. **Karakoç G, Yavuz A, Eriş Yalçın S, et al.** The significance of reverse flow in ductus venosus between sixteen and twenty weeks' gestation. *Turkish J Obstet Gynecol* 2017;14:23-27.
8. **Crovetto F, Crispi F, Scazzocchio E, et al.** First-trimester screening for early and late small-for-gestational-age neonates using maternal serum biochemistry, blood pressure and uterine artery Doppler. *Ultrasound Obstet Gynecol* 2014;43:34-40.
9. **Triunfo S, Crovetto F, Scazzocchio E, et al.** Contingent versus routine third-trimester screening for late fetal growth restriction. *Ultrasound Obstet Gynecol* 2016;47:818-818.
10. **Papageorghiou AT, Christina K, Nicolaides KH.** The role of uterine artery Doppler in predicting adverse pregnancy outcome. *Best Pract Res Clin Obstet Gynaecol* 2004;18:383-396.
11. **Papageorghiou AT, Yu CKH, Cicero S, et al.** Second-trimester uterine artery Doppler screening in unselected populations: a review. *J Matern Fetal Neonatal Med* 2002;12:78-88.
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;178:701-711.
13. **Morris RK, Selman TJ, Verma M, et al.** Systematic review and meta-analysis of the test accuracy of ductus venosus Doppler to predict compromise of fetal/neonatal wellbeing in high risk pregnancies with placental insufficiency. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2010;152:3-12.
14. **Odibo AO, Zhong Y, Goetzinger KR, et al.** First-trimester placental protein 13, PAPP-A, uterine artery Doppler and maternal characteristics in the prediction of pre-eclampsia. *Placenta* 2011;32:598-602.
15. **Hoodbhoy Z, Hasan BS, Mohammed N, Chowdhury D.** Impact of pre-eclampsia on the cardiovascular health of the offspring: a cohort study protocol. *BMJ Open* 2018;8:e024331.
16. **Yazıcıoğlu HF, Demirbas Ersu R, Dülger Çetin Ö, et al.** P15.04: Ductus venosus Doppler waveform analysis: a new tool for the early prediction of preeclampsia? *Ultrasound Obstet Gynecol* 2005;26.
17. **Seravalli V, Block-Abraham DM, Turan OM, et al.** First-trimester prediction of small-for-gestational age neonates incorporating fetal Doppler parameters and maternal characteristics. *Am J Obstet Gynecol* 2014;211:261.e1-e8.