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The role of first trimester uterine artery Doppler in the prediction of preeclampsia

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Abstract

Objective: Our aim was to assess the relationship between first-trimester uterine artery pulsatility index (UtA PI) and the development of preeclampsia.

Methods: Uterine artery pulsatility index measurements were recorded in 412 nulliparous women with singleton pregnancies at 11+0 to 13+6 weeks of gestation. Predicted detection rates for preeclampsia and early preeclampsia were calculated for threshold UtA PI values.

Results: Preeclampsia and early preeclampsia were present 9.4% and 3.1% of pregnancies respectively. Mean UtA PI was 2.5±0.9 in group who developed preeclampsia and 1.7±0.5 in non-preeclamptic group (p<0.001). Receiver-operating characteristics (ROC) curve analysis for prediction of preeclampsia and early preeclampsia for UtA PI, the area under curve was 0.79 and 0.83, respectively. In predicting preeclampsia, the sensitivity, positive prediction value and negative prediction value of UtA PI at 2.56 threshold value for 5% false positivity were found as 45.5%, 50% and 94.4%, respectively. The sensitivity, specificity, positive prediction value and negative prediction value of 2.56 threshold value of uterine artery pulsatility index in early-onset preeclampsia prediction were found as 63.6%, 93.3%, 23.3% and 98.8%, respectively. The sensitivity, positive prediction value and negative prediction value of UtA PI at 2.72 threshold value for 5% false positivity in predicting early-onset preeclampsia were found as 45.5%, 23.8% and 98.2%, respectively. The sensitivity, specificity, positive prediction value and negative prediction value at 2.72 threshold value of uterine artery pulsatility index in predicting preeclampsia were found as 33.3%, 96.9%, 52.4% and 93.4%, respectively.

Conclusion: Uterine artery Doppler at 11-14 weeks of gestation identifies about 65% of women who develop early preeclampsia.

Key words: Preeclampsia, uterine artery Doppler, uterine artery pulsatility index.

İlk trimester uterin arter Doppler incelemesinin preeklampsi öngörüsündeki yeri

Amaç: Bu çalışmada ilk trimesterde uterin arter pulsatilite indeksi (UtA PI) ölçümünün preeklampsi gelişimi ile olası ilişkisini incelemek amaçlanmıştır.

Yöntem: Dört yüz on iki nullipar tekil gebenin 11+0 ile 13+6 gebelik haftasında UtA PI ölçümleri kaydedildi. Preeklampsi ve erken başlangıçlı preeklampsi öngörüleri için eşik UtA PI değerleri için saptama oranları hesaplandı.

Bulgular: Olguların %9.4'ünde preeklampsi ve %3.1'inde erken başlangıçlı preeklampsi tespit edildi. Preeklampsi gelişen grupta ortalama UtA PI 2.5±0.9 iken preeklampsi gelişmeyen grupta ortalama UtA PI 1.7±0.5 olarak saptandı (p<0.001). Uterin arter pulsatilite indeksi değerinin preeklampsi ve erken başlangıçlı preeklampsi ile ilişkisini işlem karakteristik (ROC) eğrisi ile değerlendirdiğimizde; ROC eğrisi altında kalan alan sırasıyla 0.79 ve 0.83 idi. Preeklampsiyi öngörmede %5 yalancı pozitiflik için UtA PI'nin 2.56 eşik değerindeki duyarlılığı %45.5, pozitif kestirim değeri %50 ve negatif kestirim değeri %94.4 olarak bulundu. Uterin arter pulsatilite indeksi 2.56 eşik değerinin erken başlangıçlı preeklampsi öngörüsündeki duyarlılığı %63.6, özgüllüğü %93.3, pozitif kestirim değeri %23.3 ve negatif kestirim değeri %98.8 bulundu. Erken başlangıçlı preeklampsiyi öngörmede %5 yalancı pozitiflik için UtA PI'nin 2.72 eşik değerindeki duyarlılığı %45.5, pozitif kestirim değeri %23.8 ve negatif kestirim değeri %98.2 olarak bulundu. Uterin arter pulsatilite indeksi 2.72 eşik değerinin preeklampsi öngörüsünde duyarlılığı %33.3, özgüllüğü %96.9, pozitif kestirim değeri %52.4 ve negatif kestirim değeri %93.4 bulundu.

Sonuç: On bir ila on dört hafta uterin arter Doppleri tek başına erken başlangıçlı preeklampsi olgularının yaklaşık %65'ini tespit edilebilmektedir.

Anahtar sözcükler: Preeklampsi, uterin arter Doppler, uterin arter pulsatilite indeksi.

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Introduction

Preeclampsia (PE), is one of the most significant reasons of maternal-perinatal mortality and morbidity which affects about 2% of all pregnant women.[1,2] Today, identifying pregnants who are under risk in terms of serious complications such as PE has become one of the essential purposes of perinatal medicine. Although the physiopathology of PE and its complications are not fully understood yet, impaired placentation is the most supported hypothesis.[3,4] Histological studies support that preeclampsia occur due to the decrease in spiral artery invasion of trophoblasts causing resistance uteroplacental circulation.[5] Even though preeclamptic clinic findings appear after 20 weeks of gestation, trophoblastic invasion responsible for pathogenesis occur at first trimester.[6] Therefore, first trimester uterine artery Doppler evaluation may be a good non-invasive method to predict preeclampsia at advanced periods of pregnancy reflecting abnormal trophoblastic invasion. This study aims to examine possible relations of PE development with the measurement of uterine artery pulsatility index (UtA PI) at first trimester.

Methods

This study was conducted through the antenatal follow-up of 412 nulliparous women with singleton pregnancies referred to Department of Perinatology, Zeynep Kamil Training and Research Hospital, Istanbul for routine pregnancy follow-up between December 2011 and December 2012. The cases between 11+0 and 13+6 weeks of gestation were informed about the study, and their consents were obtained. The detailed medical histories of the cases were received including age, body mass index, medical background (PE history, chronic hypertension, thrombophilia, antiphospholipid syndrome, diabetes mellitus), medication history, conception methods (spontaneous, ovulation induction, IVF). Crown-rump length (CRL), UtA PI, and nuchal translucency (NT) were measured by the transabdominal ultrasound, and fetal anomaly screening was carried out. For UtA PI measurement by Doppler ultrasound, sagittal cross-section of uterus was taken, and cervical canal and internal servical os were defined. Both uterine arteries were defined by using color mapping while transducer was directed from one side to another side of cervix at internal os level. Pulsed wave Doppler was carried as insonation angle being below 50°, and sampling interval including entire vessel by 2 mm. Mean left and right UtA PI values were calculated. Ultrasonographic examinations were carried out by minor program assistants of perinatology department. Preeclampsia is defined by the International Society for the Study of Hypertension in Pregnancy as gestational hypertension above 90 mmHg on two separate occasions 4 hours apart accompanied by significant proteinuria of at least 300 mg in a 24-hour collection of urine or proteinuria of +2 on dipstick after 20 weeks of gestation in a previously normotensive woman.[7] Early preeclampsia and late preeclampsia were defined as the preeclampsia developing before and after 34 weeks of gestation, respectively.

SPSS 11.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Distribution of data was tested by Kolmogorov-Smirnov test. ANOVA test was used for the analysis of parametric data, and Mann-Whitney U test for the analysis of non-parametric data. The relationship of UtA PI value with preeclampsia was evaluated by ROC curve. $p<0.05$ was considered statistically significant.

Results

A total of 412 nulliparous women with singleton pregnancies were included to this study, and gestational results of 352 cases (85.4%) were reached. Four cases were excluded due to fetal anomaly, and 3 cases due to fetal death and miscarriage. The results of 53 cases could not be obtained. Mean maternal age was 28±4.2 years and the median gestational day on which ultrasound carried out was found as 84.4±2.3 days. PE developed in 33 (9.4%) of the cases. In 11 (3.1%) of these cases, early-onset PE was identified. Descriptive characteristics of the groups are given in the **Table 1**. UtA PI measurement could be done in all pregnants as defined. While UtA PI value was 2.5±0.9 in the group developing preeclampsia, it was found as 1.7±0.5 in the group not developing PE ($p<0.001$). Mean UtA PI in early and late PE cases was found as 2.7±0.8 and 2.4±1.0, respectively and no significant difference was detected ($p=0.15$). Also, there was no difference between early and late PE cases and cases without PE in terms of maternal age and gestational day with on which ultrasound carried out.

When we evaluate UtA PI value with PE by ROC curve, we found that the area under the influence of ROC curve was 0.79 (95% CI 0.70-0.88), and standard error was 0.046 ($p<0.001$) (**Fig. 1**). The sensitivity, positive prediction value and negative prediction value of UtA PI at 2.56 threshold value for 5% false positivity in predicting preeclampsia were found as 45.5%, 50% and

Table 1. Descriptive characteristics of the groups.

	Groups	N	Mean	Std. dev.	Std. error	Minimum	Maximum
Maternal age	Without PE	319	27.9	4.1	0.23	18	41
	Late PE	22	28.2	5.5	1.17	19	42
	Early PE	11	29.8	4.1	1.25	23	37
GD with ultrasound	Without PE	319	89.6	4.3	0.24	77	97
	Late PE	22	90.2	4.6	0.99	81	97
	Early PE	11	91.6	4.1	1.24	84	97
UtA PI	Without PE	319	1.7	0.5	0.03	0.57	5.04
	Late PE	22	2.4	1.0	0.20	1.20	4.76
	Early PE	11	2.7	0.8	0.25	1.56	3.77
Birth week	Without PE	319	39.2	1.1	0.06	35	42
	Late PE	22	39.1	1.6	0.33	36	42
	Early PE	11	32.9	2.3	0.69	29	36
Birth weight (g)	Without PE	319	3353.6	423.6	23.72	2050	4420
	Late PE	22	2982.5	389.4	83.01	2130	3800
	Early PE	11	1804.3	355.8	107.28	1220	2250
1st min. Apgar score	Without PE	319	7.2	0.9	0.05	4	9
	Late PE	22	6.2	1.2	0.25	4	9
	Early PE	11	4.9	1.5	0.46	2	8
5th min. Apgar score	Without PE	319	8.8	0.9	0.05	4	10
	Late PE	22	7.7	1.4	0.30	5	10
	Early PE	11	6.6	1.2	0.36	5	9

GD: gestational day, **PE:** preeclampsia, **UtA PI:** uterine artery pulsatility index

94.4%, respectively. The sensitivity, specificity, positive prediction value and negative prediction value of 2.56 threshold value of uterine artery pulsatility index in early-onset preeclampsia prediction were found as 63.6%, 93.3%, 23.3% and 98.8%, respectively (**Table 2**). When we evaluate UtA PI value with early-onset PE by ROC curve, we found that the area under the influence of ROC curve was 0.83 (95% CI 0.71-0.95), and standard error was 0.062 (p<0.001) (**Fig. 2**). The sensitivity, positive prediction value and negative prediction value of UtA PI at 2.72 threshold value for 5% false positivity in predicting early-onset preeclampsia were found as 45.5%, 23.8% and 98.2%, respectively. The sensitivity, specificity, positive prediction value and negative prediction value at 2.72 threshold value of uterine artery pulsatility index in predicting preeclampsia were found as 33.3%, 96.9%, 52.4% and 93.4%, respectively (**Table 2**). It was found that the evaluation of UtA PI was more significant for early-onset PE screening.

Discussion

In this study, our findings showed that first trimester UtA PI value in cases with PE were significantly difference than the cases without PE. The findings showed the relationship of UtA PI with late-onset preeclampsia more than early-onset preeclampsia, and they support that the etiologies of early- and late-onset preeclampsia

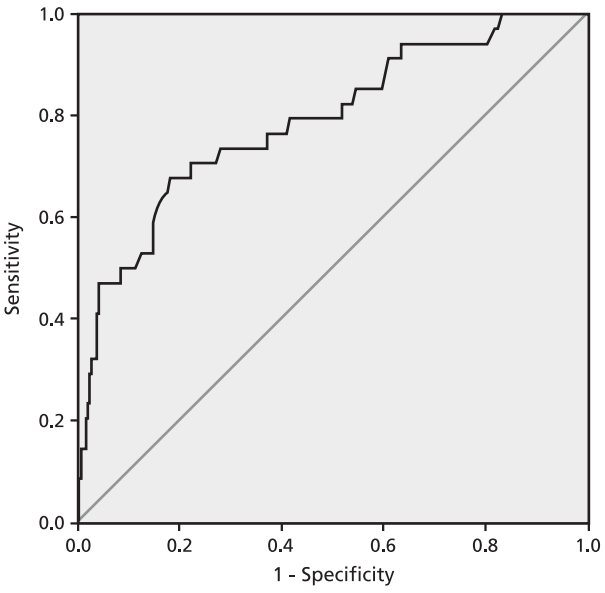

Fig. 1. Receiver operating characteristic (ROC) curve of the relationship between UtA PI value and preeclampsia.

Table 2. Threshold UtA PI values for preeclampsia and early-onset preeclampsia predictions.

Threshold		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
UtA PI ≥2.56	PE	45.5	95.3	50	94.4
	Early-onset PE	63.6	93.3	23.3	98.8
UtA PI ≥2.72	PE	33.3	96.9	52.4	93.4
	Early-onset PE	45.5	95.3	23.8	98.2

NPV: negative prediction value, **PE:** preeclampsia, **PPV:** positive prediction value, **UtA PI:** uterine artery pulsatility index

conditions may be different. The incidence of preeclampsia is 9.4%, and it is higher than the rates reported in the literature.[1,2] Patients under risk in terms of PE being nulliparous seem to explain the high incidence rate.

Additional findings of the study showed that UtA PI evaluation is more significant in early-onset PE screening, and they support the literature. UtA PI threshold values in PE and early-onset PE prediction for 5% false positivity were found as 2.56 and 2.72, respectively. While the sensitivity values of UtA PI at 2.56 threshold value for the prediction of PE and early-onset PE were 45.5 and 63.3 respectively, they were 33.3% and 45.5% for 2.72 threshold value of UtA PI. There are many studies evaluating uterine artery Doppler performance alone or together with maternal characteristics and biochemical parameters for PE prediction in first trimester. Martin et al. evaluated 3045 pregnant women at 11-14 weeks of gestation, they could only perform uterine artery Doppler measurement on 96% of the cases, and they found mean PI 95th percentile value of uterine artery as 2.35 which did not change significantly according to the week of gestation. The sensitivity of this value in terms of preeclampsia is 27%, and this rate was reported as 600% for preeclampsia which will require delivery before 32 weeks of gestation.[8] Gomez et al. reported in their study of the first trimester uterine artery Doppler performed on 999 low-risk patients that the sensitivity of PI value for preeclampsia was 24% when 95th percentile was taken as cut-off independent from the week of gestation.[9] In the study of Rizzo et al. including 348 nulliparous patients, the sensitivity values of abnormal mean UtA PI (>2.35) for predicting PE and the PE which will require delivery before 32 weeks of gestation were found as 50% and 66.7%, respectively. Similar to the results of our study, PE prevalence of the population analyzed including nulliparous patients expected to be higher explains the high sensitivity.[10] In the study of Plasencia et al., the area under the influence of ROC curve for the performance of first trimester UtA PI in preeclampsia screening was found as 0.677 and 0.895, respectively for early- and late-onset preeclampsia. Similar to our study, it was reported that UtA PI analysis was more significant in the early-onset PE screening.[11] Consequently, in first trimester uterine artery Doppler studies, weaker efficiency was reported for the preeclampsia prediction when compared with late second trimester uterine Doppler findings.[8,9,12] Especially for identifying severe preeclampsia cases which will require delivery before 34 weeks of gestation, uterine artery Doppler at 22-24 weeks of gestation is a safe method and it can especially predict more than 90% of severe cases.[13,14]

However, although the identification of patients with preeclampsia risk at second trimester improves pregnancy outcomes by more frequent maternal-fetal follow-up in terms of clinical findings of the disease and fetal growth restriction, it will decrease the efficiency of the prophylactic therapies such as low-dose

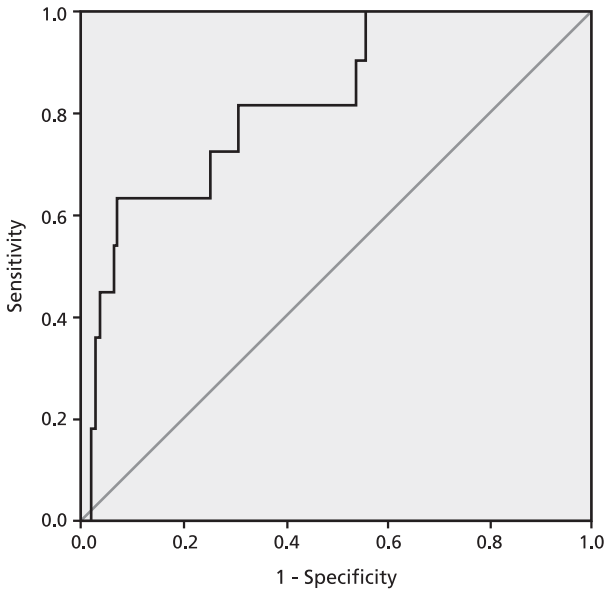

Fig. 2. Receiver operating characteristic (ROC) curve of the relationship between Ut-PI value and early-onset preeclampsia.

of aspirin. Therefore, identifying the high risk group at first trimester instead of second trimester will improve the efficiency of preventive treatment.[15] The recent studies have shown that using uterine artery Doppler as the screening method for the preeclampsia prediction in combination with maternal characteristics (maternal history, age, race etc.) and biochemical parameters (pregnancy-associated plasma protein-A, placental growth factor, placental protein 13 etc.) will help to predict about 90% of cases with early-onset preeclampsia which will especially require delivery before 34 weeks of gestation.[16-18]

This study showed that using uterine artery Doppler alone at first trimester for the prediction of early preeclampsia could not reach the sensitivity rate obtained by uterine artery Doppler carried out at 22-24 weeks of gestation or when combined with maternal characteristics and biochemical parameters. However, on the other hand, UtA PI measurement is a method which is easily applied especially for identifying cases with early preeclampsia. High negative predictive rate of screening may be used to identify low-risk group in terms of perinatal complications.

Conclusion

It has been found out that the evaluation of uterine artery pulsatility index is more significant for early-onset PE screening. Close follow-up of these cases and preventive treatments such as low-dose of aspirin may decrease the frequency of early-onset preeclampsia and related morbidity.

Conflicts of Interest: No conflicts declared.

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