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# Uterine Doppler velocimetry of the uterine arteries in the second and third trimesters for the prediction of gestational outcome

## *Doplervelocimetria da artéria uterina no segundo e terceiro trimestres para predição dos resultados gestacionais*

Original Article

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**Palavras-chave**
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## Abstract

**PURPOSE:** The aim of this longitudinal study was to investigate the value of uterine artery Doppler sonography during the second and third trimesters in the prediction of adverse pregnancy outcome in low-risk women. **METHODS:** From July 2011 to August 2012, a total of 205 singleton pregnant women presenting at our antenatal clinic were enrolled in this prospective study and were assessed for baseline demographic and obstetric data. They underwent ultrasound evaluation at the time of second and third trimesters, both included Doppler assessment of bilateral uterine arteries to determine the values of the pulsatility index (PI) and resistance index (RI) and presence of early diastolic notch. The endpoint of this study was assessing the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of Doppler ultrasonography of the uterine artery, for the prediction of adverse pregnancy outcomes including preeclampsia, stillbirth, placental abruption and preterm labor. **RESULTS:** The mean age of cases was 26.4±5.11. The uterine artery PI and RI values for both second (PI: 1.1±0.42 *versus* 1.53±0.59, p=0.002; RI: 0.55±0.09 *versus* 0.72±0.13, p=0.000 respectively) and third-trimester (PI: 0.77±0.31 *versus* 1.09±0.46, p=0.000; RI: 0.46±0.10 *versus* 0.60±0.14, p=0.010 respectively) evaluations were significantly higher in patients with adverse pregnancy outcome than in normal women. Combination of PI and RI >95$^{th}$ percentile and presence of bilateral notch in second trimester get sensitivity and specificity of 36.1 and 97% respectively, while these measures were 57.5 and 98.2% in third trimester. **CONCLUSIONS:** According to our study, it seems that uterine artery Doppler may be a valuable tool for the prediction of a variety of adverse outcomes in second and third trimesters.

## Resumo

**OBJETIVO:** O objetivo do presente estudo longitudinal foi avaliar o valor da ultrassonografia Doppler das artérias uterinas no segundo e terceiro trimestres de gestação para a predição de desfecho adverso da gravidez em mulheres de baixo risco. **MÉTODOS:** De julho de 2011 até agosto de 2012, 205 gestantes de feto único atendidas em nossa clínica de pré-natal foram incluídas no presente estudo prospectivo e avaliadas em termos de dados demográficos e obstétricos. As pacientes foram submetidas à avaliação de ultrassom durante o segundo e terceiro trimestres, incluindo avaliação Doppler das artérias uterinas bilaterais, visando determinar os valores do índice de pulsatilidade (IP) e do índice de resistência (IR), bem como a presença de incisura diastólica precoce. O desfecho do presente estudo foi a avaliação da sensibilidade, especificidade, valor preditivo positivo (VPP) e valor negativo preditivo (VNP) da ultrassonografia Doppler das artérias uterinas para a predição de desfechos adversos da gravidez, incluindo pré-eclâmpsia, natimortalidade, descolamento prematuro da placenta e trabalho de parto prematuro. **RESULTADOS:** A média de idade das gestantes foi de 26,4±5,11 anos. Os valores de IP e IR das artérias uterinas para o primeiro (IP: 1,1±0,42 *versus* 1,53±0,59, p=0,002; IR: 0,55±0,09 *versus* 0.72±0.13, p=0,000, respectivamente) e para o terceiro trimestre (IP: 0,77±0,31 *versus* 1,09±0,46, p=0,000; IR: 0,46±0,10 *versus* 0,60±0,14, p=0,010, respectivamente) foram significativamente maiores em pacientes com desfecho adverso da gravidez em relação às mulheres com desfecho normal. A combinação de IP e IR > percentil 95 e a presença de incisura bilateral apresentou sensibilidade e especificidade de 36,1 e 97%, respectivamente, no segundo trimestre e de 57,5 e 98,2% no terceiro trimestre. **CONCLUSÕES:** Com base no presente estudo, o *Doppler* das artérias uterinas parece ser ferramenta valiosa para a predição de uma variedade de desfechos adversos no segundo e terceiro trimestres de gestação.

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## Introduction

Preeclampsia, Intrauterine Growth Restriction (IUGR), abruption and stillbirth and other related complications are the consequence of defect in normal placentation during pregnancy[1]. In fact impaired placentation results in increased impedance to flow in uteroplacental circulation leading to hypoxemia and necrosis[2]. These complications are major causes of maternal and perinatal mortality[3]. The epidemiologic study of adverse pregnancy outcomes shows a higher rate of these complications in developing countries than in developed ones[4]. Predicting the risk of these outcomes helps obstetricians to consider appropriate antenatal surveillance and therapeutic intervention[5].

In normal pregnancy the resistance in the uterine artery flow decreases with advancing gestational age. Failure to get a low resistant circulation is associated with a subsequent risk of pregnancy adverse outcome[1]. Uteroplacental perfusion adequacy can be examined indirectly by uterine artery Doppler examination[6]. The fact that uterine artery Doppler velocimetry is a non-invasive technique which can be easily added to the current routine ultrasound examination without significant extra costs, plus its ability to determine a group of at-risk patients who would benefit from increased care, makes it an eligible candidate for a potential screening tool in predicting adverse pregnancy outcomes[7-9]. Previous studies have shown that uterine artery Doppler could improve screening efficacy for the prediction of adverse pregnancy outcomes in the first[10,11] and second[12,13] trimester of pregnancy with different sensitivity and specificity. Recently, some studies have continued uterine artery indices measurement in the third trimester of pregnancy[1,14]. However, many studies were retrospective or cross-sectional in design and could not truly show the relationship between uterine artery indices and the risk of adverse outcome[2,15,16]. It seems reasonable that serial evaluation of uterine artery Doppler velocimetry in second and third trimesters could help to determine normal development of fetal growth and deserve as a good predictor of pregnancy complications.

The aim of this prospective longitudinal study was to investigate the sensitivity, specificity, positive and negative predictive value of uterine artery Doppler ultrasonography indices including Resistance Index (RI) and Pulsatility Index (PI) in second and third trimesters for prediction of pregnancy complications.

## Methods

### Study population

Between July 2011 and August 2012, to a total of 250 singleton pregnant women attending our perinatal clinic for routine antenatal care were offered to participate in the project. Inclusion criteria were singleton pregnancies with normal fetuses, not taking aspirin, heparin, metformin or antihypertensive drugs. Cases with concomitant maternal diseases (*e.g.* morbid obesity, chronic hypertension, renovascular or connective tissue diseases) and those pregnancies that resulted in fetuses with structural or chromosomal abnormalities or Rh immunization were excluded from the study. Of 250 recruited participants who fulfilled the entry criteria, 205 women were able to complete the study and their data were included in the final analyses. Forty-five patients were excluded for different reasons, including lack of satisfaction for incorporation in the study and lack of complete records. The entire study protocol has been reviewed and approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences. Informed written consent was obtained from all study participants.

All recruited women were assessed at the 1st trimester screening for baseline demographic and obstetric data including age, parity, Body Mass Index (BMI) and past medical events. Smoking, alcohol and drug use were also determined.

### Study design

This was a single center observational prospective study conducted in the gynecology department of Tajrish Hospital in Tehran, Iran. Sample size was determined after consideration of type 1 statistical error <5% and type 2 statistical error <20%.

### Sonographic assessment

All pregnant women underwent ultrasound evaluation at the time of second trimester (15–20 weeks of gestation) as well as third trimester (30–34 weeks of gestation). During that scan, gestational age was confirmed by fetal crown-rump length measurement. All sonographic examinations were performed trans-abdominally by a single expert obstetric sonographer using a Hitachi EUB 525 Color Doppler® ultrasound scanner (Gyeonggi-do, South Korea) with multi-frequency volumetric trans-abdominal transducer. For ultrasound examination, a trans-abdominal transducer was placed on the lower quadrant of the abdomen, angled medially, and the color Doppler mode was used to identify the uterine artery where it crosses-over with the external iliac artery. The insonation was performed approximately 1 cm distal to the crossover point with a maximum angulation of 30º. The pulsed-wave Doppler was used to obtain waveforms. The calculation of the PI and RI of the uterine artery is made from a wave similar to at least three other symmetrical consecutive waveforms. The presence of early diastolic notch was also noted. A notch was considered to be present when there was a clearly defined upturn of the flow velocity waveform at the beginning of diastole, which was present in all four waveforms on both

occasions that each uterine artery was sampled. The mean PI and RI of the two uterine arteries were calculated manually by arithmetic mean between the PI and RI values of the left and right arteries respectively.

### Study outcomes

All pregnancy outcomes were obtained from the delivery suite database. Fetal and neonatal status and morbidity including baby Apgar scores, fetal distress or fetal death and admission to the neonatal intensive care unit were determined. All the examinations and data recording were performed by two senior resident physicians. The primary endpoint of this study is assessing the sensitivity and specificity of Doppler ultrasonography of the uterine artery, for the prediction of adverse pregnancy outcomes. Adverse outcomes included developments of preeclampsia (defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy[17]; recording of two diastolic blood pressure greater than 90 mmHg at least 4 hours apart in previously normotensive women, and proteinuria with minimum of 300 mg in 24 hours, or 2 readings of at least 2+ protein on dipstick analysis of urine), and birth weight less than the tenth percentile for gestation requiring delivery before 34 weeks. Other adverse outcomes were stillbirth, placental abruption (defined as presence of retro placental clot at delivery or vaginal bleeding leading to emergency delivery), preterm labor (labor 20–37 weeks of gestation), Apgar scores at one and five minutes less than 7, and gestational hypertension (blood pressure of 140/90 mmHg persistent after delivery).

### Statistical analysis

The sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Values (NPV) of uterine artery RI and PI in the prediction of adverse pregnancy outcomes were calculated by using the IBM SPSS version 18® software package (SPSS, Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation (SD); categorical data were expressed as numbers and percentages. Student *t*-test, Mann-Whitney U-test, and $\chi^2$ test or Fisher's exact test were used as appropriate.

## Results

Two hundred and five pregnant women were able to complete the study and their data were included in the final analyses. The mean age of the entire group was 26.4±5.11 (range 16 to 42 years). At the time of birth, the mean±SD of gestational age and birth weight were 268.2±22.3 days and 3051.5±657.0 g, respectively. The complete demographic characteristic and outcome data are shown in Table 1.

Mean PI and RI in our population was 1.2 and 0.6 respectively at second trimester and it was 0.85 and 0.5 at third trimester. The values of uterine artery PI and RI for both second and third trimesters evaluations were significantly higher in patients who developed pregnancy complications than in normal women (Table 2). Also, the prevalence of bilateral notches in patients with subsequent complications is significantly higher than those with normal pregnancies (55.5 *versus* 36.7% for second trimester and 35 *versus* 15% for third trimester evaluation).

Mean PI>95$^{th}$ percentile for gestational age at 15–20 weeks' gestation and at 30–34 weeks' gestation were present in 43 (21%) and 19 (9.5%) patients, respectively. The uterine artery 90$^{th}$, 95$^{th}$ and 97.5$^{th}$ RI percentiles were calculated to be 0.76, 0.80 and 0.82 at second trimester and (0.66, 0.7 and 0.72) at third trimester, respectively.

Sensitivity, specificity, PPV and NPV of uterine artery Doppler ultrasonography parameters for predicting the pregnancies adverse outcomes are summarized in

**Table 1.** Demographic characteristics and outcome data of the study population

| Characteristic | n (%) |
|---|---|
| Maternal age (years) - Mean±SD | 26.4±5.11 |
| Body mass index (kg/m²) - Mean±SD | 24.9±8.16 |
| Parity | |
| Nulliparous | 104 (50.7) |
| Multiparous | 101 (49.3) |
| Smoking >5/day | 4 (2) |
| History of previous abortion | 48 (23.4) |
| Pregnancy adverse outcome | 36/205 (17.6) |
| Preeclampsia | 7 (3.4) |
| Preterm labor | 8 (3.9) |
| Birth weight below tenth percentile | 23 (11.2) |
| Intrauterine fetal death | 2 (1) |
| Placental abruption | 1 (0.5) |
| Apgar scores at one and five minutes <7 | 9 (4.4) |

**Table 2.** Demographic characteristics and description of Doppler ultrasound findings in normal pregnancies *versus* pregnancies with adverse outcome

| Parameter | Normal pregnancies Mean±SD | Complicated pregnancies Mean±SD | p-value |
|---|---|---|---|
| n | 169 | 36 | |
| Demographic data | | | |
| Maternal age (years) | 25.5±3.1 | 26.9±8.5 | |
| Body mass index (kg/m²) | 24.1±3.2 | 25.2±8.8 | |
| Parity (%) | | | |
| Nulliparous - n (%) | 85 (50.3) | 19 (53) | |
| Multiparous - n (%) | 84 (49.7) | 17 (47) | |
| Second trimester | | | |
| PI | 1.1±0.42 | 1.53±0.59 | 0.002* |
| RI | 0.55±0.09 | 0.72±0.13 | 0.000* |
| Bilateral notches (%) | 36.7 | 55.5 | 0.041** |
| Third trimester | | | |
| PI | 0.77±0.31 | 1.09±0.46 | 0.000* |
| RI | 0.46±0.10 | 0.60±0.14 | 0.010* |
| Bilateral notches (%) | 15 | 35 | 0.011** |

*Mann-Whiney U-test. **$\chi^2$ test. PI: pulsatility index; RI: resistance index.

**Table 3.** Screening characteristics of uterine artery resistance indices during second and third trimesters for adverse pregnancy outcome

| Characteristic | Mean RI >95th percentile | Mean PI >95th percentile | PI and mean RI >95th percentile and bilateral notch |
|---|---|---|---|
| **Second trimester** | | | |
| Sensitivity (%) | 77.2 | 48.8 | 36.1 |
| Specificity (%) | 89.6 | 90.7 | 97 |
| PPV (%) | 47.2 | 58 | 72.2 |
| NPV (%) | 97 | 86.9 | 87.7 |
| **Third trimester** | | | |
| Sensitivity (%) | 58 | 63.1 | 57.5 |
| Specificity (%) | 95.8 | 89.5 | 98.2 |
| PPV (%) | 53.3 | 38.7 | 75 |
| NPV (%) | 87.6 | 95.8 | 87.3 |

RI: resistance index; PI: pulsatility index; PPV: positive predictive value; NPV: negative predictive values.

Table 3. The sensitivity for predicting adverse outcomes for mean RI>95th percentile in third trimester was 58%. It increased to 77.2% at second trimester. The sensitivity of RI to predict complicated pregnancy in both trimesters was higher than sensitivity of PI and combined RI, PI and bilateral notch. On the other hand, the value of specificity to detect adverse outcome was higher when RI, PI and bilateral notch values were combined.

## Discussion

This study evaluated clinical usefulness of uterine artery color Doppler ultrasound as a predictor of adverse outcomes in pregnancy. In line with previous findings[1,16], our results also showed that uterine artery PI and RI values were significantly higher in patients who eventually developed pregnancy complications than in women with normal outcome. This finding was encountered for both second and third trimesters. The sensitivity of mean RI>95th percentile in second trimester was higher than third trimester (77.2 *versus* 58.0%), which suggests the valuable role of second trimester's uterine Doppler sonography in screening complicated pregnancy. After the combination of uterine indices, the value of sensitivity did not differ from each index alone in third trimester (57.5 *versus* 58.0%), but decreased in second trimester (36 *versus* 77%). With regards to specificity, although each parameter (PI, RI or presence of bilateral notches) may provide a good diagnostic yield for the adverse pregnancy outcome, combination of all parameters together may result in a great specificity. As it is evident in Table 3, a mean PI and mean RI>95th percentile along with presence of bilateral notches may produce a positive predictive value of 88%. This positive predictive value is acceptable since our subjects were not selected from high-risk population.

We realize that the study could have some weaknesses. The main bias is that the study has low number of patients. To decrease the sonographic measurement bias, all women were assessed by one experienced radiologist. Participants in this study were not confined to high-risk population, which could enhance the external validity of our research; however, the results of the study could not be generalized to all population.

Screening abilities of color Doppler ultrasound in assessing single certain outcomes such as stillbirth[18], preeclampsia and fetal growth restriction[19] were extensively addressed. In a study by Singh and colleagues, which showed elevated second-trimester Doppler indices, a proxy for impaired placentation, they are more strongly associated with stillbirth than conventional risk factors[18]. This is while in that study; stillbirth was the only primary outcome. In another study by Coleman et al.[20] adverse outcomes were defined as development of preeclampsia and Small for Gestational Age (SGA). In that study, just high-risk women were included and it has been shown that uterine artery Doppler waveform analysis performed best in the prediction of severe adverse outcome and was better than clinical risk assessment in the prediction of preeclampsia and SGA babies. The definition of adverse pregnancy outcome in the current study was similar to Jamal et al., including preeclampsia, IUGR, preterm delivery, placental abruption and fetal death[1]. The combination of several different adverse outcomes is more clinically relevant and may help obstetrician for a better clinical judgment. Jamal and colleagues reported a sensitivity of 60% for the mean PI>95th percentile for gestational age and/or bilateral notches in predicting a severe adverse outcome[1]. In another study by Harrington et al. the sensitivity for an adverse outcome in screen-positive women of low-risk group was 33.3% for a specificity of 92.8% and a positive predictive value of 24.4%[16].

In the present study, the presence of bilateral uterine artery notches in complicated and normal pregnancies was compared. The prevalence of bilateral notches in patients with subsequent complications was significantly higher than those with normal pregnancies. Jamal et al. showed a prevalence of bilateral notch of 20% in complicated pregnancies compared to 4.5% in normal ones[1]. This was in agreement with ours. Evaluation of bilateral notch presence is usually performed along with the RI and PI, but there exist studies that solely included this item to predict adverse pregnancy outcome. Mires et al.[21] have shown that the presence of bilateral uterine arterial notching is associated with a significantly increased risk of adverse pregnancy outcome. In concordance with another study that showed a strong positive predictive value in high-risk populations[22], in recent research, combination

of bilateral notch to other indices resulted in a good positive predictive value in normal population.

The benefit of detecting such screen positive pregnancy is that they will form an ideal group for prophylactic trials such as low-dose aspirin. Also, it helps health care resources to target women with abnormal Doppler results for a better antenatal surveillance[16,23].

The results of this study suggest that uterine artery Doppler may be a valuable screening tool for the prediction of a variety of adverse outcomes in second and third trimesters. Further studies with larger sample size will be necessary to determine whether this information could be incorporated into the routine antenatal care of pregnant women.

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