The Relationship Between Elevated Maternal Uric Acid Level and Bilateral Early Diastolic Notching at Uterine Arteries at Second Trimester and Pregnancy Complications

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Abstract

Objective: The aim of this study was to evaluate the relationship between maternal uric acid level, abnormal uterine artery waveform at second trimester and adverse pregnancy outcome.

Methods: We evaluated 319 women with Doppler sonography at 20-26 weeks of gestation. The presence of early diastolic notching at uterine arteries and maternal serum uric acid levels were determined. Pregnancy induced hypertension was defined as new-onset elevated blood pressure ≥140 mmHg systolic or ≥90 mm/Hg diastolic after 20 weeks of gestation. Small for gestational age was defined as birth weight <10th centile. Delivery <37 weeks was termed as preterm.

Results: The number of cases with PIH, SGA and preterm delivery were significantly higher in the group of bilateral notching (n: 145). In cases with bilateral notching mean uric acid level was significantly higher (3.08±0.88 versus 2.58±0.76 mg/dl). The number of the cases which developed PIH (P=0.016), small for gestational age- birth weight (P=0.0013) and fetal demise (P=0.02) were higher in the highest quartile of uric acid level (>3.4- 6.2 mg/dl). Maternal serum level of uric acid showed significant negative correlation with birth weight (r:-0.24, 95% confidence interval for r: -0.34 to-0.14, P<0.0001). Using >3.4mg/dl as a cut off value for uric acid level we could detect the cases with pregnancy induced hypertension with a sensitivity of 40.4%, specificity 79.8%, and for gestational age birth weight with a sensitivity of 44.2%, specificity 80.45%.

Conclusion: The presence of bilateral notching at uterine arteries at second trimester is related with pregnancy induced hypertension, small for gestational age, preterm delivery and elevated maternal uric acid level. Maternal serum uric acid level at second trimester may be used in the prediction pregnancy induced hypertension and small for gestational age birth weight.

Keywords: Uric acid, Doppler ultrasonography, pregnancy induced hypertension, Small for gestational age, fetal demise.

İkinci trimester yüksek maternal ürik asit değerlerinin uterin arterlerde bilateral erken diyastolik çentiklenme mevcudiyeti ve gebelik komplikasyonları ile ilişkisi

Amaç: Bu çalışmamın amacı ikinci trimester maternal ürik asit değerleri ile anormal uterin arter daralma formunun kötüşü gebelik sonucu ile iliskisini araştırmaktır.


Bulgular: Bilateral çentiklenme bulunan (n:145) grupta gebelikte bağılı hipertansiyon, gebelik haftasına göre küçük ve erken doğum olgularının sayısı anlamlı olarak yüksekti. Bilateral çentiklenme bulunan olgularda ortalama ürik asit değerleri anlamlı olarak yüksekti (3.08±0.88’e karşılık 2.58±0.76 mg/dl). Ürik asit değerleri en yüksek olan dörtte birlikte grupta (>3.4-6.2 mg/dl) PIH (P=0.016), SGA doğum kilosu (P=0.0013) ve fetal kayıp (P=0.02) gelişen olguların sayısı anlamlı olarak yüksekti. Maternal serum ürik asit değerleri doğum kilosu ile anlamlı negatif korelasyon göster込んで idi (r:-0.24, %95 güven aralığı (-0.34-0.14), P<0.0001). Ürik asit değerleri >3.4
Introduction

Pre-eclampsia and intrauterine growth restriction are important obstetrical complications which are suggested to be caused by impaired placenta-tion. The failure to undergo physiological vascular changes is reflected by the high impedance to the blood flow at uterine arteries. Uterine artery Doppler screening identifies women at high risk for developing complications.[1] Combinations of biochemical and ultrasonographic markers might improve the predictive performance of single markers.[1-4]

Increased uric acid levels generally precedes the onset of hypertension and proteinuria in preeclampsia.[8] Hyperuricemia in pregnant women without proteinuria is at least as good a predictor of fetal morbidity as hypertension and proteinuria.[9] Postpartum normalization of blood pressure in preeclamptics has also been shown to be directly related to uric acid levels.[10] It has been speculated that uric acid may play direct roles in the pathological processes of preeclampsia at both the level of the placenta and maternal vasculature.[8]

The aim of this study was to evaluate the relationship between maternal uric acid level, abnormal uterine artery waveform at second trimester and pregnancy induced hypertension (PIH), small for gestational age (SGA) birth weight, preterm delivery and fetal demise.

Methods

Study Design and Population

Between January 2009 and February 2010, women attending for second trimester anomaly screening at 20-26 weeks of gestation were enrolled in the study. Baseline demographic information and medical history were collected. A total of 360 cases with a singleton pregnancy without preexisting diabetes, hypertension, renal disease or major fetal anomalies were examined with transabdominal Doppler ultrasonography (Logic 400). The presence or absence of early diastolic notching at uterine arteries was noted for both sides.

All of the women were asked to provide blood samples for the investigation of serum uric acid levels at the day of examination. Uric acid was measured using an uricase based colorimetric assay (Architect C16000) with a lower detection limit of 1mg/dl.

Pregnancy induced hypertension (PIH) was defined as new-onset elevated blood pressure ≥140 mmHg systolic or ≥90 mm/Hg diastolic after 20 weeks of gestation. Normotensive women were those without gestational blood pressure elevations. Neonatal outcomes assessed included birth weight and birth weight centile. Small for gestational age (SGA) was defined as birth weight <10th centile. Gestational age was determined by obstetrical assessment, using early ultrasound data where available. Delivery <37 weeks was termed as preterm and <28 weeks severe preterm.

Statistical Analysis

The collected data were analysed with use of the MedCalc for Windows, version 8.1.00 (MedCalc Software, Mariakerke, Belgium). Data were presented as means ± standard deviations or numbers of subjects and percents. Student’s t-test was used for continuous variables and Chi-square test or Fisher exact test for categorical variables, while one-way ANOVA was used to compare the variables of four groups. Correlation between maternal uric acid level and birth weight was assessed by Pearson's correlation coefficient. The efficiency of serum uric acid levels in predicting PIH and SGA was examined with the analysis of the area under the receiver operator characteristic (ROC) curves. A P value of <0.05 was regarded as significant.
Results
A total of 319 cases were available for analysis with a mean gestational age at sampling of 22.3±1.3 weeks and uric acid concentration of 2.81 ± 0.85 mg/dl. Bilateral early diastolic notching (BLN+) was detected in 145 of the cases and 174 of the cases were found to have bilateral or unilateral absent early diastolic notching (BLN- or ULN-). Mean maternal age and the percentage of cases after 30 years was significantly higher in the group of BLN+, significantly higher percent of the cases were nullipares (Table 1).

The number of cases with PIH, SGA and preterm delivery were significantly higher in the group of BLN+. Mean birth weight and gestational age at delivery were significantly higher in the group with normal Doppler finding. Mean uric acid level was significantly higher in the group of BLN+ (Table 2).

We evaluated uric acid concentration by quartile for the entire study population, comparing the highest quartile to the lower three quartiles. The number of the cases in the highest quartile was significantly higher for the group with BLN+ (Table 3).

The number of the cases which developed PIH, SGA birth weight and fetal demise were higher in the highest quartile of uric acid level. In this group mean birth weight was lower than the other quarr-
tiles. The number of preterm deliveries did not show any significant difference (Table 4).

Maternal serum level of uric acid showed significant negative correlation with birth weight (r: -0.24; 95% confidence interval for r: -0.34 to -0.14, P<0.0001). Scatter diagram for uric acid levels, birth weight the presence of PIH is presented in Figure 1.

We analyzed the predictive value of second trimester maternal uric acid level for PIH (AUC:0.622, P=0.006) and SGA birth weight (AUC: 0.65, P=0.0003) with Roc curve. Using 3.4 mg/dl as a cut off value we could detect the cases with PIH with a sensitivity of 40.4% and specificity 79.8%, SGA with a sensitivity of 44.2% and specificity 80.45% (Figures 2 and 3).

**Discussion**

In this study we evaluated the relationship between second trimester maternal uric acid levels and the presence of bilateral early diastolic notching at uterine arteries. In our study population mean uric acid level and the number of cases with various pregnancy complications were higher in the group of BLN+. In the group of women with

<table>
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<th>Group 1 (n=80)</th>
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<td>10</td>
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Table 4. Doppler findings, maternal and neonatal prognosis according to the quartiles of uric acid.

**Figure 1.** Scatter diagram of the cases showing the correlation of uric acid and birth weight (colored points indicate the cases with PIH).
Figure 2. ROC curve analysis of uric acid levels for the prediction of PIH (AUC:0.622, P=0.006).

Figure 3. ROC curve analysis of uric acid levels for the prediction of SGA (AUC:0.65, P=0.0003).
an uric acid level at the highest quartile the percentage of cases with PIH, SGA birth weight and fetal demise were significantly higher.

Abnormal uterine artery waveforms were reported to be a better predictor of pre-eclampsia than of intrauterine growth restriction. Pulsatility index alone or combined with notching was advised to be used in clinical practice.[9] Bilateral uterine notching between 23 and 25 weeks' gestation was reported to be an independent risk factor for the development of early-onset preeclampsia and gestational hypertension and suggested to be considered in the assessment of risk for the development of these pregnancy complications.[10] The addition of uterine Doppler waveform analysis to the monitoring profile of women at risk of preeclampsia, small for gestational age, intrauterine death and preterm delivery was reported further define those in a higher risk group.[11] In this study we found that bilateral notching at uterine arteries at second trimester was related with PIH, SGA, preterm delivery and fetal demise. Therefore we also suggest that the presence of bilateral notching should be considered as a risk factor.

As previously reported the increase in uric acid antedates the reduction of glomerular filtration and hypovolemia in PIH.[12] An elevation in serum uric acid has been associated with an increased risk for the development of hypertension. Even mild hyperuricemia causes hypertension and renal injury with stimulation of the renin-angiotensin system and inhibition of neuronal NO synthase.[13] It was suggested that women who develop preeclampsia come into pregnancy with elevated uric acid as part of the metabolic syndrome or that uric acid production is increased in early pregnancy. Elevated concentration of uric acid in preeclamptic women is not simply a marker of disease severity but rather contributes directly to the pathogenesis of the disorder.[14]

Uric acid could contribute to failed placental bed vascular remodeling by impeding trophoblast invasion with resultant reduced placental perfusion, setting the stage for ischemia reperfusion injury to the placenta.[15] In this study we found that the number of cases with bilateral notching was significantly higher in the group of women with an uric acid in the highest quartile at second trimester. This result indicates the possible relationship between impaired placentation and high maternal uric level before the clinical appearance of pregnancy complications.

Myers et al. evaluated maternal uric acid levels at 22 and 26 weeks and concluded that these time points were remote from the diagnosis of preeclampsia and this might contribute to the lack of differences.[15] In our study population at the same time point we could predict PIH by using an uric acid level of 3.4 mg/dl with a sensitivity of 40.4% and specificity 79.8%.

A striking increase in the odds for small gestational age infants in preeclamptic women with increasing serum uric acid concentration has been reported.[6,16] Lower birth weight of children born to mothers found to have hyperuricemia (>58.3 mg/l) for more than 2 weeks was reported as a consequence of hyperuricemia.[17] In our study population serum level of maternal uric acid showed a significant negative correlation with birth weight and the number of the cases with SGA birth weight was significantly higher in the group of highest quartile of uric acid. Elevated uric acid was also recognized many years ago as a better predictor for fetal risk than blood pressure in preeclampsia.[18,19] In our study the risk of fetal demise was higher either in the group with elevated maternal uric acid level at second trimester.

**Conclusion**

The presence of bilateral notching at uterine arteries at second trimester is related with PIH, SGA and preterm delivery and elevated maternal uric acid level. Maternal serum uric acid level at second trimester may be used in the prediction PIH and SGA birth weight.

**References**


