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MATERNAL-FETAL MEDICINE

The value of uterine artery Doppler and NT-proBNP levels in the second trimester to predict preeclampsia

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Abstract
Objective To determine the maternal serum N-Terminal proBNP levels in predicting development of preeclampsia.
Method Sixty-eight patients were included in the study. The study group consisted of patients with the finding of diastolic notch with abnormal pulsatility index (PI) between 21–24 weeks gestation and the control group consisted of patients without diastolic notch and normal PI. The study included high-risk patients who did not have a history of hypertensive disorder before pregnancy, heart failure, recurrent pregnancy loss, autoimmune disorder or diabetes. The groups were compared in terms of NT-ProBNP levels, development of preeclampsia, obstetric and neonatal problems.
Results There was no significant difference between groups in terms of age, gravidity, parity, uric acid levels, and NT-proBNP levels. There was significant difference between the groups in terms of week of birth, rate of cesarean section and fetal weight. Furthermore, there were significant differences between the two groups when compared in terms of obstetric and neonatal problems ($p < 0.05$). Obstetric and neonatal problems were more common in the notch with abnormal (PI) group. The NT-pro BNP levels were found to be comparable among groups. Preeclampsia was the most common obstetric problem (11.7 %). We were unable to document significant difference in patients who developed preeclampsia.
Conclusion Bilateral notch together with abnormal PI measurements in the uterine artery Doppler screening during the second trimester was associated with poor perinatal outcomes. Such an association was not significant in the NT-proBNP measurements. Larger trials focused on late-onset preeclampsia are needed to draw definitive conclusions.

Keywords NT-proBNP · Uterine artery doppler · Perinatal outcome

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Introduction

Predicting obstetric conditions with high perinatal morbidity and mortality is one of the major target areas of perinatology. Insufficient placentation is associated with poor obstetric outcomes because of the impairment of uteroplacental circulation [1]. This impairment results in defective trophoblastic invasion, insufficient vascular response, preeclampsia, and fetal growth restriction [2, 3]. One of the most commonly used non-invasive tests to evaluate uteroplacental circulation is uterine artery Doppler measurement, which is performed in the second trimester. The combination of uterine artery Doppler with biochemical markers measured in the first and second trimester has been reported to be the most appropriate screening tool [4].

A brain natriuretic peptide (BNP) is a peptide secreted when ventricles of the heart are stressed and when pressure increases [5–7]. This condition leads to water and sodium excretion from the kidneys when increased volume and resistance occur. Studies have shown that N-terminal pro-brain natriuretic peptide (NT-proBNP) levels increase in cases of preeclampsia, hypertensive pregnancies, twin pregnancies, and pregnancies complicated with pulmonary or cardiac disorders [8–11]. Previous studies usually focused on patients with preeclampsia and established final and accurate diagnoses. However, to the best of our knowledge, no prospective study has been conducted yet to evaluate NT-proBNP as an indicator for the early prediction of preeclampsia in high-risk pregnant women. Therefore, we aimed to evaluate the diagnostic value of BNP levels to predict preeclampsia and poor obstetric outcomes in patients with a notch detected in the uterine artery Doppler examination performed in the second trimester.

Materials and methods

This prospective cohort study was performed at the obstetrics and gynecology clinics of a training and research hospital. Approval for the study from the ethics committee was obtained from the hospital's training and planning committee. Patients were informed, and their written informed consent was obtained. A total of 68 patients were included in the study. Patients were initially divided into two groups. Doppler examination of the bilateral uterine arteries was performed during the 21st–24th week of pregnancy. Patients with a diastolic notch in the obstetric uterine artery together with mean pulsatility index (PI) above 90th centile were noted as abnormal Doppler group (Group A). Control group (Group B) was composed of patients with absent diastolic notch in the obstetric uterine artery and/or normal PI values. Pregnancy week was determined on the basis of the last menstruation date and ultrasonographic imaging (USI) results obtained in the first trimester. Exclusion criteria were as follows: hypertensive disease before pregnancy, history of cardiac and renal diseases, recurrent pregnancy loss, ongoing anticoagulant or aspirin therapy, presence of a known rheumatic or autoimmune disease, pregestational diabetes mellitus, and history of a low-weight birth infant. NT-proBNP levels (VIDAS, NT-proBNP ELFA), biochemical parameters (blood glucose, urea, creatinine, uric acid, liver enzymes), blood count values, blood pressure, and proteinuria in total urine analysis were determined when Doppler ultrasonographic examinations were performed during the 21st–24th week, and the results were recorded. USI, biochemical analyses, and urine protein and blood pressure measurements were performed during routine pregnancy follow-up, and the results were recorded. Pregnancy week at delivery, mode of delivery, neonatal weight as centiles, gender, and obstetric and neonatal problems were noted. Obstetric problems such as preeclampsia, abruptio placentae, prematurity, oligohydramnios and IUGR, and neonatal problems including respiratory distress syndrome (RDS), intrauterine fetal demise, were recorded.

NT-proBNP and the other laboratory parameters measured in both groups were compared according to the development of preeclampsia and obstetric and neonatal problems.

Data were represented as mean ± standard deviation, range, and percentage as appropriate. Pearson's Chi-square test and Student's t test were used for the statistical analysis of qualitative and quantitative parameters, respectively. Non-parametric data were analyzed with the Mann–Whitney U test. A p value of 0.05 was set to test statistical significance. Analysis was conducted using SPSS version 16.0 (Chicago, Illinois) statistical software package.

Results

A total of 68 patients were included in the study. The mean age was 28.1 ± 5.8 years; mean number of pregnancies was 2.4 ± 1.4; mean number of parities was 0.9 ± 0.9; mean pregnancy week at delivery was 37.6 ± 3.4 weeks; mean birth weight was 2,874.9 ± 764.5 g; mean uric acid level was 3.5 ± 0.8 mg/dl; and mean NT-proBNP value was 34.8 ± 0.8 pg/dl.

The reported adverse obstetric outcomes included to the analyses were composed of one ablatio placentae case, two cases of oligohydramnios and intrauterine growth restriction (IUGR), and eight cases of preeclampsia. Preeclampsia was the most common obstetric problem. Of the eight preeclampsia cases, seven were in the abnormal doppler group and one was in the control group (Table 1).

Neonatal problems included two cases of intrauterine fetal death (2.9 %), seven cases of premature +RDS (10.2 %), and six cases of RDS (8.8 %). RDS was the most common neonatal problem. All but one of the cases with RDS diagnosis was discharged from the neonatal unit within 5 days (Table 2).

No statistically significant difference was found between the abnormal Doppler group (Group A) and control group (Group B) with respect to age, number of pregnancies and parities, uric acid levels, and NT-proBNP levels ($p > 0.05$) (Table 3). Pregnancy week at delivery was significantly different between the two groups ($p < 0.001$). Patients in the abnormal Doppler group gave birth in the early weeks of pregnancy, and fetal weights were low. Moreover, proportion of SGA neonates with a birth weight below the 10th centile in the abnormal Doppler group was higher than that of the control group. A comparison of the two groups with respect to adverse obstetric outcomes revealed a statistically significant difference ($p < 0.05$) (Table 3). Prematurity rate was statistically significant between the groups ($p < 0.001$).

The NT-proBNP levels were found to be comparable between the Group A and Group B ($p > 0.05$). We also evaluated the NT-proBNP levels between patients who developed preeclampsia and those who did not (Fig. 1). Although we observed a higher trend of NT-proBNP levels in the preeclampsia group, this difference was not statistically different ($p > 0.05$). We also did not find any significant association between NT-proBNP levels and obstetric outcomes. We further analyzed the NT-proBNP levels among patients who developed early-onset (<34 weeks) or late-onset preeclampsia and pregnants who

Table 1 Obstetrical outcome of the followed pregnancies

	Group A ($n = 18$) notching with PI > 90th centile (%)	Group B ($n = 50$) absent notching and/or normal PI (%)	Total (n: 68) (%)
Preeclampsia	7 (38.8)	1 (2)	8 (11.7)
Ablatio placenta	0	1 (2)	1 (1.4)
Oligohydramnios and IUGR	1 (5.5)	1 (2)	2 (2.8)
Prematurity	8 (44.4)	6 (12)	14 (20.5)

IUGR intrauterine growth restriction

Table 2 Neonatal outcome of the followed pregnancies

	Group A ($n = 18$) notching with PI > 90th centile (%)	Group B ($n = 50$) absent notching and/or normal PI (%)	Total (n:68) (%)
IU exitus	1 (5.5)	1 (2)	2 (2.8)
Prematurity + RDS	6 (33.3)	1 (2)	7 (10.3)
RDS	3 (16.6)	3 (6)	6 (8.8)

IU in-uterine, *RDS* respiratory distress syndrome

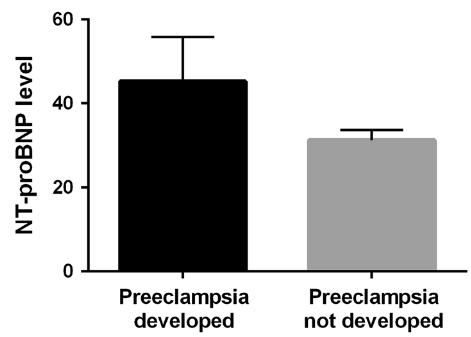

Fig. 1 NT-proBNP levels between patients who developed preeclampsia and those who did not. ($p > 0.05$; mean NT-proBNP levels according to the development of preeclampsia)

Table 3 Demographic features, NT-proBNP levels and pregnancy features of Notching with PI > 90th centile and Absent notching and/or normal PI

	Group A ($n = 18$) notching with PI > 90th centile	Group B ($n = 50$) absent notching and/or normal PI	p value
Age	28.0 ± 6.6	28.2 ± 5.7	0.913
Gravidity	2.5 ± 1.7	2.3 ± 1.3	0.613
Parity	0.9 ± 0.9	1 ± 0.9	0.952
Week of birth	35.7 ± 4.1	38.3 ± 3.0	**0.021**
Uric acid level(mg/dl)	3.7 ± 1	3.3 ± 0.6	0.164
NT-ProBNP (pg/dl)	34.3 ± 19.0	31.9 ± 19.7	0.654
	Group A ($n = 18$) notching with PI > 90th centile (%)	Group B ($n = 50$) absent notching and/or normal PI (%)	p value
Adverse obstetrical outcome	8 (44.4)	3 (6)	**0.001**
SGA babies			
<10th centile	10 (55.6)	10 (20)	**0.005**
Mode of delivery			
Vaginal delivery	3 (16.6)	23 (46)	**0.028**
C-section	15 (83.4)	27 (54)	
Fetal gender			
Male	8 (44.4)	32 (64)	0.148
Female	10 (55.6)	18 (36)	

NT-proBNP N-terminal pro-brain natriuretic peptide, *C-section* cesarean section, *PI* pulsatility index, *SGA* small for gestational age

Bold values are statistically significant (p < 0.05)

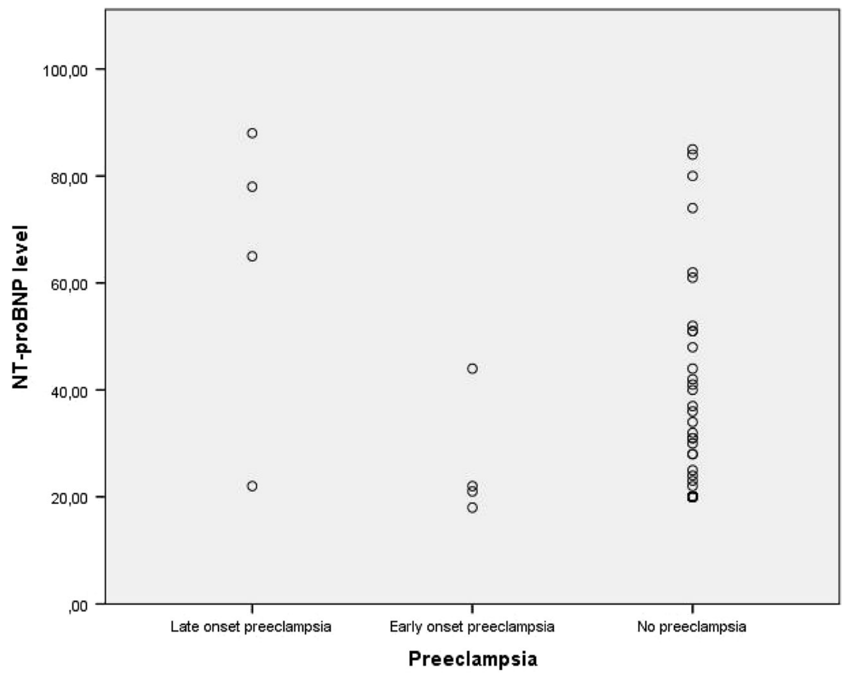

Fig. 2 NT-proBNP levels among patients who developed early-onset or late-onset preeclampsia and pregnants who did not developed preeclampsia

did not develop preeclampsia (Fig. 2). This comparison interestingly revealed a possible but not significant trend of high proBNP levels in patients with late-onset PE compared to early-onset PE.

Discussion

The study evaluated the serum NT-proBNP levels between patients with and without abnormal uterine artery Doppler evaluation along with elevated PI, performed in the second trimester. The study did not find any association between NT-proBNP levels when measured in the 21st–24th week of pregnancy and the development of preeclampsia in later pregnancy. However, the detection of a diastolic notch together with elevated PI during the uterine artery Doppler screening performed in the second trimester appeared to be a valuable examination. These results indicate that the addition of the NT-proBNP measurement at the beginning of the second trimester to the presence of abnormal uterine artery Doppler findings does not lead to a more effective detection of poor obstetric outcomes, including preeclampsia. However, our relatively low sample size hampered us to drive definitive conclusions for the predictive role of NT-proBNP measurement on predicting late-onset preeclampsia.

Normally, the volume of intravascular space physiologically increases during pregnancy, reaching up to 50 % as pregnancy progresses. This condition results in an increase in left ventricular wall tension and end-diastolic diameter [12]. Furthermore, the addition of insufficient placentation and high-resistance placental circulation to maternal cardiac distress may increase the cardiac effects and levels of BNP as a neurohormone released from the ventricles of the heart. BNP has been investigated in various studies. Kale and colleagues found NT-proBNP levels in preeclamptic women to be prominently higher than those observed in normotensive pregnancies; they concluded that the increase in tension is parallel to the increase in NT-proBNP levels and that such high values show the severity of left ventricular diastolic dysfunction [8]. In another study conducted by Fleming et al., normotensive and hypertensive pregnancies were compared, and NT-proBNP levels and left ventricular filling pressure were found to be high in the hypertensive group [13].

In the present study, as expected, adversed obstetric outcomes including preeclampsia were more prevalent among patients with abnormal uterine artery Doppler than among those in the normal group. Moreover, this patient group was associated with an earlier week of birth and higher rate of C-section.

The relevant literature shows that uterine artery resistance is associated with poor pregnancy outcomes [14, 15, 16]. Abnormal Doppler findings are considered to reflect defective trophoblastic function and are, therefore, trophoblastic-impaired secretory biomarkers. Consequently, some serum biomarkers are used along with Doppler findings to predict poor obstetric outcomes. Some of these biomarkers can be analyzed within the first trimester. Biomarkers that are measured within the second trimester have been associated with poor perinatal outcomes. Dugoff et al. [17] compared decreased PAPP-A levels with perinatal outcomes in the First and Second Trimester Evaluating Risk trial and demonstrated the relationship between decreased levels and adverse perinatal outcomes. Aside from determining these placental markers, measuring the Doppler parameters and serum homocysteine level in the second trimester was found to be useful, that it increased the sensitivity, as shown in a study comparing homocysteine and Doppler findings [18].

A recent study of Kleinrouweler et al. [19] revealed that addition of PI or RI and bilateral notching improves the identification of preeclampsia risk. Besides, uterine artery notch positivity continuing after the 26th week was considered a risk factor for poor perinatal outcomes [20, 21]. In this manner, we compared the impact of preeclampsia prediction of NT-proBNP with notch positivity together with elevated PI values. Unlike in other studies, NT-proBNP levels were not different with respect to the development of preeclampsia in later pregnancy [8, 13, 22]. The lack of difference may be related to some reasons. In the present study, NT-proBNP levels were measured during the 21st–24th week. However, Fleming et al. and Kale et al. [8, 13] reported their results after 34–35 weeks. This period is when placentation is completed. The reflection of highly resistant feto-placental circulation, which developed because of insufficient trophoblastic invasion, on the mother's heart and the time taken to complete this adaptation period could be a reason. The resistant wave forms detected on the Doppler increased the preload of the heart, resulting in tension that affected the ventricular walls and increased the ventricular filling pressure. Moreover, the release of prohormone-BNP, which is further cleaved to BNP and NT-proBNP, was induced. NT-proBNP is more stable than BNP and has a longer half-life. In this respect, performing a single measurement may not have provided the expected result. The low number of enrolled patients was another limitation of this study.

Interestingly, we observed a higher but insignificant trend of NT-proBNP levels among patients who were destined to develop preeclampsia. Moreover, a further comparison for the early and late preeclampsia, defined as the onset of the disease before or after 34 weeks gestation, revealed a similar result indicating late-onset preeclampsia to be more suitable for prediction using NT-proBNP levels. This difference may reflect the fact proposed by Verlohren et al. that there are two different types of late-onset preeclampsia [23]. They hypothesize that the pathophysiology of a subgroup of late-onset preeclampsia patients may be related with maternal cardiac dysfunction and it later result in placental hypoxemia which leads to preeclampsia. This explanation seems to be coherent with our finding that NT-proBNP levels have a higher trend in patients that were destined to develop late-onset preeclampsia. Taking into account that BNP is secreted when cardiac function alters, we hypothesize that a more specific trial with a larger case size may uncover the insignificant trend found in our research.

In conclusion, the detection of a bilateral notch together with abnormal PI measurements in the uterine artery Doppler screening during the second trimester was associated with poor perinatal outcomes. Such an association was not significant in the NT-proBNP measurements. NT-proBNP assessment during second trimester may have a predictive value for the prediction of late-onset preeclampsia with an underlying cardiac function alteration. Larger trials focused on late-onset preeclampsia are needed to draw definitive conclusions.

Conflict of interest The authors stated that they did not have conflict of interests.

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