The Association between N-terminal Pro-Brain Natriuretic Peptide Levels in the Umbilical Vein and Amniotic Fluid Volume Abnormalities

Associação entre níveis de peptídeo natriurético pró-cerebral N-terminal na veia umbilical e as anormalidades do volume de líquido amniótico

Ali Ozgur Ersoy[1] Sibel Ozler[1] Efser Oztas[1] Ebru Ersoy[1] Merve Ergin[2] Salim Erkaya[1] Dilek Uygur[1]

[1] Department of Obstetrics and Gynecology, Zekai Tahir Burak Women's Health Care, Training and Research Hospital, Ankara, Turkey
[2] Department of Biochemistry, Ataturk Education and Research Hospital, Ankara, Turkey

Address for correspondence Ali Ozgur Ersoy, MD, Department of Obstetrics and Gynecology, Zekai Tahir Burak Women's Health Care, Training and Research Hospital, Talatpasa Bulv. Hamamonu, 06230, Altindag, Ankara, Turkey (e-mail: draliersoy@gmail.com).

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Abstract

Purpose The amniotic fluid volume (AFV) is known as a predictor for the wellness of a fetus. We aimed to investigate whether N-terminal pro-brain natriuretic peptide (NTproBNP) levels reflect AFV abnormalities in otherwise normal fetuses.

Methods We recruited 24 women with isolated oligohydramnios, 23 women with isolated polyhydramnios, and 36 women with normal AFV at a tertiary referral center. NT-proBNP levels in umbilical venous samples and the individual characteristics of the three groups were compared. One-way ANOVA and Kruskal–Wallis analysis of variance were used for multi-group comparisons of continuous variables. When a significant difference was detected, the Scheffe test was performed as a post-hoc analysis. Proportions were compared using the Chi-square ($\chi 2$) test.

Results Maternal age, body mass indices, weight gained in pregnancy and NT-proBNP levels were similar among the three groups. Apgar scores at 1 and 5 minutes significantly correlated with NT-proBNP levels in all newborns (Spearman's r = 0.23; $p = 0.03$ and Spearman's r = 0.24; $p = 0.02$, respectively). The umbilical venous NT-proBNP levels did not differ between newborns who needed mechanical ventilation and those who didn't ($p = 0.595$).

Conclusions NT-proBNP is a biomolecule that may provide insights into the pathogenesis of fetal circulatory problems and subsequent renal failure. Further investigations are warranted.

Keywords
- amniotic fluid volume
- oligohydramnios
- polyhydramnios
- pregnancy
- renal function

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Resumo

Objetivo Investigar se os níveis de peptídeo natriurético pró-cerebral N-terminal (NT-proBNP) refletem anormalidades no volume de líquido amniótico (VLA) em fetos normais.

Métodos Reunimos 24 mulheres com oligoidrâmnios isolados, 23 com poli-hidrâmnios isolados, e 36 com VLA normal em um centro de referência. Comparamos os níveis de NT-proBNP em amostras venosas umbilicais e características individuais em três grupos. Usamos análise de variância simples (One-way ANOVA) e a análise de variação Kruskal–Wallis para comparação de variáveis contínuas em múltiplos grupos. Quando identificada uma diferença significativa, o teste de Scheffe foi aplicado como uma análise *post-hoc*. Comparamos proporções usando o teste Qui-quadrado ($\chi 2$).

Resultados Idade fértil, índice de massa corporal, ganho de peso na gestação e níveis de NT-proBNP foram similares nos três grupos. Apgar em 1 e 5 minutos correlacionaram significativamente com os níveis de NT-proBNP em todos os recém-nascidos (Spearman's r = 0,23; $p = 0,03$ e Spearman's r = 0,24; $p = 0,02$, respectivamente). Os níves de NT-proBNP venoso umbilical não se distinguiram entre os recém-nascidos que precisaram de ventilação mecânica e aqueles que não precisaram ($p = 0,595$).

Conclusões NT-proBNP é um candidato biomolecular que pode contribuir na patogênese de problemas circulatórios fetais e subsequente insuficiência renal. São necessárias futuras investigações.

Palavras-chave

- volume do líquido amniótico
- oligoidrâmnios
- poli-hidrâmnios
- gravidez
- função renal

Introduction

Amniotic fluid volume (AFV) is influenced by various fetal organs, although the vast majority of amniotic fluid abnormalities is idiopathic. Amniotic fluid (AF) abnormalities are known to be associated with potential health problems in the fetus and the neonate.[1] The AF is provided primarily by the fetal urine, and the major route of AF clearance occurs via fetal swallowing during the second part of pregnancy.[2] Various mechanisms, such as placental insufficiency, fetal renal anomalies and fetal obstructive uropathies can cause oligohydramnios, while maternal diabetes mellitus, fetal polyuria, isoimmunization, and some congenital anomalies, such as esophageal atresia and duodenal atresia, can cause polyhydramnios.[1] An ovine study demonstrated that the volume of AF swallowed by the fetus each day is a determinant of the AF volume, but the swallowing is not the major regulator of AF volume.[3] In addition, another ovine study demonstrated that the fluid excreted from the fetal lungs failed to substantially contribute to the AF volume.[4] Although various mechanisms have been suggested to contribute to the pathogenesis of isolated polyhydramnios and oligohydramnios, the exact mechanism that underlies these abnormalities remains to be determined.

Brain natriuretic peptide (BNP) is produced in cardiomyocytes and released into the circulation system in response to atrial and ventricular distention. The precursor of the pro-brain natriuretic peptide (ProBNP) performs different functions in the maintenance of cardiovascular, renal, and endocrine stability, and is cleaved into two molecules. One of these molecules is NT-proBNP, and the other molecule is BNP.[5] BNP and NT-proBNP are released into the plasma in equimolar concentrations.[6]

Recent years have seen advances in assessing the renal effects of natriuretic peptides. It was showed that lower glomerular filtration rates occur in association with higher NT-proBNP levels.[5,7] Also, the severity of cardiac dysfunction was shown to be associated with higher NT-proBNP levels.[8] We investigated this topic in the context of the AFV, as the AFV is a clinically relevant variable in fetal health surveillance and a function of the fetal renal and circulatory systems. Thus, we aimed to investigate NT-proBNP levels in patients with and without AFV abnormalities.

Methods

Eighty-three singleton pregnant women who were past 28 weeks of gestation were included in this prospective case-control study. All of the included women visited the Zekai Tahir Burak Women's Health Care Training and Research Hospital in Ankara, where there is a tertiary referral center for perinatology, between August and December 2014. Recruitment was performed at the time of delivery. The study was approved by the Institutional Review Board (approval date/number: 28.04.2014/37), and the universal principles of the Helsinki Declaration were applied.[9] All pregnant women in the study gave written informed consent to participate. Of the 83 included patients, 24 consecutive women were diagnosed with isolated oligohydramnios, 23 consecutive women were diagnosed with isolated polyhydramnios, and the remaining 36 women, who had normal AFV, were recruited as a control group with no matching. All of the recruited women were the ones who had been examined comprehensively with the use of ultrasonography for a fetal anomaly scan by a senior perinatologist between the gestational ages of 18 and 22 weeks. All participants attended regular

antenatal visits. Women were excluded from the study for the following reasons: any form of coexisting fetal health abnormalities (previously diagnosed fetal cardiac, circulatory, renal or other anatomic abnormalities) detected via ultrasound; any detected Doppler waveform abnormalities in the uterine, umbilical and middle cerebral arteries (MCA); any sign of fetal anemia, intrauterine growth restriction (IUGR), or rupture of the membranes; any previously diagnosed maternal systemic disease (diabetes mellitus, cardiovascular, thyroidal, renal, or hepatic diseases, or any autoimmune disease); and the use of various drugs/substances that are likely to affect the circulatory system of the fetus (painkillers, alcohol, tobacco). All ultrasonographic evaluations were performed using a Voluson 730 Expert and a 3–5 MHz convex transducer (GE Healthcare Systems, Kretztechnik, Zipf, Austria).

The diagnosis of oligohydramnios was made when the AF index was below 5 cm. The diagnosis of polyhydramnios was made when the AF index was above 24 cm.[10] All diagnoses were confirmed by measuring the actual AFV during delivery.

Age (years), body mass index (BMI) (kg/m^2), weight gain during pregnancy (kg), obstetric history characteristics, hemoglobin value (g/dL), the length of postpartum hospitalization and total hospitalization (hours), and the AF index (mm) were recorded. BMI was calculated as the weight in kilograms divided by the height in square meters (kg/m^2).

Umbilical venous blood samples (3 mL) were obtained from the newborn of each participant just after the expulsion phase of delivery and transferred to the laboratory within 20 minutes. Serum samples were separated by centrifugation at 5,000 rpm (2,236 g) for 10 minutes. The serum samples were stored at -80°C until use. The serum NT-proBNP levels were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (USCNK, Wuhan, Hubei, PRC) and reported in pg/mL. The minimum detectable dose of this kit was 14 pg/mL; the intra-assay and inter-assay variances were lower than 10% and 12% respectively.

The hemoglobin levels of the women were analyzed using an LH780 hematological analyzer (Beckman Coulter, Fullerton, CA, USA) within two hours of blood sampling and reported in g/dL.

The variables related to perinatal outcomes were birth weight (g), gestational week at delivery, Apgar scores at 1 and 5 minutes, the need for the neonatal intensive care unit (NICU), and the need for mechanical ventilation.

Statistical Analysis

The distributions of the variables were assessed using the Kolmogorov–Smirnov test or the Shapiro–Wilk test. Continuous variables were presented as the mean and standard deviation (SD) or the median (range). Categorical variables were presented as the number (percentage). One-way ANOVA and Kruskal–Wallis variance analysis were used for multi-group comparisons of continuous variables. When a significant difference was detected, the Scheffe test was performed as a post-hoc analysis. If the observed differences were significant, pair-wise comparisons were based on the Mann–Whitney U-test or the Bonferroni correction to determine which subgroups differed. Proportions were compared using the Chi-square (χ^2) test. Pearson's correlation coefficients were calculated for normally distributed continuous variables, and Spearman's rank correlation coefficients were calculated for non-normally distributed continuous variables. All analyses were conducted using SPSS software version 17.0 for Windows (SPSS, Chicago, IL, USA). In all analysis, two-tailed P-values of < 0.05 were considered to be statistically significant.

Results

The three groups were similar in terms of age, BMI, gestational weight gain, maternal hemoglobin concentration, and the obstetric history characteristics of the patients, as shown in ►**Table 1**. The AF indices of the patients were significantly different as a result of the categorization ($p < 0.001$). The serum NT-proBNP levels were also similar among the three groups (►**Fig. 1**, ►**Table 2**).

The route of delivery and the indications for cesarean section (CS) did not differ among the three groups ($\chi^2 = 1.86$; $p = 0.39$ and $\chi^2 = 3.02$; $p = 0.93$). In addition, the serum NT-proBNP levels were similar among patients who delivered by vaginal route and cesarean section ($p = 0.77$).

Both the birth weight and the gestational week at delivery differed significantly among the groups, and both of these parameters were consistent with the following ranking, with a descending trend among the three groups: Normal AFV > Polyhydramnios > Oligohydramnios (►**Table 2**). The Apgar scores at 1 and 5 minutes differed significantly among the groups, and both of these parameters were consistent with the following ranking, with a descending trend among the three groups: Normal AFV > Oligohydramnios > Polyhydramnios (►**Table 2**).

The need for mechanical ventilation occurred more frequently in the oligohydramnios group but did not differ significantly among the three groups ($\chi^2 = 4.92$; $p = 0.08$). The umbilical venous NT-proBNP levels exhibited no significant correlation with the amniotic indices of the patients ($n = 83$; Spearman's r = 0.2; $p = 0.07$). The umbilical venous NT-proBNP levels exhibited no correlation with the hemoglobin concentrations of the patients ($n = 83$; Spearman's r = −0.142; $p = 0.199$).

No correlation was observed between the birth weights and NT-proBNP levels of the newborns in our study ($n = 83$; Spearman's r = 0.08; $p = 0.42$). Similarly, no correlation between gestational weeks at delivery and NT-proBNP levels was observed for all patients included in the study (Spearman's r = 0.05; $p = 0.63$) or for the patients with normal AFV (Spearman's r = 0.07; $p = 0.67$). The Apgar scores at 1 and 5 minutes were positively correlated with NT-proBNP levels in all newborns (Spearman's r = 0.237; $p = 0.031$ and Spearman's r = 0.24; $p = 0.029$ respectively). The umbilical venous NT-proBNP levels did not differ between newborns who needed mechanical ventilation and those who didn't ($p = 0.595$).

Table 1 Comparison of demographic and clinical characteristics among the three groups

Characteristics	Oligohydramnios ($n = 24$)	Polyhydramnios ($n = 23$)	Normal Amniotic Volume ($n = 36$)	*p* value
Age (years)	25.5 ± 3.5	25.3 ± 3.8	26.5 ± 3.4	0.6
BMI (kg/m^2)	28.5 ± 1.6	28.7 ± 1.8	28.8 ± 1.8	0.8
WG during pregnancy (kg)	10.6 ± 2.7	11.0 ± 3.1	10.5 ± 2.2	0.7
Gravidity	2 (1–6)	2 (1–4)	2 (1–5)	0.3
Parity	1 (0–4)	1 (0–3)	1 (0–4)	0.7
Living child	1 (0–4)	1 (0–2)	1 (0–4)	0.6
Abortus	0 (0–1)	0 (0–1)	0 (0–2)	0.1
D&C	0 (0–1)	0 (0–1)	0 (0–1)	0.9
Amniotic index (mm)	34.2 ± 10.4	257.48 ± 7.0	125.8 ± 25.1	$< 0.001^*$
Hemoglobin (g/dL)	11.9 ± 1.2	11.90 ± 1.01	12.0 ± 1.3	0.9
Postpartum Stay (h)	37.4 ± 11.5	37.78 ± 12.1	36.5 ± 14.3	0.9
Total Stay (h)	55.8 ± 15.9	58.17 ± 19.5	52.08 ± 16.8	0.4

Abbreviations: BMI, body mass index; D&C, dilatation and curettage; g, grams; GW, gestational week; h, hours; MV, mechanical ventilation; WG, weight gain.
Note: The data are expressed as the mean ± standard deviation or the median (range).
* indicates that the difference is significant at the 0.05 level.

Discussion

The similarity of the three groups with respect to demographic variables such as maternal age, BMI, gestational weight gain, obstetric history characteristics and maternal hemoglobin concentration increased the value of the comparisons. As NT-proBNP has previously been reported in association with renal and cardiac effects, in this study we hypothesized that proBNP may be associated with abnormal AFV. We suspected that the fluid volume in the fetal body and the volume load to the fetal heart may be associated with the AFV regardless of the source of AF (such as swallowing or intramembranous flow). We found no significant correlation between the AFV and the NT-proBNP levels of our participants, but we generated some interesting findings.

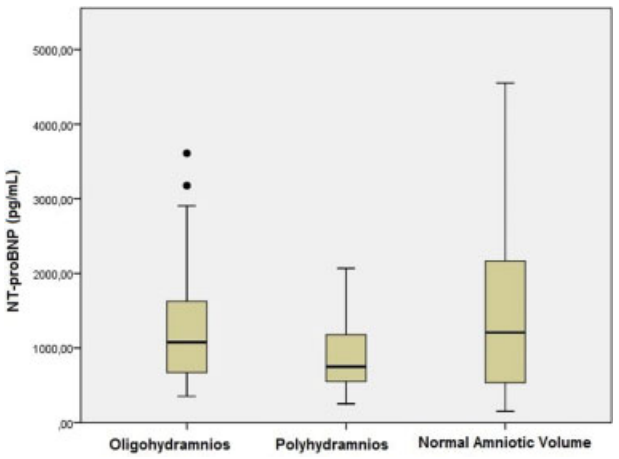

Fig. 1 The concentration of NT-proBNP (pg/mL, Y-axis) and changing levels of NT-proBNP in cord venous sera in the three groups (X-axis).

One of these findings was the observation that the Apgar scores at 1 and 5 minutes differed significantly among the groups; both of these parameters could be ranked as follows, with a descending trend among the groups: Normal AFV > Oligohydramnios > Polyhydramnios. Although Apgar scores are widely recommended only for evaluating the need for neonatal resuscitation, it has been reported that low Apgar scores were associated with neonatal death and cerebral palsy.[11] Another interesting finding was that the NT-proBNP levels exhibited a positive correlation with the Apgar scores at 1 and 5 minutes. In a study performed by Arad et al, it was reported that higher NT-proBNP levels were associated with low Apgar scores at 1 minute.[12] That study included early preterm deliveries prior to 32 weeks of gestation, in contrast to our study. Compared with our study, higher umbilical venous NT-proBNP levels were reported in that study. Fetal blood NT-proBNP levels have been reported to decline with advancing gestational age in a low-risk population.[13] Thus, the difference in NT-proBNP levels between the study performed by Arad et al and our study may have originated from the different gestational ages of the included patients.[12]

Renal failure and a low glomerular filtration rate are coincident with cardiac or circulatory failure. We performed our study based on these inferences.[14] Recent years have seen advances in testing for the renal effects of natriuretic peptides. Anwaruddin et al[15] demonstrated that lower glomerular filtration rates occurred in association with higher NT-proBNP levels. Similarly, two other studies demonstrated that both BNP and NT-proBNP could be elevated in patients with renal dysfunction.[16,17] Various studies reported that NT-proBNP levels are associated with renal function and the glomerular filtration rate (GFR) to a greater degree than BNP levels; this difference occurs due to differences in the

Table 2 Comparison of perinatal outcomes and umbilical venous N-terminal pro-brain natriuretic peptide levels among the three groups

Characteristics	Oligohydramnios ($n = 24$)	Polyhydramnios ($n = 23$)	Normal Amniotic Volume ($n = 36$)	p value
NT-Pro-BNP level (pg/mL)	1298.4 ± 900.6	923.12 ± 518.5	1551.18 ± 1148.9	0.1
GW at delivery (weeks)	37.0 ± 2.5	37.48 ± 1.7	39.19 ± 1.3	$< 0.001^*$
Birth weight (g)	2856.6 ± 738.4	3314.35 ± 428.8	3450 ± 400.5	0.003^*
Male newborn	10 (41.7%)	11 (47.8%)	17 (47.2%)	0.8
Apgar1	7 (4–9)	7(3–9)	7.5 (6–9)	0.02^*
Apgar5	9 (6–10)	9 (5–10)	9.5 (8–10)	0.01^*
Need for NICU [n (% within group)]	7 (29.2%)	4 (17.4%)	3 (8.3%)	0.1
MV [n (% within group)]	3 (12.5%)	1 (4.3%)	0	0.08

Abbreviations: GW, gestational week; g, grams; Apgar1, Apgar score at 1 minute; Apgar5, Apgar score at 5 minutes; NICU, neonatal intensive care unit; MV, mechanical ventilation.
Note: The data are expressed as the number (%), the median (range) or the mean ± standard deviation.
* indicates that the difference is significant at the 0.05 level.

dependence of the clearance of these peptides on renal function.[7,18,19]

Sahin et al[20] demonstrated that NT-proBNP has substantial efficacy for the identification of hemodynamic alterations. In addition, those authors stressed that this parameter might be useful for screening at-risk groups. Abnormal function and volume loading of the left ventricle[21] and pressure load on the left ventricle may elevate the BNP level in newborns with congenital heart diseases.[22] Circulating NT-proBNP levels in fetuses with cardiac defects have been reported as higher than in healthy fetuses.[23] Thus, to ensure equality among groups, at the beginning of this study we excluded patients whose fetuses had congenital cardiac anomalies. In addition, we excluded patients who were diagnosed with IUGR because the levels of NT-proBNP can be altered by this condition.[24]

In a study by Merz et al,[25] it was demonstrated that amniotic fluid levels of NT-proBNP are of fetal origin. They attributed it predominantly to fetal renal functions, but the exact origin in the fetal body remained to be elucidated.[25]

NT-proBNP levels were demonstrated to accurately reflect renal function when the cardiac and circulatory status are normal.[5,26] It's been demonstrated that these levels were also superior to BNP, likely because the clearance of NT-proBNP is more dependent on kidney function, while the clearance of BNP can be performed by other pathways.[27]

Due to the reported interference of NT-proBNP with anemia status, we excluded patients with any sign of fetal anemia (such as fetuses with abnormal MCA Doppler waveform or fetal hydrops). In addition, this diagnosis was confirmed at the neonatal evaluation.[28] Nayer et al[6] reported that the levels of natriuretic peptides were affected by the weight and age of the patient. However, we did not find any association between NT-proBNP levels and the weights of the newborns. Merz et al[13] demonstrated that a decline in fetal blood NT-proBNP levels occurred with advancing gestational age in a low-risk population. In contrast, we found no correlation between NT-proBNP levels and gestational age among both the group of patients with normal AFV and the total samples of patients included in this study. Bakker et al[29] and Bar-Oz et al[30] reached the same inferences as our study related to the lack of correlations between NT-proBNP levels and the gestational age and mode of delivery.

The low number of cases represents a major limitation of our study. The small sample size was caused by the lack of isolated cases. Birth weight and gestational week at delivery were not homogeneous among the three groups, and the similarity of the NT-proBNP levels observed among the groups may have arisen from these variations. These factors represent another limitation of our study.

In conclusion, we found no association between the AFV abnormality and the cord NT-proBNP level, but we found that NT-proBNP levels correlated with the Apgar scores at 1 and 5 minutes. We propose that NT-proBNP may be a biomolecule with the potential to provide insights into the pathogenesis of circulatory problems and subsequent renal failure during the fetal period. Placental and amniotic fluid levels may be useful for determining the biological role of NT-proBNP in the future. Further investigations with larger population sizes are warranted to elucidate the molecular mechanisms associated with NT-proBNP and the effects of this peptide on fetal and neonatal well-being.

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