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# Umbilical arterial N-terminal pro-B-type natriuretic peptide levels in preeclampsia, fetal growth restriction, preterm birth and fetal distress

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**Summary**

*Objective:* To evaluate fetal cardiopulmonary stress in pregnancies complicated by preeclampsia (PE), fetal growth restriction (FGR), preterm birth (PT), and fetal distress (FD) using umbilical arterial blood N-terminal pro-B-type natriuretic peptide (NT-proBNP). *Materials and Methods:* The study included 146 blood samples that were drawn from umbilical arteries at the time of delivery (20 cases of PE, 11 cases of FGR, 31 cases of PT, 23 cases of FD, and 61 cases of gestational age-matched controls) and analyzed. The main outcome measures included neonatal birthweight, cord pH, and umbilical arterial NT-proBNP. *Results:* The umbilical arterial NT-proBNP levels were significantly higher in the PE, FGR, PT, and FD groups than in the control group. The umbilical arterial NT-proBNP levels were negatively correlated with gestational age, birthweight, and umbilical arterial pH. *Conclusions:* Umbilical arterial NT-proBNP levels are elevated in stressful fetal conditions and have the potential to be considered as a marker for fetal cardiopulmonary stress.

*Key words:* Cardiopulmonary state; Fetal stress; NT-proBNP; Marker; Umbilical artery.

## Introduction

The cardiovascular status of the newborn infant is highly unstable during the transition period from the environment in utero, especially during fetal stressful conditions, and can affect postnatal cardiovascular function. Thus, detection of the hemodynamic index, which is a surrogate for antenatal stress, is important and studies about this have increased recently.

A number of imaging techniques, such as echocardiography, cardiac magnetic resonance imaging (MRI), and computed tomography (CT) are available for the detection of heart failure. Also, the use of biomarkers, including cardiac troponin I (TnI), high-sensitive C-reactive protein (hs-CRP), cystatin C, brain natriuretic peptide/N-terminal pro-B-type natriuretic peptide (BNP/NT-proBNP) are becoming increasingly popular in the process of screening and diagnosis [1-3]. These biomarkers are cost-effective, non-invasive technique, and minimize trauma to the patients with sensitivities and specificities surpassing clinical and radiologic methods. Among the biomarkers, the plasma NT-proBNP has been reported to be significantly associated with the severity of heart failure, left atrial size, the degree of ventricular diastolic dysfunction, left ventricular hypertrophy, and the pressure gradient between the aorta and left ventricle [4]. Another study reported that the plasma NT-proBNP level has high specificity for asymptomatic left ventricular dysfunction [5]. Thus, the plasma NT-proBNP level is an important parameter in the evaluation of the severity of heart failure, prognosis, and treatment response [4, 6]. However, the knowledge and evaluation about the marker as a parameter for fetal cardiopulmonary stress is limited. Therefore, the authors evaluated fetal cardiopulmonary stress in pregnancies complicated by preeclampsia (PE), fetal growth restriction (FGR), preterm birth (PT), and fetal distress (FD) using umbilical arterial blood NT-proBNP at the time of delivery compared with a healthy control group.

## Materials and Methods

From July 2007 to June 2009, the authors enrolled 146 blood samples drawn from the umbilical artery at the time of delivery and corresponding maternal serum NT-proBNP at the time of admission for delivery in this prospective observational study. Informed consent was obtained from all gravidas prior to venipuncture. The inclusion criteria included the following: singleton pregnancy; PE, FGR without PE, PT, FD, and gestational age (GA) matched controls. The exclusion criteria were as follows: overlapping groups; birth before 28 weeks gestation, twin pregnancy, and fetuses with major anomalies. NT-proBNP levels were compared with perinatal factors and short-term postnatal variables.

The diagnosis and classification of PE was based on the criteria suggested in the 2000 National High Blood Pressure Education Program Working Group Report in High Blood Pressure in Pregnancy [7]. Any case that fulfilled only the minimum criteria for PE

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Table 1. — *Comparison of cord NT-proBNP levels between the PE, FGR, and control groups.*

| | PE | *p* value | FGR without PE | *p* value | Controls |
|---|---|---|---|---|---|
| Patient no. | 20 | | 11 | | 61 |
| Age (years) | 31.8 ± 5.3 | 0.956 | 30.2 ± 4.5 | 0.212 | 32.1 ± 3.4 |
| Parity | 0.80 ± 1.15 | 0.946 | 0.45 ± 0.52 | 0.467 | 0.57 ± 0.50 |
| BMI (kg/m²) | 26.6 ± 2.8 | 0.212 | 25.6 ± 4.6 | 0.707 | 25.7 ± 3.4 |
| GA (days) | 258.8 ± 17.0 | 0.181 | 265.5 ± 23.3 | 0.305 | 263.1±14.0 |
| Birthweight (gram) | 2498.0 ± 726.8 | 0.006 | 2367.3 ± 573.1 | 0.001 | 2994.8 ± 502.1 |
| Cord pH | 7.29 ± 0.11 | 0.000 | 7.31 ± 0.14 | 0.026 | 7.39 ± 0.04 |
| NT-proBNP (pg/ml) | 8432.4 ± 12607.7 | 0.000 | 1524.5 ± 1774.9 | 0.065 | 906.1 ± 812.6 |

BMI is defined as the individual's body weight divided by the square of the height. GA: gestational age at delivery.

Table 2. — *Comparison of cord NT-proBNP levels between the FD and control groups.*

| | Fetal distress | Controls | *p* value |
|---|---|---|---|
| Patient no. | 23 | 37 | |
| Age (years) | 29.1 ± 3.8 | 32.0 ± 3.4 | 0.010 |
| Parity | 0.57 ± 0.51 | 0.62 ± 0.49 | 0.667 |
| BMI (kg/m²) | 25.4 ± 4.4 | 26.3 ± 3.1 | 0.148 |
| GA (days) | 246.2 ± 34.7 | 257.8 ±1 4.9 | 0.767 |
| Birthweight (grams) | 2573.5 ± 913.0 | 2871.1 ± 567.0 | 0.287 |
| Cord pH | 7.32 ± 0.10 | 7.39 ± 0.04 | 0.001 |
| NT-proBNP (pg/ml) | 2541.3 ± 3175.8 | 1025.1 ± 985.2 | 0.003 |

Table 3. — *Comparison of cord blood NT-proBNP levels between the PT and control groups.*

| | Preterm birth | Controls | *p* value |
|---|---|---|---|
| Patient no. | 31 | 45 | |
| Age (years) | 30.1 ± 3.6 | 32.5 ± 3.5 | 0.007 |
| Parity | 0.68 ± 0.48 | 0.82 ± 0.94 | 0.991 |
| BMI (kg/m²) | 25.7 ± 3.8 | 25.6 ± 3.3 | 0.619 |
| GA (days) | 234.5 ± 23.6 | 269.8 ± 7.4 | 0.000 |
| Birthweight (grams) | 2141.6 ± 617.8 | 3212.0 ± 340.7 | 0.000 |
| Cord pH | 7.34 ± 0.11 | 7.39 ± 0.04 | 0.034 |
| NT-proBNP (pg/ml) | 2463.6 ± 2752.1 | 648.5 ± 327.3 | 0.000 |

Table 4. — *Correlation coefficients between the cord blood NT-proBNP levels, GA, birth weight, cord blood pH, and maternal NT-proBNP serum levels.*

| | GA | Birthweight | Cord pH | Maternal serum NT-proBNP |
|---|---|---|---|---|
| Cord NT-proBNP (log) | - 0.445* | - 0.544* | - 0.392* | 0.011 |

(blood pressure ≥ 140/90 mm Hg after 20 weeks gestation and proteinuria ≥ 300 mg/24 hours or ≥ 1+ protein in dipstick analysis) was defined as PE. The newborns with birth weights < 10$^{th}$ percentile for GA was defined as FGR. The clinical diagnosis of PT birth was made on delivery after 28 weeks gestation and before 37 completed weeks gestation due to spontaneous preterm labor and preterm rupture of membranes. FD was diagnosed on a non-assuring fetal heart rate (absent baseline FHR variability with recurrent late decelerations or bradycardia) before delivery or umbilical arterial pH < 7.2 at the time of delivery [8].

All study groups were independent and did not overlap. Umbilical arterial blood was obtained at the time of delivery and all blood samples were collected in vacutainers (REF 367820). After clot and serum were completely separated, an aliquot of serum was frozen immediately at -70°C and thawed at the time of assay, which was performed within eight weeks after sampling. The electrochemiluminescence immunoassays of all samples were performed. Comparison of the mean NT-proBNP levels was performed with Mann-Whitney U test. The correlation between NT-proBNP levels and clinical factors, such as GA, birthweight, umbilical arterial pH, maternal age, and maternal body mass index (BMI) was analyzed with Pearson's correlation coefficient. Multivariate analysis was performed to find independent factors affecting NT-proBNP using multiple linear regression analysis. SPSS was used for all statistical analyses.

## Results

Table 1 shows the maternal characteristics and cord NT-proBNP levels of the PE, FGR, and GA matched control groups. There were no statistical differences in patient age, parity, BMI, and GA among the three groups; however, birthweight and cord pH were significantly higher in the control group. The cord NT-proBNP levels were significantly higher in the PE group than the control group, and higher in the FGR group than the control group, but without statistical significance.

Table 2 shows the maternal characteristics and cord NT-proBNP levels between the FD and GA matched control groups. There were no statistical differences in factors between the two groups except patient age, cord pH, and cord NT-proBNP. The cord NT-proBNP levels were significantly higher in the FD group than the control group.

Table 3 shows maternal characteristics and cord NT-proBNP levels of the PT and control groups (GA ≥ 37 completed weeks). There were no statistical differences in parity and BMI among the groups; however, patient age, GA, birthweight, and cord pH were higher in the control group. The cord NT-proBNP levels were significantly higher in the PT group than the control group.

As a result, the cord NT-proBNP levels were higher in the PE, PT, and FD groups than the control group. Furthermore,

the cord NT-proBNP levels were higher in the FGR group than the control group ($p = 0.065$), suggesting borderline statistical significance. The present findings indicate that the cord NT-proBNP levels were negatively correlated with the GA (CC = - 0.445), neonatal birth weight (CC = - 0.544) and umbilical arterial pH (CC = -0.392). The cord NT-proBNP levels were not correlated with the maternal serum NT-proBNP (CC = 0.011, Table 4).

## Discussion

In complicated pregnancies, the cardiovascular status of the newborn is highly unstable during the transition period from the fetal environment. Using antenatal markers that reflect the fetal condition, treatment can be applied before the fetal condition deteriorates and becomes irreversible. Increasing evidence suggests an association between the levels of NT-proBNP in the newborn and the clinical condition [9].

BNP is synthesized in the ventricles and stored as proBNP. This prohormone is then cleaved to active BNP and inactive NT-proBNP, both of which are co-released into the circulation. These peptides are secreted in response to cardiac volume and pressure overload and cause vasodilation, natriuresis, diuresis, and inhibition of the renin-angiotensin system [10]. NT-proBNP has a longer half-life (60-120 minutes) compared to BNP (20 minutes), remains in the blood stream longer, and is stable under a range of storage conditions, thereby rendering NT-proBNP more suitable than BNP for routine clinical monitoring [11]; therefore, NT-proBNP was recently accepted as a more stable and reliable alternative to BNP [12]. Soon after birth, there is no significant difference in plasma NT-proBNP concentrations between umbilical cord blood and neonatal peripheral venous blood [13]. After a marked increase during the first few days of life, NT-proBNP levels decrease steadily and become stable after several days. This is known to result from neonatal cardiopulmonary maturation [14].

In a study involving preterm-delivered neonates with birth weight ≤ 1,500 g and GA ≤ 24 weeks, Sanjeev *et al.* reported that elevation of the plasma BNP accurately detects the presence of patent ductus arteriosus (PDA) in premature infants based on echocardiograms and BNP determinations. Successful closure is reflected by a corresponding decrease in the BNP level. Using a BNP cut-off of 70 pg/ml, BNP was shown to be a useful screening tool for diagnosis and monitoring the efficacy of treatment of PDA [15]. In a study involving 253 healthy controls (11 neonates, 24 infants, and 68 children) and 154 patients with congenital heart disease (ventricular septal defect [VSD], n = 91; PDA, n = 29; atrial septal defect [ASD], n = 34). Kunii *et al.* reported that BNP levels were well-correlated with the severity of disease based on echocardiograms and cardiac catheterizations. In patients with VSDs, it appears that BNP levels may be useful in evaluating surgical indications; specifically, BNP levels between 20 and 35 pg/ml are the appropriate cut-off value [16]. Walsh *et al.* studied 38 children from one to 36 months of age undergoing surgical repair of cardiac lesions. The NT-proBNP levels were measured preoperatively and after surgical intervention and were assessed for predictive value of postoperative outcomes. The preoperative levels correlated with the complexity of surgical repair, as measured by cardiopulmonary bypass time, and with postoperative measures, including inhaled oxygen requirements and duration of mechanical ventilator use. NT-proBNP levels can be a prognostic indicator in pediatric patients after surgery for congenital heart repair [17]. Rocha *at al.* evaluated the NT-proBNP level in neonates with and without respiratory distress syndrome (RDS) at a mean GA of 30 weeks. NT-proBNP was significantly increased directly related to the increasing severity of RDS in neonates, suggesting a close relationship to the functional impairment of pulmonary hemodynamic changes [18]. Thus, NT-proBNP levels facilitate screening, determining the severity of disease, treatment response, and prognosis of patients with cardiac dysfunction or related conditions [19-21]. The plasma concentrations of NT-proBNP are influenced by several factors, such as demographic factors, clinical situations, medical management, and hemodynamic effects [22]. Because these confounding factors limit the interpretation of an elevated NT-proBNP, further investigation for evaluation of cardiac function should be done.

In the present authors' previous study, they reported that NT-proBNP levels were significantly higher in patients with mild and severe PE than in the patients with gestational hypertension and the healthy control patients. This may reflect ventricular stress and/or subclinical cardiac dysfunction associated with PE [23]. In the current study they documented a correlation between the NT-proBNP level and stressful fetal conditions. The NT-proBNP levels were significantly higher in the PE, PT, and FD groups than in the control group. The NT-proBNP levels were higher in the FGR group than the control group, but showed borderline statistical significance. After synthesis in the ventricles, BNP and NT-proBNP are secreted in response to cardiac volume and pressure overload [10]. There is a study suggesting NT-proBNP placental transport is based on the difference of cord NT-proBNP levels in FGR and appropriate-for-gestational-age (AGA) pregnancies [24]. In the present study, however, the cord NT-proBNP levels were not correlated with the maternal serum NT-proBNP. Therefore the authors suggest that NT-proBNP does not pass the placenta, and the natriuretic peptides are considered to be very sensitive markers for cardiac stress not affected by maternal factor. A stressful intrauterine environment appears to induce the fetus to produce large amounts of NT-proBNP. Thus, NT-proBNP may be a useful surrogate for antenatal cardiopulmonary stress in stressful fetal conditions [25].

The present study had some limitations. First, the sample size of the study was relatively small. Second, the authors did not determine the NT-proBNP levels based on the mode

of delivery and anesthetic methods for cesarean sections in the current study. However, in their previous report, they documented that there was no statistical significance by comparison of the mean NT-proBNP values between the cesarean and vaginal delivery groups. With respect to the method of anesthesia, there was no significant difference, too [26].

The strength of the study, however, was that a general evaluation of NT-proBNP in various stressful fetal conditions was conducted. The extant literature with respect to NT-proBNP in PE, FGR, PT, and FD groups is limited, as is the general evaluation in various stressful situations.

Umbilical arterial NT-proBNP levels have the potential to be considered as a marker for fetal cardiopulmonary stress. Based on the results of NT-proBNP measurement, other imaging techniques for cardiac evaluation are required. Although the NT-proBNP level is not a stand-alone test, the NT-proBNP level provides valuable information quickly with respect to detecting an infant requiring intervention. The potential benefit of the NT-proBNP level in neonates is immense. Further large-scale studies of neonatal outcomes evaluating echocardiographic results, use of ventilatory support, perinatal mortality, and long-term outcomes associated with NT-proBNP levels are needed**.**

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