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PLASMA CONCENTRATIONS AND CORRELATIONS OF NATRIURETIC PEPTIDES AND OXYTOCIN DURING LABOR AND EARLY POSTPARTUM PERIOD

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Abstract

Context. Natriuretic peptides (NP) and oxytocin (OT) play an important role in cardiovascular and hydro-electrolytic homeostasis. Changes in NP levels and their roles in cardiovascular adaptations in pregnancy and labor have not been clear.

Objective. The present study aimed to investigate the changes and correlations in plasma levels of atrial natriuretic peptide (ANP), C-type natriuretic peptide (CNP), B-type natriuretic peptide (BNP) and OT during labor and the postpartum period.

Study design. Blood samples were collected from 29 healthy pregnant women in the active phase of spontaneous labor, 15 minutes after delivery and 3 hours postpartum. Plasma levels of OT and the stable N-terminal fragments of NPs (NT-proANP, NT-proCNP, NT-proBNP) were measured using enzyme or electrochemiluminescence immunoassays.

Results. The plasma levels of NT-proANP and NT-proCNP significantly decrease 3 hours postpartum compared to the active phase of labor and to 15 minutes after delivery. The plasma NT-proBNP levels significantly higher after delivery and 3 hours postpartum compared to the active phase of labor. A significant correlation exists between OT and NT-proANP levels during the active phase of labor and 15 minutes after delivery.

Conclusions. The data show that during labor and postpartum, the plasma concentrations of the NPs change differently. Elevations in NT- proBNP after delivery suggest that BNP may be involved in postpartum adaptations. The correlations between OT and ANP levels indicate that OT may be partly responsible for the increased levels of ANP and may have a role in the modification of the cardiovascular system.

Key words: Natriuretic peptides, Oxytocin, Pregnancy, Labor, Postpartum.

INTRODUCTION

The natriuretic peptides (NPs) are regulatory hormones involved in volume homeostasis, vascular tone, cardiovascular remodeling, regulating hydroelectrolyte balance, inducing hypotension, natriuresis and diuresis as well as cardio protection in myocardial ischemia both as circulating hormones and as local autocrine and/or paracrine factors. These peptides promote reductions in blood pressure, increases in sodium excretion, and suppression of renin and aldosterone secretion (1). Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are produced in the heart. Hypervolemia-induced stretch of the atria and ventricles induces the release of ANP and BNP into the circulation (2). Oxytocin (OT) and ANP act in concert to control vascular homeostasis and the body's internal environment; it is possible that the protective effect of OT is mediated through endogenous ANP (3). C-type natriuretic peptide (CNP) is synthesized within a broad range of tissues including the heart, vascular endothelium, central nervous system, reproductive and skeletal tissues (4-6). Recent studies demonstrate that CNP is a novel endothelium-derived hyperpolarizing factor that complements the actions of other endothelial vasorelaxant mediators such as nitric oxide and prostacyclin (7). The expression of the CNP receptor in the human uterus suggests a possible action in reproduction (8).

Oxytocin is one of the most important hormones involved in human parturition by triggering uterine contractions (9). Recent evidence suggests that OT is involved in the regulation of cardiovascular functions (10, 11). Some researchers have shown that OT and OT receptors are present in the heart as well (12). In another study, OT synthesis and release were reported in all four chambers of the heart. The study demonstrated that cardiac OT is structurally identical to that found in the hypothalamus, which thereby indicates that cardiac OT is derived from the same

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gene and is an active form of OT (13). The OT and OT receptors in atrial myocytes directly and/or via the release of the cardiac hormone atrial natriuretic peptide (14) can regulate the force of cardiac contractions (15).

The cardiovascular system undergoes important adaptations during pregnancy and parturition. During pregnancy blood volume, stroke volume, heart rate and cardiac output increase, while systemic vascular resistance and systemic blood pressure decrease. During labor cardiac output and stroke volume, stimulated by pain and increased blood volume, increase further. After delivery, cardiac output initially increases, but begins to decrease within the first hours (16, 17). The cardiovascular changes usually persist for 2–3 weeks postpartum and reach nonpregnant levels in 12 weeks (18-20). The mechanisms regulating pregnancy-induced volume and hemodynamic changes are not completely understood. The gestational hormones as well as arginine vasopressin, and the renin-angiotensin-aldosterone system have been shown to play an important role in pregnancy-induced adaptations (21). Despite the growing data on the role of NPs in the regulation of blood pressure and volume homeostasis, studies examining the changes in NPs during pregnancy and labor are limited and the data obtained from these studies are conflicting. The present study was designed to examine the changes in plasma levels of OT, ANP, BNP and CNP during labor and the early postpartum period and to find out if a relation exists between OT levels and NPs.

PATIENTS AND METHODS

Patients

The hospital ethics committee of Marmara University School of Medicine and of Zeynep Kamil Women and Children's Diseases Education and Research Hospital approved this study. For determination of NP values during labor and postpartum, 29 healthy singleton pregnant women without a history of cardiovascular disease, hypertension or pulmonary disease who had been admitted to the delivery room and had delivered vaginally were enrolled in the study. Blood samples were collected from the women in the supine posture after receipt of informed consent. None of the women received analgesia during labor. Most of the women did undergo induction or augmentation of labor (Synpitan Forte 5 IU/mL IV Ampoule. Deva Corp. Turkey). The pregnants were not on any medications except iron supplementation.

Blood samples

For determination of NP and OT values during labor and postpartum, blood samples were collected at three separate times: 1) the active phase of spontaneous labor (cervical dilatation ≥ 4 cm); 2) within 15 minutes after vaginal delivery; and 3) three hours after vaginal delivery. For comparison and correlation between the different stages, only paired sets of measurements were considered.

Blood was collected into chilled tubes containing EDTA (1mg/mL) and aprotinin (500KIU/mL) and kept on ice until the plasma was separated (at 4°C, at 2000×g for 15 minutes) and subsequently stored at -80°C until assayed.

Biochemical analysis

Plasma levels of the more stable amino terminal fragment of the NPs were measured. Plasma concentrations of NT-proANP, NT-proCNP (Biomedica, Austria) and OT (Phoenix, USA) were measured with an enzyme immunoassay (EIA). NT-proBNP (Roche Diagnostics, Germany) concentration was assayed with an electrochemiluminescence immunoassay (ECLIA) on the Elecsys 2010 system. Oxytocin EIA was preceded by a solid-phase extraction using a SEP-COLUMN containing 200 mg of C18 (Phenomenex 200mg, USA) (22).

Statistical analysis

Results are expressed as mean ± standard deviation (SD) and $p<0.05$ was taken to indicate a significant difference between groups. Statistical comparisons of paired tests were performed by repeated measures of analysis of variance (ANOVA). The Pearson correlation test was used to investigate the linear associations of plasma NT-proANP, NT-proBNP, NT-proCNP and oxytocin levels. Data were analyzed by IBM SPSS 20 software.

RESULTS

Mean±SD age of the pregnants was 26.3±3.3 years, and the gestational age was 38.5±1.9 weeks.

NP and OT values during labor and postpartum:

The plasma level of NT-proANP (mean ± SD) in the active phase of labor was 2.08±1.16 nmol/L then rose to 2.34±1.08 nmol/L 15 minutes after delivery and declined to 1.55±0.80 nmol/L 3 hours postpartum, which was significantly ($p<0.05$, $p<0.001$, n=29) lower than that seen at the active phase and after delivery (Fig. 1b, Table 1).

The plasma level of NT-proBNP in the active phase of labor was 5.19±3.01 pmol/L and then rose to 6.14±3.48 pmol/L 15 min after delivery, being significantly higher compared to the active phase, and then rising to 6.64 ± 4.26 pmol/L at 3 hours postpartum, which was significantly (p<0.05, p<0.01, n=29) higher than that seen after delivery (Fig. 1c, Table 1).

The plasma level of NT-proCNP in the active phase of labor was 3.79±1.82 pmol/L, declined to 3.63±1.86 pmol/L after delivery, and to 3.19±1.70 pmol/L 3 hours postpartum, which was significantly (p<0.01, p<0.05, n=29) lower than that seen at the active phase and after delivery (Fig. 1d, Table 1).

The plasma OT levels showed great variations. The mean ± SD of OT concentration was highest (74.56±82.99 pg/mL) after delivery, being significantly different from those seen at the active phase of labor (24.29±15.73 pg/mL) and 3 hours postpartum (53.35±75.79 pg/mL) (p<0.01, p<0.05, n=29) (Fig. 1a, Table 1).

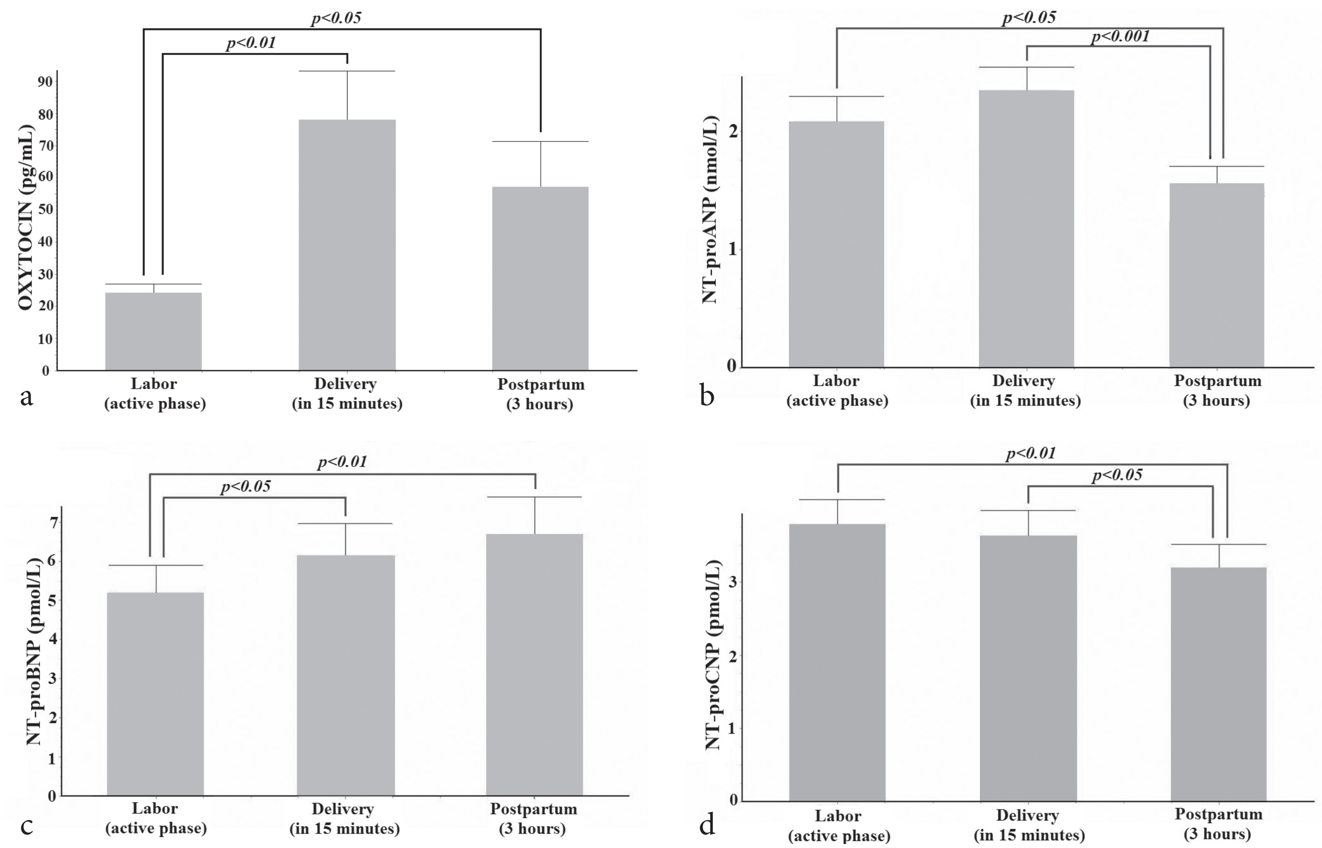

Figure 1 a-d. Plasma Oxytocin, NT-proAtrial Natriuretic Peptide, NT-proB-type Natriuretic Peptide, and NT-proC-type Natriuretic Peptide levels of pregnant women in the active phase of labor, right after delivery in 15 min and 3 hours postpartum. Bars represent Mean±SD obtained from the measurement of the paired samples (n=29 for oxytocin, NT-proANP, NT-proBNP and NT-proCNP).

Table 1. Concentrations (Mean±SD) of oxytocin, NT-proANP, NT-proBNP, NT-proCNP in plasma of normal pregnant women during labor, 15 minutes after delivery and 3 hours postpartum

	Labor (active phase)	**Delivery (in 15 minutes)**	**Postpartum (3 hours)**
Oxytocin	n=29	n=29	n=29
(pg/mL)	24.29±15.73	74.5 ±82.99 [a]	53.35±75.79 [b]
NT-proANP	n=29	n=29	n=29
(nmol/L)	2.08 ±1.16	2.34 ±1.08	1.55 ±0.80 [bc]
NT-proBNP	n=29	n=29	n=29
(pmol/L)	5.19 ±3.01	6.14 ±3.48 [a]	6.64 ±4.26 [b]
NT-proCNP	n=29	n=29	n=29
(pmol/L)	3.79 ±1.82	3.63 ±1.86	3.19 ±1.70 [bc]

a, b and c showed statistical significance at the p<0.05 level.
a Labor *vs*. Delivery, b Labor *vs*. Postpartum, c Delivery *vs*. Postpartum

Correlation between plasma oxytocin and NP levels:

A significant correlation (r=0.44, p<0.01) between oxytocin and NT-proANP levels at the active phase of labor was found (Fig. 2). Also a significant correlation (r=0.40, p<0.05) between oxytocin levels and NT-proANP levels at 15 min after delivery was found (Fig. 3). However, there was no correlation among oxytocin, NT-proBNP and NT-proCNP levels at any phase.

DISCUSSION

This study is the first to investigate the changes in plasma levels of the three NPs and OT in the same group of women during labor and postpartum, and also the first to demonstrate a correlation between OT and ANP levels in women during labor.

The NPs are secreted as pro-peptides and cleaved to give the physiologically active peptide and the inactive amino terminal fragment NT-proNP.

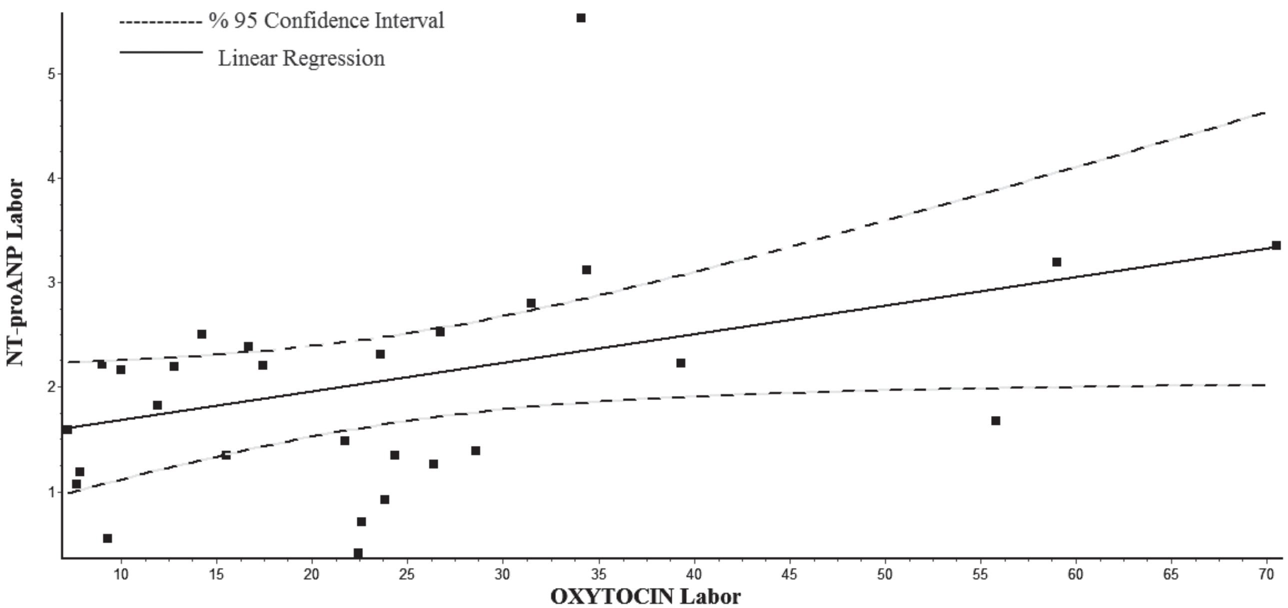

Figure 2. Correlation between the NT-proANP and oxytocin levels during the active phase of labor.

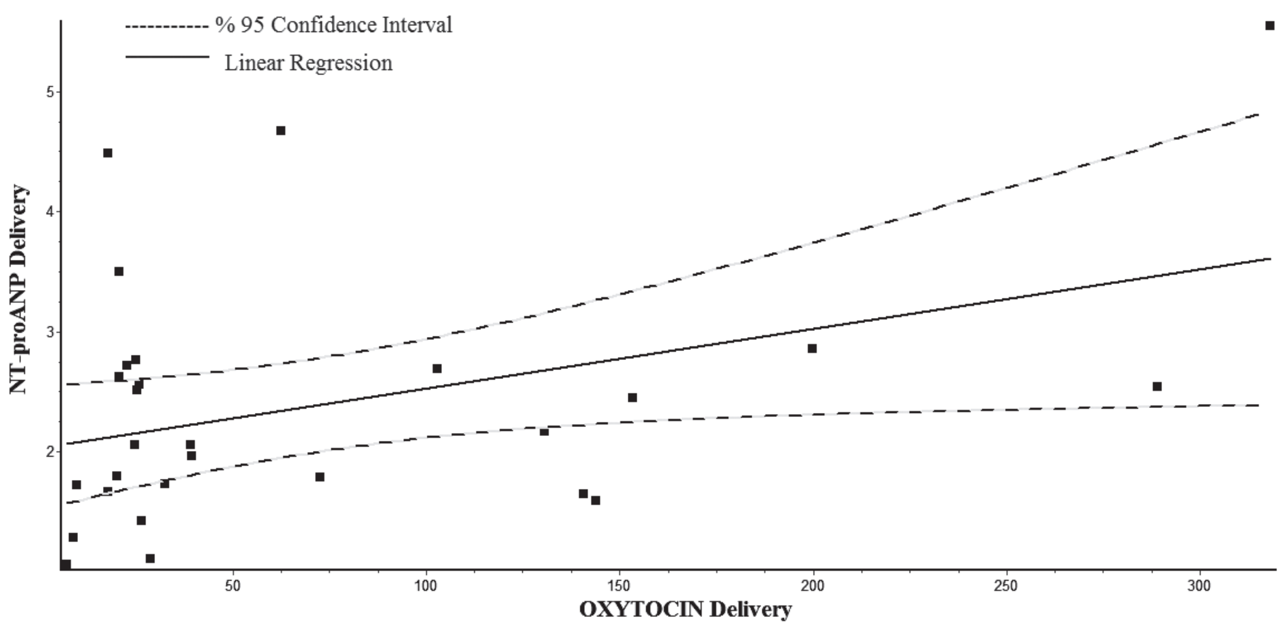

Figure 3. Correlation between the NT-proANP and oxytocin levels in 15 minutes after delivery.

Previous studies have shown that the measurement of NT-proNPs provide valid information similar to active NPs (23-26).

Previously the plasma levels of ANP have been measured in many studies to investigate its physiological role during normal gestation and especially its possible role in pre-eclampsia. A few studies examining changes in NP levels have reported that ANP levels decrease (27) whereas some others have reported that ANP levels do not change during normal pregnancy (28, 29). However, most of the studies have reported increases in ANP levels with advancing gestation (30-34). The wide variation in previously reported circulating levels of ANP during pregnancy may be due to differences in methods and/or antibody specificity.

Less is known about the changes in levels of NPs during delivery and postpartum periods. Our study indicates that ANP levels reach peak values in 15 minutes after delivery and begin to decrease early postpartum. Yoshimura *et al*. measured plasma ANP levels 30 minutes after separation of the placenta and reported significant increases compared to term pregnancy values. They also observed a significant decline in the late postpartum (5-72 h) period (34). In contrast, Wong *et al*. showed that plasma ANP levels in pregnant women increased significantly in the active phase of the first stage of labor but decreased during and after delivery towards control levels (35). Elevations in plasma ANP levels during labor and in the early postpartum period may be explained by the hemodynamic changes such as increased blood volume. Yet another potential mechanism involved in ANP release may be the increased OT levels. According to our data, plasma OT levels were the highest in the immediate postpartum period coinciding with the highest ANP levels, showing a statistically significant correlation. In fact, the hormone oxytocin is not directly related to birth, and contrary to popular opinion, it is not among the factors that initiate birth. Oxytocin is mostly secreted in the early postpartum period in order to prevent uterine bleeding after the delivery is completed. It is well known that OT is released during parturition and breast-feeding to promote uterine contraction and milk ejection (36). However, the evidence from recent studies suggests that OT is also involved in regulation of cardiovascular functions and water/electrolyte balance (37). It has been proposed that part of the effect of OT on the cardiovascular system results from its ANP-releasing action and thus partly from the natriuretic effect of ANP (15). Therefore, elevations in OT levels, both physiologically and pharmacologically, during labor may be partly responsible for the increased levels of ANP and may have a role in the modulation of the cardiovascular system via ANP in humans during labor besides promoting uterine contractions.

Our data indicate that plasma levels of BNP significantly increased during labor and postpartum periods.

In most of the earlier studies, levels of ANP and BNP increased postpartum. Both ANP and BNP have potent diuretic effects, and help mediate the diuresis noted in the early postpartum period (38). To our knowledge, there are no previous studies measuring the NP levels 15 minutes after delivery, although there are a few studies providing data on BNP values in the postpartum period at different time points. Our data also demonstrates that BNP levels significantly increase after delivery and at 3h postpartum compared to the active stage of labor although all the values are below the levels that may indicate any cardiac dysfunction. Lev-Segie *et al*. have reported a 2-fold increase in BNP levels within 28 hours after delivery compared to predelivery levels (39). Yoshimura *et al*. reported that the plasma level of BNP increased 30 minutes after separation of the placenta, and more in the late postpartum period (34). Our results are consistent with the previous studies that reported significant increase in BNP levels in the postpartum period but indicate that elevation in BNP levels begins earlier, during the active phase of labor.

Since cardiovascular parameters show their greatest changes within the postpartum period it is not surprising to find an increase in BNP levels reflecting pressure/volume overload (19). Persisting elevations in the postpartum period may indicate that BNP is involved in postpartum hemodynamic readaptations.

There are few studies of the changes in CNP levels during pregnancy and labor. This may be due to problems in measurement related to the low circulating plasma levels and rapid catabolism of CNP. However, the relatively recent possibility of the assessment of the more stable NT-proCNP has contributed to the investigation of CNP (26). Our results indicate that plasma CNP levels decline significantly in the early postpartum period compared to the active phase and right after delivery. This data are consistent with the results of Stepan *et al*. who investigated CNP levels during pregnancy, in the active phase of labor and 24 hours postpartum in a smaller group of subjects (40, 41). The decline in CNP levels after delivery may suggest that this peptide is not involved in postpartum hemodynamic adaptations but may have a role during labor.

This study has several limitations, the size of the study group is relatively small and the non-pregnant control group was not available to compare the pregnant and non-pregnant levels, although, preconception levels of NT-proANP, NT proBNP and NT proCNP were not available in the present study patients.

In conclusion, an overview of the data show that during early postpartum NT-proANP and NT-proCNP levels decline while NT-proBNP levels rise. These results indicate that BNP is involved in postpartum hemodynamic adaptation. The correlations existing between OT and ANP levels during labor suggest that OT may be partly responsible for the increased levels of ANP and may have a role in the modification of the cardiovascular system besides promoting uterine contractions. More research is required to clarify the physiological importance of NPs in labor and postpartum.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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