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SERUM LEVELS OF N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE IN HYPERTENSIVE DISORDERS OF PREGNANCY

Svitlana O. Ostafiichuk, Nataliia V. Drohomyretska, Yuliya B. Motsyuk, Oksana M. Zhukuliak, Yaroslav S. Zadorozhniy

Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine

Abstract

Introduction. Hypertensive disorders of pregnancy (HDP) are among the leading causes of maternal and perinatal morbidity and mortality. This necessitates improvement of early diagnostic and prognostic approaches. Impaired cardiovascular adaptation, increased vascular resistance, and endothelial dysfunction play key roles in their pathogenesis. N-terminal pro-brain natriuretic peptide (NT-proBNP), a biomarker reflecting myocardial hemodynamic load, appears promising; however, its prognostic value in gestational hypertension (GH) and preeclampsia (PE) remains to be fully established.
Aim. To evaluate the association between serum NT-proBNP levels and the development of HDP and to assess its prognostic potential.
Materials and methods. A total of 119 pregnant women were enrolled and divided into three groups: 61 women with HDP (46 with GH and 15 with moderate PE), 48 women at high risk of HDP, and 25 women with uncomplicated pregnancies (control group). All participants underwent clinical examination, 24-hour blood pressure (BP) monitoring, and serum NT-proBNP measurement using enzyme-linked immunosorbent assay. Statistical analysis was performed using Statistica 12 and MedCalc®.
Results. NT-proBNP levels were 3.4-fold higher in women with GH compared to controls (196.41 ± 17.28 vs. 56.16 ± 6.62 pg/mL, p = 0.000) and 4.7-fold higher in women with PE compared to controls (264.73 ± 9.13 vs. 56.16 ± 6.62 pg/mL, p = 0.000). NT-proBNP levels were 1.3-fold higher in PE compared to GH (p = 0.000). In the high-risk group, women who subsequently developed HDP had significantly higher NT-proBNP levels in the second trimester compared to controls (87.71 ± 8.56 vs. 56.16 ± 6.62 pg/ mL, p = 0.006) and compared to women who remained normotensive (87.71 ± 8.56 vs. 62.79 ± 5.50 pg/mL, p = 0.018). A strong positive correlation was observed between NT-proBNP levels and mean daily systolic BP in women with HDP (r = 0.81, p = 0.000) and a moderate positive correlation in the high-risk group (r = 0.54, p = 0.000).
Conclusions. Elevated NT-proBNP levels are associated with HDP. NT-proBNP may serve as an informative biomarker for early detection, risk stratification, and clinical monitoring of patients with GH and PE.

Keywords: **pregnancy, gestational hypertension, preeclampsia, NT-proBNP, endothelial dysfunction**

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are among the leading causes of maternal and perinatal morbidity and mortality, affecting approximately 8-10% of pregnancies. The development of HDP is primarily associated with inadequate physiological cardiovascular adaptation during pregnancy. O'Driscoll et al. suggest that the hemodynamic abnormalities observed in gestational hypertension (GH) reflect both women's pre-existing cardiovascular (CV) vulnerability and the chronic hemodynamic load imposed by pregnancy [1]. These changes, which correlate with the severity of the clinical course, can emerge as early as the first trimester and may be detected before the onset of clinical symptoms. Importantly, such hemodynamic disturbances can persist for years postpartum, increasing long-term cardiovascular risk [2].

HDP are associated with increased left ventricular mass, concentric hypertrophy, and elevated systemic vascular resistance compared with physiological pregnancy. In women with chronic hypertension, systemic vascular resistance remains persistently

elevated, and intravascular volume expansion is limited throughout pregnancy. In contrast, data on hemodynamic changes in GH remain inconsistent [3]. In preeclampsia (PE), studies report a reduction in stroke volume and myocardial function indices compared with normotensive pregnancies, and heart failure may develop in nearly half of PE cases [4]. Both PE and GH exert a substantial adverse impact on the cardiovascular system, with the most pronounced changes observed during early onset or in severe clinical courses. Researchers increasingly recognize pregnancy as a «window of opportunity» for identifying women at high cardiovascular risk, highlighting the importance of investigating HDP pathogenesis and implementing early screening for high-risk groups to reduce the incidence of pregnancy complications and future cardiovascular morbidity [5, 6].

N-terminal pro-brain natriuretic peptide (NT-proBNP), a biomarker reflecting endothelial dysfunction, has attracted particular attention in the literature. Ventricular cardiomyocytes synthesize NT-proBNP in response to mechanical stress rather than direct myocardial injury [7]. The association between NT-proBNP levels and GH remains controversial: some studies report increased NT-proBNP with the severity of PE, whereas others find no significant association [8, 9]. Establishing the relationship between circulating NT-proBNP levels and HDP may provide insight into the mechanisms underlying cardiovascular dysfunction in GH and PE and holds promise for improving early diagnosis and prognostic evaluation of these conditions.

AIM

To evaluate the association between serum NT-proBNP levels and the development of HDP and to assess its prognostic potential.

MATERIALS AND METHODS

A prospective study was conducted from 2022 to 2025 at the Department of Obstetrics and Gynecology of the Ivano-Frankivsk National Medical University and the Ivano-Frankivsk Perinatal Center. A total of 119 pregnant women were enrolled. The first group included 61 women with HDP, of whom 46 (75.4%) had gestational hypertension (GH) and 15 (24.6%) had moderate preeclampsia (PE). The second group comprised 48 women at high risk of HDP (with a history of HDP during a previous pregnancy). The control group included 25 women with uncomplicated pregnancies. In the second group, 14 women (29.2%) subsequently developed HDP in the third trimester, while 34 women (70.8%) remained normotensive until delivery.

The mean age was 30.19 ± 5.07 years (95% CI: 28.50-31.88) in the first group, 32.18 ± 5.11 years (95% CI: 29.44-34.92) in the second group, and 26.93 ± 4.71 years (95% CI: 25.10-28.76) in the control group. The proportion of women over 30 years of age, with higher education, and primarily engaged in mental work was significantly higher in the first and second groups compared to controls ($p < 0.05$ for all comparisons) (Table 1).

Table 1

Characteristics of the Examined Women

Indicanntors	First group (n=61)		Second group (n=48)		Control group (n=25)		p
	Abs.	%	Abs.	%	Abs.	%	
Parity							
– primiparous	53	86.9	0	0.0	14	56.0	
– multiparous	8	13.1	48	100.0	11	44.0	0.004^{1-3}
Age, years							
18-24	3	4.9	4	8.3	3	12.0	
25-30	25	41.0	15	31.3	15	60.0	
31-34	21	34.4	19	39.6	5	20.0	
- 35 and >	12	19.7	10	20.8	2	8.0	
Education							
– higher	47	77.0	38	79.2	13	52.0	0.041^{1-3}
– secondary	10	16.4	9	18.8	10	40.0	0.033^{2-3}
– no education	4	6.6	1	2.1	2	8.0	0.038^{1-3}
Employment							
– mental work	38	62.3	32	66.7	9	36.0	0.047^{1-3}
– physical work	9	14.8	7	14.6	10	40.0	0.023^{2-3}
– pupils, students	2	3.3	0	0.0	2	8.0	0.022^{1-3}
– housewives	12	19.7	9	18.8	4	16.0	0.031^{2-3}
Average daily systolic BP, mm Hg	146.77±3.47		129.47±3.69		113.11±4.01		0.000^{1-3} 0.000^{2-3}
Average daily diastolic BP, mm Hg	96.83±3.46		80.08±4.26		69.54±3.01		0.000^{1-3} 0.000^{2-3}

Notes: 1 – first group, 2 – second group, 3 – control; $p < 0.05$ was considered statistically significant.

Inclusion criteria: women aged 18 years and older with a singleton pregnancy, diagnosed with GH or PE, or at high risk of HDP (history of HDP in a previous pregnancy), with no history of chronic hypertension, severe somatic or mental disorders.

Exclusion criteria: age under 18 years, multiple pregnancy, use of assisted reproductive technologies, current eclampsia, HELLP syndrome, chronic hypertension, endocrine disorders, metabolic syndrome, chronic kidney or liver disease, moderate to severe anemia, autoimmune disorders, and mental illnesses.

Daily blood pressure (BP) monitoring was performed using the Dia Card system (Solveig, Ukraine). Laboratory analyses were conducted in a certified laboratory at the Ivano-Frankivsk Perinatal Center. Serum NT-proBNP concentrations (pg/mL) were measured by enzyme-linked immunosorbent assay using a UNscience kit (P. R. China, Cat. No.: CP02005, Hubei, China).

Statistical analyses were performed using Statistica 12 (Serial Number: STA999K347150-W) and MedCalc® (https://www.medcalc.org/calc/). Continuous variables are presented as meanstandard deviation (M ± SD) with 95% confidence intervals (CI). Differences between two independent groups were evaluated using Student's t-test, with $p < 0.05$ considered statistically significant. Pearson's correlation coefficient (r) was used to assess the presence, strength, and direction of relationships between selected parameters. To reveal the presence, strength, and direction of the relationship between the selected parameters, Pearson's paired correlation (r) was used.

RESULTS

NT-proBNP levels were significantly higher in women with GH compared to controls, with a 3.4-fold increase (196.41 ± 17.28 pg/mL vs. 56.16 ± 6.62 pg/mL, p = 0.000), and in women with PE compared to controls, with a 4.7-fold increase (264.73 ± 9.13 pg/mL vs. 56.16 ± 6.62 pg/mL, p = 0.000) (Fig. 1a). NT-proBNP concentrations were also 1.3 times higher in the PE group compared with the GH group (p = 0.0009).

For predicting the development of GH, an NT-proBNP threshold of ≥ 171 pg/mL demonstrated a sensitivity of 83.3% (95% CI: 79.8-86.8) and a specificity of 75.0% (95% CI: 69.3-80.3).

In the second group, during the second trimester of pregnancy, NT-proBNP levels were not significantly different from controls (70.06 ± 13.08 pg/mL vs. 56.16 ± 6.62 pg/mL, p = 0.34). However, among women who subsequently developed HDP, NT-proBNP levels were 1.4 times higher compared to women who remained normotensive (87.71 ± 8.56 pg/mL vs. 62.79 ± 5.50 pg/mL, p = 0.018) and 1.6 times higher compared to controls (87.71 ± 8.56 pg/mL vs. 56.16 ± 6.62 pg/mL, p = 0.006) (Fig. 1b). No significant difference in NT-proBNP levels was observed in women of the second group who remained normotensive until delivery compared with controls (62.79 ± 5.50 pg/mL vs. 56.16 ± 6.62 pg/mL, p = 0.44).

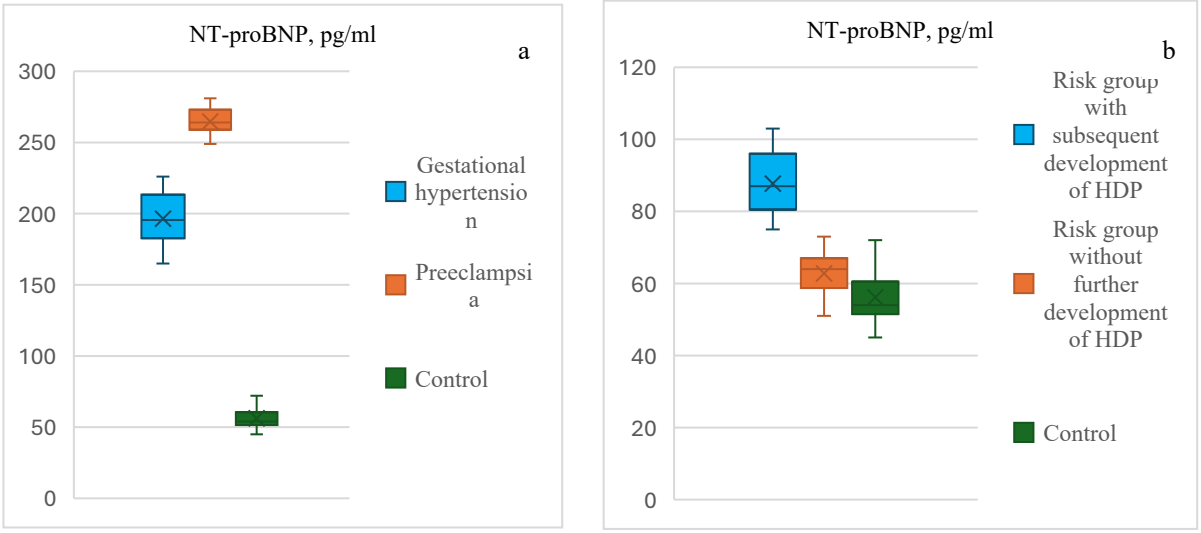

Figure 1. NT-proBNP levels in study groups. a – women with gestational hypertension, preeclampsia, and control (normotensive) patients, expressed in pg/mL; b – high-risk group, subdivided into participants with or without subsequent development of hypertensive disorders of pregnancy (HDP), expressed in pg/mL; p < 0.05 was considered statistically significant.

The study demonstrated a strong positive correlation between average daily systolic BP and NT-proBNP levels in the first group (r = 0.81, p = 0.000) (Fig. 2a), indicating that NT-proBNP concentrations increase with the severity of hypertension. A moderate positive correlation was also observed in the second group (r = 0.54, p = 0.001) (Fig. 2b), suggesting a relationship between NT-proBNP levels and BP even within the normotensive range.

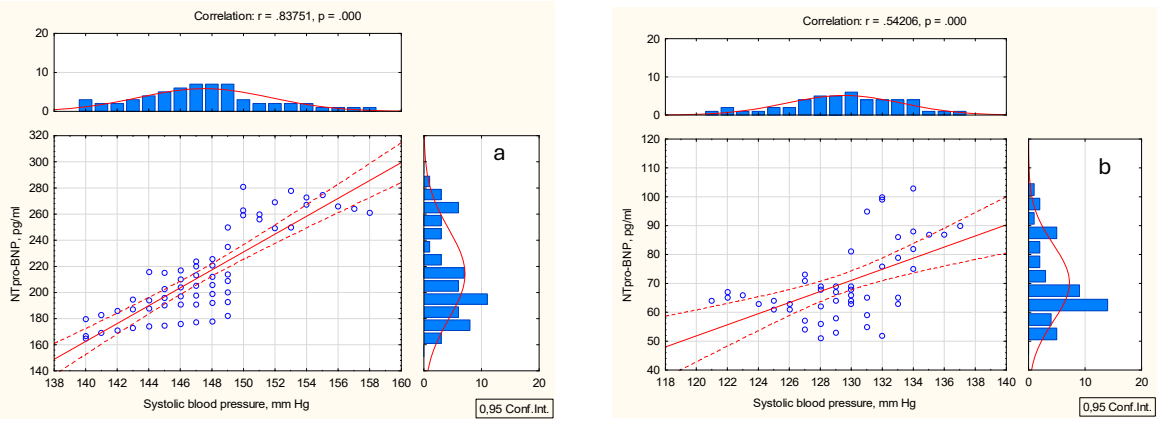

Figure 2. Correlation between NT-proBNP levels and average daily systolic blood pressure; a – first group (women with HDP), b – second group (high-risk women).

DISCUSSION

Our study demonstrated significantly higher NT-proBNP levels in pregnant women with GH and PE compared to normotensive controls. Similarly, Nguyen et al. reported elevated NT-proBNP levels in women with PE relative to controls, with higher concentrations observed in severe PE compared to moderate PE. These authors emphasized that women with severe PE face an increased risk of both immediate and long-term cardiovascular complications [10]. In our cohort, a strong positive correlation was observed between average daily systolic BP and NT-proBNP levels, indicating that NT-proBNP concentrations increase with hypertension severity.

Rusoi et al. also demonstrated that NT-proBNP concentrations are elevated in PE patients compared to healthy pregnant women. Cardiac overload induces increased secretion of cardiomyocyte natriuretic peptides, including ANP, BNP, and NT-proBNP. Among these, NT-proBNP has a long half-life and persists in systemic circulation, making it an informative biomarker of cardiac dysfunction. Elevated NT-proBNP reflects impaired left ventricular diastolic function, systolic dysfunction, and structural myocardial changes. Vascular changes characteristic of PE differ from physiological pregnancy adaptations and are marked by a predominance of vasoconstriction, which increases afterload on the heart, thereby altering left ventricular function and morphology. Consequently, elevated NT-proBNP levels in women with PE reflect increased cardiac workload due to heightened afterload [11].

In women at high risk who subsequently developed HDP, NT-proBNP concentrations were higher compared to both women who remained normotensive and controls. However, conflicting results have been reported. Takahashi et al., in a retrospective study, found that NT-proBNP concentrations in early pregnancy were lower in women who later developed HDP after 35 weeks compared to those who remained normotensive, suggesting that lower early NT-proBNP may reflect defective vascular adaptation and an increased risk of late-onset hypertension [12]. Conversely, Álvarez-Fernández et al. reported higher NT-proBNP levels in women who developed late-onset PE compared to those without complications [13]. Palmrich et al. confirmed the prognostic value of NT-proBNP, showing that elevated levels reliably predict severe adverse pregnancy outcomes in women with PE, particularly in early-onset cases [14].

Tihtonen et al. reported increased NT-proBNP in PE compared with women with chronic hypertension and normotensive pregnancies. During PE, elevated peripheral resistance increases afterload and ventricular stress, which in turn stimulates NT-proBNP secretion as a compensatory mechanism. Natriuretic peptides, including NT-proBNP, contribute to BP regulation through natriuresis, diuresis, and vasodilation, suggesting that elevated BP itself stimulates NT-proBNP production [15]. Our findings, consistent with those of Kumari et al., indicate that PE, rather than hypertensive status, is the primary factor driving NT-proBNP elevation [16]. Additional contributors may include increased plasma volume and venous congestion.

CONCLUSIONS

Elevated serum NT-proBNP levels are associated with the development of HDP. NT-proBNP may serve as an accessible and informative biomarker for early detection, risk stratification, and ongoing monitoring of women with GH and PE.

Perspectives for Further Research. NT-proBNP levels were measured at specific time points rather than longitudinally throughout pregnancy. Further conduct of serial measurements may provide a more detailed understanding of dynamic changes in biomarker levels and their temporal relationship with the onset and

progression of hypertensive disorders. Further research with longitudinal biomarker assessment will clarify the prognostic value of NT-proBNP in HDP. Such knowledge will provide an evidence base for the development of effective methods for risk prediction and management of pregnant women with GH and PE.

COMPLIANCE WITH ETHICAL REQUIREMENTS

The study was conducted in accordance with the ethical principles of the World Medical Association and the Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, as well as the Universal Declaration on Bioethics and Human Rights. The study was approved by the Ethics Committee of Ivano-Frankivsk National Medical University (Protocol No. 130/22, 23.11.2022). Prior to the initiation of the study, all participants received comprehensive information regarding the study objectives, methodology, and benefits of participation. Enrollment was based on the principle of voluntary informed consent, and all participants signed a written informed consent form before data collection. Participants were informed of their right to withdraw from the study at any time without providing a reason and without any consequences.

In accordance with confidentiality requirements, all data were collected anonymously and processed in compliance with applicable data protection legislation, including the General Data Protection Regulation (GDPR). Personal information was strictly protected and used exclusively for the purposes of this study. The data were analyzed and presented in aggregated form to ensure participants' confidentiality.

Study Limitations. Limitations of this study are connected with relatively small sample size, particularly in the subgroup of women with moderate preeclampsia, may limit the generalizability of the findings and reduce statistical power for subgroup analyses. Also, this was a single-center study conducted at one Perinatal Center, which may restrict the external validity of the results to other populations and healthcare settings. Future multicenter studies with larger cohorts are warranted to validate these findings and to further clarify the prognostic value of NT-proBNP in HDP.

Primary Data and Materials. This study is based on original clinical data obtained from enrolled participants. The datasets generated and/or analysed during the current study are not publicly available due to ethical and confidentiality restrictions but are available from the corresponding author upon reasonable request and with permission of the relevant institutional authority.

Declaration of AI use. The authors declare that no artificial intelligence tools or generative AI technologies were used in the preparation of this manuscript.

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The authors declare that they have no conflicts of interest related to this study.

AUTHOR CONTRIBUTIONS

Ostafiichuk S. O.[A, D, C, E, F]

Drohomyretska N. V.[A, B, F]

Motsyuk Yu.B.[A, B]

Zhukuliak O. M.[A, B]

Zadorozhniy Ya.S.[B, D]

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Резюме

РІВНІ СИРОВАТКОВОГО N-КІНЦЕВОГО ПРОМОЗКОВОГО НАТРІЙУРЕТИЧНОГО ПЕПТИДУ (NT-PROBNP) ПРИ ГІПЕРТЕНЗИВНИХ РОЗЛАДАХ ВАГІТНОСТІ

Світлана О. Остафійчук, Наталія В. Дрогомирецька, Юлія Б. Моцюк, Оксана М. Жукуляк, Ярослав С. Задорожний

Івано-Франківський національний медичний університет, м. Івано-Франківськ, Україна

Вступ. Гіпертензивні розлади вагітності (ГРВ) є однією з провідних причин материнської та перинатальної захворюваності і смертності, що зумовлює необхідність удосконалення методів ранньої діагностики та прогнозування цих станів. Важливу роль у їхньому патогенезі відіграють порушення серцево-судинної адаптації, підвищення судинного опору та розвиток ендотеліальної дисфункції. Перспективним біомаркером, який відображає гемодинамічне навантаження на міокард, є N-кінцевий промозковий натрійуретичний пептид (NT-proBNP), однак його прогностична цінність при гестаційній гіпертензії (ГГ) та прееклампсії (ПЕ) потребує подальшого вивчення.

Мета. Встановити асоціацію між сироватковим рівнем NT-proBNP та розвитком ГРВ та оцінити його можливості як прогностичного маркера.

Матеріали та методи. Обстежено 119 вагітних, яких розподілено на три групи: 61 вагітна жінка з ГРВ (з них 46 осіб мали ГГ, 15 – помірну ПЕ); 48 вагітних із високим ризиком їх розвитку та 25 жінок із нормальною вагітністю. Усім пацієнткам проводили клінічне обстеження, добове моніторування артеріального тиску (АТ) та визначення сироваткового рівня NT-proBNP імуноферментним методом. Статистичну обробку результатів здійснювали із застосуванням Statistica 12 (Serial Number: STA999K347150-W) та MedCalc®.

Результати. Встановлено вищі рівні NT-proBNP у вагітних з ГГ порівняно з контролем в 3,4 раза (196,41 ± 17,28 проти 56,16 ± 6,62 пг/мл, p = 0,000), у жінок з ПЕ порівняно з контролем в 4,7 раза (264,73 ± 9,13 проти 56,16 ± 6,62 пг/мл, p = 0,000), у групі з ПЕ проти пацієнток з ГГ в 1,3 раза (p = 0,000). У групі високого ризику у жінок, у яких згодом розвинулися ГРВ, рівень NT-proBNP був в 1,6 раза вищим уже в другому триместрі відносно контролю (87,71 ± 8,56 проти 56,16 ± 6,62 пг/мл, p = 0,006) та в 1,4 раза був вищим порівняно з вагітними без наступного розвитку гіпертензії (87,71 ± 8,56 проти 62,79 ± 5,50 пг/ мл, p = 0,018). Виявлено позитивний кореляційний зв'язок між рівнем NT-proBNP та середньодобовим систолічним АТ в першій (r = 0,81, p = 0,000) і другій групах (r = 0,78, p = 0,000).

Висновки. Підвищення рівня NT-proBNP асоціюється з розвитком ГРВ. NT-proBNP може розглядатися як інформативний біомаркер для раннього виявлення і стратифікації ризику, а також моніторингу пацієнток з ГГ і ПЕ.

Ключові слова: **вагітність, гестаційна гіпертензія, прееклампсія, NT-proBNP, ендотеліальна дисфункція**

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