



The Investigation of NT-proBNP Values in Third-Trimester Gestational Diabetes Women Without Cardiovascular Disease

Kardiyovasküler Hastalığı Olmayan Üçüncü Trimesterdeki Gestasyonel Diabetes Mellitus Olan Kadınlarda NT-Probnp Değerlerinin Araştırılması

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ABSTRACT

Objective: The clinical utility and importance of natriuretic peptides during pregnancy in women with gestational diabetes mellitus (GDM) and no known cardiovascular disease are not well-known. We aimed to investigate N-terminal pro-B-type natriuretic peptide (NT-proBNP) values in women with gestational diabetes in the third trimester without cardiovascular disease.

Methods: This study included pregnant women in the third trimester who were referred to our outpatient cardiology clinic for dyspnea assessment between August and September 2024. Patients were classified into two groups: the GDM group (n = 31) and the control group (n = 20). NT-proBNP values and clinical and laboratory parameters were compared between the two groups.

Results: No differences were observed between the two groups with respect to age, height, weight changes during pregnancy, or biochemical and echocardiographic parameters. Weight and body mass index were significantly elevated in the GDM group. NT-proBNP values were higher in the GDM group than in the control group. However, there were no statistically significant differences in NT-proBNP values between the two groups [28.9 (4–258) pg/mL vs. 18 (4–230) pg/mL, p = 0.331].

Conclusion: We found that NT-proBNP values were similar in gestational and non-gestational pregnant women in the third trimester without cardiovascular disease.

Keywords: Gestational diabetes mellitus, NT-proBNP, body mass index, third trimester

Öz

Amaç: Kardiyovasküler hastalığı olmayan gestasyonel diyabeti olan gebelerde natriüretik peptitlerin klinik kullanımı ve önemi iyi bilinmemektedir. Biz bu çalışmada üçüncü trimesterdeki gestasyonel diyabetes mellitusu (GDM) olan ve kardiyovasküler hastalığı olmayan kadınlarda N-terminal pro-B tipi natriüretik peptid (NT-proBNP) değerlerini ile ilgili boşluğu doldurmayı amaçladık. Bu konu kapsamlı bir şekilde araştırılmamıştır.

Yöntemler: Nefes darlığı ile ayaktan kardiyoloji kliniğine Ağustos-Eylül 2024 tarihlerinde başvuran üçüncü trimesterdeki gebe kadınlar çalışmaya dahil edildi. Hastalar iki gruba ayrıldı: GDM grup (n = 31) ve kontrol grubu (n = 20).

Bulgular: Yaş, boy, gebelikteki kilo değişimi, biyokimyasal ve ekokardiyografik parametreler bakımından iki grup arasında fark saptanmadı. Kilo ve vücut kitle indeksi GDM grubunda anlamlı olarak yüksek saptandı. Numerik olarak NT-proBNP değerleri GDM grubunda daha yüksek saptandı. Ancak istatistiksel olarak iki grup arasında NT-proBNP değerleri açısından anlamlı bir fark yoktu [28.9 (4-258) pg/mL vs. 18 (4-230) pg/mL, p = 0.331].

Sonuç: Çalışmamızda NT-proBNP değerlerini kardiyovasküler hastalığı olmayan üçüncü trimester gebelerde gestasyonel diyabet olsun olmasın benzerdi.

Anahtar Sözcükler: Gestasyonel diabetes mellitus, NT-proBNP, vücut kitle indeksi, üçüncü trimester

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INTRODUCTION

Pregnancy is generally a physiological state characterized by enhanced beta-cell function and insulin resistance, mediated primarily by placental secretion of diabetogenic hormones (1). These changes develop and are most prominent during the third trimester. Gestational diabetes mellitus (GDM) develops in pregnant people whose pancreatic beta-cell function is insufficient to overcome the insulin resistance associated with pregnancy (2).

Type 2 diabetes mellitus is a chronic disease and one of the main risk factors for heart failure (3). Despite normal heart function and structure, diabetes mellitus increases the risk of heart failure. However, unlike type 2 diabetes mellitus, GDM is generally a temporary condition. GDM is also associated with increased risks of adverse pregnancy outcomes and their morbidities and metabolic effects. Furthermore, there is no well-established relationship between GDM and natriuretic peptides that indicates elevated ventricular filling pressure.

Despite the wide use of natriuretic peptides in the non-pregnant population for the diagnosis and prognosis of cardiovascular disease, the clinical utility of natriuretic peptides in pregnant women remains less well understood. There are no recognized reference values for natriuretic peptides in pregnant women. Some physiologic adaptations during pregnancy may impact natriuretic peptide levels. N-terminal pro-B-type natriuretic peptide (NT-proBNP) may be produced by fetal membranes and may generate myometrial tissue during pregnancy (4). Moreover, pregnant women undergo several hemodynamic and cardiac structural changes, including increases in plasma volume and cardiac output and enlargement of the left and right ventricles (5). These changes may impact NT-proBNP levels during pregnancy. Furthermore, the clinical utility of natriuretic peptides in pregnant women with GDM is not well known. In contrast to prior studies, which primarily evaluated unselected or asymptomatic pregnant women, the present study focuses specifically on pregnant women in the third trimester referred for cardiology evaluation because of dyspnea and compares NT-proBNP levels between women with and without GDM, all without known cardiovascular disease. For this reason, we aimed to investigate the effect of NT-proBNP values in third-trimester GDM patients.

MATERIALS AND METHODS

Study Population

Pregnant women in the third trimester who were referred from the obstetrics department to the cardiology outpatient clinic were enrolled in the study between August and September 2024. We enrolled 51 pregnant women in the third trimester who were aged and gt ; 18 years. Both the GDM and control groups comprised pregnant women in the third trimester who were referred to the cardiology outpatient clinic for evaluation of dyspnea. Participants with a history of cardiovascular and systemic diseases such as hypertension, coronary artery disease, valvular heart disease (including more than mild mitral and/or tricuspid regurgitation), chronic renal disease, and chronic inflammatory disease were excluded. Additionally, twin pregnancies were excluded. Women were excluded if they had preexisting diabetes, an abnormal glucose screening result before 24 weeks' gestation, prior gestational

diabetes, a history of stillbirth, or multifetal gestation. All women with GDM received medical nutrition therapy. All the women who participated in the study provided written informed consent. Approval was obtained from the Ethics Board of the University of Health Sciences Türkiye, Ankara Etlik City Hospital (approval number: AESH-BADEK-2024-788, date: 30.10.2024).

Measurement of NTproBNP, laboratory, and echocardiographic parameters NT-proBNP was measured in a blood sample (Roche Diagnostics) at our outpatient cardiology clinic. Additionally, hemograms, hemoglobin A1c (HbA1c), and routine biochemical tests, including fasting glucose, urea, creatinine, uric acid, and electrolytes, were recorded.

GDM was diagnosed using the Carpenter–Coustan criteria at the 24th week of gestation (6). According to these criteria, GDM was defined as a fasting glucose level of greater than or equal to 95 mg per deciliter (5.3 mmol per liter) and two or more timed glucose measurements exceeding the following thresholds: 1-hour: 180 mg per deciliter (10.0 mmol per liter); 2-hour: 155 mg per deciliter (8.6 mmol per liter); and 3-hour: 140 mg per deciliter (7.8 mmol per liter). Pregnant women with a negative 50-g glucose challenge screening test formed the control group.

Transthoracic echocardiography was performed in all study patients using a GE S60 ultrasound system. The investigated echocardiographic parameters were the dimensions of the left atrium; the end-diastolic and end-systolic dimensions; the interventricular septum and posterior wall; and the ejection fraction.

Statistical Analysis

SPSS 19.0 software was used for statistical analyses. Shapiro-Wilk test was used to determine whether the data were normally distributed. For continuous variables, mean $\pm$ standard deviation or median (minimum–maximum) values were used; for categorical variables, frequencies or percentages were used where appropriate. An independent-samples t-test or the Mann-Whitney U test was used to compare continuous variables between two groups. Spearman's correlation analysis was performed to determine the relationship between continuous variables. $p < 0.05$ was considered statistically significant for all tests.

RESULTS

Thirty-one patients in the GDM group and twenty in the control group were enrolled in the study. Baseline characteristics and laboratory parameters are shown in Table 1. Age was similar between the two groups (32 ± 5.8 vs. 31.6 ± 4.6 ; $p = 0.834$). Similarly, no differences were found in current weight, weight changes during pregnancy, and weeks of pregnancy between the two groups. Weight and body mass index (BMI) were significantly high in the GDM group. Kidney function, electrolytes, and hemogram parameters were similar between the two groups. Although NT-proBNP levels were numerically higher in the GDM group, the difference was not statistically significant [28.9 (4–258) vs. 18 (4–230) pg/mL; $p = 0.331$]. As mentioned before, all women with GDM received medical nutrition therapy. Only five women with GDM were on insulin therapy, which indicates insulin-requiring GDM (irGDM). Due to the small number of irGDM cases, we did not separate the GDM group into “received medical nutrition” and “irGDM” subgroups.

Fasting glucose was higher in the GDM group, as expected (97 ± 19 vs. 84 ± 15 ; $p = 0.050$). The HbA1c level was slightly higher in the GDM group than in the control group ($5.0\% \pm 0.39$ vs. 4.5% , $p < 0.001$). However, both HbA1c values were within normal limits.

All echocardiographic parameters considered similar between the two groups are shown in Table 2. Correlation analyses were performed to assess the relationships between NT-proBNP values and BMI, HbA1c, and fasting glucose (Table 3). We did not observe any correlation between NT-proBNP values and the variables considered.

DISCUSSION

In our study, NT-proBNP values did not differ between gestational and non-gestational diabetes in the third trimester. Normal levels of NT-proBNP are not well established, and there are no recognized reference values in pregnancy. However, NT-proBNP levels in pregnant women were approximately twice those in non-pregnant women, particularly in the first trimester (7). It may be related to the volume status and to placental production of NT-proBNP. However, the clinical utility of natriuretic peptides during pregnancy in women with or without GDM is not well known. In addition, whether a relationship exists between NT-proBNP and glucose metabolism merits consideration.

BNP and its inactive N-terminal fragment (NT-proBNP) are released in response to cardiac strain and are commonly used to evaluate suspected heart failure. The systemic effects of natriuretic peptides are well described in the literature, including diuresis, natriuresis, vasodilatation, and regulation of salt-water balance and maintenance of volume status (8). It has been suggested that the natriuretic peptide system is involved in glucose metabolism and plays a role in diabetes. Experimental data suggest that low levels of atrial natriuretic peptide (ANP) promote the development of insulin resistance and diabetes through activation of the renin-angiotensin system, leading to increased oxidative stress and inflammatory responses, disrupting signaling pathways between insulin and angiotensin and impairing glucose transport (9).

Chang et al. (10) found a strong association between NT-proBNP levels and both heart failure and preeclampsia. However, they did not find any significant differences in NT-proBNP levels in pregnancies complicated by arrhythmia, pregnancy-induced hypertension, postpartum hemorrhage, or adverse fetal/neonatal events.

It is well-established in the literature that obesity is inversely associated with NT-proBNP levels, effectively suppressing them (11). In our study, despite the GDM group having a significantly higher BMI, they exhibited numerically higher, though not statistically significant, NT-proBNP levels. This suggests that the volume overload or subclinical effects induced by GDM may have attenuated the

Table 1. Baseline characteristics of all study patients.

Variables	GDM group (n = 31)	Control group (n = 20)	p-value
Age, years	32 ± 5.8	31.6 ± 4.6	0.834
Weight, kg	83 ± 10	72 ± 13	0.004
Height, cm	161.2 ± 7	161 ± 6	0.958
BMI, kg/cm ²	32 ± 4	27 ± 5.3	0.005
HbA1c, %	5.0 ± 0.39	4.5 ± 0.36	<0.001
Weight changes during pregnancy, kg	10.2 ± 5.9	8 ± 5.7	0.229
Week of pregnancy	31.0 ± 3.2	30.2 ± 3.5	0.224
Fasting glucose, mg/dL	97 ± 19	84 ± 15	0.050
NT-proBNP, pg/mL	28.9 (4–258)	18 (4–230)	0.331
Urea, mg/dL	13 (7–28)	15 (6–20)	0.117
Creatinin, mg/dL	0.5 ± 0.1	0.5 ± 0.08	0.958
Sodium, mEq/L	137 ± 1.7	136 ± 1.5	0.134
Potassium, mEq/L	4.1 ± 0.30	4.1 ± 0.37	0.822
TSH	1.98 ± 0.8	2.3 ± 1	0.250
Uric acide, mg/dL	3.9 ± 0.8	3.5 ± 1.3	0.315
White blood count, 10 ³ /mCL	10.2 ± 2.9	10.6 ± 2.6	0.639
Hemoglobin, g/dL	11.4 ± 2.1	11.7 ± 1.2	0.601
MCV, fL	89 (80–97)	88 (60–98)	0.815
RDW, fL	42 ± 10	44 ± 5	0.476
Platelet count, 10 ³ /mCL	228 ± 54	231 ± 47	0.882
MPV, fL	10 (9–12)	11 (9–13)	0.103
PCT, %	0.27 ± 0.11	0.24 ± 0.05	0.359

BMI: Body mass index, GDM: Gestational diabetes mellitus, MCV: Mean corpuscular volume, PCT: Plateletcrit, RDW: Redcell distrubation width, TSH: Thyroid stimulating hormone, HbA1c: Hemoglobin A1c.

Table 2. Echocardiographic parameters among two groups.

Variables	Gestational diabetes mellitus group (n = 31)	Control group (n = 20)	p-value
Left atrial diameter, mm	34 ± 2.8	33 ± 2.7	0.361
End diastolic diameter, mm	45 (40–50)	44 (37–49)	0.442
End systolic diameter, mm	25 (24–30)	27 (24–30)	0.162
Interventricular septum, mm	9 (8–11)	9 (7–11)	0.351
Posterior wall, mm	9 (8–10)	9 (7–11)	0.398
Left ventricular ejection fraction %	60.7 ± 1.8	60	0.110

Table 3. Bivariate correlation analysis with NT-proBNP value.

	r	p
HgA1c	0.043	0.786
BMI	0.027	0.071
Fasting glucose	0.075	0.231

r: correlation coefficient, BMI: Body mass index, HbA1c: Hemoglobin A1c, NT-proBNP: N-terminal pro-B-type natriuretic peptide.

known suppressive effect of obesity. Minhas et al. (11) investigated NT-proBNP levels in pregnant women without known cardiovascular disease, stratified by pregnancy status and trimester. According to their findings, the prevalence of elevated NT-proBNP (>125 pg/mL) was 20.0% among pregnant women in the first trimester, 2.4% among women in the third trimester, and 8.0% among non-pregnant women. Additionally, NT-proBNP was 44% higher in the first trimester of pregnancy than in non-pregnant women [absolute difference, 26.4 pg/mL; 95% confidence interval (CI): 11.2–41.6]. Further, among pregnant women, adjusted NT-proBNP was 46% lower [absolute difference 22.2 pg/mL (95% CI: 36.9 to 7.5)] in women in the third trimester compared with women in the first trimester. According to the study researcher's explanation that NT-proBNP decreases to lower levels by the third trimester, increased ventricular size and remodeling may contribute to the resolution of the initial rise in natriuretic peptide levels. They also found that NT-proBNP was inversely associated with BMI and systolic blood pressure.

According to the current literature, a study similar to ours exists. In this study, NT-proBNP was significantly lower in patients with irGDM than in controls in the subgroup analysis (35 ± 25 pg/mL vs. 53 ± 43 pg/mL; p = 0.012). However, they found that NT-proBNP levels were similar between women with GDM receiving medical nutrition therapy and the control group, as our study findings indicated. If we compare our study with the mentioned study, they did not exclude cardiovascular disease or report echocardiographic parameters. The mean gestational age was higher than in the other study (30 vs. 28 weeks). Due to the small number of women with irGDM, we did not perform any statistical analyses comparing women with irGDM and those with medical nutrition therapy GDM.

From a cardiology perspective, dyspnea in late pregnancy is common but non-specific and often prompts referral to exclude underlying cardiac disease. In this symptomatic third-trimester cohort, NT-

proBNP values did not differ significantly between women with and without GDM, suggesting that GDM itself does not materially confound NT-proBNP levels in this setting. Accordingly, when evaluating pregnant women in the third trimester who present with dyspnea and have no known cardiovascular disease, NT-proBNP may retain its supportive value in identifying those who warrant closer cardiac evaluation, rather than reflecting glycemic status alone. These findings may help clinicians interpret NT-proBNP more confidently in pregnant women with dyspnea and may underscore that biomarker results should be integrated with clinical assessment and echocardiography.

The present study has several strengths. First, its design enabled standardized and systematic collection of clinical, laboratory, and echocardiographic data. However, several limitations should be acknowledged. Given the small number of women with irGDM, we could not perform a subgroup analysis. Another limitation was that we did not evaluate hemodynamic parameters, such as pulse and systolic and diastolic blood pressure, which may affect NT-proBNP levels.

Additionally, we did not evaluate the concentrations of other enzymes or components of the natriuretic pathway that might help explain the mechanisms underlying our findings, such as BNP, ANP, and cyclic guanosine monophosphate (cGMP).

These findings may serve as a basis for future studies involving larger cohorts, including women in the final month of pregnancy, when the risk of pregnancy-associated cardiomyopathy is particularly high.

Study Limitations

This study has certain limitations. First, the fact that the research was conducted at a single center and had a relatively small sample size (n = 51) may limit the generalizability of the findings. Due to the cross-sectional design of the study, it is not possible to assess the cause-effect relationship and the temporal course of changes in NT-proBNP levels. Second, cardiac hemodynamic indicators such as heart rate, diastolic and systolic blood pressure were not examined in the pregnant women included in the study. Investigating these parameters could have helped to better understand the relationship between NT-proBNP levels and cardiac load. Finally, the number of GDM cases receiving insulin therapy was low (n = 5); therefore, subgroup analyses to evaluate the effect of insulin therapy on NT-proBNP could not be performed. Additionally, physical factors that could affect NT-proBNP levels, such as electrolyte balance, obesity

level, and changes in plasma volume, were not controlled. Cardiac hemodynamic parameters (heart rate, systolic/diastolic blood pressure) were not evaluated. Other biomarkers in the natriuretic pathway, such as BNP, ANP, and cGMP, were not analyzed in the study.

CONCLUSION

In conclusion, NT-proBNP values did not differ between gestational and non-gestational pregnant women in the third trimester without cardiovascular disease. For this reason, our findings suggest that third-trimester NT-proBNP levels in women with uncomplicated GDM are not significantly different from those in healthy pregnant controls, indicating that GDM does not introduce additional bias in the cardiac evaluation of these patients.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Board of the University of Health Sciences Türkiye, Ankara Etlik City Hospital (approval number: AESH-BADEK-2024-788, date: 30.10.2024).

Informed Consent: All the women who participated in the study provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S., Concept: B.K., E.P.O., Design: B.K., E.P.O., Data Collection or Processing: M.A., B.M., Analysis or Interpretation: B.K., Literature Search: M.A., B.K., E.P.O., Writing: M.A., B.K.

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