

ORIGINAL RESEARCH ARTICLE

Maternal and umbilical cord blood N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in pregnancies affected by COVID-19: A case-control study

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Abstract

This study aimed to compare maternal and umbilical cord blood pro-BNP levels in pregnant women with a history of COVID-19 infection and to evaluate possible cardiac effects during pregnancy. In this prospective case-control study conducted between January and October 2023, 88 pregnant women were included: 44 with a history of COVID-19 infection after the second trimester and 44 healthy controls. Women with diabetes, hypertension, heart disease, or severe pregnancy complications were excluded. Maternal venous and umbilical cord arterial blood samples were collected immediately after delivery, and pro-BNP levels were measured using standard laboratory procedures. Maternal pro-BNP levels were significantly higher in the COVID-19 group, whereas cord blood pro-BNP levels did not differ significantly between groups. Obstetric and neonatal outcomes were similar. These findings suggest that prior COVID-19 infection may cause subclinical maternal cardiac stress, while placental mechanisms may protect the fetus from cardiac involvement. (*Afr J Reprod Health* 2026; 30 [18]: 38-45).

Keywords: SARS-CoV-2; maternal cardiac stress; placental protection; perinatal outcomes; cardiovascular biomarker

Résumé

Cette étude visait à comparer les taux de pro-BNP dans le sang maternel et le sang du cordon ombilical chez des femmes enceintes ayant des antécédents d'infection par la COVID-19, ainsi qu'à évaluer les effets cardiaques potentiels durant la grossesse. Dans le cadre de cette étude cas-témoins prospective menée entre janvier et octobre 2023, 88 femmes enceintes ont été incluses : 44 ayant contracté la COVID-19 après le deuxième trimestre et 44 témoins en bonne santé. Les femmes atteintes de diabète, d'hypertension, de cardiopathie ou de complications graves de la grossesse ont été exclues. Des prélèvements de sang veineux maternel et de sang artériel du cordon ombilical ont été effectués immédiatement après l'accouchement, et les taux de pro-BNP ont été mesurés selon les procédures de laboratoire standard. Les taux de pro-BNP maternels étaient significativement plus élevés dans le groupe COVID-19, alors qu'aucune différence significative n'a été observée entre les groupes concernant les taux de pro-BNP dans le sang du cordon. Les issues obstétricales et néonatales étaient similaires. Ces résultats suggèrent qu'une infection antérieure par la COVID-19 pourrait induire un stress cardiaque maternel infraclinique, tandis que des mécanismes placentaires pourraient protéger le fœtus d'une atteinte cardiaque. (*Afr J Reprod Health* 2026; 30 [18]:38-45).

Mots-clés: SARS-CoV-2 ; stress cardiaque maternel ; protection placentaire ; issues périnatales ; biomarqueur cardiovasculaire

Introduction

COVID-19 infection primarily affects the respiratory system but is known to cause various complications both during the acute phase and the post-infectious period. Although vertical transmission from mother to fetus has not been definitively established, placental involvement may

contribute to complications such as intrauterine growth restriction, threatened miscarriage, and preterm birth. However, the impact of the virus on fetal cardiac function remains unclear.^{1,2} It has been suggested that COVID-19 infection during pregnancy increases the resistance of the uterine and umbilical arteries, potentially harming the fetus. Additionally, increased risks of gestational

hypertension, preeclampsia, eclampsia, myocardial infarction, and cardiomyopathy have been reported.³

Brain natriuretic peptide (BNP) is encoded by a gene located on the distal arm of chromosome 1 and is derived from the 108-amino acid prohormone proBNP. Natriuretic peptides, including BNP, are neurohormones secreted from atrial and ventricular myocytes in response to increased wall tension due to volume and pressure overload. BNP exerts various biological effects, including natriuresis and vasodilation, thereby regulating extracellular fluid volume and blood pressure.⁴ The main stimulus for BNP release is increased wall tension, especially in the ventricles. BNP is widely used as a marker of myocardial stress in conditions such as cardiomyopathy, ischemic heart disease, and other critical illnesses.⁵

In neonates, elevated plasma BNP levels have been reported in several conditions, such as patent ductus arteriosus (PDA), persistent pulmonary hypertension, and congenital heart disease.^{6,7} Plasma levels of BNP and proBNP are closely correlated, but proBNP has a longer half-life due to resistance to degradation by neutral endopeptidases, making it easier to measure. Its levels are less affected by transient conditions like body position or exercise. Moreover, in patients using enzyme inhibitors, proBNP measurement is more reliable than BNP.⁸

BNP is also recognized as a biomarker for the severity of COVID-19 infection. It can reveal cardiac injury in patients with COVID-19 even in the absence of pre-existing cardiac conditions.^{9,10} Furthermore, hypoxic stress in maternal COVID-19 infection may lead to changes in fetal circulation and alterations in BNP secretion.¹¹

The present study aims to compare pro-BNP levels in maternal and umbilical cord blood samples in pregnant women with a history of COVID-19 infection, in order to assess potential cardiac involvement using this biochemical marker.

Methods

This prospective case-control study was conducted at the Department of Obstetrics and Gynecology, Tuzla State Hospital, Istanbul, Turkey, between January 2023 and October 2023. The study population consisted of unvaccinated pregnant women aged 18–40 years who contracted COVID-

19 after the second trimester and did not require intensive care. A history of COVID-19 infection during pregnancy was confirmed through review of the participants' medical records, based on a documented positive real-time polymerase chain reaction (RT-PCR) test performed according to the national diagnostic guidelines. At the time of delivery, none of the participants had active COVID-19 infection. Women were excluded if they had known cardiac disease, hypertension, pregestational diabetes, a history of first trimester COVID-19 infection, vaccination, or any perinatal complications such as preeclampsia, gestational diabetes mellitus, intrahepatic cholestasis of pregnancy, or premature rupture of membranes.

Demographic and obstetric data such as maternal age, body mass index (BMI), gravidity, parity, and gestational age at delivery were retrieved from hospital records. Laboratory data (hemogram, CRP) and clinical information including birth weight, neonatal sex, and Apgar scores (1st and 5th minute) were collected at the time of delivery. No formal a priori sample size calculation was performed because this was an exploratory prospective case-control study. Nevertheless, all eligible participants meeting the inclusion criteria during the study period were consecutively enrolled. No randomization or matching procedures were performed because of the observational design of the study. Standardized eligibility criteria, consecutive enrollment of all eligible participants, and uniform laboratory procedures were applied to minimize selection and measurement bias.

Following delivery, the umbilical cord was clamped and cut, and 5 mL of blood was collected from the umbilical artery. An additional 5 mL maternal venous blood sample was obtained immediately postpartum. Blood samples were placed into biochemistry tubes, centrifuged at 9000 rpm for 10 minutes using a NF 1200R refrigerated centrifuge (Nüve, Ankara, Türkiye). The separated plasma was stored at -80°C until analysis. After sufficient sample size was reached, maternal and umbilical cord blood BNP levels were measured using a commercially available Human Pro Brain Natriuretic Peptide (pro-BNP) ELISA Kit (SunRed Biotechnology Co., Ltd., Shanghai, China; Catalog No. 201-12-1288) according to the manufacturer's instructions. The assay was performed using an ELK800 microplate reader and a BioTek 50 TS

microplate washer, and the results were analyzed using KC Junior software.

Data analysis

Statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used to assess normality. The Mann–Whitney U test was applied for nonparametric data. Levene’s test was used to evaluate homogeneity of variances.

Ethical consideration

The study received approval from the Institutional Clinical Research Ethics Committee (Approval No: 2015-KAEK-77-23-03 Date: 29.03.2023) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. Data were expressed as mean $\pm$ standard deviation, median (25th–75th percentile), or number and percentage as appropriate. Categorical variables were analyzed using chi-square and cross-tabulation tests, while continuous variables were compared using Mann–Whitney U test. A p-value of <0.05 was considered statistically significant

Results

A total of 88 pregnant women were included in the study, with 44 (50%) in the COVID-19 group and 44 (50%) in the control group. There were no significant differences between the two groups in terms of maternal age ($p=0.289$), body mass index (BMI) ($p=0.314$), gravidity ($p=0.154$), or parity ($p=0.887$). Smoking rates were also similar (39% vs. 41%; $p=0.769$) (Table 1).

Gestational age at delivery, mode of delivery, birth weight, neonatal sex, 1st and 5th minute Apgar scores, and NICU admission rates were comparable between the two groups (all $p > 0.05$). Although the rate of cesarean delivery was higher in the control group (72% vs. 61%; $p=0.262$) and male birth rate was slightly higher (54% vs. 50%; $p=0.674$), these differences were not statistically significant.

Table 1: Baseline demographic and obstetric characteristics of the study population

Parameter	Control Group	COVID-19 Group	P
Age (years)	29.3 $\pm$ 5.7	31.2 $\pm$ 10.2	0.289
BMI (kg/m ²)	26.4 $\pm$ 11.2	23.9 $\pm$ 11.8	0.314
Gravidity	2.8 $\pm$ 1.2	2.4 $\pm$ 0.9	0.154
Parity	1.2 $\pm$ 0.7	1.2 $\pm$ 0.7	0.887
Smoking (n (%))	17 (39%)	18 (41%)	0.769

Table 2: Delivery outcomes and neonatal characteristics in COVID-19 and control groups

	Control Group	COVID-19 Group	P
Gestational age at delivery (weeks)	38.5 $\pm$ 0.9	38.6 $\pm$ 0.9	0.829
Mode of delivery (C-section)	32 (72%)	27 (61%)	0.262 ^a
Birth weight (g)	3299.5 $\pm$ 419.2	3305.1 $\pm$ 463.5	0.953
Neonatal sex (male)	24 (54%)	22 (50%)	0.674 ^a
Apgar score at 1 min	8.3 $\pm$ 0.8	8.3 $\pm$ 0.8	0.900
Apgar score at 5 min	9.5 $\pm$ 0.6	9.5 $\pm$ 0.5	0.857
NICU admission	3 (6.81)	4 (9.09)	0.541

NICU admission rates were also similar (6.8% in the control group vs. 9.1% in the COVID-19 group; $p=0.541$) (Table 2). A Chi-square test (cross-tabulation) was used for categorical variables; values are expressed as n (%). NICU = neonatal intensive care unit. There were no significant differences between groups in CRP levels, hemoglobin concentration, neutrophil count, lymphocyte count, platelet count, neutrophil-to-lymphocyte ratio (NLR), or platelet-to-lymphocyte ratio (PLR) (all $p > 0.05$). Although CRP levels were higher in the COVID-19 group (7.51 ± 1.58 vs. 6.02 ± 3.45 ; $p=0.651$) and platelet counts were lower (195.13 ± 51.81 vs. 215.60 ± 53.30 ; $p=0.075$), neither reached statistical significance (Table 3).

Importantly, maternal pro-BNP levels were significantly higher in the COVID-19 group compared to the control group (779.85 ± 598.25 vs. 553.29 ± 334.12 ; $p=0.031$). Umbilical cord pro-BNP levels were also higher in the COVID-19 group, but the difference did not reach statistical significance (827.69 ± 623.27 vs. 680.97 ± 432.76 ; $p=0.203$) (Table 3).

Table 3: Comparison of maternal and cord blood laboratory parameters between groups

	Control Group	COVID-19 Group	p
Hemoglobin (g/dL)	10.7 ± 1.5	10.8 ± 1.4	0.590
Neutrophils (×10 ³ /μL)	14.3 ± 11.5	13.5 ± 10.4	0.749
Lymphocytes (×10 ³ /μL)	1.7 ± 0.6	1.5 ± 0.5	0.143
Platelet count (×10 ³ /μL)	215.6 ± 53.3	195.1 ± 51.8	0.075
NLR	8.9 ± 7.8	8.9 ± 6.2	0.962
PLR	134 ± 68	128.1 ± 49.8	0.640
CRP (mg/L)	6 ± 3.4	7.5 ± 1.5	0.651
Maternal pro-BNP (pg/mL)	553.2 ± 334.1	779.8 ± 598.2	0.031
Umbilical cord pro-BNP (pg/mL)	680.9 ± 432.7	827.6 ± 623.2	0.203

pro-BNP = pro-B-type natriuretic peptide; CRP = C-reactive protein; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio.

Discussion

Since the emergence of COVID-19, its potential impacts on both pregnant women and fetuses have been a significant concern. Several studies^{12–14} have shown that COVID-19 infection during pregnancy can lead to adverse obstetric outcomes such as intrauterine growth restriction, preterm labor, fetal distress, early pregnancy loss, and stillbirth. Yaghoobpoor et al.¹⁵ reported that cardiovascular complications such as hypertension, preeclampsia, eclampsia, cardiomyopathy, and myocardial infarction were more common in pregnant women infected with COVID-19. The infection is known to cause myocardial injury, myocarditis, acute myocardial infarction, heart failure, arrhythmias, and thromboembolic events, which may be difficult to distinguish from typical pregnancy-related cardiac complaints.¹⁶ As a result, the Brazilian Society of Cardiology¹⁷ recommended including pro-BNP testing as part of routine evaluation in pregnant women with heart disease. The present study contributes to the growing body of evidence regarding the potential cardiovascular effects of COVID-19 during pregnancy by evaluating both maternal and umbilical cord pro-BNP levels. These findings provide additional insight into maternal cardiac stress and fetal cardiovascular status following maternal SARS-CoV-2 infection.

Previous studies^{18,19} in adults with COVID-19 have demonstrated increased levels of biomarkers such as myohemoglobin, CK-MB, pro-BNP, and cardiac troponin I. A meta-analysis focusing on maternal cardiovascular complications found that 22% of 31 infected pregnant women had elevated troponin and 30% had increased pro-BNP

levels.²⁰ Umbilical cord blood pro-BNP levels have been examined in conditions involving placental insufficiency such as intrauterine growth restriction and preeclampsia. These conditions were associated with increased pro-BNP levels in the fetus, likely due to hypoxia and cardiac stress.^{21,22} COVID-19 may cause maternal hypoxia, intervillous malperfusion, and thrombosis in the placenta, which could also influence pro-BNP levels. In line with our findings, Besimoglu et al.²³ found higher cord blood pro-BNP levels in neonates born to COVID-19-positive mothers. Moreover, higher pro-BNP levels and increased neonatal morbidity and mortality have been reported in moderate to severe maternal infections.^{23,24}

Evidence suggests that vertical transmission of SARS-CoV-2 through the placenta is rare.^{25–27} In a study of 101 placentas, only 15 tested positive for SARS-CoV-2 by PCR, and no adverse neonatal outcomes were observed in those cases. This may be due to PD-L1 positivity in chorionic villi, which could mitigate immune-mediated placental damage.²⁸ The intervillous space, enriched with maternal lactoferrin, plays a protective role against placental inflammation and infection. Lactoferrin expression is altered in pathologic pregnancies such as preterm birth and preeclampsia.²⁹ Naidu et al.³⁰ also proposed that maternal lactoferrin serves as a barrier against COVID-19 during pregnancy. Furthermore, SARS-CoV-2 has a low presence in maternal blood, suggesting limited potential for direct placental infection.³¹ Shanes et al.³² concluded that placental pathologies in COVID-19 are more likely associated with maternal infection and inflammation than fetal infection. A study by

Kirlangic *et al.*³³ showed reduced maternal serum BDNF levels in COVID-19-infected pregnancies, while umbilical cord BDNF levels remained similar to those in healthy pregnancies, supporting the idea of fetal protection by the placenta.

A systematic review investigating laboratory parameters in pregnant women with COVID-19 reported that 81% exhibited elevated neutrophil counts, 69% showed increased CRP levels, and 59% had lymphopenia.³⁴ Similarly, another study comparing the immune responses of pregnant women with and without COVID-19 found significantly higher neutrophil counts, lower lymphocyte levels, and increased CRP concentrations during the infection.³⁵

Studies measuring pro-BNP levels from cord blood in neonates born to mothers with prior COVID-19 infection are scarce in the literature. The increased incidence of maternal hypoxia, associated with the heightened risk of respiratory failure in COVID-19-positive pregnancies, may contribute to an elevated risk of neonatal complications. Although vertical transmission has not been definitively confirmed, even in the presence of viral transfer, the placental barrier is thought to mitigate adverse fetal outcomes through its protective functions.^{11–13}

In the present study, although maternal pro-BNP levels were significantly elevated in the COVID-19 group, no significant differences were observed in umbilical cord pro-BNP levels or Apgar scores between groups. These findings support the hypothesis that the placenta provides an effective defense mechanism for the fetus. Additionally, the comparable pro-BNP levels across groups may be explained by the predominantly mild nature of COVID-19 cases in this cohort. Unlike previous studies that focused on active infection, the participants in our study had recovered from COVID-19 by the time of delivery. As such, laboratory markers including neutrophil and lymphocyte counts, CRP, and hemoglobin were similar between groups. This is likely due to the resolution of acute inflammation by the time of sample collection.

This study has several strengths, including its prospective case-control design, the inclusion of RT-PCR-confirmed COVID-19 pregnancies, and the simultaneous assessment of maternal and umbilical cord blood pro-BNP levels, which

enabled evaluation of both maternal and fetal cardiovascular responses.

This study has several limitations. The sample size was relatively small, and only mild cases were included. The infection occurred during earlier trimesters and was not active at the time of birth, which may have influenced biomarker expression. Moreover, other potential confounding factors such as maternal nutrition, psychological stress, and comorbid conditions were not assessed. Given that COVID-19 is associated with hypoxia, the lack of hypoxia-related biomarker analysis is also a notable limitation. Furthermore, because all participants had recovered from COVID-19 before delivery, these findings may not be generalizable to pregnancies complicated by active or severe infection. Finally, maternal cardiac involvement was assessed solely using pro-BNP measurements without echocardiographic evaluation or other functional cardiac assessments, which should be considered when interpreting the findings.

From a clinical perspective, the findings suggest that maternal pro-BNP may be a promising biomarker for detecting subclinical cardiac stress in pregnancies with a history of COVID-19 infection. However, routine clinical use cannot yet be recommended, and larger prospective multicenter studies including patients with varying disease severities are required before these findings can be translated into clinical practice.

Conclusion

Despite these constraints, this study demonstrated that maternal pro-BNP levels were significantly higher in women with prior COVID-19 infection compared to controls, suggesting subclinical cardiac stress during pregnancy. Although umbilical cord pro-BNP levels were higher in the COVID-19 group, the difference was not statistically significant. Furthermore, similar Apgar scores and neonatal outcomes reinforce the notion that the fetal cardiovascular system may remain unaffected. Future multicenter prospective studies including larger populations, varying disease severities, and comprehensive cardiac assessments are warranted before pro-BNP can be recommended as a routine biomarker for cardiovascular monitoring in pregnancies affected by COVID-19.

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Conflict of interest

The authors have stated no conflict of interest. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Artificial intelligence (AI)

No artificial intelligence tools were used in this writing, analysis or preparation of this manuscript.

Informed consent

Informed consent was obtained from all individuals included in this study.

Data statement

The data used to support the findings of this study are available on request from the corresponding author.

Contribution of authors

BNAH, MMK, EE, OSS, MCO and CA contributed to the conception and design of the study. MMK and BNAH developed the project and methodology. OSS, EE and MMK collected and curated the data. MCO and CA analyzed the data. BNAH prepared the first draft of the manuscript, and MMK edited and supervised the work. All authors reviewed previous versions and read and approved the final manuscript.

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