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Evaluation of maternal serum and umbilical cord brain-derived neurotrophic factor (BDNF) levels in COVID-19-infected pregnancies

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Abstract. – OBJECTIVE: COVID-19 is a disease that affects and damages the neurological system. The aim of this study was to evaluate the fetal neurodevelopmental status through maternal serum and umbilical cord BDNF levels.

PATIENTS AND METHODS: In this prospective study, 88 pregnant women were evaluated. Demographic and peripartum characteristics of the patients were recorded. Samples were collected from pregnant women for maternal serum and the umbilical cord BDNF levels during delivery.

RESULTS: In this study, 40 pregnant women hospitalized with COVID-19 formed the infected group and 48 pregnant women without COVID-19 formed the healthy control group. Demographic and postpartum characteristics were similar in both groups. Maternal serum BDNF values were significantly lower in the COVID-19 infected group (1597.0 ± 337.3 pg/ml) than in the healthy group (1783.2 ± 394.1 pg/ml) (p=0.019). Fetal BDNF levels were 1794.9 ± 440.3 pg/ml in the healthy group and 1691.0 ± 368.6 pg/ml in COVID-19 infected pregnant women group and statistically similar between groups (p=0.232).

CONCLUSIONS: Results showed that while maternal serum BDNF levels decreased in the presence of COVID-19, there was no difference in umbilical cord BDNF levels. This may be an indication that the fetus is not affected and is protected.

Key Words:
COVID-19, BDNF, Brain-derived neurotrophic factor, Neurodevelopment, Fetus, Brain.

Introduction

Coronavirus is a single-stranded RNA virus, which has caused two previous outbreaks: severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012. With the increase in cases of atypical pneumonia in December 2019, it was redefined by the WHO as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19)[1]. The most common symptoms of COVID-19 disease are fever, cough, shortness of breath, muscle pain, headache, diarrhea, runny nose, and loss of smell and taste[2]. COVID-19 affects not only respiratory functions but also cardiovascular, renal, and nervous system functions[3]. In addition, neuropsychiatric problems such as major depressive disorder (MDD), posttraumatic stress syndrome, anxiety disorders, obsessive-compulsive disorder, and insomnia have been reported[4,5].

Brain-Derived Neurotrophic Factor (BDNF) acts on the existing neurons of the central nervous system and peripheral nervous system. While supporting the differentiation and growth of newly formed nerve cells and synapses, it ensures the continuation of the vitality of existing neurons. Furthermore, there are several aspects of learning and memory processing associated with BDNF, including the persistence and storage of memories[6]. Because BDNF crosses the blood-brain barrier, changes in BDNF serum levels may also occur due to changes in the central nervous system and cerebrospinal fluid[7]. People suffering from MDD often have below average BDNF levels, which recover following effective antidepressant treatment[8]. Asgarzadeh et al[9] found that COVID-19 patients with neurological symptoms had lower levels of BDNF than the control group. Another study[10] also focused on the potential link between MDD and BDNF reduction in those with COVID-19. In this study, we hypothesized

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that decreased oxygen saturation and systemic inflammation caused by COVID-19 may affect both the maternal and fetal brains and neuronal development. Hence, we aimed to evaluate maternal serum and umbilical cord BDNF levels in COVID-19-infected pregnant women. This is the first study to evaluate COVID-19 effects on fetal neurological development, especially through umbilical cord BDNF levels.

Patients and Methods

The Marmara University Faculty of Medicine Ethics Committee approved this prospective case-control study (Approval No. 09.2022.47). Written informed consent was obtained from all participants and the study was designed in accordance with the Declaration of Helsinki.

Study Population

Pregnant women who delivered in the Obstetrics Clinic of Tuzla State Hospital between February 1, 2022, and August 1, 2022 were between the ages of 18-40, had a COVID-19 infection during pregnancy, and did not have perinatal risk factors were included in the study as the COVID-19 group. The gestational age was calculated according to the last menstrual period.

Patients with multifetal pregnancies, fetal structural anomalies, gestational hypertension, preeclampsia, eclampsia, pregestational diabetes, gestational diabetes mellitus, placenta invasion anomalies, fetal growth restriction, prematurity, preterm premature rupture of membranes, urgent need for cesarean section (fetal distress), maternal systemic disease, and iron deficiency anemia were excluded. The control group included healthy pregnant women without any infection or perinatal risk factors. The study population flow chart is illustrated in Figure 1.

The pregnant women who met the inclusion criteria signed an informed consent form. Height, weight, age, birth week, gravida, parity, smoking, ethnicity, previous C/S history, and hemogram values of the patients were recorded in the prenatal period. In addition, the use of drugs when pregnant women had COVID-19, their history of hospitalization, and their history of intensive care unit admission were recorded. Hospitalized moderate COVID-19 cases were included in the

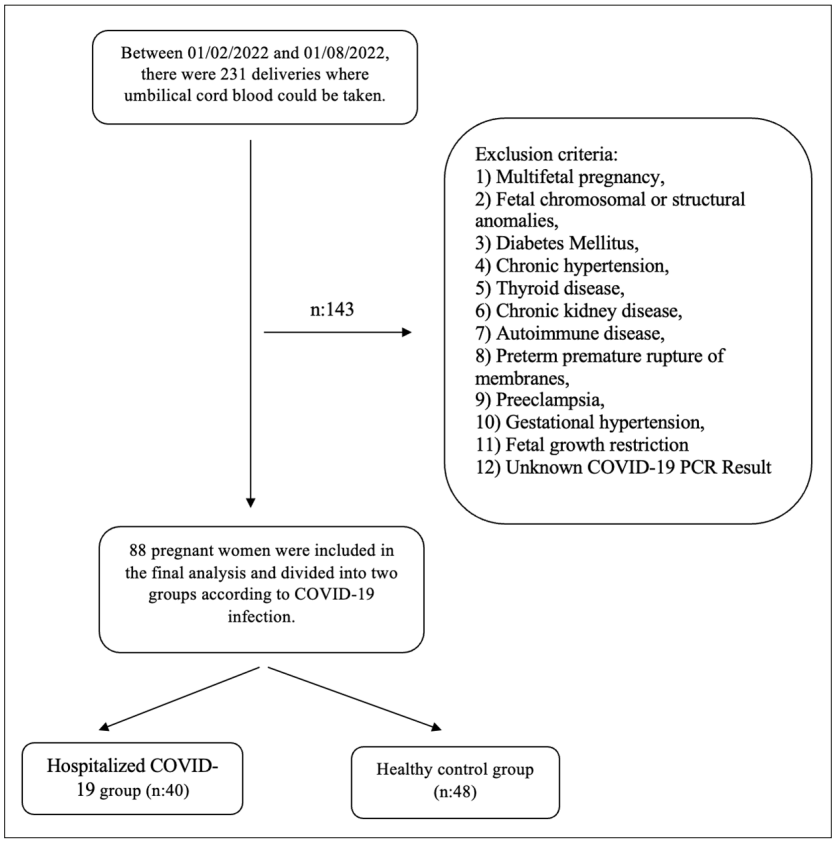

Figure 1. Study population selection.

study because those with severe COVID-19 were complicated with a need for the intensive care unit, poor prognosis, and mortality.

A throat swab was used to determine a positive COVID-19 infection, which was assessed using a real-time reverse transcriptase-polymerase chain reaction assay. American Thoracic Society/Infectious Diseases Society of America guidelines were used to divide positive COVID-19 cases into mild, moderate, or severe[11].

Primary Outcome of the Study

The primary outcome of the study was the assessment of maternal and umbilical cord BNDF levels in COVID-19-infected pregnant women.

Biochemical Analyses and Data Collection

After delivery, a 5-cc blood sample was taken from the maternal venous blood into a biochemistry tube. In addition, a 5-cc blood sample was taken from the venous blood of the umbilical cord after clamping following delivery of the baby. Samples were collected by a single physician for standardization purposes (MMK). The samples were centrifuged at 9000 rpm for 10 minutes and the serum was stored under suitable conditions at -80 °C. In the after-delivery period, the mode of delivery, birth weight, fetal gender, and fetal 1 and 5-minute APGAR scores were recorded. When the desired number of patients was reached, BDNF levels were determined using the kit and enzyme-linked immunosorbent test [Finetest, Human BDNF (Brain-Derived Neurotrophic Factor) ELISA Kit, EH0043].

Statistical Analysis

The normality of the data was assessed using the Shapiro-Wilk test. The homogeneity of variance assumption was tested with the Levene test. The values are expressed as the mean [standard deviation (SD)], or n (%). Pearson's Chi-squared test and Fisher's exact test were used to compare groups. Student's *t*-tests and *z*-tests were used for parametric comparisons, and the Mann-Whitney U test was used for nonparametric comparisons. PASW ver. 18 was used for all analyses (http:// www.spss.com.hk/statistics/). A p-value of <0.05 was accepted significant.

Results

As a result of the study, 88 pregnant women who met the inclusion criteria were analyzed. In the study, 40 pregnant women who had been hospitalized with COVID-19 formed the test group and 48 pregnant women without a COVID-19 infection formed the healthy control group. Demographic characteristics including maternal age, height, weight, BMI, gravida, parity, smoking, ethnicity, and previous C/S history were similar between the groups (p=0.275, p=0.056, p=0.757, p=0.544, p=0.122, p=0.455, p=0.515, p=0.855, and p=0.075, respectively) (Table I).

Comparison of perinatal outcomes and both maternal and umbilical cord BDNF levels between groups is illustrated in Table II. Mode of delivery (C/S), fetal gender, week of birth, preoperative hemoglobin values, and Apgar 1 min and 5 min scores showed similarities between the groups (p=0.063, p=0.401, p=0.672, p=0.752, p=0.959, and p=0.553, respectively). The maternal BDNF value was 1783.2 ± 394.1 pg/ml in the healthy group and 1597.0 ± 337.3 pg/ml in the COVID-19 infected group, which was a significant difference (p=0.019). Fetal BDNF levels were 1794.9 ± 440.3 pg/ml in the healthy group

Table I. Comparison of demographic characteristics between groups.

	Control group (n = 48)	Hospitalized COVID-19 group (n = 40)	p
Age (year)	29.17 ± 5.74	31.28 ± 10.79	0.275
Height (cm)	160.08 ± 6.53	163.07 ± 5.31	0.056
Weight (kg)	78.14 ± 13.42	77.21 ± 10.72	0.757
BMI (kg/m^2)	22.82 ± 13.85	21.03 ± 13.49	0.544
Gravida	2.88 ± 1.21	2.49 ± 1.10	0.122
Parity	1.33 ± 0.78	1.21 ± 0.80	0.455
Smoking	12 (25.00)	11 (27.50)	0.515
Ethnicity	44 (91.67)	37 (92.50)	0.855
Previous CS history	29 (60.42)	19 (47.50)	0.075

Table II. Comparison of perinatal outcomes and both maternal and umbilical cord BDNF levels between groups.

	Control group (n = 48)	Hospitalized COVID-19 group (n = 40)	*p*
Delivery characteristics			
Gestational Age (Week)	38.6 ± 0.9	38.6 ± 0.9	0.672
Birth Type (C/S)[a]	35 (72%)	22 (55%)	0.063
Fetal Weight (gram)	3323.1 ± 423.2	3331.4 ± 455.9	0.931
Gender (male)[a]	24 (50%)	22 (55%)	0.401
Apgar 1	8.29 ± 0.94	8.28 ± 0.79	0.959
Apgar 5	9.54 ± 0.65	9.46 ± 0.60	0.553
Biochemical markers			
Maternal BDNF (pg/ml)	1783.2 ± 394.1	1597.0 ± 337.3	0.019
Umbilical cord BDNF (pg/ml)	1794.9 ± 440.3	1691.0 ± 368.6	0.232

[a]Evaluation was made with Chi-square test.

and 1691.0 ±368.6 pg/ml in the COVID-19 infected group, which was statistically similar between groups (p=0.232) (Figure 2).

Discussion

Recently, many obstetricians and pregnant women have been concerned about a COVID-19 infection affects the fetus. In this current study, we aimed to evaluate maternal serum and umbilical cord BDNF levels in COVID-19-infected pregnant women to provide some answers to this worrying situation. The primary results of this study are (1) maternal serum BDNF levels were decreased in the COVID-19-infected pregnant women group compared to the healthy control group and (2) umbilical cord BDNF levels were similar in the COVID-19-infected pregnant women group compared to the healthy control group.

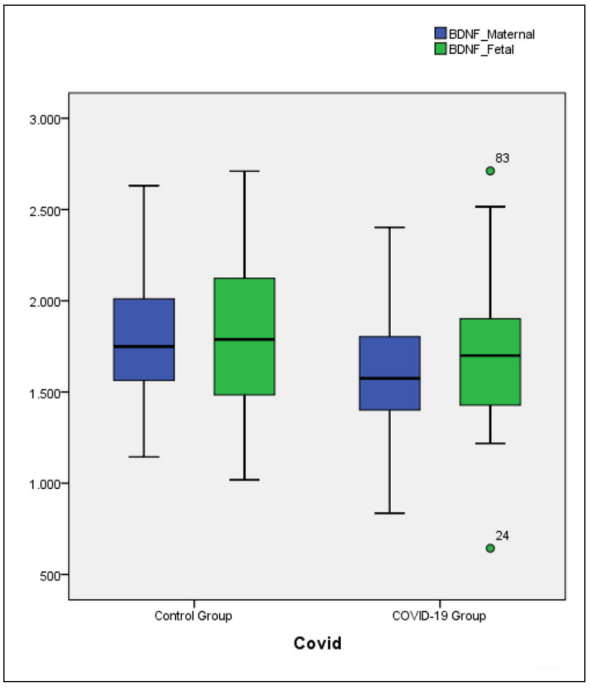

Figure 2. Box-plot of maternal serum and umbilical cord BDNF levels.

In literature it is well documented that COVID-19 was identified in maternal lung, heart and kidney specimens[12] and perinatal mortality rates are higher in COVID-19-positive pregnant women than in negative ones is an important issue for obstetric care[13]. Meta-analyses show that COVID-19 infection increases the risk of premature birth, stillbirth, preeclampsia, and premature rupture of membranes[14]. In a meta-analysis of 13 publications, babies born to mothers who had COVID-19 were at risk for premature birth, neonatal pneumonia, and respiratory distress syndrome[15]. In another study, neonatal outcomes following a COVID-19 infection were preterm birth, fetal distress, intrauterine growth retardation, miscarriage, and perinatal death[16]. The hospitalization rates for the neonatal intensive care unit were examined for cases of COVID-19-positive pregnant women. Although the hospitalization rates are higher in COVID-19-positive pregnant women, this is generally explained by preterm delivery in pregnant women with COVID-19 and close follow-up of the fetus[17]. In studies[18] examining the neonatal outcomes of pregnant women who had COVID-19 during another delivery, an increase in the neonatal intensive care rate, an increase in

the cesarean section rate, low birth weight, and a decrease in the APGAR score were observed. Nevertheless, a neurodevelopmental evaluation has not yet been made.

Studies[19] show that damage to the placental barrier caused by severe maternal hypoxia in pregnant women with COVID-19 leads to a fetal intrauterine infection. Despite the absence of local viral placental infection, pregnant women with COVID-19 develop villous trophoblast necrosis, inflammatory infiltration, and fibrinoid accumulation in the placenta[20]. Considering the development of placental barrier damage, the question of whether the fetal blood-brain barrier is affected emerges. BDNF is involved in neurodevelopment and the regulation of neuronal survival and proliferation[21,22]. BDNF is also involved in learning and memory processes as a neurotrophic protein that acts in the hippocampus and cortex[6]. Looking at the literature, the relationship between patients with COVID-19 and serum BDNF levels has been clearly demonstrated. Altered BDNF levels cause common neurological complications in COVID-19 patients, such as impaired consciousness, headache, and altered smell and taste[23,24]. Asgarzadeh et al[9] found that those COVID-19 patients with dyspnea, fever, and diarrhea had higher serum BDNF levels, whereas those with low BDNF levels experienced cough, chest pain, and fatigue/muscle pain. The oxygen requirement was higher for patients with low levels of BDNF than for other patients[9]. In COVID-19 patients, BDNF levels negatively correlated with central nervous system (CNS) symptoms[25,26]. These results add pieces of evidence to the growing body of information regarding BDNF's protective role against hypoxia-related injuries in the CNS[25,26]. It also suggests that dysregulated BDNF due to hypoxia is a potential pathological pathway for the neurological disorders of COVID-19[27]. Using rat studies, Gilmore et al[28] investigated maternal infections that affect the fetal brain in a neurodevelopmental sense. As a result of the study, it was observed that BDNF levels decreased significantly in the placenta and fetal liver/spleen, but they did not monitor changes in BDNF levels in the fetal or neonatal brain. They have argued that cytokines produced in response to infections can alter early brain development[28].

In this study, we hypothesized that decreased oxygen saturation and systemic inflammation caused by COVID-19 may affect both the maternal and fetal brain and neuronal development. Unlike the studies in the literature, the present study is the first to evaluate BDNF levels in the umbilical cord in women with COVID-19 in the presence of pregnancy, and especially to evaluate the fetus. Maternal BDNF values were significantly decreased in pregnant women who had a COVID-19 infection, but there was no difference in umbilical cord BDNF values between those who had COVID-19 and healthy pregnancies. First, many pregnant women are concerned about how the fetus is affected by COVID-19 infection. We may speculate that in the absence of prematurity and other pregnancy complications, fetal neurodevelopment is not affected by COVID-19 infection. Secondly, it is known that postpartum depression (PPD) is a common social and mental health problem. This illness often progresses into major depression, which causes an increased risk for morbidity and mortality among the underdiagnosed[29]. During the COVID-19 pandemic, both the rates and, severity of PPD and anxiety symptoms have worsened among women seeking treatment for PPD[30]. The decreased maternal serum BDNF levels reported here may be related to the increased rates and severity of PPD. Therefore, it is possible to recommend that all pregnant women with COVID-19 be screened for PPD in the early postpartum period. This, of course, will be an approach that will increase the quality of life of patients.

Limitations

We are aware that there are some limitations of our study. Considering that COVID-19 causes hypoxia and inflammation, a combination of inflammation and hypoxia markers with BDNF levels may show more clearly the disease severity effects on the central nervous system. We hope that our study will lead to future studies in which inflammation and hypoxia markers will be combined. Secondly, the neurodevelopmental process is of multifactorial origin. Many vitamins, hormones, stress, and genetic factors play a role in this process. BDNF is just one of the important laboratory parameters. This study evaluated the neurodevelopmental process only using BNDF values. Neither the questionnaire nor other genetic or biochemical values were examined. Finally, it is possible to say that the small sample size and the cross-sectional design are other limitations of the study.

Conclusions

Our results indicated that although maternal serum BDNF levels decreased in COVID-19-infected pregnant women, no difference was found in umbilical cord BDNF levels compared to the healthy group. It can be speculated that the fetal blood-brain barrier had fetal protective effects against inflammation and maternal hypoxia. Of course, further studies are needed to clarify this situation.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Informed Consent
Informed consent was obtained from all participants.

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Ethics Approval
All interventional procedures in this study were performed in accordance with both ethical and Helsinki Declaration standards. The Marmara University Faculty of Medicine Ethics Committee approved this prospective case-control study (Approval No. 09.2022.47).

Authors' Contribution
All authors have accepted responsibility for the entire content of this manuscript and approved its submission. MM Kirlangic study conception and design, data collection, manuscript writing, data analysis; E Sahin study conception, design and supervision; M Eraslan Sahin manuscript editing and supervision; OS Sade and BN Arici Halici data collection; S Kutuk data analysis.

Availability of Data and Materials
The data set analyzed to generate the findings for this study are available from the corresponding author upon reasonable request

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