

# Evaluation of neurological and cardiac development of newborn infants born to mothers infected with COVID-19

Murat Ayar<sup>1</sup>, Hande Gazeteci Tekin<sup>2</sup>, Yeliz Sevinç<sup>3</sup>, Deniz Öztekin<sup>4</sup>, Özgür Olukman<sup>1</sup>

<sup>1</sup> Department of Pediatrics, Division of Neonatology, İzmir Bakırçay University Çiğli Training and Research Hospital, Turkey

<sup>2</sup> Department of Pediatrics, Division of Pediatric Neurology, İzmir Bakırçay University Çiğli Training and Research Hospital, Turkey

<sup>3</sup> Department of Pediatrics, Division of Pediatric Cardiology, İzmir Bakırçay University Çiğli Training and Research Hospital, Turkey

<sup>4</sup> Department of Obstetrics and Gynecology, Division of Perinatology, İzmir Bakırçay University Çiğli Training and Research Hospital, Turkey

## ORCID ID of the author(s)

MA: 0000-0002-7695-8915  
HGT: 0000-0002-4407-164X  
YS: 0000-0003-1802-1742  
DÖ: 0000-0002-4213-7254  
ÖÖ: 0000-0003-4006-0465

## Corresponding Author

Murat Ayar  
Yeni Mahalle, 8780/1. Sk. No:18, 35620 Çiğli,  
İzmir, Turkey  
E-mail: muratayar45@gmail.com

## Ethics Committee Approval

This study was approved by İzmir Bakırçay University, Ethical Committee on Noninvasive Clinical Research (Date:24.06.2021, Number: 4329-3380).

All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

## Conflict of Interest

No conflict of interest was declared by the authors.

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## Abstract

**Background/Aim:** In the coronavirus disease 2019 (COVID-19) pandemic, which has been affecting the world for the last 2 years, pulmonary, cardiovascular, and neurological adverse effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been reported. These negative influences entail a risk for fetal progress. In this study, by performing a detailed clinical evaluation, postnatal ultrasonography, and echocardiography, we aimed to investigate potential neurological and cardiac complications of newborns born to pregnant women infected with COVID-19.

**Methods:** This prospective and cross-sectional study was conducted between January and July 2021. Newborn infants (0–28 days postpartum) born to mothers with proven COVID-19 infection by positive RT-PCR test during pregnancy were enrolled. Fetal cardiac development was evaluated by a pediatric cardiologist with an echocardiographic examination. Fetal neurologic evaluation was performed by a pediatric neurologist using both neurologic examination and transfontanelle ultrasonography (TFUS). Infants were reevaluated every 2 months until 6 months of age.

**Results:** Thirty-three female and 32 male infants born to 64 pregnant women, one being a twin birth, were included in the study. Seven women developed COVID-19 infection in the first trimester, 11 in the second trimester, and 46 in the third trimester. Neurological examination and TFUS were normal in all newborns except one with microcephaly. The etiologic cause could not be detected in this infant, and his neurodevelopment was normal in the follow-up. The cardiac examination did not reveal any significant disorders. Eleven infants failed the standard “Auditory Brainstem Response” (ABR) hearing screening test, so a second test was performed. Only two infants required further investigation after the second test.

**Conclusion:** We did not observe any neurologic and cardiologic teratogenic effects associated with COVID-19 infection during pregnancy.

**Keywords:** Newborn, COVID-19, Neurodevelopment, Cardiac functions

## Introduction

Infections during pregnancy threaten the health of both the mother and the developing fetus [1]. Viral intrauterine infections transmitted from the maternal genitourinary system and other infections can be detected in approximately 2.5% of all live births [2]. The effect of intrauterine infections on the fetus varies according to the infectious agent, gestational week, and maternal immune response. These infections may cause prematurity, intrauterine growth retardation, stillbirth, or severe congenital malformations [1-4]. The newborn infant may be completely asymptomatic or show subclinical or clinical symptoms soon after birth. The effects of some infections can be detected as systemic complications in long-term follow-up. However, the most important reasons for neonatal morbidity and mortality remain neurologic and cardiac complications [3-4]. In the last 2 years, during the coronavirus disease 2019 (COVID-19) pandemic affecting over 17 million people worldwide and over 5 million people in our country, pulmonary, cardiovascular, and neurological side effects of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus are clearly stated [4-6, 7, 8]. These adverse effects may pose a risk to fetal growth. However, there is limited data on this infection's fetal and maternal outcomes [6-9]. In our country, there are studies on the clinical course of the disease in the neonatal period [9, 10].

This study investigates potential neurologic and cardiac complications of newborns born to mothers infected with COVID-19.

## Materials and methods

This prospective cross-sectional study was conducted between January and July 2021. This was the time when COVID-19 infection was most common in our country. Newborn infants (0–28 days postpartum) born to mothers with proven COVID-19 infection by positive RT-PCR test during pregnancy were enrolled. Physical examinations of the infants were performed immediately after birth. Fetal cardiac development was evaluated by a pediatric cardiologist with an echocardiographic examination. Fetal neurologic evaluation was performed by a pediatric neurologist. TFUS was performed for all infants. Infants were reevaluated every 2 months until they were 6 months old. Infants with abnormal cardiac or neurologic clinical or radiological evaluation were examined concerning their preliminary diagnosis.

This study was approved by İzmir Bakırçay University, Ethical Committee on Noninvasive Clinical Research (Date:24.06.2021, Number: 4329-3380).

### Statistical analysis

Statistical analysis was performed with IBM SPSS 25.0 package program. All statistical tests were two-sided. The Kolmogorov-Smirnov test was used to check the normality assumption. Values were expressed as mean (SD) or median (min-max) as appropriate. According to the distribution type of the variable, a comparison of independent means was performed with the Mann-Whitney U test or Student's t-test, whereas a comparison of dependent means was performed with the paired Student's t-test or Wilcoxon test. Categorical variables were expressed as frequency and related percentage values and were

compared by the Chi-square test or Fisher's exact test. Spearman correlation analysis was carried out to assess the relationship between the degree of high serum unconjugated bilirubin level and heart rate variability parameters. *P*-values < 0.05 were considered statistically significant.

## Results

Sixty-five infants born to 64 COVID-19 infected pregnant women, one being a twin birth, were evaluated. Of these infants, 33 (51%) were female, and 32 (49%) were male. Seven (11%) women were diagnosed with COVID-19 infection in the first trimester and 46 (72%) women in the second trimester. After the initial diagnosis, 57 women were followed in the outpatient departments, and seven (11%) were hospitalized. Only one patient required intensive care. While two hospitalized women were diagnosed in the first trimester and required emergency treatment, five were diagnosed after 36 weeks of gestation. Antiviral treatment with favipiravir was administered to all hospitalized women, except for two women diagnosed in the first trimester. None of the pregnant women followed in the outpatient clinics received treatment. There was no correlation between the trimester at which the diagnosis was made and the week of gestation at which the delivery took place (*P* = 0.13).

Sixteen (25%) of 65 newborns were hospitalized in the neonatal intensive care unit (NICU). Seven (43%) of the hospitalized infants had respiratory problems. Other causes of hospitalization were prematurity, early-onset neonatal sepsis, and feeding problems. Only one (1.5%) infant in the whole study group showed positive RT-PCR test from nasopharyngeal swab samples taken within the first 24 h after birth. Most neurological examination results were normal, except for physiological hypotonia in one infant and familial microcephaly in another. These two infants showed normal neurodevelopment. We did not have any patients with hearing loss.

Echocardiographic examination in the first week revealed patent ductus arteriosus (PDA) in 33 newborns (51%), patent foramen ovale (PFO) in 32 newborns (49%), and tricuspid valve insufficiency in three newborns (4.6%), ventricular septal defect (VSD) was found in three newborns (4.6%), atrial septal defect (ASD) in two newborns (3%), and peripheral pulmonary stenosis (PPS) in two newborns (3%). In the follow-up, all PDAs closed spontaneously compatible with physiological development.

## Discussion

No transplacental infection was observed in studies evaluating newborns born to COVID-19 infected mothers. Placenta cultures were negative in all cases. However, during vaginal delivery, exposure of the infant to both stools and respiratory secretions of infected mothers is possible. In the recent literature, most infected pregnant women are diagnosed in the third trimester [6]. In newborns whose PCR test is positive from a nasopharyngeal swab immediately after birth, there is a possibility of this contamination by the postpartum, intrauterine, or transplacental route and the distinction cannot be made definitively. However, the absence of an increase in the frequency of congenital anomalies and dysmorphic features in newborn infants born to infected mothers suggests that this

transition occurs mostly during birth or that the transplacental transition does not affect the baby. Only one newborn in our study had PCR positivity, which we thought was due to contamination during delivery. Although this patient had transient tachypnea in the first few days of life, she recovered quickly enough to be discharged from the NICU on postnatal day 7.

Complications of SARS-CoV-2 infection during pregnancy are defined as premature rupture of membranes (PPROM), preterm birth, preeclampsia, hypertension, and gestational diabetes mellitus (GDM) [6, 7]. In our study, GDM was found in five pregnant women, PPRM in two, and placental dysfunction and abnormal flow in four.

Complications observed in infants of COVID-19 infected women include respiratory distress syndrome, transient tachypnea of the newborn, congenital pneumonia, early or late-onset neonatal sepsis, low birth weight, diffuse intravascular coagulation, birth asphyxia, and perinatal death [7, 8]. In our study, there were 20 preterm (31%) and five term neonates with transient tachypnea, four infants with early-onset neonatal sepsis, and three infants with indirect hyperbilirubinemia.

Congenital heart disease (CHD) is the most common congenital anomaly in the neonatal period and is responsible for 28% of all major congenital anomalies. Various septal and valve anomalies were detected in ten newborns in our study. However, this condition was not more common than in the general population.

Neurological involvement is in the form of headaches and anosmia in most adults. However, the evaluation of COVID-19 exposure in newborn infants can only be in terms of observing intrauterine effects, dysmorphology, seizures, tone, and consciousness. No neurological abnormalities were observed except familial microcephaly in one patient and physiological hypotonia in another.

A multicenter study including 125 newborns from our country reported 26% prematurity and 13% low birth weight [7]. In our study, it was noticed that all infants of mothers with COVID-19 infection in the first trimester, when organogenesis is most active, were born to full-term, and these infants did not have any neurological and cardiological problems. Two infants of mothers with COVID-19 infection in the second trimester were born as a middle (medium)-preterm. In our study, we found no evidence of an increase in preterm birth or vertical transmission with COVID-19.

As a result, in our single-center and limited study, no teratogenic impact related to intrauterine COVID-19 infection was determined. But in case of a possible correlation, new large-scale studies are needed.

#### Limitation

This is a single-center, time-limited, and case number-limited study.

#### Conclusion

This study could not demonstrate a teratogenic effect of COVID-19 infection.

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