Clinical and Experimental Health Sciences

The Assessment of the Neurological Development of Infants with Prenatal COVID-19 Exposure

Senem Ayça[1], Semra Yüksel[2], Hatice Yaşar Nacat[3], Pınar Arıcan[4]

[1] Haseki Sultangazi Training and Education Hospital, Department of Pediatric Neurology, İstanbul, Türkiye.
[2] İstanbul Başakşehir Çam ve Sakura City Hospital, Department of Obstetrics and Gynecology, İstanbul, Türkiye.
[3] Gaziosmanpaşa Training and Education Hospital, Department of Obstetrics and Gynecology, İstanbul, Türkiye.
[4] Başakşehir Çam ve Sakura City Hospital, Department of Pediatric Neurology, İstanbul, Türkiye.

Correspondence Author: Senem Ayça
E-mail: senemkaleci85@gmail.com

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ABSTRACT

Objective: The effects of prenatal coronavirus 2019 disease (COVID-19) exposure on the infantile neurological development are unknown. It has been considered that the inflammatory, thrombotic, and vascular changes occurred in the placentas taken from pregnant women diagnosed with COVID-19 and the inflammatory nature of COVID-19 infection may lead to negative obstetric and neurological events. We aimed to assess the potential neurological effects of prenatal COVID-19 exposure on the infant.

Methods: The present study included 2–12-month-old infants born to women with positive real-time reverse transcription polymerase chain reaction test results for COVID-19 from the population of pregnant patients under routine follow-up. The neurological examinations and the Denver II Developmental Screening Test (DDST II) were performed for 41 infants aged 2–12 months to assess the neurological effects of prenatal COVID-19 exposure.

Results: The average gestational age of the infants was 38.7 ± 1.9 weeks, and the average birth weight was 3198 ± 543 g. Eight of the infants had a history of hospitalization in the neonatal intensive care unit. The neurological examination and the neuromotor development of 40 (96%) infants were normal for their age group. Only one infant had abnormal neurological examination and DDST II result.

Conclusion: The findings of the study suggest that prenatal COVID-19 exposure has no negative neurological impact on infants. Long-term prospective studies with larger sample sizes are needed for more comprehensive assessment of the neurological effects of prenatal COVID-19 exposure on the infants.

Keywords: COVID-19, infant, Denver II Developmental Screening Test

1. INTRODUCTION

The effects of COVID-19 infection on the developing fetus are still unknown, and vertical transmission has been shown to be uncommon in case reports. However, evidence for placental and fetal infection has been reported (1). Inflammatory, thrombotic, and vascular changes have been observed in placentas collected from pregnant women diagnosed with COVID-19, and the inflammatory nature of COVID-19 infection may cause adverse obstetric and neonatal events during pregnancy (2,3).

Long-term neurological effects may occur in a fetus that has been exposed to endometrial inflammation and placental changes due to COVID-19 infection. Therefore, this study was conducted to evaluate the possible neurological effects of prenatal exposure to COVID-19 on the infant.

2. METHODS

In this prospective study, infants aged 2–12 months born to women who had a positive COVID-19 real-time reverse transcription-polymerase chain reaction (RT-PCR) test taken from nasopharyngeal or oropharyngeal swab samples during pregnancy were included. All the pregnant women were under routine follow-up at the Gaziosmanpaşa Training and Education Hospital, Department of Obstetrics and Gynecology. Medical treatment was administered to pregnant women who were not suitable for outpatient treatment.

Infants were evaluated in the pediatric neurology department of Haseki Sultangazi Training and Education Hospital during the postnatal 2–12 months between June and August 2021. Data regarding comorbidities, smoking history, gestational week of the COVID-19 infection, severity of the disease, history of hospitalization, gestational week, birth weight, birth history, and history of hospitalization in the neonatal

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intensive care unit were collected and recorded. Neurological examination of all the infants was performed by one pediatric neurologist. The DDST II was administered to all infants by one child development specialist. Cranial imaging by ultrasound was performed for all infants.

2.1. Denver II Developmental Screening Test

Denver II Developmental Screening Test, which is used to follow the developmental stages of children and for early detection of abnormal situations, is the detailed version of the Denver Developmental Screening Test (DDST), which is standardized and used in Turkey. The Denver test was developed by Frankenburg and Dodds in 1990 (4). In Turkey, a standardization study was conducted by Anlar, Yalaz, Bayoğlu, and Denver II started to be used in 2011.

This test consists of 4 parts and 134 items. The following areas are evaluated: personal social emotional development, fine motor development, language development, and gross motor development. The results of the DDST II test are classified as either normal, suspicious, abnormal, or untestable.

2.2. Statistical Analysis

SPSS version 22.0 (IBM Corp., Armonk, New York, USA) was used in the analysis of the data. Data are expressed as percentage, mean ± standard deviation, or median (minimum–maximum). The Kolmogorov–Smirnov test was used to analyze the conformity of parametric data with normal distribution.

2.3. Ethics committee

Ethics committee approval dated 26.05.21 and numbered 05-2021 was obtained from the Health Sciences University, Haseki Training and Research Hospital, Clinical Research Ethics Committee. Written informed consent was obtained from the infants' parents.

3. RESULTS

The average age of mothers in this study was 30.6 ± 5.6 years. Diabetes mellitus was diagnosed in two pregnant women and celiac disease was diagnosed in one pregnant woman, one of the pregnant women was a thalassemia carrier, and two mothers were smokers. The mean gestational week at which mothers were diagnosed with COVID-19 was 22.4 ± 10.2 weeks. The distribution of mothers according to the trimester in which the diagnosis of COVID-19 was made was 27% in the first trimester, 39% in the second trimester, and 34% in the third trimester (Table 1). Seven mothers had a history of hospitalization due to COVID-19. Among the remaining 34 mothers, 2 were asymptomatic and 32 had mild-moderate symptomatic COVID-19 disease.

The average age of the 41 infants with prenatal exposure to COVID-19 was 5.3 ± 3.3 months; 22 infants were female and 19 were male. The average gestational age of the infants was 38.7 ± 1.9 weeks, and the average birth weight was 3198 ± 543 g. Eight of the infants had a history of hospitalization in the neonatal intensive care unit (Table 2). Neurological examinations were normal in 40 infants. Head circumference percentiles were in the normal range. No pathology was detected during transfontanelle ultrasonography. Neuromotor development was normal and, according to the DDST II, partial social emotional development, fine motor development, language development, and gross motor development were normal for the infants' ages. The mother of one of the infants had diabetes, and the infant was intubated for 1 day and hospitalized in the neonatal intensive care unit for 17 days due to low APGAR scores and respiratory distress. In this infant, hypotonicity and neuromotor developmental delay were present upon neurological examination; he could not roll over (prone to supine), did not respond to affection, and did not follow moving objects with his eyes. One infant was delivered at the 27th gestational week and weighed 1300 g at birth. Findings that were compatible with periventricular leukomalacia were observed on cranial magnetic resonance imaging in this infant. The neurological examination of this infant was normal at the fifth month of age but long term developmental evaluation is needed. Six infants had history of hospitalization in the intensive care unit due to hyperbilirubinemia (2/6), sepsis (2/6), dehydration (1/6), and transient tachypnea of the neonate (1/6). Neurological examinations and the DDST II scores of these infants were normal for their ages. One infant had grade 1 intracranial hemorrhage that was revealed during transfontanelle ultrasonography. No pathology was detected during transfontanelle ultrasonography of the other infants.

Table 1. *Demographic characteristics of pregnant women diagnosed with COVID-19.*

Age (mean ± SD) (years)	30.6 ± 5.6
Body mass index (mean ±SD) (kg/m^2)	29.3 ± 6.0
Smoking (n, %)	3 (7)
Gestational week of COVID-19 diagnosis	(4–39)
Trimester of COVID-19 diagnosis (n, %)	
First	11 (26)
Second	16 (39)
Third	14 (34)
Medication taken during infection (n, %)	17 (41)
Gestational week of birth (mean ± SD) (n, %)	38.7 ± 1.9

SD:Standart deviation.

Table 2*. Characteristics of infants with prenatal COVID-19 exposure.*

Sex (n, %)	
Female	22 (54)
Male	19 (46)
Age (mean ± SD) (months)	5.3 ± 3.3
Birth weight (mean ± SD) (gr)	3198 ± 543
NICU history (n, %)	8 (19)
Neurological examination normal (n, %)	40 (98)
DDST score normal (n, %)	40 (98)

SD:Standart deviation.

4. DISCUSSION

Infection response during pregnancy is associated with short – and long-term adverse effects on the infant by causing maternal immune activation and inflammation (5,6). As a result of maternal immune activation, proinflammatory cytokines, such as interleukin-1β, interleukin-6, and tumor necrosis factor α, can cross the placental barrier and trigger fetal immune response (7,9). This may lead to neurological effects and long-term problems like autism spectrum disorder in the offspring (10). No studies have yet been reported on neurodevelopmental outcomes for autism spectrum disorder that the childrren are still in infantile period. To evaluate the possible neurological effects of this immune response on infants, a detailed neurological examination and DDST II were performed on infants aged 3–12 months. In our study, signs of neurological involvement were found in only one infant.

It was observed that pregnant women with severe COVID-19 infection had an increased risk of cesarean delivery, hypertensive pregnancy disorders, and preterm birth when compared with asymptomatic patients (11). In another study, when women with COVID-19 were compared with uninfected women, the frequency of preterm birth and intrapartum fetal distress was significantly increased in women with symptomatic COVID-19 infection (12).

Fetal stress, preterm birth, and need for hospitalization in the neonatal intensive care unit can cause neurological involvement and neuromotor developmental delay in the infant during the neonatal period and beyond. In our study, one patient who was born at the 27th gestational week and had periventricular leukomalacia. Another patient had a diabetic mother and had neurological involvement after birth with low Apgar scores, respiratory distress, and hypotonicity and neuromotor developmental delay on neurological examination. The relationship between these findings and COVID-19 infection is unclear. To predict this relationship, there is a need for detailed studies examining the pathophysiology of fetal involvement in COVID-19. In our study, neurological examinations and DDST II scores were normal in all infants, except one.

In utero exposure to viral pathogens is a risk factor for direct infection of fetal tissues. Transplacental infection of the fetus by COVID-19 is yet to be proven exactly. COVID-19 has a neurotropism and direct viral neuroinvasion of the central nervous system through physical contact is a controversial topic. The relationship between neuroinvasion and the risk for neurodevelopmental disorders is still unknown.

Limitations of this study include a small number of children and short-term neurodevelopmental follow-up. Additional investigation of the placenta post-delivery would be helpful in evaluating the impact of direct viral infection on placental and fetal tissues.

5. CONCLUSION

In conclusion, although we did not find any evidence of short-term neurological effects on the infants in our study, long-term prospective studies are needed to elucidate these neurological effects.

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