



Infants infected with SARS-CoV-2 and newborns born to mother diagnosed with COVID-19: clinical experience

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Abstract

Background Almost every day, new information about the COVID-19 pandemic continues to emerge. COVID-19 presents a mild clinical picture in children. However, how it goes in newborns and pregnant is still entirely unclear.

Aims To present the clinical course of SARS-CoV-2 positive newborns and outcomes of babies born to mothers diagnosed with COVID-19.

Methods The present cohort-study examined two groups. The first group includes fourteen newborns born to mothers diagnosed with COVID-19. The second group evaluates twelve newborns infected with SARS-CoV-2.

Results Fourteen infants born to mothers diagnosed with COVID-19 were not infected with SARS-CoV-2. They had no symptoms and pathological laboratory findings. Additionally, forty-one newborns suspected of COVID-19 were evaluated, and 12 of them were detected to be infected with SARS-CoV-2. The most common symptoms were feeding intolerance (vomiting or refusing to feed, 58%), cough (50%), elevated fever (42%), and respiratory distress (42%).

Conclusion We did not come across any signs of vertical SARS-CoV-2 transmission. COVID-19 diagnosed newborns entirely healed with conservative treatment.

Keywords Newborn · Pregnancy · SARS-CoV-2 · Vertical transmission

Introduction

A new virus from the beta-coronavirus family was isolated in the severe viral pneumonia epidemic in China's Wuhan region in December 2019. It was named as 2019 Novel Coronavirus (2019-nCoV), and the disease as Coronavirus Disease 2019 (COVID-19) by World Health Organization (WHO) [1]. 2019-nCoV spread worldwide, and then, WHO announced that the COVID-19 had become a Global Pandemic in March 2020 [1]. Moreover, the virus type was identified as novel severe acute respiratory syndrome

coronavirus 2 (SARS-CoV-2) [2]. The genetic sequence of SARS-CoV-2 was revealed at the beginning of the epidemic [2]. The reverse transcription-polymerase chain reaction (RT-PCR) test widely was started to use detecting viral nucleic acid after the disease symptoms appeared. The test was highly successful in the detection of both symptomatic patients and asymptomatic carriers [3].

There is still not enough information about people at risk in this pandemic. Exactly 90% of the children are asymptomatic. Symptomatic children are also mildly affected by the disease, and death is rare. However, 6.7% of under one age may have severe clinical presentation [4]. Babies of pregnant women diagnosed with COVID-19 may be at risk. However, it is reported that vertical transmission of the 2019-nCoV is rare [5]. Newborn babies whose mothers were diagnosed with COVID-19 just before birth have a contamination risk. Although the infection is often asymptomatic in children, the clinical onset is not evident in newborns, especially in premature infants. It is reported that unstable body temperature and respiratory and cardiovascular findings may be observed in newborns with COVID-19 [6]. Therefore, close follow-up is substantial in COVID-19 suspected cases.

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Laboratory findings may include lymphopenia, thrombocytopenia, elevated C-reactive protein (CRP), D-dimer, ferritin, creatine kinase (CK), alanine aminotransferase (ALT), or aspartate aminotransferase (AST) levels. SARS-CoV-2 nucleic acid material can be detected from the samples of upper (nasopharyngeal or oropharyngeal swabs) and lower respiratory tracts (tracheal aspirate or bronchoalveolar lavage), blood, and stool [6].

In newborns, due to insufficient information, the course of the disease is not known entirely yet. This study aimed to present the outcomes of newborns infected with SARS-CoV-2 and sought to share the clinical features of babies born to mothers diagnosed with COVID-19 in our clinic.

Methods

Data collection: The present study was performed with newborns admitted to our clinic between April and December 2020. Two groups were examined in the study. First, it was evaluated a group consisted of fourteen newborns born to mothers diagnosed with COVID-19. Second, it was handled twelve newborns infected with SARS-CoV-2. This group included all SARS-CoV-2 infected newborns less than 1 month old.

All newborn babies were hospitalized and followed up in the neonatal intensive care unit (NICU). We enrolled the demographic data of all mothers and their newborn babies. The perinatal characteristics, clinical features, and laboratory findings were also recorded.

Laboratory assessment: The values that CRP > 1.58 mg/dL, D-dimer \geq 0.5 ug/ml, and serum ferritin > 400 ng/ml were considered as elevated. The RT-PCR test was performed with the nasopharyngeal sample obtained on admission in all patients. Bio-Speedy SARS-CoV-2 Double Gene RT-qPCR Kits (Bioeksan Istanbul Technical University Ari Teknokent Company, Istanbul, Turkey) were used for RT-PCR tests. Babies born to mothers diagnosed with COVID-19 have been undergone a second test after 2 days afterward. The babies infected with SARS-CoV-2 have undergone RT-PCR tests every 3 days until two negative results were obtained consecutively.

Statistical analysis: Data were analyzed using SPSS 21 for Windows. Percentage distributions were obtained.

Ethical approval: The study was approved by the Turkish Ministry of Health scientific research commission (2020–11-04T10_01_50) and by the chief physician of our clinic ethically (2020/983).

Results

Fourteen newborns born to mothers diagnosed with COVID-19 were admitted to NICU. Five of them were detected in referral hospitals. However, we verified all patients with a PCR test. Fifty percent of the babies were delivered via

Table 1 The demographic and physiologic characteristics of newborns

Features	<i>n</i> = 14 Newborns born to mothers diagnosed with COVID-19	<i>n</i> = 12 Newborns infected with SARS-CoV-2
Gender, <i>n</i> (%)		
Male	8 (57)	8 (67)
Female	6 (43)	4 (33)
Delivery type, <i>n</i> (%)		
Cesarean section	7 (50)	8 (67)
Spontaneous vaginal	7 (50)	4 (33)
Gestational age (week)	38.6 ± 1.4	38.0 ± 1.8
Age on admission (day)	0	21.8 ± 10.1
Birth weight (g)	3466 ± 443	3262 ± 558
Preterm labor, <i>n</i> (%)	1 (7)	3 (25)

The parameters are presented as mean ± standard deviation (SD)

COVID-19 Coronavirus Disease 2019, *SARS-CoV-2* novel severe acute respiratory syndrome coronavirus 2

cesarean section, and one of them was preterm. None of the babies born in our clinic needed resuscitation in the delivery room, and early cord clamping was performed. All babies were isolated and followed for any signs of disease. They were fed with breast milk according to isolation rules. We evaluated all patients in terms of COVID-19 and its effects with a PCR test and other laboratory tests. None of the babies born to mothers diagnosed with COVID-19 was infected with SARS-CoV-2. Also, their RT-PCR tests, which were obtained 12 h after birth and 2 days later, were negative. Laboratory findings such as complete blood count (CBC), CRP, ferritin, D-dimer, and liver enzymes remained normal. We did not observe any symptoms in all babies and did not use any medications. Besides, all mothers with COVID-19 had mild symptoms and findings. They were not treated with any specific treatment. One baby was referred to our clinic due to perinatal asphyxia. The baby was not infected with SARS-CoV-2 and discharged on day 14 with healing without any neurologic impairment in short-term results.

On the other hand, forty-one newborns suspected of COVID-19 were evaluated with a RT-PCR test, and 12 of them were detected to be infected with SARS-CoV-2. Three of them were late-preterm. The index case was the mother of six babies. In others, index cases were father, grandmother, or caregiver. We could not find an index case for three patients. Table 1 shows the demographic and physiologic characteristics of all newborns suspected and infected with SARS-CoV-2 on admission.

The most common clinical findings in newborns infected with SARS-CoV-2 were feeding intolerance (vomiting or refusing to feed, 58%), cough (50%), high fever (42%), and respiratory distress (42%). The clinical features of the patients

infected with SARS-CoV-2 are summarized in Table 2. Any patient had no findings of neurologic or cardiac.

Two babies infected with SARS-CoV-2 needed a mechanical ventilator. However, one of both had a severe clinical condition and needed invasive mechanical ventilation. This patient had signs of pneumonia on the X-ray, mildly elevated D-dimer, CRP, and ferritin, and got a combined antibiotic treatment with Vancomycin and Meropenem. However, the baby was not treated with any anticoagulant agent or specific drug for COVID-19. The patients whose clinic or laboratory findings were suggesting sepsis were treated with empiric antibiotics (firstly ampicillin-sulbactam or ampicillin + cefotaxime; if there is no clinical response, teicoplanin + meropenem).

The laboratory features of the patients infected with SARS-CoV-2 on the first-day admission to NICU were summarized in Table 3. Laboratory findings commonly assessed in newborns infected with SARS-CoV-2 were elevated D-dimer (92%), ferritin (42%), and CRP (8%). However, our patients had no elevated liver enzyme. The highest CRP value measured was 7.4 mg/dL. It was observed that the CRP level reached its highest level in the median of 1.5 (IQR 25–75, 0–8) days. RT-PCR positivity continued up to the median of 10 (IQR 25–75, 5–12.3) days, and the longest was 35 days. RT-PCR and CRP course of patient summarized in Table 4.

Discussion

A newborn infected with SARS-CoV-2 causes a big concern for healthcare providers. Clinical course and treatment of the disease are still unclear in childhood. It is

Table 2 The clinical features of the newborns infected with SARS-CoV-2

Features and findings	n %
Clinical	
Feeding intolerance (vomiting or refusing to feed)	7, 58
Cough	6, 50
Fever	5, 42
Respiratory distress	5, 42
Mechanic ventilation support	2, 17
Laboratory and radiological	
D-Dimer (>0.5 ug/ml)	11, 92
Pneumonia findings on X-Ray	6, 50
Ferritin (>400 ng/ml)	5, 42
Hyperbilirubinemia	2, 17
C-reactive protein (>1.58 mg/dL)	1, 8
Elevated liver enzymes	0, 0

SARS-CoV-2 novel severe acute respiratory syndrome coronavirus 2

Table 3 Laboratory findings of patients infected with SARS-CoV-2 on the first-day admission to NICU

Findings	Median (IQR 25–75)	Mean ± SD
Leucocyte ($10^3/\mu\text{L}$)	8.5 (5.8–12.0)	8.9 ± 3.8
Lymphocyte ($10^3/\mu\text{L}$)	4.6 (2.4–7.4)	4.7 ± 2.5
Platelet ($10^3/\mu\text{L}$)	364 (294–434)	465 ± 347
C-reactive protein (mg/dL)	0.11 (0.03–0.26)	0.54 ± 1.17
Ferritin (ng/mL)	383 (326–527)	593 ± 562
D-dimer (ug/mL)	1.16 (0.6–2.8)	1.71 ± 1.46

NICU neonatal intensive care unit, IQR interquartile range, SD standard deviation

unknown whether treatment is necessary or the effectiveness and the long-term consequences of its medical treatments. In fact, there is also no specific treatment or approach in newborns for now.

Pregnancy affects the physiology and immunity of women. Although it is thought that pregnant women may have worse outcomes compared with non-pregnant [7], a large meta-analysis argues otherwise [8]. We did not observe severe clinical findings in any of the puerperal women. It is seen that in the literature, 68.9% of gynecologists prefer cesarean section for COVID-19 diagnosed pregnant because of maternal troubles, fetal death, and neonatal asphyxia risks [7, 9]. In the present study, the cesarean section rate was 50% in mothers diagnosed with COVID-19. Besides, Turkey's cesarean section rate is around 50% for now [10], similar to our study's status. A study states that delivery management should be determined according to medical indications and recommends vaginal delivery if there are no indications [11]. Furthermore, another study indicated that vertical SARS-CoV-2 transmission is all seen after cesarean delivery [12]. None of the babies delivered by cesarean were infected with SARS-CoV-2.

The researches show that the preterm labor risk was increased in pregnant women diagnosed with COVID-19 [7, 13]. Likewise, the preterm labor rate was found 7% in the present study, like a meta-analysis found 6% [12–14]. However, it is known that it may extend up to 30% [13]. It is also known that COVID-19 may cause an increase in the perinatal asphyxia risk in pregnant women [9]. In our study, one baby, born to a mother diagnosed with COVID-19, had a perinatal asphyxia clinic, also had a negative SARS-CoV-2 test. The baby healed with full body-cooling and conventional support therapy, and the clinical condition was right in the short term.

Vertical transmission of the SARS-CoV-2 is rare [5, 7]. According to a systematic review, some studies have detected SARS-CoV-2 negative in the placenta, cord blood, and breast milk [15]. However, there is some evidence that SARS-CoV-2 RNA can be seen in the placenta, breast

Table 4 CRP and RT-PCR course of newborns infected with SARS-CoV-2

Findings	Min/Max	Median (IQR 25–75)
CRP level (mg/dL)	0.02/7.4	0.14 (0.08–0.65)
Time that CRP reached to maximum (days)	0/8	1.5 (0–8)
Time that CRP remained elevated (> 0.5 mg/dL)	0/19	0 (0–1.25)
Time that RT-PCR test remained positive	2/35	10 (5–12.3)

CRP C-reactive protein, RT-PCR reverse transcription-polymerase chain reaction, IQR interquartile range, Min minimum, Max maximum

milk, and fetal blood [9]. SARS-CoV-2 positivity has been reported in several newborns born to mothers diagnosed with COVID-19 [16–18]. Even the transmission ratio is reported as low as 1% in a study [19] and 3.9% in a meta-analysis [12]. In an article evaluating the effects of COVID-19 in pregnancy, the outcomes of some research were summarized. As a result, it was mentioned that SARS-CoV-2 is a candidate for the TORCH (for toxoplasmosis, others [including syphilis], rubella, cytomegalovirus, and herpes simplex virus) list due to its intrauterine effects [20]. Although the possibility of vertical transition is still not clear, neonates born to mothers diagnosed with COVID-19 should be separated and isolated [15]. Nevertheless, have no symptoms; these newborns should be followed up in the hospital [6] and performed a RT-PCR test. None of the babies were found positive for SARS-CoV-2 with an RT-PCR test in the present study. Although clinical and laboratory findings were mentioned in this article [20], we did not also detect any elevated acute phase reactants and unusual laboratory findings that signed an infection. However, we could not analyze the amniotic fluid and cord blood samples.

On the other hand, in children infected with SARS-COV-2, it is reported that the rate at which transmission route could not be detected is 12% [21]. This rate was determined as 25% in our study because analyzing an RT-PCR test for every patient with no contact history but with suspected sepsis. Additionally, it is also reported that the disease remains asymptomatic up to one-third of children but causes a critical illness in 6% of all pediatric patients with COVID-19 and more than 11% of infants under one-year-old [22]. The most common symptoms in childhood are fever above 37.5 °C (41.5–76%) and cough (45–54%) [22, 23]. However, it may be accompanied by fatigue, myalgia, nasal congestion, runny nose, sneezing, sore throat, headache, dizziness, vomiting, and abdominal pain. A minority of children only have a cough or diarrhea [23, 24]. In newborns, shortness of breath, cough, fever, vomiting, and other gastrointestinal symptoms are prominent [24, 25]. The most common symptoms reported in SARS-CoV-2 positive newborns are respiratory distress 41–60%, fever 20–49%, cough 27–33%, feeding intolerance 40%, vomiting 10%, and tachycardia 10% [26, 27]. Besides, feeding intolerance is found at 50% in another study [27]. The most common symptoms were feeding intolerance and

vomiting (58%), cough (50%), and elevated fever (42%), and respiratory distress (42%) in this study. Another study also reported that 20% of patients developed RDS, and one patient had a pneumothorax [18]. A study performed by Kanburoglu et al. stated that some of the patients needed oxygen support (41%), noninvasive ventilation (16%), and mechanical ventilation (3%) in a larger patient group [28]. In our study, five of the babies (42%) had respiratory distress, and the two of them needed mechanical ventilation.

In the present study, 50% of the infants diagnosed with Covid-19 had pneumonic infiltration on X-ray. A study performed by Soysal et al. in children reported that the pneumonic infiltration rate is 29% on X-ray, and ground-glass opacities rate is 41% on thorax computed tomography (CT) [21]. It was observed that the CRP levels were elevated in 7% of our patients. Additionally, D-dimer was elevated in 92% of patients in our study. However, Soysal et al. reported elevated D-dimer levels as 31% in symptomatic children with COVID-19 [21]. They have also observed that the CRP levels were higher in symptomatic patients (38%) than asymptomatic ones (11%) [21].

COVID-19 is not just a disease that affects the respiratory system. Therefore, patients should be evaluated systemically. It is indicated that liver enzymes, kidney functions, cardiac biomarkers, and abdominal ultrasonography may be performed [6]. Also, the liver enzymes were found elevated in 2–10% of patients in children [21]. None of these investigations found pathological in our study. About 20% of patients had thrombocytopenia in some studies [26, 27], but our patients' laboratory findings had no thrombocytopenia.

It is reported that the children diagnosed with COVID-19 were found RT-PCR test positive about 17% at post-diagnosis seventh days and 7% at post-diagnosis 12–14 days [21]. Similarly, RT-PCR positivity disappeared median 10 days in our research. However, the RT-PCR remained positive in one patient for 35 days, but it did not affect the clinic. In some patients, RT-PCR positivity remained for weeks. Some tests may also be performed to exclude other agents like influenza and respiratory syncytial viruses [6]. In this respect, none of our patients had a positive result.

Additionally, Herpes Simplex Virus (HSV) was detected in one patient, but it did not worsen the clinical condition with acyclovir treatment. The cerebrospinal liquid had no

HSV-DNA, but blood tests were found HSV-DNA positive. HSV co-infection did not adversely affect the COVID-19 clinic.

There is no consensus yet regarding COVID-19 treatment in the neonatal period. The general recommendation is maintaining homeostasis and following up with blood tests and chest x-ray if necessary. The effectiveness of antiviral drugs in the treatment of disease is unknown. Antibiotherapy is recommended if there is a possible or proven bacterial infection, but empirical or overuse of antibiotics is not recommended. In selected severe cases, corticosteroids or intravenous immunoglobulin may be tried [6], but these treatments should not be considered for every patient as the effectiveness has not been proven [29]. According to a study, antiviral agents (Remdesivir, Lopinavir, Ritonavir) may be used by considering the benefit-harm principle [29]. But we do not know the long-term effects of these agents. Two babies had a respiratory failure in our study. Both of them were recovered with mechanical ventilation assistance, supportive care, and combined antibiotic therapy. None of them needed steroids or surfactant.

The present study has several limitations. It contains a small number of newborns. Also, it is a single-site study. Both of them limit the capability to generalize the results. Therefore, the results should be interpreted with caution. Nevertheless, it provides essential information about both vertical transmission and how SARS-CoV-2 infection progresses in newborns. Multicenter studies with more participants can give significant results.

In conclusion, COVID-19 presents a mild clinical course in children. However, how it goes in newborns and pregnant is still unclear. Vertical transmission was not observed for SARS-CoV-2. The RT-PCR test negativity for SARS-CoV-2 was especially striking in all babies born to mothers with COVID-19. Whether the mother's COVID-19 affects the baby is a question that we do not know the answer to yet. SARS-CoV-2 may be symptomatic in newborns. Besides, severe clinical conditions are also possible. Although symptomatic treatment successfully resolved the troubles with clinical conditions, the clinical course and details of treatment in newborn babies are situations that will become clear over time.

Author contributions AY; study design, data collecting, IK; study design, data collecting, writing, MAV; statistic, writing, revising, corresponding.

Data availability It is available.

Declarations

Ethical approval The study was approved by the Turkish Ministry of Health scientific research commission (2020–11-04T10_01_50) and by the chief physician of our clinic ethically (2020/983).

Conflict of interest The authors declare no competing interests.

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