

Perinatal Transmission and Clinical Outcomes of Neonates Born to SARS-CoV-2-Positive Mothers

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Abstract

Background: The aim of the study was to investigate the clinical outcomes and rate of virus detection in neonates born to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive mothers.

Methods: This prospective study included neonates born to SARS-CoV-2-positive mothers, documenting their viral polymerase chain reaction results and clinical outcomes.

Results: Of the 130 neonates born to 122 SARS-CoV-2-positive mothers, 12% tested positive. Most (62%) neonates were delivered via cesarean section at an average gestational age of 36 weeks, with a birth weight of 2,900 g. Only 38% neonates required admission. SARS-CoV-2-positive infants were born at a significantly lower gestational age; had a significantly lower birth weight; and had significantly higher admission rates, surfactant therapy, and bradycardia than SARS-CoV-2-negative infants. There was no significant difference in mortality rates.

Conclusion: This study documents perinatal transmission of SARS-CoV-2. It reports for the first time the occurrence of neonatal bradycardia as a complication of maternal SARS-CoV-2 infection. Despite that, neonates born to SARS-CoV-2-positive mothers had relatively good short-term outcomes.

Keywords: Neonate; COVID-19; Clinical outcome; Perinatal transmission

Introduction

Coronavirus disease 2019 (COVID-19) is an emerging disease that was detected for the first time among humans in December 2019. Its manifestations range from asymptomatic forms to death [1]. Due to the imposed restrictions and country lockdown, Jordan was not affected by the first wave of the pandemic [2]. However, starting on November 2021, the second wave devastated the country, with cumulative cases exceeding 600,000 cases [3].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19, is mainly transmitted via respiratory droplets or direct contact route [4]. However, vertical transmission from mothers to babies is controversial [5]. With regard to breastfeeding, it is unclear whether breast milk is a vector for virus transmission, although it was declared by the World Health Organization (WHO) and other worldwide organizations that mothers who wish to breastfeed can do so provided that they practice hygiene precautions [6].

Neonatal and pediatric patients infected with SARS-CoV-2 are mostly asymptomatic or present with mild illness [7]. In the neonatal period, the symptom presentation is quite variable, ranging from mild symptoms, such as nasal congestion, to fever, respiratory distress, hypoactivity, sepsis, and even death [8].

This prospective study aimed to compare the clinical outcomes, rates of virus detection, and presence of symptoms between SARS-CoV-2-positive and -negative neonates born to SARS-CoV-2-positive mothers.

Materials and Methods

This was a prospective observational study on neonates born to SARS-CoV-2-positive mothers at the Jordan University Hospital from March 2020 to April 2021.

This study was approved by the deanship of scientific research at the University of Jordan and by the ethical committee of the Jordan University Hospital (reference number 10-2020-8558). The study was performed in accordance with the Declaration of Helsinki. A structured data sheet was used to collect the demographic and clinical data of the included newborns.

Nasopharyngeal swabs were collected from the neonates according to the neonatal intensive care unit (ICU) protocol. At the beginning of the pandemic, the first swab was collected

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Table 1. Clinical and Demographic Data of Neonates Born to SARS-CoV-2-Positive Mothers

Characteristics	All newborns (n = 130)	SARS-CoV-2-positive (n = 16)	SARS-CoV-2-negative (n = 112)	P value
Gestational age (weeks)	36 (29 - 41)	35 (3)	37 (2.5)	0.004
Gestational age < 34 weeks	24 (18.46%)	5 (31.25%)	19 (17.0%)	0.180
Birth weight (g) (mean ± SD)	2,900 ± 653	2,400 ± 748	2,790 ± 627	0.025
Cesarean section	81 (66%)	10 (62%)	71 (62%)	1.000
Male sex	58 (45%)	6 (37.5%)	51 (45.53%)	0.596
Apgar scores (mean)				
First minute	8	7	8	
Fifth minute	9	9	9	
Neonatal ICU admission	50 (38%)	11 (68%)	39 (34%)	0.014
Bradycardia	5 (3.85%)	3 (18.8%)	2 (1.8%)	0.014
Respiratory support	33 (25.38%)	7 (43%)	26 (22%)	0.122
Non-invasive	29	5	24	0.036
Invasive	4	2	2	0.076
Surfactant therapy	5 (3.85%)	4 (25%)	1 (0.9)	0.001
Hyperbilirubinemia	18 (13.85%)	6 (37%)	12 (10%)	0.011
High C-reactive protein	7 (5.4%)	3 (18.8%)	4 (3.6%)	0.042
Received antibiotics in the first 48 h with negative cultures	30 (23.1%)	9 (56%)	21 (18.8%)	0.003
Breastfeeding	60 (46.1%)	8 (50%)	52 (45%)	0.796
Mortality	3 (2.3%)	1 (6%)	2 (1.8%)	0.332

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SD: standard deviation; ICU: intensive care unit.

at delivery and after 48 h after delivery. A few months later, this protocol was modified, with the first swab collected at 24 h of age, followed by the second swab at 72 h of age. The SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) test was used as the diagnostic test.

Neonates who did not require neonatal ICU admission were taken care of according to the international recommendation, adopting a room-in policy. The mothers were also counselled about breastfeeding and allowed to decide whether to breastfeed or to give formula. At discharge, the parents were instructed to return to the hospital if they developed symptoms. They were asked to contact health professionals at the neonatal unit via telephone if they had any concerns.

Statistical analysis

The data were analyzed using Excel 2010 (Microsoft; Redmond, Washington, USA). The frequency, mean, and standard deviation were calculated. Fisher's exact test was used to compare the frequencies. A two-tailed *t*-test was used to compare the mean and standard deviation. Statistical significance was set at $P < 0.05$.

Results

A total of 130 neonates born to 122 SARS-CoV-2-positive

mothers were included. Only six of the included mothers were diagnosed before Jordan's second wave of COVID-19 epidemic in November 2020. Sixteen mothers (13%) were symptomatic at the time of delivery. Among the neonates, 16 were SARS-CoV-2-positive based on results of RT-PCR tests using nasopharyngeal swabs. Eight (50%) neonates were positive on the first swab. Two (1.5%) had equivocal results. Most (62%) neonates were delivered via cesarean section, and 58 neonates were male (45%). The average gestational age was 36 weeks (range, 29 - 41 weeks), and the average birth weight was 2,900 g (range, 980 - 3,900 g). Only 38% neonates required admission to the neonatal ICU, mostly due to prematurity (Table 1).

SARS-CoV-2-positive neonates were born at a significantly lower gestational age than SARS-CoV-2-negative neonates (35 vs. 37 weeks; $P = 0.004$). Further, SARS-CoV-2-positive neonates had significantly lower birth weight (2,400 vs. 2,790 g; $P = 0.025$). However, there was no significant difference in the number of premature neonates aged < 34 weeks in both groups. Moreover, SARS-CoV-2-positive neonates had significantly higher rates of neonatal ICU admission (68% vs. 34%, $P = 0.014$), surfactant therapy (25% vs. 0.9%, $P = 0.000$), C-reactive protein level elevation (18.8% vs. 3.6%, $P = 0.041$), and antibiotic therapy requirement (56% vs. 18.8%, $P = 0.003$) than SARS-CoV-2-negative neonates. They also had significantly higher rates of neonatal hyperbilirubinemia (37% vs. 10%, $P = 0.011$) and bradycardia (18.8% vs. 1.8%, $P = 0.014$) than SARS-CoV-2-negative neonates. However, there was no

difference in the mortality rates between SARS-CoV-2-positive and -negative neonates (Table 1).

A multiple linear regression analysis was performed to examine whether the prematurity, neonatal SARS-CoV-2-positive status, or low birth weight variables significantly predicted admission. Low birth weight was found to be the most significant factor to predict admission to the neonatal unit with P value of 0.087, 0.085, and < 0.001 , respectively.

Discussion

Perinatal transmission of SARS-CoV-2 has been reported previously [9-11]. However, the exact route of transmission has not been documented. SARS-2-CoV-2 has been detected in the amniotic fluid, supporting its hematogenous spread through the placenta or through the aspiration and ingestion of maternal amniotic fluids [12]. Transmission can also occur later via breastfeeding [13] or from household contacts. However, evidence supporting vertical transmission has been increasing [14].

Transplacental transmission might have more severe outcomes if it occurs during the early stages of pregnancy, a gray zone that needs further investigation. In a study investigating the placental pathology in mothers with severe COVID-19, they found that the placentas showed an increased rate of decidual arteriopathy and other features of maternal vascular malperfusion, which reflect abnormalities in oxygenation within the intervillous space associated with adverse perinatal outcomes. The study further concluded that these changes were associated with hypertensive disorders of pregnancy and preeclampsia and may reflect a systemic inflammatory or hypercoagulable state influencing placental physiology [15]. Another study revealed an increased risk of miscarriages in the first trimester among pregnant SARS-CoV-2-positive women [16].

However, regarding perinatal SARS-CoV-2 infection, the route of transmission, whether transplacental or during birth, may be determined based on the duration before positive tests or whether clinical symptoms are observed. However, this will require a longer duration of isolation and outpatient follow-up and more serial testing in neonatal infants whose initial test results were negative. This places more strain on an already exhausted neonatal service.

The rate of transmission in our cohort was 12%, much higher than previously reported rates [10, 11, 16]. The National Registry for Surveillance and Epidemiology of Perinatal COVID-19 Infection reported a transmission rate of only 1.9% [10]. Similarly, in a large population-based cohort study in the UK, only 5% of the neonates born to SARS-CoV-2-infected mothers were infected [9]. In a Spanish cohort, the perinatal acquisition rate was 6.9% [16]. Various factors may explain the differences, but it may be mainly due to the differences in the COVID-19 illness stage among mothers at the time of delivery, which could potentially affect the rate of perinatal transmission due to the different intensities of viremia. Another theory that requires further investigation is the difference in the virus variant, as most of our cohort ($n = 116$) were recruited

after November 2020, when Jordan started detecting cases of the UK variant [17], a more transmissible and potentially more lethal variant [18].

Our neonates were only tested during the first 72 h of life; hence, data on neonates who tested positive later could not be reviewed. One of our neonates was born at 30 weeks of gestation. His mother was SARS-CoV-2-positive before 6 weeks and 8 days prior to delivery. The neonate presented with respiratory distress syndrome, but his condition improved after administration of surfactant therapy. At the age of 9 days, he developed severe respiratory distress, requiring 100% oxygen. A thorough investigation was conducted. Septic workup and echocardiography revealed normal results, but he was tested positive for SARS-CoV-2 on the RT-PCT test using nasopharyngeal swab. This case might represent perinatal transmission or postnatal transmission from the visiting parent or the neonatal unit staff. However, none of the other babies in the unit was positive, and none of the staff who took care of him were positive. In another case, the mother was tested 2 days prior to delivery, and the neonate had negative nasopharyngeal swab results at 24 h of age. However, the parents did not return for the follow-up swab. The neonate presented at 19 days of age with mild respiratory symptoms and was later tested positive for SARS-CoV-2. Although these cases were more likely due to postnatal infection, perinatal transmission is a possibility.

The neonates born to SARS-CoV-2-positive mothers had good outcomes. One-third (38%) neonates required admission to the neonatal ICU, mostly (48%) due to prematurity (gestational age < 35 weeks). The second most common cause of admission was respiratory distress, seen in 30% neonates. There were three mortalities (2%), with one death due to respiratory failure and prematurity and another due to pulmonary hypertension. The third baby had intrauterine growth restriction and pancytopenia; bone marrow aspiration revealed hemophagocytic lymphohistiocytosis, a complication that can be attributed to the strong activation of the immune system after a severe infection (Table 1).

Neonates born to SARS-CoV-2-positive mothers can develop complications due to factors not directly related to the infection, such as maternal hypoxemia, preeclampsia, and placental hypoperfusion [11]. These complications might be due to the passage of inflammatory cytokines [19], which can be attributed to sepsis-like symptoms and elevated C-reactive protein levels (Table 1). Although these morbidities are relatively common during the neonatal period, affected newborns need long-term follow-up, especially for monitoring their neurodevelopmental status.

Among the SARS-CoV-2-positive newborns, 11 (68%) required admission to the neonatal ICU, mostly due to prematurity; the rate of neonatal ICU admission was significantly higher in SARS-CoV-2-positive newborns than in SARS-CoV-2-negative newborns ($P = 0.014$). This might be attributed to the fact that the positive newborns were more premature (35 vs. 37 weeks, $P = 0.004$) and had lower birth weights than the negative newborns (2,400 vs. 2,790, $P = 0.025$). This finding might also explain why the SARS-CoV-2-positive neonates required more surfactant therapy ($P < 0.0007$). However, there was no significant difference in the number of premature in-

fants aged ≤ 34 weeks, which places them at higher risk of respiratory distress syndrome, between the two groups (31% vs. 17%, $P = 0.18$).

Bradycardia was reported in both groups, although there were significantly more cases among SARS-CoV-2-positive patients than in SARS-CoV-2-negative patients. The electrocardiogram showed sinus bradycardia, while the electrolyte and thyroid function tests showed normal findings. The echocardiogram was normal. Severe acute respiratory syndrome coronavirus from the 2002 outbreak was associated with sinus bradycardia in up to 15% patients [20]. Several studies have also linked the SARS-CoV-2 to bradycardia [21]. However, the exact mechanism is unknown. This may be due to direct SARS-CoV-2 infiltration into myocardial cells and the dedicated conduction system. It may also be due to the collateral damage from the activation of the inflammatory system and the resulting cytokine storm [22]. As such, the passage of maternal cytokines might explain the bradycardia in SARS-CoV-2-negative group. Another suggested mechanism for bradycardia is the activation of the angiotensin-converting enzyme 2 receptor, specifically in the sino-atrial nodal cells, leading to conduction disturbances [23]. However, this mechanism might not apply to newborns due to the lower expression and decreased affinity of the angiotensin-converting enzyme 2 receptor [24].

The milder disease observed in neonatal patients might be attributed to multiple factors, such as the following: lower intensity of exposure to SARS-CoV-2; weaker adaptive immunity, decreasing the severity of the inflammation responsible for most tissue damage; and relatively lower expression, affinity, and distribution of the angiotensin-converting enzyme 2 receptors, which facilitate SARS-CoV-2 entry into cells [25].

Our study limitation is its single center nature, and the lack of some of the maternal data. However, it provides evidence on the vertical transmission of the SARS-CoV-2. We also proved that the neonatal population is not at risk of severe illness, but long-term complications are unknown.

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Conflict of Interest

The authors have no conflict of interest to declare.

Informed Consent

Patient consent was waived due to the observational nature of

this study, in addition to the absence of patients' identifiers.

Author Contributions

Conceptualization: Manar Al-Lawama. Data curation: Manar Al-Lawama, Noor Ghanim, Ayah Irsheid and Hiba Qtaishat. Formal analysis: Manar Al-Lawama, Noor Ghanim, Ayah Irsheid and Hiba Qtaishat. Methodology: Manar Al-Lawama and Eman Badran. Project administration: Manar Al-Lawama. Resources: Manar Al-Lawama, Eman Badran, Iyad Al-Ammouri and Ghada Massad. Supervision: Manar Al-Lawama. Writing original draft: Manar Al-Lawama, Noor Ghanim, Ayah Irsheid and Hiba Qtaishat. Writing review and editing: Iyad Al-Ammouri, Enas Al-Zyadneh, Montaha Al-Iede, Amira Daher and Fares Bakri.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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