

Vertical transmission of SARS-CoV-2 Infection, epidemiology and risk factors

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ABSTRACT

Objective:SARS-CoV-2 infection can affect people of all ages. Little is still known about the impact of COVID-19 on pregnant women and neonates and whether it can be transmitted from the mother to the neonate is still a conflicted issue. This study was designed to determine the rate vertical transmission of COVID-19 and variables associated with increased risk of transmission.

Method: A prospective study was done during the period from March 2020 to January 2022 in one of the leading national pandemic centers in Jordan, Queen Alia Military Hospital. All neonates born to SARS-CoV-2 positive mothers were included in the study. The following data were gathered for each neonate: age of the mother, maternal vaccination status, clinical severity of maternal infection, mode of delivery and the indication, presence of prolonged rupture of the membrane for more than 18 hours , gestational age at delivery, birth weight, gender, admission to neonatal unit, and the result of the reverse transcriptase-polymerase chain reaction (RT-PCR) nasopharyngeal swabs of each neonate, according to the protocol.

Result:357 neonates were delivered to 344 women who were diagnosed with COVID-19 infection within 14 days before the delivery. 110 neonates (30.8%)were admitted to the intensive care unit. The vertical transmission rate was 2.8%. The severity of the maternal disease and the duration of the maternal symptoms before the delivery were associated with an increased risk of transmission of the infection. A high rate of cesarean sections (61%) and premature deliveries (27.5%) were observed in pregnant women with COVID-19 infection.

Conclusion: Vertical transmission of COVID -19 is possible with third trimester maternal infection but occurs in the minority of cases. The risk of transmission is increased with increasing severity of maternal infection and long duration of symptoms. Hence, testing neonates born to COVID-19-infected mothers is vital.

Keywords: Vertical transmission, neonates, COVID-19.

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INTRODUCTION

COVID-19 is a disease caused by SARS-CoV-2, a member of the Coronaviridae family, transmitted mainly through air droplets [1,2].It was declared a public health emergency by the World Health Organization on January 30, 2020.[3]

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Since then, there has been a concern about the effect of SARS-CoV-2 infection on pregnant ladies and neonates delivered by mothers who are positive at the time of delivery. Perinatal SARS-CoV-2 transmission routes include transplacental, through contact with infected secretions during delivery and respiratory droplets after delivery, and breast milk [4]. Low rates of virus positivity in relevant biological specimens (placenta, amniotic fluid, vaginal secretion, and breast milk) suggest that perinatal transmission is uncommon [4-6].

COVID-19 research efforts have built on earlier research on severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), that both are caused by coronaviruses. At the beginning of the disease, many experts tried to compare it with similar coronaviruses such as SARS and MERS, as no known cases of vertical transmission had been noted, although the number of cases reported was small [7]. However, with the presence of angiotensin-converting enzyme 2 receptor in the placenta, which is considered the receptor for SARS-CoV-2, and the presence of immunoglobulin M (IgM) antibodies for SARS-CoV-2 in the blood of neonates which cannot cross the placenta, raise the possibility of vertical transmission of COVID-19 [8].

Current knowledge about the effect of SARS-CoV-2 infection in pregnant women and neonates has been collected largely from case reports, case series, and population surveillance systems in high-income countries and a few studies from developing countries where the income and social situation have a major impact on maternal and neonatal health outcome.

To the best of our knowledge, few large cohort studies have addressed the vertical transmission of SARS-CoV-2 in pregnant women and investigated the risk factors for transmission to neonates delivered by those women. Given the low incidence of vertical transmission of SARS-CoV-2, identifying associated risk factors can be challenging, especially with the small number of neonates involved in the studies. Our study was designed to address this issue in a hospital considered to be one of the leading national pandemic centers in a developing country.

METHOD

This is a prospective study conducted during the period from March 2020 to January 2022 in one of the major hospitals in Jordan—Queen Alia Military Hospital, which selected to be a referral hospital for SARS-CoV-2 patients since the start of the pandemic, with a capacity of more than 400 beds. High-risk SARS-CoV-2-positive pregnant women were referred to our hospital from all over the country, especially those needing intensive care for respiratory support in the form of CPAP or ventilator support.

All neonates born to SARS-CoV-2-positive mothers were included in the study. The inclusion criteria were 1- gestational age of 24-42 weeks, 2- Mother developed Covid positive within 30 days before delivery. and the exclusion criteria were 1- unknown maternal status for Covid 19 infection 2- death or early discharge before obtaining the PCR test. Nasopharyngeal swabs for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction RT-PCR testing were obtained from neonates at the age of 48 hours, and if specimens were positive, tests were repeated after 7 days. Neonates who did not need to be admitted to the neonatal intensive care unit (NICU) were admitted to the nursery unit and were separated from their mothers until discharge from the

hospital; visitors were forbidden from entering the unit and breastfeeding was encouraged after discharge from the hospital with proper precautions, including hand hygiene and a mask. Mothers were given a contact number to call if symptoms developed.

Immediately after delivery, neonatal isolation was performed without delayed cord clamping or skin-to-skin contact, according to hospital policy. All neonates were given a bath after delivery to reduce the contamination with amniotic fluid. Parents alone were able to visit the neonatal intensive care unit if they were polymerase chain reaction (PCR) negative for COVID-19, according to NICU protocol.

The following data were gathered for each neonate: gestational age, birth weight, gender, age of the mother, mode of delivery and the indication, need for admission, clinical conditions of the mother, the intensity of pneumonia and level of lung involvement, complete blood count (CBC) for the mothers, vaccination status of the mother, presence of prolonged rupture of the membrane for more than 18 hours and the result of the reverse transcriptase-polymerase chain reaction (RT-PCR) nasopharyngeal swabs of each neonate, according to the protocol.

Electronic medical records were used to collect the maternal data. The primary study outcome was the newborn SARS-CoV-2 test results. Vertical transmission was defined as positive SARS-CoV-2 test results on the initial newborn swab, and postnatal transmission was defined as subsequent positive SARS-CoV-2 test results after the first week of life, either during hospitalization or after discharge, which was not the scope of this study.

Infection control protocol policy in our hospital for the healthcare worker was strict temperature measurement and symptom-reporting, followed by a reverse transcriptase-polymerase chain reaction (RT-PCR) test. Randomized nasopharyngeal swabs for health care workers were obtained weekly. If a neonate tested positive for COVID-19, we reviewed whether any healthcare worker in the unit was symptomatic or tested positive during the previous 14 days.

We used Excel 2010 to analyze the data and the Fisher exact test to compare dichotomous variables. A two-tailed *t*-test was used to compare the mean and standard deviation. Two-sided $P < 0.05$ indicated significance.

The study was approved by the Human Research Ethics Committee of the Royal Medical Services, Amman, Jordan. Waiver of Informed Consent was obtained, and confidentiality was ensured at all levels.

RESULT

357 neonates were delivered to 344 women diagnosed with COVID-19 infection within 14 days before the delivery. None of the pregnant ladies were vaccinated for COVID-19. 110 neonates(30.8%)were admitted to the neonatal intensive care unit (NICU). The vertical transmission rate was 2.8%,with 10 neonates tested positive for COVID-19 by nasopharyngeal swap by RT-PCR. None of the healthcare workers in the neonatal unit were symptomatic or tested positive by PCR for COVID-19within 14 days before the neonates tested positive.

Table I shows the possible risk factors that we investigate, could be associated with an increased risk of vertical transmission of SARS-COV-2 before the delivery. There was a significantly high percentage of cesarean delivery61% (210/344) among the total number of women infected with SARS-COV-2 at the time of delivery. Eight out the ten of the neonates (80%) who developed COVID-19 were delivered by cesarean section, but was not statistically significant with respect to possibility of increase risk of vertical transmission. Maternal age ranged from 19 to 43 years. The total number of premature babies born to COVID-19-infected women was high 101/357 (28.1%). We found that the prematurity, severity of infection in the mothers, duration of symptoms before delivery and lymphopenia during the infection of the mothers were significant risk factors for vertical the transmission of COVID 19.

Risk factors	All neonate for COVID 19 positive mothers (357)	Positive for COVID 19 neonates (10)	Negative for COVID 19 neonates (347)	Test value	P value
Male: Female	200:157 (56.02%/43.9%)	5:5 (50%/50%)	195:152 (56.03%/43.68%)	0.151	0.697 ^a
Maternal age (mean)	30.2±11.3	32.6±5	29.8±10.5	0.839	0.402 ^b
Caesarean delivery*	210/344(61%)	8/10(80%)	202/334(60.5%)	1.556	0.212 ^a
Premature delivery* <37 wk (344 women)	98/344 (28.5%)	6/10(60%)	92/334(27.5%)	5.020	0.025 ^a
sBirth weight <2.5 kg	75/357 (21.01%)	4/10 (40%)	71/347(20.05%)	2.236	0.135 ^a
Moderate to severe infection in the mother	82/357 (23%)	9/10 (90%)	73/347 (21%)	26.126	<0.001 ^a
Duration of symptoms before delivery (Mean)	4.52±4.1	11.3±3.75	4.52±3.95	5.358	<0.001 ^b
Lymphopenia in the mother < 4*	58/344 (16.86%)	4/10 (40%)	54/334 (16.2%)	3.934	0.047 ^a
Prolonged rupture of membrane >18 hr	11/357 (3.08%)	0/10	11/347 (3.1%)	--	1.00 ^c

Table 1: Risk factors that is possibly associated with increase vertical transmission of SARS-COV-2.*it was related to the total number of mothers with positive Covid 19(344 women)a= chi square test , b= independent t test, c= fisher exact test

Chart 1 shows the distribution of the neonates according to their gestational age. 40% of the infected neonates were full term, compared to the uninfected full term neonates (73.5%). The vertical transmission according to gestational age was as follows: <28 wks, 28-32wks, 33-37wks, and >37 wks were 4.76%, 14.29%, 3.57%, and 1.5%, respectively.

The severity of maternal infection affected the vertical transmission of SARS-COV-2 infection (chart 2). The vertical transmission according to the severity of infection in the asymptomatic mothers was 0/193 (0%), mild in 1/82 (1.2%), moderate in 5/43 (11.6%), and severe in 4/39 (10.3%).

The duration of symptoms persistence in the mothers before delivery affected the vertical transmission, which was concordant with the neonates (80%) infectivity, where the mothers experienced symptoms for more than 10 days before admission (chart 3).

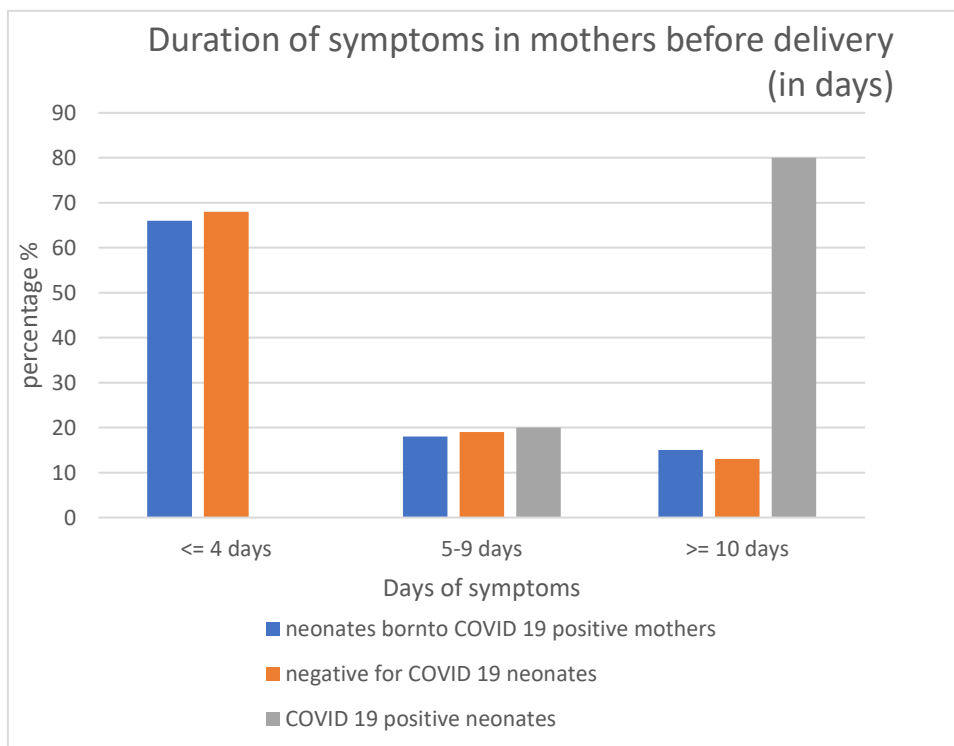


Chart 2: Severity of COVID infection in the mother and its relation with neonatal infection.

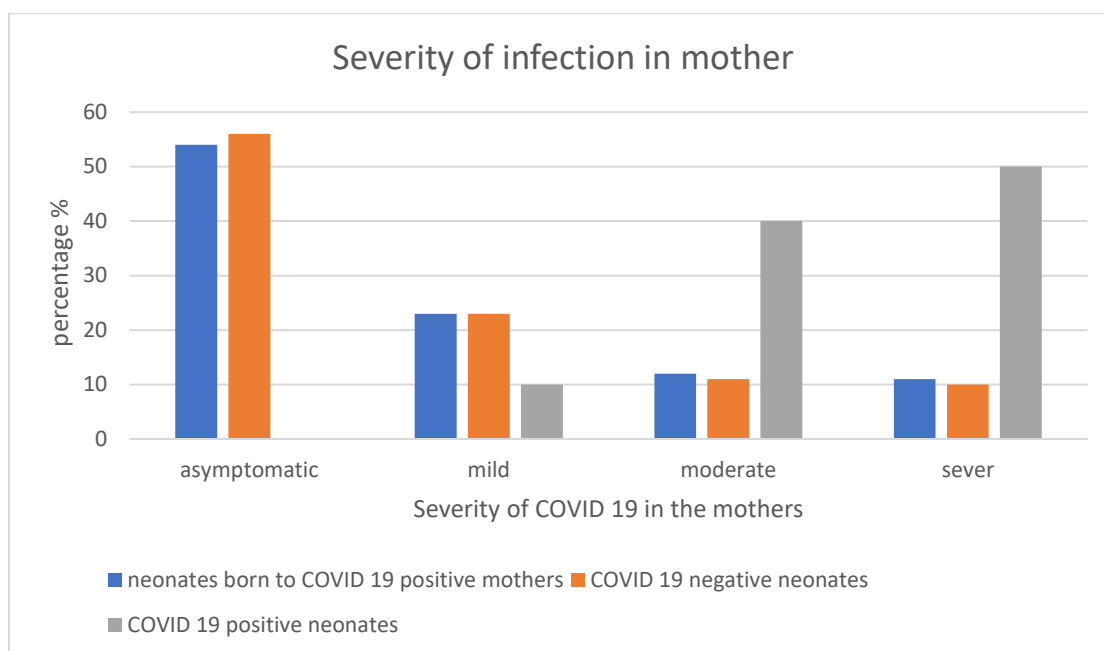


Chart 3: duration of symptoms of COVID 19 in the mothers before delivery and its relation to COVID 19 in neonates.

DISCUSSION

The first reported case of COVID-19 in Jordan was in March 2020. Four waves of the disease had followed. By the time of writing of this study, the total number of cases in Jordan had reached 1,141,048 according to the Jordanian Ministry of Health [9]. The vaccination program for the SARS-COV-2 vaccine started in January 2021 with priority for the elderly and those with co-morbidities. This explained why none of the pregnant ladies in our study were vaccinated against COVID-19. Further, the uncertainty about the safety of the vaccine for pregnant women at the beginning of the vaccination program had a major impact on the avoidance of vaccination by pregnant ladies.

Vertical transmission is defined as the transmission of the infectious pathogen from the mother to the fetus during the antepartum and intrapartum periods, or to the neonate during the postpartum period via the placenta *in utero*, body fluid contact during childbirth, or through direct contact owing to breastfeeding after birth [10]. Severe acute respiratory syndrome coronavirus 2 viral RNA testing in neonatal cord blood was positive in 2.9% of the samples (1/34), 7.7% of the placenta samples (2/26), 0% of the amniotic fluid (0/51), 0% of the urine samples (0/17), and 9.7% of the fecal or rectal swabs (3/31) [10].

In our study, we investigate SARS-COV-2 transmission from the mother to neonate antepartum and intrapartum, but not postpartum, as we separate the neonate from the mother after delivery, and visitors were

forbidden from entering the Unit except the parents if they have PCR negative certification for SARS-COV-2. The neonates were given formula milk during hospitalization, but the mothers were encouraged to breastfeed after discharge, as most of the studies demonstrate the absence of SARS-CoV-2 in breast milk [11-13]. A strict infection control policy was applied in the unit. We included in the study only neonates positive for SARS-COV-2 infection during hospitalization and not those who return to the hospital after discharge.

The vertical transmission of SARS-COV-2 infection was 2.8%, which is in line with most of the published studies [14]. In a large meta-analysis study, 936 tested neonates were included. It indicated a pooled proportion of 3.2% (95% confidence interval) for vertical transmission [10]. Another meta-analysis study which included 405 neonates delivered to SARS-COV-2-positive women showed that the pooled incidence of vertical transmission was 1.6% [15]. This can be explained by the finding that placental cells co-expressing ACE2 and TMPRSS2 proteins, required for SARS-CoV-2 viral cell entry, are rare [16]. Data from the National Registry for Surveillance and Epidemiology of Perinatal COVID-19 infection (NPC-19) showed that the rate was 1.9%, as they included 2287 neonates delivered to COVID-19-positive mothers, of whom 44 neonates were positive for COVID-19 [17].

E. Mullins et al. [18] report the outcome of infected pregnancies (4005 women) from a collaboration formed early during the pandemic between the investigators of two registries: the UK and Global Pregnancy and Neonatal Outcomes in COVID-19 (PAN-COVID) study and the American Academy of Pediatrics (AAP) Section on Neonatal-Perinatal Medicine (SONPM) National Perinatal COVID-19 Registry. They found that cesarean delivery occurred in 47.9%, and 38.3% of the cases, respectively. The high rate of cesarean section in our study during the first wave of COVID-19 (from October to late December 2020) was due to the policy of hospitals to perform PCR for COVID-19 for all patients before entering the theater, so the patients found positive for COVID-19 were transferred to our hospital for cesarean delivery. During the third and fourth wave of COVID-19 infection, a high percentage of cesarean sections were mainly indicated due to moderate to severe respiratory infection, based on the need for oxygen and respiratory support and chest-computed tomography (CT) scan in pregnant women, as the policy was to terminate the pregnancy to improve the respiratory status of the mother. Despite an increase in the rate of cesarean sections, the mode of delivery of pregnant women infected with SARS-CoV-2 could not increase or decrease the risk of infection for newborns [14].

The gender of the neonates and the presence of prolonged rupture of the membrane did not affect the rate of vertical transmission. Preterm deliveries (<37 weeks of gestational age) were 28.5% of the total deliveries in our study, which is considered high, compared to other studies [18-22], who showed an increased rate of premature deliveries; however, in our study, it is higher than reported, as most of the mothers who were symptomatic and needed respiratory support were transferred to our hospital for the benefit of the mother. In the third and fourth COVID-19 waves, the most common cause of premature deliveries was poor maternal respiratory status. We found that prematurity is a risk factor for increase vertical transmission in our study this is due to abundance of angiotensin-converting protein 2 (ACE-2) receptors in the placenta in early gestation which is associated with increase in rate of transmission in earlier gestation and they diminish across gestational age [23].

There was no difference in the mean maternal age of neonates positive for COVID-19 and those who were negative, but we found positive relationship between the duration of infection in the mother and the vertical transmission, where a duration of > 10 days was associated with an increasing rate of vertical transmission.

The severity of the maternal disease and its relationship to the vertical transmission of SARS-CoV-2 is a debatable issue. Some studies found no correlation [24-25], but in our study the severity of the disease and the

duration of symptoms before the delivery were the most significant risk factors for vertical transmission. This could be explained by the fact that mothers presenting with severe COVID-19 symptoms may have higher SARS-CoV-2 viral loads [26], which could make them more prone to transmit the infection to their neonates.

The vertical transmission of COVID-19 in the third trimester of pregnancy seems possible but occurs at a very low frequency (2.8%). The risk increased with prematurity, severity of infection in the mothers, long duration of symptoms before delivery and lymphopenia during the infection of the. further studies are needed to establish the effect on neonates.

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