IS VERTICAL TRANSMISSION OF SARS-CoV-2 INFECTION POSSIBLE IN PRETERM TRIPLET PREGNANCY? A CASE SERIES

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Abstract: There is limited data regarding the vertical transmission (VT) of severe acute respiratory syndrome-coronavirus-2 infection. We report the first case of VT in preterm triplet pregnancy, with all triplets positive for severe acute respiratory syndrome-coronavirus-2 at 20 hours and day 5 of life. This report reiterates the need for an expedited formulation of a simple, standardized, and reproducible international case definition and classification for VT.

Key Words: COVID-19 pregnancy, intrauterine infection, neonates, SARS-CoV-2, vertical transmission

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The novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), is one of the worst pandemics the human race has ever experienced. COVID-19 infection affects all age groups, including newborn infants and pregnant women. Most of the SARS-CoV-2 infections in pregnancy are mild, occur in the third trimester, and 1% develop severe disease.[1] COVID-19 infection in the third trimester of pregnancy may be associated with premature rupture of membranes and preterm delivery.[2] The precise incidence of vertical transmission (VT) of SARS-CoV-2 infection is unknown. A systemic review of 18 studies comprising 114 pregnant women with COVID-19 infection demonstrated a lack of VT.[3] A recent study, contrary to the previous one, revealed that the human placenta minimally expresses the angiotensin-converting enzyme 2 receptors (aid in viral cell attachment), and also for an enzyme transmembrane serine protease known as type II (TMPRSS2) (essential for viral replication); this may explain the low occurrence of VT.[4] There is limited convincing data regarding the VT of SARS-CoV-2 and systematic analysis of published studies reported only 28 cases of possible VT from 665 COVID-19 positive mothers.[5] We report the first case of VT in preterm trichorionic triamniotic triplet pregnancy, with all triplets, tested positive for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (RT-PCR) from nasopharyngeal and throat swabs, taken at 20 hours and day 5 of life. The mother's timeline of infection indicates that COVID-19 possibly triggered preterm labor.

CASE SERIES

Thirty-year-old Omani primigravida woman conceived by in vitro fertilization with trichorionic triamniotic triplets. During this pregnancy, she developed gestational thrombocytopenia and was treated for hypothyroidism, with thyroxin 50 mcg once daily. Her serology screening was negative for HIV, Hepatitis B, and syphilis. Her high vaginal swab was positive for group B Streptococcus infection and received 3 doses of intravenous cefazolin. She was on regular antenatal follow-up, and her last antenatal scan done at 31 weeks gestation was reported as normal.

In July 2020, at 32 weeks and 5 days gestational age, she presented to the local health center with high-grade fever and flu-like symptoms. She had a history of direct contact with her husband and her brother, both of whom were diagnosed with COVID-19 4 days ago. RT-PCR of her nasopharyngeal swab was positive for SARS-CoV-2 infection. She received 2 doses of dexamethasone for early preterm labor. She presented the following day to the delivery ward at Khoula Hospital, Muscat, in active labor. She underwent emergency cesarean section for malpresentation of the triplets: triplet 1 transverse, triplet 2 breech, and triplet 3 breech. The cesarean section was performed under spinal anesthesia in a negative pressure operation theater, with all airborne, droplet, and contact precautions. The membranes were ruptured for all the triplets at operation. The neonatal team attended the delivery, and resuscitation was carried out as per the institutional and international infection prevention and control guidelines. The triplets were separated from the mother immediately after cutting the cord and were taken into a separate isolation room.

Triplet 1 was a baby boy, born vigorous, with birth weight (BW) of 1910 g (64th centile) and did not require any resuscitation at birth. Triplet 2 was a baby girl, born vigorous, with BW 1390 g (13th centile), and required nasal continuous positive airway pressure at birth. Triplet 3 was a baby boy, born vigorous, with BW of 1630 g (31st centile). The Apgar scores for all triplets were 8 and 9 at 1 and 5 minutes. The umbilical cord was clamped immediately, and no skin to skin contact given for all triplets. The babies were transported in closed incubators and admitted to the neonatal intensive care unit (NICU) in a negative pressure isolation room, after observing the recommended COVID-19-specific precautions. On admission to NICU, triplet 2 required nasal intermittent positive ventilation and got weaned to nasal continuous positive airway pressure at 8 hours. She came off from respiratory support on day 3 of life. Triplets 1 and 3 did not require any respiratory support. The nasopharyngeal swabs were positive for all triplets, by RT-PCR for SARS-CoV-2 at 20 hours and day 5 of life. From day 2 of life, all triplets were fed exclusive preterm formula with good tolerance. All the triplets showed no temperature instability or COVID-19-related symptoms and were discharged home after 3 weeks of an uneventful stay. The placental examination of 1 of our triplets showed evidence of chorioamnionitis with fibrin deposition, but we were unable to perform the SARS-CoV-2 specific advanced investigations. Table 1 outlines the laboratory test results of all triplets. Neonatal follow-up at 4 weeks of age revealed normal growth and development.

DISCUSSION

All 3 preterm infants born to the mother with acute COVID-19 infection showed evidence of SARS-CoV-2 in nasopharyngeal swabs by RT-PCR at 20 hours of age and remained positive on day 5. It indicates the possibility of either (a) transplacental VT, (b) colonization of nasopharynx by swallowed infected amniotic fluid in utero or during cesarean section, (c) postnatal acquisition, or (d) a false-positive test. The probability of postnatal (nosocomial) transmission is extremely low, due to the strict compliance with COVID-19 infection prevention protocols during cesarean section and in the NICU isolation room. After delivery, the babies were

TABLE 1. Laboratory Test Results

Number	Gender	Weight (g)	WBC (10^9/L)	Lymph (10^9/L)	Hb (g/dL)	Platelet (10^9/L)	ALT (IU/L)	RT-PCR (day 1)	RT-PCR (day 5)
Triplet 1	Male	1910	6.7	3.2	16.5	333	5.1	Positive	Positive
Triplet 2	Female	1390	7.11	3.1	15.3	192	5.5	Positive	Positive
Triplet 3	Male	1630	7.16	3.13	12.9	271	6.4	Positive	Positive

ALT indicates alanine aminotransferase; g, gram; Hb, hemoglobin; IU, international units; L, liter; RT-PCR, reverse transcriptase-polymerase chain reaction; WBC, white blood cell.

separated immediately from their mother, without skin to skin contact, and fed exclusive preterm formula. Moreover, all 3 preterm infants acquiring a positive test twice at the same time almost rules out the possibility of a postnatal or nosocomial acquisition. The chances of false-positive tests are low in a scenario of high pretest probability (COVID-19 positive mother). Besides, for a test with high specificity (95%) but moderate sensitivity (70%), a negative test would have been more misleading. Evidence of SARS-CoV-2 in amniotic fluid, placenta, or virus-specific antibodies in babies would have confirmed VT. Unfortunately, we could not do these tests as our expert thought it would not change the patient management and will be a burden on already compromised resources during the pandemic.

Our triplets were born preterm at 32 weeks and 5 days of gestational age. The average gestational age of delivery for triplet pregnancy is 33.0±2.7 weeks, and virtually all deliver before 37 weeks.[6] The timeline of infection in our triplets' mother indicates that she was exposed to COVID-19 positive contacts 4 days before the advent of her symptoms and delivered within 48 hours of her onset of symptoms, suggesting a possible role COVID-19 infection in triggering preterm labor. In a prospective study from the United Kingdom of 427 women confirmed positive for COVID-19, 27% delivered preterm.[7] However, 1 systematic review and metaanalysis showed no significant association between COVID-19 infection and preterm delivery.[8]

Since SARS-CoV-2 is a new infection, the essential diagnostic criteria, biologic mechanisms, and clinic implications of vertical versus horizontal transmission in neonates are not well defined. Recently, Blumberg et al[9] and Shah et al[10] defined and classified the VT of SARS-CoV-2 infection. According to Blumberg et al classification, our triplet babies qualify as confirmed "vertical intrauterine transmitted SARS-CoV-2 infection." However, as per Shah et al, in the absence of evidence of virus from the placenta, amniotic fluid, or neonatal blood, our triplets cannot be classified as confirmed intrauterine transmission. Since viremia with SARS-CoV-2 infection is very rare, we agree with Blumberg et al definition of VT. Evidence of the virus from the amniotic or neonatal blood should be optional if the virus is detected in the nasopharynx in 2 samples taken after birth, each 24 hours apart. In 28 reported neonates of possible or confirmed VT, only 1 neonate developed SARS-CoV-2 viremia.[5] We speculate that the portal of entry of SARS-CoV-2 in the fetus is primarily via the respiratory tract, by swallowed infected amniotic fluid and rarely transplacental via an umbilical vein.

Both these classifications are complex and not validated in different clinic settings. The timeline and types of biologic samples essential to establish intrauterine VT are also different. There is an urgent need to standardize the definition of "vertical transmission" for better case detection, communication, and prognosis of SARS-CoV-2 infection in pregnancy and neonates. Most of the reported neonatal cases were asymptomatic,[5] except one which presented with neurologic manifestation following neonatal viremia with neuroimaging showing vascular inflammation similar to some of the adult SARS-CoV-2 infections.[11] Since most of these cases were asymptomatic, we assume that the need and urgency for taking samples at delivery or in the first few hours of life may be lacking, resulting in under investigations and underreporting of VT.

CONCLUSIONS

Our preterm triplets and the literature review demonstrate that VT of SARS-CoV-2 infection is possible, rare, and often asymptomatic. We reiterate the necessity for the collection of appropriate samples, at prescribed times, to differentiate in utero VT from peri or postnatal transmission. There is an urgent need for an expedited formulation of a simple, standardized, and reproducible international case definition and classification of VT.

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