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. COVID-19 infection in the third trimester of pregnancy may be associated with premature rupture of membranes and preterm delivery. 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. A recent study, contrary to the previous one, revealed that the human placenta minimally expresses the angiotsensin-converting enzyme 2 (ACE2) 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. There is limited convincing data regarding the vertical transmission (VT) of SARS-CoV-2 and systematic analysis of published studies reported only 28 cases of possible VT from 665 COVID-19 positive mothers. We report the first case of VT in preterm trichorionic trisomic 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 trisomic 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 Khouda 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 of 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 chorionic villi 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
separated immediately from their mother, without skin to skin con-
tact, 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 man-
agement 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 metaanaly-
sis showed no significant association between COVID-19 infection
and preterm delivery.8

Since SARS-CoV-2 is a new infection, the essential diag-
nostic criteria, biologic mechanisms, and clinic implications of
vertical versus horizontal transmission in neonates are not well
defined. Recently, Blumberg et al9 and Shah et al10 defined and clas-
sified the VT of SARS-CoV-2 infection. According to Blumberg et
al classification, our triplet babies qualify as confirmed “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,9 except one which pre-
sented 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 tak-
sing samples at delivery or in the first few hours of life may be lack-
ing, resulting in under investigations and underreporting of VT.

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 reproduc-
ible international case definition and classification of VT.

CONCLUSIONS

Our preterm triplets and the literature review demonstrate
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definition for SARS-CoV-2 infection in pregnant women, fetuses, and neo-

TABLE 1. Laboratory Test Results

<table>
<thead>
<tr>
<th>Number</th>
<th>Gender</th>
<th>Weight (g)</th>
<th>WBC (10⁹/L)</th>
<th>Lymph (10⁹/L)</th>
<th>Hb (g/dL)</th>
<th>Platelet (10⁹/L)</th>
<th>ALT (IU/L)</th>
<th>RT-PCR (day 1)</th>
<th>RT-PCR (day 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triplet 1</td>
<td>Male</td>
<td>1910</td>
<td>6.7</td>
<td>3.2</td>
<td>16.5</td>
<td>333</td>
<td>5.1</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Triplet 2</td>
<td>Female</td>
<td>1390</td>
<td>7.11</td>
<td>3.1</td>
<td>15.3</td>
<td>192</td>
<td>5.5</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Triplet 3</td>
<td>Male</td>
<td>1630</td>
<td>7.16</td>
<td>3.13</td>
<td>12.9</td>
<td>271</td>
<td>6.4</td>
<td>Positive</td>
<td>Positive</td>
</tr>
</tbody>
</table>

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