Article published online: 2024-02-18

Likely Vertical Transmission of Neonatal SARS CoV-2 Infection

Andre A. Robinson, MD[1] Samantha Feder, MD[2] Sushma Krishna, MD[3] Lois Brustman, MD[4]

[1] Department of Obstetrics and Gynecology, Mount Sinai West, New York, New York
[2] Department of Obstetrics and Gynecology, NewYork-Presbyterian/Weill Cornell Medical Center, New York, New York
[3] Department of Neonatology, Mount Sinai West, New York, New York
[4] Department of Maternal-Fetal Medicine, Mount Sinai West, New York, New York

Address for correspondence Andre Robinson, MD, Department of Obstetrics and Gynecology, Mount Sinai West, 1000 10th Avenue, New York, NY 10019 (e-mail: andrealbertrobinson@gmail.com).

AJP Rep 2024;14:e62–e65.

Abstract

Maternal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can affect placental function, but the possibility of intrauterine transmission has been debated. Several authors have published inclusion criteria for vertical transmission, but few reports exist that are able to meet the suggested requirements. Despite the fact that the majority of fetuses born to infected mothers do well, others become critically ill. We present a case of likely intrauterine transmission of a neonate born to a mother who was recently symptomatic with a positive SARS CoV-2 polymerase chain reaction (PCR). The parturient complained of decreased fetal movement and presented at $31^{2/7}$ weeks' gestation with a biophysical profile score of 2/10 and required an emergency cesarean delivery. The neonate went on to develop severe leukopenia with signs of sepsis with a positive SARS CoV-2 PCR on day 4 of life and an otherwise pan-negative workup. Meeting criteria for transplacental transmission requires timely collection of several diagnostic studies that are not standard of care. Further research is needed to support the notion that intrauterine/transplacental infection is possible. Collection swabs should be obtained soon after delivery to help diagnose neonatal infection because early diagnosis is crucial to help identify opportunities for intervention.

Keywords
- vertical
- transmission
- CoV-2
- SARS
- COVID-19
- neonatal
- sepsis
- thrombocytopenia
- infection

A year has passed since the emergence of the coronavirus disease 2019 (COVID-19). Scientists across the world have detailed the infectious properties of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulting in global policy change on how to reduce the spread of the disease. However, there remains a poor understanding of neonatal infection, and intrauterine transmission was initially presumed to be unlikely. More recently, objective findings such as fetal swabs and placental immunohistochemistry have been described to support the idea that congenital infection is possible. The motivation for providing evidence to support congenital infection was lacking because it was thought to be unlikely[1,2] and the majority of fetuses born to infected mothers do well.[3,4]

Maternal SARS-CoV-2 infection has the potential to impact a pregnancy at any gestational age. Even in the absence of fetal infection, fetal and maternal malperfusion at the level of the placenta has been demonstrated.[5,6] When it comes to

received
May 20, 2020
accepted
October 22, 2023

DOI https://doi.org/10.1055/s-0044-1779030.
ISSN 2157-6998.

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

infection in the third trimester, there is conflicting evidence on the potential implications for the fetus and the impact on the neonate.

One early study in Wuhan, China was the first to investigate fetal outcomes of nine symptomatic women who tested positive for SARS-CoV-2 in the third trimester. The authors found no evidence of intrauterine infection based on amniotic fluid, cord blood, and neonatal throat swab samples.[7]

Since then, there have been conflicting opinions about whether intrauterine, or transplacental, infection is likely. Research is limited given that infant infection is rare, approximately 4% as quoted in one systematic review,[8] and screening for fetal infection at the time of birth is not a current standard of care. It is important to note that infant infection includes postnatal infection and, in fact, none of 28 neonates who tested positive met criteria for intrauterine infection criteria described by Shah et al.[9] This guideline published in May 2020 was written to help determine congenital versus intrapartum versus postnatal infection. Huntley et al[10] defined vertical transmission with a positive neonatal nasal swab immediately after birth or a positive immunoglobulin M result for SARS-CoV-2 infection in cord blood. Other authors have proposed confirmation of intrauterine transmission based on placental pathology,[11] but no consensus has been reached.

By using previously published criteria such as by Shah et al, or their own, several authors have reported transplacental transmission.[12–15] Fetal outcomes vary from asymptomatic to critically ill. In a small case series of presumed postnatal infection in eight infants who tested positive for SARS-CoV-2, the most common symptoms were fever, cough, and coryza.[16] Interestingly, four out of eight of the infants were treated for suspected sepsis with broad-spectrum antibiotics despite negative blood cultures, which suggests critical illness.

We present, what we feel to be, one of the first cases of neonatal sepsis in a neonate who tested positive for SARS-CoV-2 on day 4 of life born to a mother who was also recently infected. The possibility of intrauterine infection cannot be ruled out in this case based on maternal symptoms and fetal outcome in the absence of other etiologies, despite our lack of placental polymerase chain reaction (PCR) or immunohistochemistry.

Case Report

A 36-year-old nulliparous woman without significant medical history was admitted for fetal monitoring at $31^{6/7}$ weeks' gestation after complaining of decreased fetal movement for 24 hours. She reported a history of positive COVID-19 testing by nasopharyngeal swab at an outside urgent care 9 days prior, after a previous known exposure. Symptoms included low-grade fever, cough, headache, and chills which were resolved 3 days prior to presentation to the hospital.

A biophysical profile (BPP) was performed, 2/10 (amniotic fluid volume: 2, breathing: 0, movement: 0, tone: 0, nonstress test (NST): 0), and decision was made to proceed with an emergency cesarean delivery under general anesthesia for new-onset thrombocytopenia. Maternal complete blood count (CBC) prior to delivery was significant for leukopenia with a white blood cell (WBC) count of 5 K/μL and thrombocytopenia with a platelet (Plt) count of 55 K/μL. Her previous WBC and Plt counts 1 month prior had been 7.6 and 161 K/μL, respectively. Cefazolin 2 g was administered prior to delivery; no steroid or magnesium was administered.

Membranes were ruptured at delivery and amniotic fluid was meconium stained. A female infant was delivered breech weighing 1,485 g (appropriate for gestational age at 35%tile). The infant received positive pressure ventilation in the delivery room with good response in heart rate and respiratory effort. Apgar scores were 4 and 7 at 1 and 5 minutes, respectively. Venous cord blood gas showed a pH of 6.96 with a base deficit of 20.8 mEq/L. Newborn arterial blood gas at 1 hour of life showed a pH of 6.98, glucose of 24 mg/dL, and lactate of 17.5 mmol/L.

The infant was transported to the neonatal intensive care unit and admitted into a negative pressure isolation room. All personnel that entered were required to wear complete personal protective equipment (PPE) including N95 mask and face shield. The infant was placed on nasal continuous positive airway pressure, requiring 45% fraction of inspired oxygen (FiO_2) with signs of significant clinical respiratory distress including tachypnea and retractions, but without hemodynamic instability. The physical examination was otherwise unremarkable with no hemodynamic instability. For suspected respiratory distress syndrome (RDS), the infant received surfactant with good response and was weaned to minimal oxygen 25% FiO_2, with marked improvement in her respiratory effort. Subsequent chest X-ray showed mild RDS. Blood cultures and CBC were sent, and the infant was started on ampicillin/gentamicin per standard rule out sepsis protocol.

Umbilical catheters were urgently placed and repeat arterial blood gas showed improvement in metabolic acidosis 7.19/25/135/-17, lactate 13.3. Blood gasses were trended every 3 to 4 hours thereafter and showed resolution of acidosis by 18 hours of life (pH 7.40/28/75/-6, lactate 3.6). Basic metabolic panel and liver function tests did not reveal kidney or liver injury.

The neonate's initial CBC showed mild thrombocytopenia 140 K/μL, normal WBC 20 K/μL, and hematocrit (Hct) 56.8%. However, WBC and Plt counts declined significantly and by 40 hours of life, the WBC was 2.1 K/μL and Plt count 20 K/μL. Intravenous immunoglobulin (IVIG) was administered for possible autoimmune thrombocytopenia based on the history of maternal thrombocytopenia. However, thrombocytopenia worsened to 15 K/μL thereafter. The infant received a Plt transfusion of 20 mL/kg. Ultrasound of fetal head showed bilateral germinal matrix hemorrhage. Plt count improved after transfusion to 221 K/μL and rapidly declined again within 48 hours to 43 K/μL for which the infant received a second Plt transfusion of 20 mL/kg. The Plt level again declined to a nadir of 73, but rose to more than 400 prior to discharge without a third transfusion.

There was an underlying suspicion of fetal infection of SARS CoV-2 based on fetal presentation and maternal

underlying history. The infant was treated with a 7-day course of antibiotics based on a suspicion of neonatal sepsis of leukopenia and thrombocytopenia despite normal C-reactive protein and negative blood cultures. Nasopharyngeal swab for SARS-CoV-2 reverse transcription (RT)-PCR was sent on day of life (DOL) 4 and resulted as positive with a cycle threshold value of 16.37. PCR testing of other viruses were negative including salivary cytomegalovirus and blood testing for herpes simplex virus types 1 and 2, toxoplasma gondii, parvovirus B19, and enterovirus. On DOL 19, the neonate's COVID-19 antibody titer was elevated 1:2,880.

The infant was weaned off respiratory support by 11 days of life and discharged home at 26 days of life.

Discussion

There are two interesting clinical scenarios that may be related to maternal SARS-CoV-2 infection. One being the in utero events that required immediate delivery and the other being neonatal sepsis that cannot be explained by other etiologies. The perception of decreased fetal movement, low BPP, and eventual fetal bradycardia was initially thought to be secondary to maternal illness, given the proximity of her positive PCR test. Placental damage is well documented in the literature and placental vasculopathies such as intervillous fibrin depositions and ischemic necrosis of the villi may compromise fetal perfusion.[14,17] However, these events may in fact be explained by fetal illness if we accept that vertical transmission is possible.

Given the limited evidence to support intrauterine transmission of SARS-CoV-2 from mother to infant, classification systems have been proposed. One published guideline considers timing of viral PCR by nasopharyngeal swab, neonatal blood or cord blood, and amniotic fluid to help distinguish congenital, intrapartum, or postpartum infections of the neonate.[9] Our ability to meet criteria for a confirmed or probable case of congenital infection is limited by two factors. First, the nasopharyngeal swab was collected on DOL 4 and neither the placenta nor amniotic fluid was tested. Despite the absence of viral PCR confirmation within 12 hours of birth, we suspect that the clinical presentation and laboratory abnormalities seen may be best explained by vertical transmission SARS-CoV-2 from mother to infant.

Out of an abundance of safety precautions, several hospital policies are in place to protect the neonate from infection. In this instance, we feel that the likelihood of postpartum infection is unlikely given that all staff wore full PPE including N95 masks during delivery and while caring for the neonate in a negative pressure isolation room. Furthermore, the mother was kept away from the infant until DOL 3, which was 14 days after her positive PCR test.

Laboratory abnormalities including leukopenia and thrombocytopenia have been observed for patients infected with COVID-19. A study of 1,099 patients showed that 82.1% had lymphopenia, 36.2% had thrombocytopenia, and 33.7% had leukopenia.[18] Proposed mechanisms for thrombocytopenia include increased autoantibodies and destruction of Plts as well as decreased primary Plt production from hematopoietic dysfunction.[19] In this case, these explanations as they relate to SARS-CoV-2 infection should be considered and neonatal thrombocytopenia may not be explained by neonatal alloimmune thrombocytopenia or other viruses given the negative workup and unusual precipitous drop on day 1 of life. The diagnosis of autoimmune thrombocytopenia was considered, but less favored given that administration of IVIG failed to increase Plt levels. Furthermore, real-time RT-PCR cycle threshold (Ct) values represent the number of amplification cycles required for the target gene to exceed a threshold detectable level. The low cycle threshold value of 16.37 likely indicates true infant infection as opposed to residual maternal viral "colonization" as has been demonstrated in patients with COVID-19.[20]

Transmission from mother to infant remains a debated concept. Classification systems to determine likelihood of infection are helpful in understanding pathological processes, but clinical assessments should guide treatment. There is still little known about the effects of COVID-19 on intrauterine development and how these insults present on routine fetal monitoring. There is no doubt that COVID-19 has implications for the mother, fetus, and neonate, but further research is needed. This case report supports the notion of vertical transmission, though it cannot be confirmed based on currently published requirements. We feel that recognizing the potential for vertical transmission is important because anticipating clinical manifestations in the neonate are warranted. Maintaining a high index of suspicion for dangerous laboratory abnormalities in the neonate with a confirmed positive mother, for example, will allow for prompt treatment, as seen in this case.

Conflict of Interest
None declared.

References

1 Edlow AG, Li JZ, Collier AY, et al. Assessment of maternal and neonatal SARS-CoV-2 viral load, transplacental antibody transfer, and placental pathology in pregnancies during the COVID-19 pandemic. JAMA Netw Open 2020;3(12):e2030455
2 Diriba K, Awulachew E, Getu E. The effect of coronavirus infection (SARS-CoV-2, MERS-CoV, and SARS-CoV) during pregnancy and the possibility of vertical maternal-fetal transmission: a systematic review and meta-analysis. Eur J Med Res 2020;25(01):39
3 Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr 2020;9 (01):51–60
4 Zeng L, Xia S, Yuan W, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. JAMA Pediatr 2020;174(07):722–725
5 Komine-Aizawa S, Takada K, Hayakawa S. Placental barrier against COVID-19. Placenta 2020;99:45–49
6 Pulinx B, Kieffer D, Michiels I, et al. Vertical transmission of SARS-CoV-2 infection and preterm birth. Eur J Clin Microbiol Infect Dis 2020;39(12):2441–2445
7 Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020;395(10226):809–815
8 Walker KF, O'Donoghue K, Grace N, et al. Maternal transmission of SARS-COV-2 to the neonate, and possible routes for such

transmission: a systematic review and critical analysis. BJOG 2020;127(11):1324–1336
9 Shah PS, Diambomba Y, Acharya G, Morris SK, Bitnun A. Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates. Acta Obstet Gynecol Scand 2020;99(05):565–568
10 Huntley BJF, Huntley ES, Di Mascio D, et al. Rates of Maternal and Perinatal Mortality and Vertical Transmission in Pregnancies Complicated by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Co-V-2) Infection: A Systematic Review. Obstet Gynecol 2020;136(02):303–312
11 Smithgall MC, Liu-Jarin X, Hamele-Bena D, et al. Third-trimester placentas of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive women: histomorphology, including viral immunohistochemistry and in-situ hybridization. Histopathology 2020;77(06):994–999
12 Vivanti AJ, Vauloup-Fellous C, Prevot S, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun 2020;11(01):3572
13 Facchetti F, Bugatti M, Drera E, et al. SARS-CoV2 vertical transmission with adverse effects on the newborn revealed through integrated immunohistochemical, electron microscopy and molecular analyses of placenta. EBioMedicine 2020;59:102951
14 Hecht JL, Quade B, Deshpande V, et al. SARS-CoV-2 can infect the placenta and is not associated with specific placental histopathology: a series of 19 placentas from COVID-19-positive mothers. Mod Pathol 2020;33(11):2092–2103
15 Lamouroux A, Attie-Bitach T, Martinovic J, Leruez-Ville M, Ville Y. Evidence for and against vertical transmission for severe acute respiratory syndrome coronavirus 2. Am J Obstet Gynecol 2020;223(01):91.e1–91.e4
16 Ng KF, Bandi S, Bird PW, Wei-Tze Tang J. COVID-19 in neonates and infants: progression and recovery. Pediatr Infect Dis J 2020;39(07):e140–e142
17 Sharps MC, Hayes DJL, Lee S, et al. A structured review of placental morphology and histopathological lesions associated with SARS-CoV-2 infection. Placenta 2020;101:13–29
18 Guan W-j, Ni Z-y, Hu Y, et al. Clinical characteristics of 2019 novel coronavirus infection in China. N Engl J Med 2020;382:1708–1720
19 Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol 2020;99(06):1205–1208
20 Rao SN, Manissero D, Steele VR, Pareja J. A systematic review of the clinical utility of cycle threshold values in the context of COVID-19. Infect Dis Ther 2020;9(03):573–586