Fetal Inflammatory Response Syndrome Associated With Maternal SARS-CoV-2 Infection

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abstract

Amid the coronavirus disease 2019 pandemic, uncertainty exists about the potential for vertical transmission from mothers infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to the fetus in utero. In this case report, we aim to demonstrate the occurrence of a fetal inflammatory response syndrome associated with maternal SARS-CoV-2 infection resulting in neonatal morbidity. In this report we describe an infant of a SARS-CoV-2–positive mother born prematurely with late-onset fever, thrombocytopenia, and elevated levels of inflammatory markers, all of which are consistent with a systemic inflammatory response. The neonate was tested for SARS-CoV-2 by using 2 nasopharyngeal swabs 24 hours apart, and results of both were negative. The result of a full workup for additional infectious pathogens was also negative. Although initially in critical condition in the perinatal period, the infant recovered completely before discharge. We hypothesize that this systemic inflammation occurred in response to maternal viral infection in the absence of vertical transmission of the virus. During the coronavirus disease 2019 pandemic, it will be important to consider the virus as a nidus for a fetal inflammatory response syndrome and resulting morbidity, even in the setting of a negative SARS-CoV-2 testing result in the infant.

Coronavirus disease 2019 (COVID-19), the disease associated with the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), primarily impacts those with comorbidities and underlying risk factors, such as pregnancy. However, limited data exist regarding the fetal morbidity and mortality associated with SARS-CoV-2 infection during pregnancy.[1–3] By using data from previous novel coronavirus pandemics, such as severe acute respiratory syndrome and Middle East respiratory syndrome, in addition to data from the current COVID-19 pandemic, a pattern of higher rates of miscarriage, preterm birth, preeclampsia, and perinatal death has been observed in women infected with one of these novel coronaviruses during pregnancy.[1,2]

Recent meta-analyses indicate that the incidence of preterm birth at <37 weeks' gestational age (WGA) is increased in women infected with SARS-CoV-2.[4,5] Additionally, a higher rate of perinatal fetal distress and admission to the NICU has been identified in neonates born to mothers infected with SARS-CoV-2.[4,6] Despite apparent perinatal complications, the majority of these neonates are negative for SARS-CoV-2 infection.[7–9] According to a recent study, the placenta has low expression of canonical receptors necessary for viral entry, which may explain the rarity of vertical transmission of the virus.[10]

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Alternatively, the observed neonatal morbidity seems consistent with a fetal inflammatory response syndrome (FIRS) secondary to maternal viral infection, which has been described in the literature as a transient cause of perinatal morbidity.[11,12]

Here we present an infant born prematurely at 34 + 6/7 WGA with symptoms consistent with a FIRS, subsequent severe pulmonary hypertension, and respiratory failure, most likely attributed to maternal SARS-CoV-2 infection.

CASE PRESENTATION

A 32-year-old gravida 3, para 2 female patient presented at 34 + 6/7 WGA with vaginal bleeding in active labor. On presentation, she had symptoms of COVID-19 and subsequently tested positive for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR). Results of maternal infection–related laboratory tests were unremarkable: she was rubella immune, hepatitis B–negative, HIV antibody–negative, syphilis antibody–negative, and gonorrhea and/or chlamydia–negative. Group B streptococcal status was unknown, but the infant was delivered precipitously and therefore did not receive antibiotics. Because of maternal hypertension (which developed after delivery), a urine protein/creatinine ratio of 0.3, and a platelet count of 90 000 cells per μL, the mother was diagnosed with severe preeclampsia and was started on magnesium sulfate post partum. The placental pathology was remarkable for focal chronic infarcts.

At birth, the infant was hypotonic and had poor respiratory effort, which required positive pressure ventilation and subsequent intubation and mechanical ventilation. Initial arterial blood gases revealed significant metabolic acidosis (Table 1). Laboratory tests revealed mild leukocytosis, with a white blood cell count of 15 900 cells per μL, an immature/total neutrophil ratio of 0.19, and a normal platelet count of 220 000 cells per μL (Table 2). Blood cultures were obtained, and the infant was initiated on ampicillin and cefepime.

TABLE 1 Initial Arterial Blood Gases

	Birth	1 HOL	2 HOLs	3 HOLs
pH	7.00	7.07	7.14	7.17
$Pco_{2,\ mm\ Hg}$	38	35	32	30
$Po_{2,\ mm\ Hg}$	29	31	30	37
Bicarbonate, mmol/L	10	10.1	10.9	10.7
Base deficit, mmol/L	20	20	18	18
O_2 Sat, %	—	38	41	57

HOL, hour of life; O_2 Sat, oxygen saturation in serum; —, not available.

The neonate underwent a bedside echocardiogram at ~2 hours of life, which revealed suprasystemic pulmonary pressures concerning for severe pulmonary hypertension; inhaled nitric oxide (iNO) was initiated at 20 ppm. Blood pressures remained stable, and no vasoactive medications were required. The initial chest radiograph at 2 hours of life revealed diffuse bilateral granular opacities consistent with neonatal respiratory distress syndrome. He received 2 doses of surfactant, which resulted in improvement in his respiratory status; his metabolic acidosis resolved over the next 12 hours.

The neonate then became febrile (38.1°C) at 14 hours of life. Acyclovir was initiated after herpes simplex virus testing was obtained and was continued until results returned negative. Once the results of the neonatal blood cultures were negative for 48 hours, ampicillin was also discontinued. Because of the severity of the presentation, the neonate was treated with cefepime for 7 days. A respiratory viral panel was also obtained, and results were negative for all included pathogens (Table 3). A lumbar puncture was performed and revealed unremarkable cell counts and negative Gram-stain, culture, and RT-PCR results. Because of maternal SARS-CoV-2 exposure, the neonate was tested for SARS-CoV-2 per American Academy of Pediatrics (AAP) guidelines; all test results were negative.

A repeat complete blood cell count (CBC) with differential at 48 hours of life revealed a significant decline in the platelet count to 25 000 cells per μL requiring platelet transfusion. The CBC was also significant for severe lymphopenia and a significantly elevated immature/total neutrophil ratio of 0.69. The C-reactive protein (CRP) level obtained at that time was

TABLE 2 Serial CBC With Differentials

	Birth	24 HOLs	48 HOLs	72 HOLs	DOL 8
Hemoglobin, g/dL	14.4	15.2	17.1	14.3	14.5
Hematocrit, %	44.1	41.8	48.4	39.8	40.7
Platelet count, ×1000 cells per μL	220	189	25	127	98
White blood cell count, ×1000 cells per μL	15.9	9.0	4.9	3.1	9.0
Segmented neutrophils, %	42	88	29	45	42
Absolute neutrophils, ×1000 cells per μL	7.79	8.10	4.65	1.40	3.96
Absolute band count, ×1000 cells per μL	7	22	66	—	2
Lymphocytes, %	41	8	5	45	34
Monocytes, %	5	2	—	4	20
Eosinophils, %	—	—	—	6	2
CRP, mg/dL	—	—	—	6.78	0.69

DOL, day of life; HOL, hour of life; —, not applicable.

TABLE 3 Respiratory Viral Panel Components

Viruses or Bacteria Tested by RT-PCR	Viral Strains Tested
Adenovirus	—
Coronavirus strains	226E, HKU1, NL63, OC43
Metapneumovirus	—
Rhinovirus	—
Enterovirus	—
Influenza virus strains	A H1N1, A H1, A H3, B
Parainfluenza virus	1, 2, 3, 4
Respiratory syncytial virus	—
Bordetella pertussis	—
Chlamydia pneumoniae	—
Mycoplasma pneumoniae	—

—, not applicable.

also significantly elevated to 6.78 mg/dL. The CRP level continued to downtrend on subsequent laboratory tests and was within normal range (<1.0 mg/dL) by day of life 8 (Table 2).

A repeat echocardiogram on day of life 4 revealed appropriate left to right flow through a patent foramen ovale and near-normal right heart pressures; thus, iNO and mechanical ventilation were slowly weaned. The neonate was extubated to continuous positive airway pressure on day of life 5, iNO was discontinued on day of life 6, and he was weaned to room air by day of life 9. The neonate was tolerating full oral feeds on day of life 19 and was discharged from the hospital with his parents on day of life 22 with no follow-up required aside from standard prematurity care.

DISCUSSION

The literature published thus far indicates that SARS-CoV-2 is not acquired via vertical transmission.[6–8] However, there is a paucity of information regarding other potential fetal effects resulting from exposure to SARS-CoV-2 in utero. FIRS has been described in perinatal literature, originally reported in pregnancies complicated by preterm labor and preterm premature rupture of membranes.[11,12] Neonates affected by FIRS have multiorgan system involvement and higher morbidity after adjustment for gestational age, as seen in this case report. FIRS is defined by elevated interleukin 6 (IL-6) concentrations (>11 pg/mL) and is often associated with leukocytosis and neutrophilia.[11,13] Although IL-6 concentrations were not obtained in our case, the infant had significant neutrophilia, which peaked between 24 and 48 hours of life (Table 2). FIRS is also associated with increased fetal plasma concentrations of tumor necrosis factor receptors and CRP, the latter of which was seen in our patient as well (Table 2).[13]

Placental pathology often includes chorionic vasculitis or funisitis in neonates with FIRS.[14] Although funisitis was absent in our case, the chronic infarcts seen on placental pathology are consistent with vascular damage and may be attributed to inflammation secondary to maternal viral infection. The placental changes seen in our patient are consistent with those seen thus far in SARS-CoV-2–positive mothers and likely contributed to placental insufficiency and resulting perinatal depression.[10,14] However, the laboratory abnormalities seen in our patient are uncharacteristic of placental insufficiency. These findings, in addition to late-onset fever and multiorgan involvement, are more indicative of FIRS, which we hypothesize was secondary to exposure to maternal SARS-CoV-2 infection in utero and can occur in the absence of proven vertical transmission.

There is also increasing awareness of a SARS-CoV-2–related hyperinflammatory syndrome in pediatric patients, now termed multisystem inflammatory syndrome in children (MIS-C). Diagnostic criteria for MIS-C includes the following[15,16]:

- fever, laboratory evidence of inflammation, and evidence of clinically severe illness with multisystem (≥2) organ involvement requiring hospitalization;
- no alternative plausible diagnoses; and
- RT-PCR, serology, or antigen test positive for current or recent SARS-CoV-2 infection or COVID-19 exposure within the 4 weeks before onset of symptoms.

Many features of this syndrome overlap with the clinical course observed in our patient, and the neonate presented here meets the above diagnostic criteria. Our patient demonstrated fever despite receiving broad-spectrum antibiotics, significant neutrophilia, and elevated CRP levels during his illness course. He also exhibited respiratory compromise, pulmonary hypertension, and thrombocytopenia, indicative of multisystem organ involvement without a definitive microbial cause. Although our patient was SARS-CoV-2–negative by molecular assay, the significant degree of inflammation parallels that of MIS-C and likely occurred in response to maternal SARS-CoV-2 exposure in utero.

Literature on MIS-C thus far reveals a variety of hematologic abnormalities.[15,16] We suspect that the late-onset thrombocytopenia seen in this neonate was secondary to an inflammatory response associated with systemic exposure to maternal viral infection. Thrombocytopenia has been described in other cases of SARS-CoV-2 infection and may also explain the maternal

thrombocytopenia on presentation.[17] Hence, it would be prudent to monitor platelet counts in other neonates with suspected FIRS secondary to SARS-CoV-2 exposure. After transfusion, platelet counts remained stable on the follow-up CBC, supporting our hypothesis that a transient period of hyperinflammation occurred.

If this case is indicative of the clinical course of SARS-CoV-2 infection during pregnancy, perinatal fetal distress and unexpected premature birth may not be the only morbidities associated with maternal SARS-CoV-2 infection. We propose that FIRS secondary to maternal SARS-CoV-2 infection explains the neonatal morbidity seen in this case.

LIMITATIONS

This report is only one case, and uncomplicated deliveries of neonates born to SARS-CoV-2–positive mothers have been reported. We did not evaluate the presence of the virus in amniotic fluid, cord blood, or placental tissue, which could clarify the possibility of vertical transmission. Additionally, IL-6 levels were not obtained from the amniotic fluid or the fetal plasma, which would have further examined the diagnosis of FIRS.

The first neonatal RT-PCR swab was obtained at ~7 hours of life, despite AAP recommendations to collect the first sample at 24 hours of life. Additionally, the sample was collected only from the nares, despite the AAP recommendations to collect both oropharyngeal and nasopharyngeal samples by using the same swab.[18]

CONCLUSIONS

Perinatal fetal distress is a potential complication of neonates born to mothers infected with SARS-CoV-2 and may be associated with otherwise unexpected preterm birth. We hypothesize that an FIRS stimulated by maternal viral load explains the perinatal depression and subsequent metabolic acidosis, severe pulmonary hypertension, and additional hematologic abnormalities seen in this neonate. Even in the absence of vertical transmission, FIRS due to maternal SARS-CoV-2 infection could lead to significant neonatal morbidity. In infants born to mothers diagnosed with COVID-19, a SARS-CoV-2–associated FIRS should be considered.

ABBREVIATIONS

AAP: American Academy of Pediatrics
CBC: complete blood cell count
COVID-19: coronavirus disease 2019
CRP: C-reactive protein
FIRS: fetal inflammatory response syndrome
IL-6: interleukin 6
iNO: inhaled nitric oxide
MIS-C: multisystem inflammatory syndrome in children
RT-PCR: reverse transcription polymerase chain reaction
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
WGA: weeks' gestational age

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