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

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Abbreviations:
AAP: American Academy of Pediatrics
CBC: complete blood count
CRP: C-reactive protein
FIRS: fetal inflammatory response syndrome
HIV: human immunodeficiency virus
IL-6: interleukin-6
I/T ratio: immature to total neutrophil ratio
iNO: inhaled nitrous oxide
RT-PCR: Real time polymerase chain reaction
WGA: weeks gestational age

Table of Contents Summary:
This case report aims to demonstrate a possible fetal inflammatory response syndrome associated with maternal SARS-CoV-2 infection.

Contributors’ Statement Page
Dr. McCarty contributed to the acquisition of data, drafted the initial manuscript, and reviewed and revised the manuscript.
Dr. Tucker and Dr. Lee contributed to the analysis and interpretation of data and critically reviewed and revised the manuscript.
Dr. Pandey contributed to the analysis and interpretation of data and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Abstract

Amidst the COVID-19 pandemic, uncertainty exists about the potential for vertical transmission from SARS-CoV-2 infected mothers to the fetus in utero. This case report aims to demonstrate the occurrence of a fetal inflammatory response syndrome associated with maternal SARS-CoV-2 infection, resulting in neonatal morbidity. In this case report we present an infant of a SARS-CoV-2-positive mother born prematurely with late-onset fever, thrombocytopenia, and elevated inflammatory markers, all of which are consistent with a systemic inflammatory response. The neonate was tested for SARS-CoV-2 by two nasopharyngeal swabs 24 hours apart, both of which were negative. A full work up for additional infectious pathogens was also negative. Although initially in critical condition in the perinatal period, the infant recovered completely prior to 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 COVID-19 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 negative SARS-CoV-2 testing in the infant.

Introduction

COVID-19, the disease associated with the novel coronavirus SARS-CoV-2, primarily impacts those with comorbidities and underlying risk factors such as pregnancy. However, limited data exists regarding the fetal morbidity and mortality associated with SARS-CoV-2 infection during pregnancy.\textsuperscript{1-3} Using data from prior novel coronavirus pandemics such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), 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.\textsuperscript{1,2}

Recent meta analyses indicate that the incidence of preterm birth less than 37 weeks gestational age (WGA) is increased in women infected with SARS-CoV-2.\textsuperscript{4,5} Additionally, a higher rate of perinatal fetal distress and admission to the Neonatal Intensive Care Unit has been identified in neonates born to SARS-CoV-2 infected mothers.\textsuperscript{4,6} Despite apparent perinatal complications, the majority of these neonates are negative for SARS-CoV-2 infection.\textsuperscript{7-9} According to 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.\textsuperscript{10} Alternatively, the observed neonatal morbidity seems consistent with a fetal inflammatory response syndrome to maternal viral infection, which has been described in literature as a transient cause of perinatal morbidity.\textsuperscript{11,12}

Here we present an infant born prematurely at 34 6/7 WGA with symptoms consistent with a fetal inflammatory response syndrome, 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 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). Maternal infection-related laboratory tests were unremarkable: rubella immune, hepatitis B negative, HIV antibody negative, syphilis antibody negative, gonorrhea/chlamydia negative. Group B streptococcal status was unknown, but the infant delivered precipitously and therefore did not receive antibiotics. Due to maternal hypertension (which developed after delivery), urine protein to creatinine ratio of 0.3, and platelet count of 90,000 cells/mcL, the mother was diagnosed with severe preeclampsia and started on magnesium sulfate post-partum. Placental pathology was remarkable for focal chronic infarcts.

At birth the infant was hypotonic with poor respiratory effort, requiring positive pressure ventilation and subsequent intubation and mechanical ventilation. Initial arterial blood gases demonstrated significant metabolic acidosis (Table 1). Labs demonstrated a mild leukocytosis with white blood cell count of 15,900 cells/mcL, immature to total neutrophil ratio (I/T ratio) of
0.19, and normal platelet count of 220,000 cells/mcL (Table 2). Blood cultures were obtained, and the infant was initiated on ampicillin and cefepime.

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

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

Repeat complete blood count (CBC) with differential at 48 hours of life demonstrated a significant decline in platelets to 25,000 cells/mcL requiring platelet transfusion. CBC was also significant for severe lymphopenia and a significantly elevated I/T ratio of 0.69. A C-reactive protein (CRP) obtained at that time was also significantly elevated to 6.78 mg/dL. The CRP
continued to down-trend on subsequent labs and was within normal range (<1.0 mg/dL) by day of life 8 (Table 2).

Repeat echocardiogram on day of life 4 demonstrated 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 home with 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. The fetal inflammatory response syndrome (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 multi-organ system involvement and higher morbidity after adjustment for gestational age as seen in this case report. FIRS is defined by elevated IL-6 concentrations (>11 pg/mL) and 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 C-reactive protein, 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. 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. However, the laboratory abnormalities seen in our patient are uncharacteristic of placental insufficiency. These findings, in addition to late-onset fever and multi-organ 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:

- Fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization with multisystem (≥2) organ involvement; and
- No alternative plausible diagnoses; and
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or COVID-19 exposure within the four weeks prior to 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 broad-spectrum antibiotics, significant neutrophilia, and elevated CRP 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 demonstrates a variety of hematologic abnormalities. 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. 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 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 approximately 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 using the same swab.18

Conclusion

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 a fetal inflammatory response syndrome 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.

References


Table 1: Initial arterial blood gases.

<table>
<thead>
<tr>
<th></th>
<th>Birth</th>
<th>1 HOL</th>
<th>2 HOL</th>
<th>3 HOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.00</td>
<td>7.07</td>
<td>7.14</td>
<td>7.17</td>
</tr>
<tr>
<td>pCO2</td>
<td>38</td>
<td>35</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>pO2</td>
<td>29</td>
<td>31</td>
<td>30</td>
<td>37</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>10</td>
<td>10.1</td>
<td>10.9</td>
<td>10.7</td>
</tr>
<tr>
<td>Base Deficit</td>
<td>20</td>
<td>20</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>O2 Sat</td>
<td>38</td>
<td>41</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

[HOL = hours of life, pCO2 = partial pressure of carbon dioxide, pO2 = partial pressure of oxygen, O2 Sat = % oxygen saturation in serum]

Table 2: Serial CBC with differentials.

<table>
<thead>
<tr>
<th></th>
<th>Birth</th>
<th>24 HOL</th>
<th>48 HOL</th>
<th>72 HOL</th>
<th>DOL 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>14.4</td>
<td>15.2</td>
<td>17.1</td>
<td>14.3</td>
<td>14.5</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>44.1</td>
<td>41.8</td>
<td>48.4</td>
<td>39.8</td>
<td>40.7</td>
</tr>
<tr>
<td>Platelet (K cells/mcL)</td>
<td>220</td>
<td>189</td>
<td>25</td>
<td>127</td>
<td>98</td>
</tr>
<tr>
<td>White blood count (K cells/mcL)</td>
<td>15.9</td>
<td>9.0</td>
<td>4.9</td>
<td>3.1</td>
<td>9.0</td>
</tr>
<tr>
<td>Segmented Neutrophils (%)</td>
<td>42</td>
<td>88</td>
<td>29</td>
<td>45</td>
<td>42</td>
</tr>
<tr>
<td>Absolute Neutrophils (K cells/mcL)</td>
<td>7.79</td>
<td>8.10</td>
<td>4.65</td>
<td>1.40</td>
<td>3.96</td>
</tr>
<tr>
<td>Bands (K cells/mcL)</td>
<td>7</td>
<td>22</td>
<td>66</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>41</td>
<td>8</td>
<td>5</td>
<td>45</td>
<td>34</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>5</td>
<td>2</td>
<td>-</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>C Reactive protein (mg/dL)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6.78</td>
<td>0.69</td>
</tr>
</tbody>
</table>

[HOL = hours of life, DOL = days of life]
Table 3: Respiratory viral panel components.

<table>
<thead>
<tr>
<th>Virus tested by RT-PCR</th>
<th>Viral strains tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td></td>
</tr>
<tr>
<td>Coronavirus strains</td>
<td>226E, HKU1, NL63, OC43</td>
</tr>
<tr>
<td>Metapneumovirus</td>
<td></td>
</tr>
<tr>
<td>Rhinovirus</td>
<td></td>
</tr>
<tr>
<td>Enterovirus</td>
<td></td>
</tr>
<tr>
<td>Influenza virus strains</td>
<td>A H1N1, A H1, A H3, B</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
<td>1, 2, 3, 4</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td></td>
</tr>
<tr>
<td>Bordetella pertussis</td>
<td></td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td></td>
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</tbody>
</table>
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