*Case Report*

# Extremely Preterm Infant Born to a Mother With Severe COVID-19 Pneumonia

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## Abstract

Little is known about the effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on pregnant women, fetuses, and neonates, especially when the virus is contracted early in pregnancy. The literature is especially lacking on the effects of SARS-CoV-2 on extremely preterm (<28 weeks gestation) infants who have underdeveloped immune systems. We report the case of an extremely preterm, 25-week 5-days old infant, born to a mother with severe COVID-19 (coronavirus disease-2019) pneumonia. In this case, there is no evidence of vertical transmission of SARS-CoV-2 based on reverse transcription-polymerase chain reaction testing, despite extreme prematurity. However, it appears that severe maternal COVID-19 may have been associated with extremely preterm delivery, based on observed histologic chorioamnionitis. This is the first reported case of an extremely preterm infant born to a mother with severe COVID-19 pneumonia who required intubation, and was treated with hydroxychloroquine, azithromycin, remdesivir, tocilizumab, convalescent plasma, inhaled nitric oxide, and prone positioning for severe hypoxemic respiratory failure prior to and after delivery of this infant. The infant remains critically ill with severe respiratory failure on high-frequency ventilation, inotropic support, hydrocortisone for pressor-resistant hypotension, and inhaled nitric oxide for severe persistent pulmonary hypertension with a right to left shunt across the patent ductus arteriosus and foramen ovale. Pregnant women or women planning to get pregnant should take all precautions to minimize exposure to SARS-CoV-2 to decrease adverse perinatal outcomes.

**Keywords**

extremely preterm, COVID-19 pneumonia, respiratory failure, tuberous sclerosis

## Introduction

Little is known about the effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the fetus when the virus is contracted by the mother, especially early in gestation. While a series of 9 pregnant women demonstrated no vertical transmission of SARS-CoV-2 based on reverse transcription-polymerase chain reaction (RT-PCR) testing,[1] other studies have reported elevated neonatal immunoglobulin M (IgM) antibodies, concerning for vertical transmission,[2,3] and cases of symptomatic neonatal and infant COVID-19 (coronavirus disease-2019).[4-6] However, these reports are lacking data on extremely preterm infants (<28 weeks gestation), who have underdeveloped immune systems, and therefore may be at a greater risk. The only report that examined the effects of maternal COVID-19 in extremely preterm fetuses presented a case of miscarriage during the second trimester, at 19 weeks' gestation, that appeared related to placental infection with SARS-CoV-2.[7] We report the case of an extremely preterm infant born to a mother with severe COVID-19 pneumonia at Los Angeles County+USC Medical Center in April 2020. Verbal HIPPA (Health Insurance Portability and Accountability Act) authorization and informed consent were obtained from the patient and from a legally authorized representative for anonymized patient information to be published in this article, per the recommendations of our institutional review board.

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## Case Presentation

### Maternal Presentation

A 22-year-old primigravida mother with placenta previa and a past medical history of tuberous sclerosis and multiple associated comorbidities (pulmonary lymphangioleiomyomatosis, left ventricular hamartomas, subependymal nodules, adenoma sebaceum, left partial and right total nephrectomy for angiomyolipoma, and leiomyosarcoma) carrying a fetus at 23+6 weeks was admitted with cough, fever, emesis, and abdominal pain. Four days earlier, she had tested positive for SARS-CoV-2 at another institution. One day after her positive SARS-CoV-2 test, she was admitted for observation due to productive blood-tinged cough and tachycardia, which resolved with rest and intravenous fluids, she was treated for a urinary tract infection, and discharged home the next day. Two days after discharge, she presented with lymphopenia, elevated transaminases and lipase, and chest X-ray showed multifocal pneumonia consistent with diagnosis of COVID-19 pneumonia (Table 1).

She was admitted for acute pancreatitis in the setting of COVID-19 pneumonia. She was started on hydroxychloroquine and azithromycin. The following evening her respiratory status deteriorated, with hypoxia despite nasal cannula support, and she was transferred to the intensive care unit (ICU) for initiation of high-flow nasal cannula. Two days later, she was intubated. She was ultimately treated with sedation, paralysis, prone positioning with a RotoProne bed and doughnut to avoid pressure on the uterus and fetus, inhaled nitric oxide, remdesivir, convalescent plasma, tocilizumab (monoclonal antibody against interleukin-6), and therapeutic anticoagulation. On hospital day 14, with the fetus at 25+5, she developed preeclampsia and concern for concealed abruption in the setting of placenta previa. Given maximal maternal medical support, following multidisciplinary discussions among the intensivists, obstetrical, and neonatal care providers about resuscitation and initiating care, betamethasone for fetal lung development and magnesium sulfate for neuroprotection were begun. A few hours later, an urgent Cesarean section was performed in her ICU bed for worsening maternal status. Propofol was added to ongoing pain and sedation management. Following delivery, maternal status initially improved but was ultimately complicated by bilateral pneumothoraces requiring chest tube placement, multiple bilateral pulmonary emboli, culture negative sepsis, and failed extubation requiring tracheostomy after 27 days of intubation.

**Table 1.** Laboratory Studies for Mother.

| Blood counts morning of delivery | Result (reference range) |
|---|---|
| White blood cell count (K/cmm) | 14.1 (4.5-10) |
| Neutrophils | 87.4% |
| Lymphocytes | 7.3% |
| Monocytes | 4.5% |
| Eosinophils | 0.7% |
| Basophils | 0.1% |
| Absolute neutrophil count (K/cmm) | 12.3 |
| Absolute lymphocyte count (K/cmm) | 1.0 |
| Hemoglobin (g/dL) | 6.6[a] (12.0-14.6) |
| Hematocrit (%) | 19.5[a] (36.0-44.0) |
| Platelets (K/cmm) | 356 (160-360) |
| Coagulation studies day of delivery | |
| Partial thromboplastin time (seconds) | 61.6[b] (24.4-36.6) |
| Fibrinogen (mg/dL) | 1070 (237-481) |
| Arterial blood gas prior to delivery | |
| pH | 7.43 |
| $pCO_2$ (torr) | 39 |
| $paO_2$ (torr) | 57 |
| $HCO_3$ | 26 |
| Base excess | 1.5 |
| Lactate (mmol/L) | 0.8 |
| Initial inflammatory markers | |
| CRP (mg/L) | 229.7 (≤4.9) |
| Procalcitonin (ng/mL) | 16.10 (≤0.09) |
| Serum interleukin-6 (pg/mL) | 150.93 (<5.00) |
| Ferritin (ng/mL) | 350 (10-150) |
| D-dimer (µg/mL) | 3.27 (≤0.49) |
| SARS-CoV-2 RT-PCR | |
| Initial deep nasopharyngeal swab | Positive |
| Brocheoalveolar lavage 31 days later | Negative |

Abbreviations: CRP, C-reactive protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription-polymerase chain reaction.
[a]The patient received a packed red blood cell transfusion and hemoglobin was 7.4 g/dL prior to delivery. She also received packed red blood cell transfusion during delivery.
[b]The patient was on a therapeutic heparin drip until 6 hours prior to delivery.

### Neonatal Presentation

At 25+5 weeks, an 810 g appropriate for gestational age female fetus was delivered in a negative-pressure ICU room. All staff were wearing N-95 masks, face shields, gowns, foot covers, gloves, and bouffants. On delivery the infant was apneic, cyanotic, and with no heart rate. Amniotic fluid was meconium stained and there was a nuchal cord. Cord clamping was not delayed. The infant needed intubation, chest compressions, and 1 dose of epinephrine, with improvement in oxygen saturation and heart rate by 11 minutes of life. Apgar scores were 0, 2, 5, 5, 5 at 1, 5, 10, 15, and 20 minutes, respectively. A viral filter was used between the endotracheal tube and T-piece resuscitator to minimize aerosolization. The infant was transported in a transport isolette and admitted to a negative-pressure room in the neonatal ICU.

SARS-CoV-2 testing with RT-PCR of tracheal aspirate immediately after admission and nasopharyngeal swab at 24 hours of life were negative. Initial chest X-ray was consistent with respiratory distress syndrome. The infant was placed on high-frequency oscillatory ventilation and given surfactant. Initial laboratory values (Table 2) were significant for

**Table 2.** Laboratory Studies for Neonate.

| Blood counts | Result (reference range) |
|---|---|
| White blood cell count (K/cmm) | 11.7 (9-30) |
| Neutrophils | 48% |
| Bands | 11% |
| Lymphocytes | 28% |
| Monocytes | 12% |
| Eosinophils | 1% |
| Absolute neutrophil count (K/cmm) | 6.9 (6.0-26.0) |
| Absolute lymphocyte count (K/cmm) | 3.3 (2.0-11.0) |
| Hemoglobin (g/dL) | 12.7 (13.5-21.9) |
| Hematocrit (%) | 38.6 (42.0-60.0) |
| Platelets (K/cmm) | 209 (150-350) |
| Coagulation studies | |
| Prothrombin time (seconds) | 58.6 (11.8-14.4) |
| INR | 6.8 (0.87-1.13) |
| Partial thromboplastin time (seconds) | 98.8 (24.4-38.6) |
| Fibrinogen (mg/dL) | <60 (237-481) |
| First blood gas | |
| pH | 6.93 |
| Base deficit | −8.8 |
| Lactate (mmol/L) | 5.2 |
| Inflammatory markers | |
| CRP (mg/L) | 0.2 (≤4.9) |
| Procalcitonin (ng/mL) | 0.64 (≤0.09) |
| SARS-CoV-2 RT-PCR | |
| Tracheal aspirate DOL 0 | Negative |
| Deep nasopharyngeal swab DOL 1 | Negative |
| Deep nasopharyngeal swab DOL 10 | Negative |

Abbreviations: INR, international normalized ratio; CRP, C-reactive protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription polymerase chain reaction; DOL, day of life.

coagulopathy requiring transfusion of cryoprecipitate, fresh frozen plasma, and packed red blood cells. The complete blood count and liver enzymes were normal and remained essentially within normal limits. Repeat SARS-CoV-2 testing on day of life 10 was also negative and the infant was moved out of negative-pressure isolation per the recommendation from infectious disease consultants. The infant did not receive maternal breast milk due to multiple maternal medications and lack of breast milk supply due to severe maternal illness. Placental pathology revealed a small placenta, and fetal membranes with chorionitis, stage 1, grade 2. The infant has grade 2 intraventricular hemorrhage, patent ductus arteriosus, and remains hospitalized. She also has findings suggestive of tuberous sclerosis complex and genetic testing is pending. The mother is a known case of tuberous sclerosis complex and is heterozygous for a pathogenic variant of the *TSC2* gene.

## Discussion and Conclusion

The effects of COVID-19 on the pregnant woman and fetus are not well known, especially if the infection occurs early in pregnancy, making patient counseling and clinical decision making difficult. To our knowledge, this is the first reported case of an extremely preterm infant born to a mother with severe COVID-19 pneumonia. Though limited by one case, this report provides some information on the effects of severe COVID-19 on birth outcomes, vertical transmission, and neonatal outcomes when SARS-CoV-19 infection is confirmed during the second trimester of pregnancy.

In terms of birth outcomes, although there appears to be an increased frequency of preterm labor and cesarean delivery for abnormal fetal heart rate tracings (likely related to severe maternal illness), outcomes have only been studied for women infected in the third trimester of pregnancy.[8] In our case, severe COVID-19 pneumonia likely contributed to preterm delivery. Though this observation is only an association, it is indirectly supported by the finding of histologic chorioamnionitis, which may be due to SARS-CoV-2, as reported in another study that documented still birth in the second trimester, potentially related to SARS-CoV-2 infection of the placenta.[7] Severity of maternal hypoxic respiratory failure may have also contributed to preterm delivery. To our knowledge, this is the only report of severe COVID-19 in pregnancy needing intubation.

With regard to vertical transmission, while a series of 9 pregnant women reported no vertical transmission of SARS-CoV-2 based on PCR testing of newborn throat swabs, amniotic fluid, cord blood, and breastmilk,[1] others have reported elevated neonatal IgM antibodies, suggestive of vertical transmission in 1 and 2 neonates born to mothers with COVID-19, respectively, with the later report also showing elevated levels of the inflammatory cytokine interleukin-6 in all infants.[2,3] In our case, based on RT-PCR testing of the tracheal aspirate at birth, and nasopharyngeal swabs on days of life 1 and 10, there was no evidence of vertical transmission despite extremely preterm status and the possible presence of tuberous sclerosis complex at birth, which appears to have an effect on the development and function of the innate and adaptive immune responses.[9] However, in our case, testing of cord blood and placenta for SARS-CoV-2 was not performed due to severity of maternal illness and urgency of delivery in the ICU. Additionally, SARS-CoV-2 antibody testing is not currently available at our county institution or through the send out service to an outside laboratory. Although this additional testing may have provided more information, difficulties in diagnosing vertical transmission remains, as RNA PCR is not necessarily indicative of viable virus and IgM exhibits high cross-reactivity, which may lead to false-positive results.

Finally, with regard to the effects of SARS-CoV-2 on the neonate, other reports have documented cases of symptomatic neonatal and infant COVID-19.[4-6] In the study by Zhu et al, all infants tested negative for SARS-CoV-2 by RT-PCR of pharyngeal swabs after birth but presented with clinical symptoms, and laboratory and imaging abnormalities that could have been consistent with COVID-19.[5] In the studies

by Zeng et al, and Feld et al, the neonates and infants tested positive for COVID-19.[4,6] However, the infants in the Feld study were admitted from home, where they likely contracted the virus, making this a different population with likely horizontal acquisition of infection from the community. In our case, potential postnatal transmission was negated by isolation from all family members and lack of breastmilk feeding.

Our case also highlights the dilemma obstetricians and perinatologists have been facing during this COVID-19 pandemic related to antenatal steroids for prematurity. While there are concerns that antenatal steroids may worsen maternal condition, this has to be weighed against the benefits of steroids to the fetus.[10,11] Initial guidelines from the Centers for Disease Control and Prevention and World Health Organization recommended against corticosteroids in COVID-19 patients unless indicated for other reasons, such as the management of chronic obstructive pulmonary disease or septic shock. This is because limited studies in patients with MERS (Middle East respiratory syndrome), SARS, and influenza had shown corticosteroids to be associated with prolonged viral replication, possible harms, or higher mortality. Based on this, the American College of Obstetricians and Gynecologists altered their recommendation for corticosteroids for fetal lung maturity in COVID-19 mothers, recommending steroids only before 34+0 weeks. However many guidelines, such as those from the National Institutes of Health and World Health Organization, have now been revised or are undergoing revision, as recent new preliminary data from a large, multicenter, randomized, open-label trial for hospitalized patients in the United Kingdom (currently unpublished and undergoing peer review) has shown that dexamethasone appears to be associated with decreased mortality in patients who are severely ill (mechanically ventilated or receiving oxygen support by noninvasive methods).[12] However, the preliminary data also show that in COVID-19 patients not requiring respiratory support, corticosteroids were associated with no benefit and possible harm (nonsignificant increase in mortality), and that timing of administration of corticosteroids in relation to the onset of COVID-19 appeared to be of critical importance. Therefore, who receives steroids and at what point in illness requires serious consideration, especially in pregnant women, where the immune response may be different, and maternal versus fetal benefit has to be weighed. Due to rapidly worsening maternal status and anticipated delivery, the mother in our case received 1 dose of betamethasone 4 hours prior to delivery. More data are needed to better inform how to weigh the risks and benefits of giving antenatal steroids in COVID-19-positive pregnant women. This case additionally highlights dilemmas related to the safety of positioning pregnant patients prone, delivery to improve maternal respiratory status, and continuous versus intermittent monitoring of very preterm fetuses in the setting of maternal respiratory failure, given the unknown risks and benefits to the mother and fetus of intervening on fetal behalf.[13] Ultimately, it is clear that in cases where there is potential for maternal acute respiratory failure, ongoing goals of care discussions with the family, designation of a health care proxy, and clear and frequent communication between the intensivists, obstetric, and neonatal teams is paramount.

Limitations are the following: this is a report of a single case and amniotic fluid, placenta, cord blood, and breast milk were not tested for SARS-CoV-2. We did not find evidence of vertical transmission in this extremely preterm infant. Further studies of maternal-infant dyads are needed to understand the impact of SARS-CoV-2 on pregnancy and neonatal outcomes, especially early in pregnancy. This information will be important to help guide clinical counseling, decision making, and health policy for pregnant women and neonates.

## Author Contributions

Dr Easterlin conceptualized and designed the case report, drafted the initial manuscript, and reviewed and revised the manuscript.
Drs De Beritto, Yeh, Wertheimer, and Ramanathan conceptualized and designed the case report, reviewed and revised the manuscript, 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.

## Declaration of Conflicting Interests

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## Ethics Approval

This case report complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

## Informed Consent

Verbal HIPAA (Health Insurance Portability and Accountability Act) authorization and informed consent were obtained from the patient and from a legally authorized representative for anonymized patient information to be published in this article, per the recommendations of our institutional review board.

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