Severe COVID-19 during pregnancy and possible vertical transmission: a case report

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ABSTRACT

Introduction: Much is still unknown about the impact of COVID-19 infection in pregnancy, including clinical course and outcomes in this population, as well as the risk of vertical transmission. There are few cases of pregnant women with COVID-19 in the literature, most of them with a mild illness course. There is limited evidence about in-utero infection and early positive neonatal testing.

Case Report: A 41-year-old G3P2 with a history of previous cesarean sections and diabetes mellitus presented with a 4-day history of malaise, low-grade fever, and progressive shortness of breath. A nasopharyngeal swab was positive for COVID-19, COVID-19 serology was negative. The patient developed respiratory failure requiring mechanical ventilation on day 5 of disease onset. The patient underwent an cesarean section, and neonatal isolation was implemented immediately after birth, without delayed cord clamping or skin-to-skin contact. The neonatal nasopharyngeal swab 16 hours after delivery was positive for SARS-CoV-2 RT-PCR, and IgM and IgG for SARS-CoV-2 were negative. Maternal IgM and IgG were positive on postpartum day 4 (day 9 after symptom onset).

Conclusions: These findings have important public health implications. We report a severe presentation of COVID-19 during pregnancy. To our knowledge, this is the earliest reported positive PCR in the neonate, raising the concern for vertical transmission. We suggest pregnant women should be considered a high-risk group and minimize exposures for these reasons.

KEYWORDS: COVID-19, coronavirus, neonate, pregnancy

KEY POINTS:

- Severe COVID-19 infection in pregnancy
- Mechanical ventilation in infected pregnant patient

- Earliest positive RT-PCR of neonatal specimen
- Possible case of vertical transmission
- Undetectable maternal antibodies prior to delivery

INTRODUCTION

The ongoing pandemic of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a highly infectious disease that was first described by Huang *et al.* (1), whose report focused primarily on the main characteristics and outcomes of non-pregnant adults. The largest series of cases published describes 55 cases of pregnant women infected with COVID-19, of whom only one had a severe presentation, and there were no deaths. (2) There is still much unknown regarding the impact of the disease on pregnancy, differences in clinical course, and outcomes in this population, as well as the risk of vertical transmission.

Physiological changes during pregnancy, such as reduced functional residual volumes, diaphragm elevation, and altered cell immunity, lead to increased susceptibility to viral infections and worse outcomes. (2) In severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), up to 35% and 41% of pregnant patients required mechanical ventilation, and mortality rates were as high as 18% and 25%, respectively. (2–4) In contrast, the majority of reported cases of COVID-19 infection in pregnant patients have shown a mild or asymptomatic course of the disease, with few instances involving ICU admission, only a few reported cases requiring mechanical ventilation. (2,3,5–7)

To date, there is no concrete evidence of whether there is in-utero transmission of SARS-CoV-2. Two cases of neonates with positive RT-PCR testing soon after delivery, have been described. (2,5) However, these cases lack essential clinical data and information regarding adequate isolation, which raises the suspicion of infection in the neonatal period.

Herein, we describe a case of COVID-19 infection in a pregnant woman requiring mechanical ventilation and cesarean section, as well as a neonate with positive testing 16 hours after birth.

CASE REPORT

On March 29, 2020, a 41-year-old woman (gravida 3, para 2) was transferred to our institution at 33 weeks gestation due to respiratory insufficiency. Her medical history was remarkable for two previous cesarean sections and diabetes mellitus, previously treated with metformin and insulin up to the beginning of the current gestation. She received prenatal care at another institution.

The patient presented with a 4-day history of general malaise, fatigue, and low-grade fever, and later developed worsening shortness of breath, which prompted her to seek medical attention. She was admitted to an outside hospital and remained there for 3 days. She was then transferred to our institution for further care. Of importance, her partner and two children were symptomatic in the 15 days prior to admission. The partner tested positive for RT-PCR SARS-CoV-2 during her admission. In the emergency department, the patient's pulse was 131 beats per minute, the respiratory rate 38 breaths per minute, and the oxygen saturation 99% with a FiO2 of

approximately 90%, showing a poor ventilatory pattern. Her BMI was 35. Laboratory tests showed metabolic acidosis on arterial blood gases, pancytopenia, elevated C-reactive protein, ferritin, and slightly elevated D-dimer and glucose (Table 1). A nasopharyngeal swab was obtained for SARS-CoV-2 real-time polymerase chain reaction (RT-PCR), which was reported as positive the next day, and for Viral Filmarray and Pneumovir panel, both reported as negative for common viruses. Initial tomography is shown in Figure 1.

The patient was intubated and placed on mechanical ventilation due to severe respiratory insufficiency in the setting of suspected COVID-19. Patient was started on azithromycin, hydroxychloroquine, meropenem, vancomycin, and oseltamivir. The patient underwent a cesarean delivery due to maternal indication. The neonate weighed 2970 grams, with Apgar scores of 6 and 8. The neonate was intubated in another room due to the high level of sedation of the mother. Delayed cord clamping or skin-to-skin contact were not performed due to general depressed state of the neonate. He was immediately separated from his mother and was not exposed to family members, who were at home under strict isolation measures. Due to maternal state, maternal medical regimen, as well as lack of strong evidence, breastfeeding was not initiated. He was placed in the NICU with no other COVID-19 cases, as this was the first pediatric case at our institution making the possibility of neonatal exposure to COVID-19 very unlikely. Chest X-ray showed no abnormalities.

Baseline and follow-up neonatal serology obtained at birth analyzed by solid-phase immunochromatographic assay (Zhejiang Orient Gene Biotech Co.) yielded negative IgG and IgM titers. Nasopharyngeal swab for SARS-CoV-2 RT- PCR obtained 16

hours after delivery (as soon as the maternal PCR resulted), was reported as positive. RT-PCR repeated 48 hours later for confirmation was also positive. Maternal serology on postpartum day 1 showed negative IgG and IgM levels, followed by positive IgG and IgM on repeat testing on postpartum day 4 (day 9 after symptom onset).

The newborn required ventilatory support for 12 hours, after which he was extubated and placed on CPAP with favorable evolution, and not requiring antibiotic treatment. At the sixth day of life, the newborn presented mild respiratory difficulty and sporadic cough requiring supplemental oxygen with nasal cannula. Imaging and laboratory remain normal.

DISCUSSION

We report a severe clinical presentation of COVID-19 during pregnancy, leading to respiratory failure, mechanical ventilation, and preterm delivery. This adds to a growing body of evidence which raises concerns about possible worse maternal outcomes in pregnancy, as seen with previous coronavirus outbreaks (4,5). The most commonly described course of disease in pregnancy is that of an asymptomatic infection or mild pneumonia, and most cases resolved without undergoing delivery. (2,3,5) Few cases that prompted ICU admission and one case required invasive ventilation with extracorporeal membrane oxygenation. (2,7) It is unknown whether pregnancy-related immune regulation alters the disease course by suppressing the exaggerated inflammatory response seen in this disease and associated with a poorer prognosis. (8) It is important to mention that this patient had diabetes and class II obesity, both risk factors for severe COVID-19. We do not have

enough reported data to ascertain that pregnancy does not lead to worse outcomes, particularly in high-risk pregnant patients. (9,10)

In previous reports, most of the deliveries were performed by cesarean section. In our patient, a preterm cesarean delivery was performed due to her history of two prior cesarean sections, completed antenatal steroid course, and severe maternal pulmonary insufficiency. Different indications for cesarean section during COVID-19 infection are described, most of them related to common obstetric factors, such as history of cesarean sections, pre-eclampsia or fetal distress. There is a lack of convincing evidence that cesarean delivery is protective and vaginal delivery is not contraindicated in patients with COVID-19.(2,11)

The risk of vertical transmission remains unknown. A major finding in this case is the positive testing on RT-PCR of neonatal nasopharyngeal swab as soon as 16 hours after delivery. We believe there is a low probability of perinatal infection due to sterility of the procedure and isolation measures implemented immediately after birth, strongly raising the suspicion of in-utero transmission of SARS-CoV-2. Prior studies have failed to demonstrate maternal-fetal transmission of SARS-CoV-2, including negative testing in amniotic fluid, umbilical cord blood, vaginal swabs, and breast milk. (2,5,11–13) A case series of nine pregnant women with COVID-19 demonstrated negative nasopharyngeal swabs on all neonates. There have been two neonates with positive RT-PCR testing as early as 30 hours after delivery; however, these cases lacked sufficient clinical data or precise information regarding isolation methods, and perinatal infection could not be ruled out. (2,5)

Recently, Dong et al. and Zeng et al. reported virus-specific IgM antibodies in neonatal blood immediately after birth, with negative testing on RT-PCR of nasopharyngeal swab, in neonates with SARS-CoV-2 infected mothers. (14,15) Given that IgM does not usually cross the placental barrier due to its dimensions, it is possible that IgM was produced in the fetus in response to vertical transmission of virus. However this is not conclusive evidence, and may also be due to placental alterations allowing the passage of IgM, or false positive testing.

We found negative serology in both mother and neonate on the day of birth, and later seroconversion of the mother, likely due to the acute presentation of COVID-19. These are consistent with the serological conversion curve described in other studies in which IgM seroconverts after day 5 of illness. The evolution of serologic testing of both the mother and neonate are shown in Figure 2. Until day of life 5, the neonatal serology remains negative. This could be explained by the immaturity of the adaptive immunity in the neonatal period, especially seen in preterm neonates, which results in impaired cytokine and B cell immunoglobulin production relative to adults. (16)

Angiotensin-converting enzyme 2 (ACE2), has been described as a SARS-CoV-2 receptor in humans. There is conflicting evidence regarding the interaction of ACE2 and SARS-CoV-2 at placental level. Levy et al. (14) demonstrated transient ACE2 overexpression and increased activity in the placenta and reproductive organs in rats during pregnancy. In contrast, Zheng et al.(15) described very low expression of ACE2 in almost all human cell types of the early maternal-fetal interface, suggesting the placenta had virtually no susceptible cells to the virus.

Our report has several limitations. The lag-time to neonatal nasopharyngeal swab, due to the current national criteria for testing raises the possibility of perinatal transmission, though this was minimized by the procedures described above. We did not evaluate the presence of virus in amniotic fluid, cord blood or placental tissue, which could further clarify pathogenesis.

CONCLUSIONS

We describe a severe presentation of COVID-19 during the third trimester of pregnancy, leading to mechanical ventilation and preterm delivery, as well as positive RT-PCR in the neonate. We believe these findings have important public implications both due to the severity of disease presentation, and the concern for vertical transmission. Given this information, pregnant women should be considered a vulnerable population in which exposure is to be avoided.

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Figure 1: CT scan of the chest showing multiple consolidations in both lungs, predominantly in bases and associated with bilateral pleural effusion.

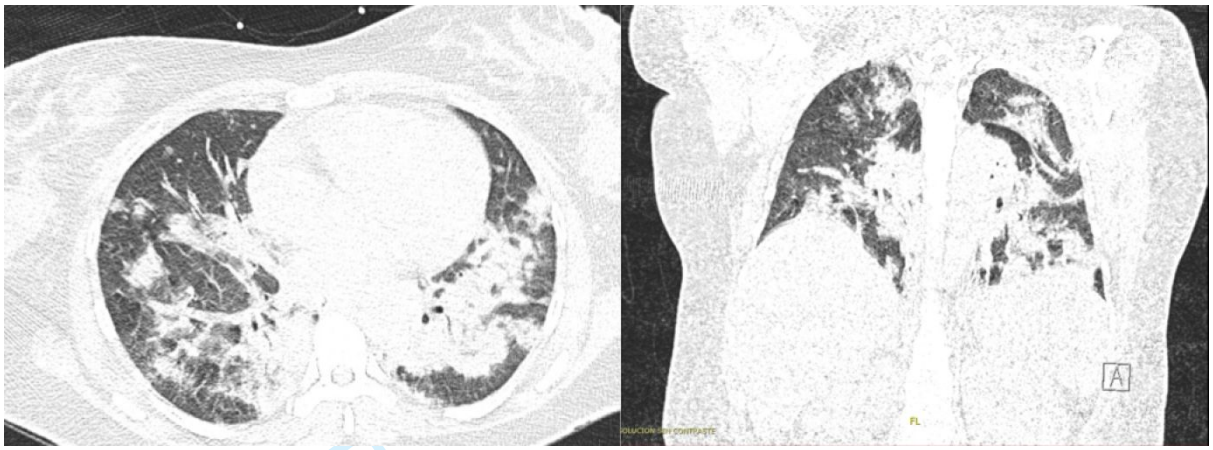


Figure 2: Timeline illustrating serologic assay results evolution in mother and neonate

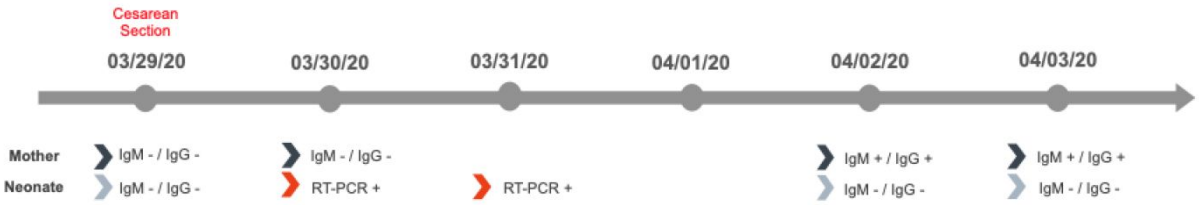
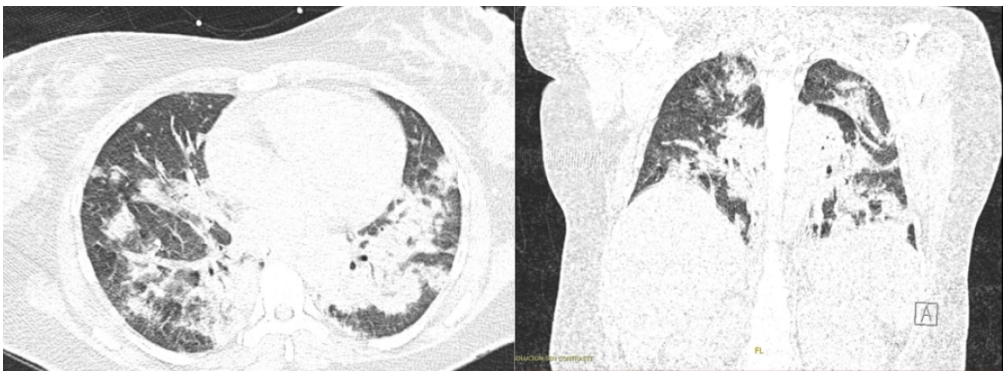


Table 1: Initial Clinical Laboratory Results

Variable	Reference Range	Result
Hemoglobin (g/dL)	12.3-15.3	10.0
White-cell count (per mm3)	4,400-11,300	3,590
Platelet count (per mm3)	149,000-409,000	116,000
Absolute lymphocyte count (per mm3)	1,000-4,000	467
C-reactive protein (mg/dL)	0.00-0.50	14.28
Procalcitonin ng/mL	<0.50	0.35
D-dimer (ug/mL)	0.00-0.50	0.79
Ferritin (ng/mL)	15.0-150.0	266.70
CPK (U/L)	26.0-155.0	17.0
Glucose (mg/dL)	70.0-100.0	105.0
Creatinine (mg/dL)	0.5-1.20	0.31
Blood urea nitrogen (mg/dL)	5.13-23.3	5.6
Total bilirubin (mg/dL)	0.00-1.20	0.41
Aspartate aminotransferase (U/L)	0.0-40.0	18.0
Alanine aminotransferase (U/L)	0.0-38.0	15.0
Sodium (mEq/L)	135.0-145.0	135.3
Potassium (mEq/L)	3.5-5.5	3.68
Chloride (mEq/L)	97.0-111.0	101.8
Arterial blood gases:		
pH	7.35-7.43	7.43
PCO2	32-43	23

PO2	80-100	196
HCO3	22.0-28.0	15.3
BE	-2.0-2.0	-7.7



CT scan of the chest showing multiple consolidations in both lungs, predominantly in bases and associated with bilateral pleural effusion.

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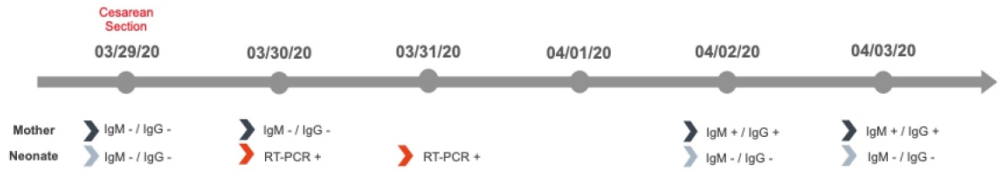

Timeline illustrating serologic assay results evolution in mother and neonate

303x95mm (144 x 144 DPI)

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