Case report

Clinical improvement of severe COVID-19 pneumonia in a pregnant patient after caesarean delivery

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SUMMARY

The clinical implications of COVID-19 in pregnancy remain unknown. While preliminary reports demonstrate that pregnant patients have a similar symptomatic presentation to the general population, the appropriate management and timing of delivery in these patients is still unclear, as pregnancy may impose additional risk factors and impede recovery in gravid patients. In this brief report, we present a case of COVID-19 in a pregnant patient with severe respiratory compromise, whose clinical status significantly improved after caesarean delivery. We also address the potential benefits of experimental therapy, including tocilizumab, a monoclonal antibody that targets interleukin-6 receptors.

BACKGROUND

COVID-19 has become a global pandemic after the first case of severe acute respiratory syndrome (SARS) coronavirus-2 (SARS-CoV-2) was reported in Wuhan, China, in December 2019. While cases continue to increase, questions about the clinical course and long-term implications of infection remain unanswered. This lack of clarity is especially concerning in obstetrics, where gravid patients have historically been at higher risk of viral respiratory infections as a result of their immunocompromised state and physiological changes of pregnancy, including diaphragm elevation, increased oxygen consumption and mucosal oedema of the respiratory tract. Pregnant patients had increased susceptibility to viral respiratory illness during the SARS coronavirus-1 (SARS-CoV-1) and Middle East respiratory syndrome (MERS) outbreaks, with high rates of complications and mortality in obstetric patients.[1] However, current SARS-CoV-2 studies have demonstrated that pregnant patients have similar clinical courses to their non-pregnant counterparts, often presenting with mild symptoms of fever, cough and dyspnoea.[2–9] Common laboratory abnormalities include lymphopenia and elevated levels of lactate dehydrogenase (LDH), ferritin and aminotransferase.[10] Bilateral ground glass opacities with patchy consolidations on chest CT scans are frequently seen in COVID-19.[7] We present a case of COVID-19 in a pregnant patient with severe respiratory compromise. This case highlights the complex interplay of pregnancy and COVID-19, and its impact on clinical management in obstetrics.

CASE PRESENTATION

A 35-year-old gravida 10 para 7 at 29 3/7 weeks gestation presented to the labour and delivery unit in Queens, New York, with a 2-week history of cough and fever, last documented at home to 38.2°C the day prior. The patient also reported dyspnoea that worsened with ambulation, myalgias and dysuria.

Her pregnancy was complicated by pyelonephritis at 13 weeks gestation, requiring intravenous antibiotics and recently diagnosed gestational diabetes mellitus (GDM) (diet controlled, type A1). Her obstetric history was significant for seven full-term vaginal deliveries and three spontaneous abortions. She also had a prior cholecystectomy and ventral hernia repair. She was otherwise medically uncomplicated.

On admission, she was afebrile, with a blood pressure of 109/56, peripheral oxygen saturation (SpO2) of 95%, respiratory rate of 23 breaths per minute and heart rate of 109 beats per minute. SpO2 with ambulation decreased to 92%. She was promptly placed in an isolation room with contact and droplet precautions. On the day of presentation, she became increasingly hypoxic, requiring 8 L/min of oxygen via nasal cannula. Fetal well-being was confirmed with a reactive non-stress test. A COVID-19 nasopharyngeal PCR test on admission was positive. Her laboratory results were significant for lymphopenia and elevated LDH, D-dimer and C reactive protein (CRP) (table 1). Her chest X-ray (CXR) findings were consistent with COVID-19, with extensive patchy airspace opacities in the middle and lower lung fields (figure 1).

TREATMENT

The Infectious Disease service was consulted and recommended hydroxychloroquine and azithromycin for 5 days with monitoring of the QT interval by ECG. They also recommended ceftriaxone to empirically treat for a urinary tract infection, pending urine culture results. Over the next 12 hours, the patient's partial pressure of oxygen on an arterial blood gas dropped from 91 to 66 mm Hg, and the patient was transferred to the surgical intensive care unit (SICU).

In the SICU, the patient's condition worsened on hospital day 2 with increasingly elevated oxygen requirements. The Infectious Disease service recommended a single administration of intravenous tocilizumab 400 mg, which is a monoclonal

Table 1 COVID-19 laboratory values

	Reference range	HD1	HD2	HD3	HD4	HD5	HD6	HD7	HD8	HD9	HD10	HD11	HD12	HD13	HD14	HD15
Procalcitonin (ng/mL)	0.02–0.10	0.16				0.08	0.11	0.12	0.20	0.18						
D-dimer (ng/mL)	0.0–243		422	680	856	1011	1249	2383	3037	2579	1384		1398	799		710
Interleukin-6 (pg/mL)	0.0–15.5	88.5				531.2	773.7	1123.1			45.3	280.9				
Lactate dehydrogenase (U/L)	135–214	230	230	246	308	438	564	517	505	428		450	437	355	359	462
C reactive protein (mg/L)	<=5.0	179.1	167.7	123.6	34.3	7.4	3.3	1.8	1.2	1.0	0.8		0.5	0.6	0.5	0.6
Alanine aminotransferase (U/L)	0–33	33				85	196	270	304	314	384	458	575	601	602	439
Creatinine (mg/dL)	0.5–1.2	0.51	0.52	0.51	0.57	0.56	0.54	0.59	0.60	0.49	0.50	0.62	0.44	0.47	0.46	0.49
Aspartate aminotransferase (U/L)	5–32	40				125	221	235	220	200	236	240	315	298	279	144
Ferritin (ng/mL)	13–150	106	97	108	118	134	130	102		62		48	47	43	46	41
Platelets ($\times 10^9$/L)	150–450	327	343	438	522	665	660	713	705	721	663	544	598	520	498	522
White blood cells ($\times 10^9$/L)	4.80–10.80	8.16	9.93	7.02	4.90	5.69	7.63	8.21	7.31	6.48	20.79	8.49	8.77	7.62	7.08	6.11
Absolute lymphocyte count ($\times 10^3$/mcL)	1.00–4.90	0.83	0.79	0.90	0.95	1.09	1.22	1.19	1.08	1.43	1.21	1.57	2.32	2.53	2.41	2.24

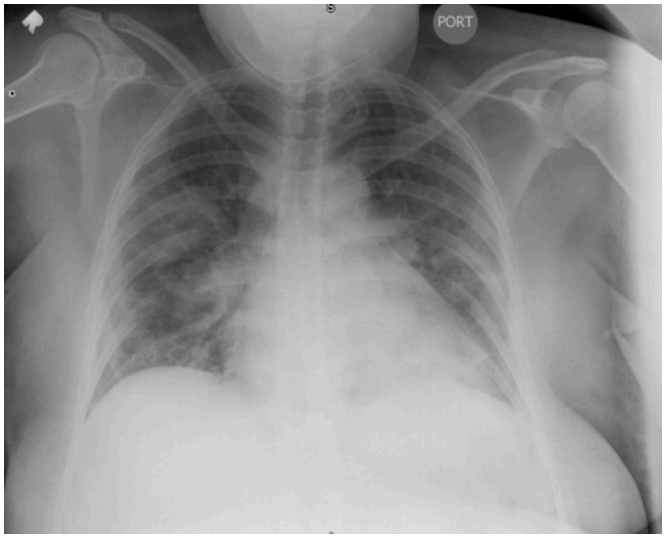

Figure 1 Chest X-ray on hospital day 1 with patchy airspace opacities in the middle and lower lung fields.

antibody that targets the interleukin-6 (IL-6) receptor.[2] Maternal Fetal Medicine was consulted about the safety of monoclonal antibodies in pregnancy and approved its use, given the low risk of birth defects in the third trimester. The Genentech Actemra Registry was also contacted for further information on known cases of gravid women exposed to tocilizumab, with preterm birth being the main risk.[11]

On hospital day 3, the patient received tocilizumab. The patient's respiratory status continued to worsen, and by hospital day 5, she required 15 L/min of oxygen through Venturi mask with desaturation of her SpO2 to the low 80th percentile on ambulation. Despite worsening respiratory status, the patient's acute phase reactants remarkably improved. CRP downtrended from 179 mg/L at admission to 7.4 mg/L by day 5. Blood cultures showed no growth and her urine culture was negative, so ceftriaxone was discontinued.

After administration of tocilizumab, the patient developed transaminitis and hypertriglyceridaemia. Although these laboratory abnormalities are known side effects of tocilizumab, a hepatitis panel was sent to rule out other causes, which was negative. Throughout her hospitalisation in the SICU from hospital day 2 to 9, the patient remained afebrile but was visibly tachypneic with increased work of breathing. The D-dimer level continued to rise, peaking at 3037 ng/mL. Given the risk of thrombotic events with COVID-19, the patient was started on an empiric heparin drip to treat for pulmonary embolism.

Because the patient remained dependent on 15 L/min of oxygen and showed signs of clinical worsening with potential imminent need for intubation, there was an interdisciplinary discussion about her treatment plan with the Obstetrics, Maternal Fetal Medicine, Infectious Disease, Critical Care, Paediatrics and Anaesthesia teams. All teams agreed on proceeding with caesarean delivery with neuraxial anaesthesia for expedited delivery, and possible intraoperative intubation if the patient was unable to tolerate prolonged supine position. With recommendations from Maternal Fetal Medicine, the patient received a single dose of betamethasone for fetal lung maturity 24 hours before delivery. Magnesium for fetal neuroprotection was deferred, given concern for maternal respiratory depression.

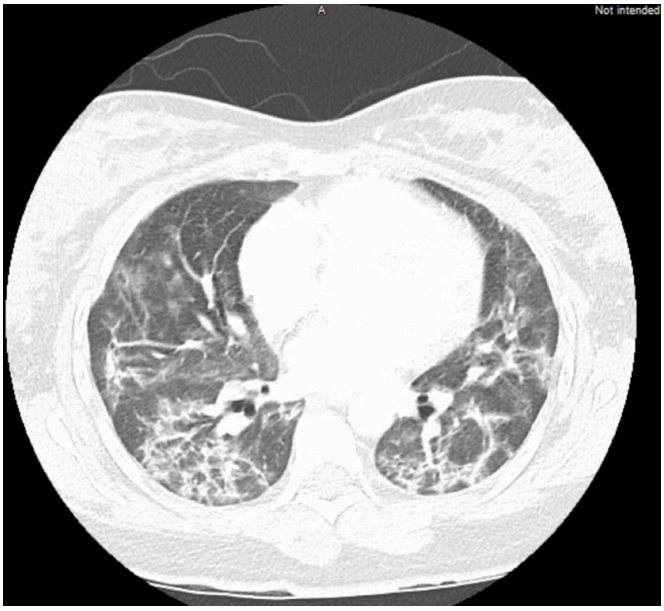

Figure 2 CT angiogram on postoperative day 4 with bilateral patchy ground glass infiltrates and small consolidations.

OUTCOME AND FOLLOW-UP

On hospital day 10, the patient underwent an uncomplicated primary caesarean delivery at 30 5/7 weeks gestation with spinal anaesthesia. All medical staff was donned in appropriate airborne personal protective equipment. The patient was maintained on 15 L/min of oxygen during the procedure and did not require intubation. The surgery lasted 45 min from skin incision to closure. A 1705 g male neonate was delivered with early cord clamping, and had Apgar scores of 9 and 9 at 1 and 5 min, respectively. The neonate was immediately transferred to the neonatal intensive care unit. He initially required supplemental oxygen to achieve adequate saturation, likely secondary to respiratory distress syndrome of prematurity, but had good oxygen saturation on room air by day of life 4. His CXR on day of life 3 showed no evidence of pulmonary disease, and COVID-19 nasopharyngeal PCR testing collected 2 hours after delivery and on day of life 3 were negative.

The patient's clinical status rapidly improved postoperatively. At 2 hours post-caesarean, she had a SpO2 to the low 90th percentile on room air, which improved to 100% on 15 L/min of oxygen in the recovery room, and significantly improved cough and work of breathing. Postoperative pain was managed with oral acetaminophen and hydromorphone. Her oxygen requirements gradually decreased, and by postoperative day 2, she was weaned to 4 L/min of oxygen via nasal cannula. She remained on therapeutic enoxaparin postpartum until she was stable enough to obtain a CT angiogram, given the continued concern for a concomitant pulmonary embolism. Her CT angiogram was negative for pulmonary embolism, but consistent with COVID-19 infection, showing extensive bilateral patchy ground glass infiltrates and small consolidations (figure 2). COVID-19 nasopharyngeal PCR tests continued to be positive on postoperative days 7, 8 and 9. However, the patient was discharged on postoperative day 9 with recommendations about use of personal hygiene precautions and quarantine at home, as she was symptomatically improved, saturating well on room air and meeting all postoperative milestones. On postoperative day 14, her COVID-19 test was negative.

DISCUSSION

As COVID-19 begins to affect more obstetric patients, determining the best treatment to optimise maternal and fetal well-being becomes ever more important. While there are no established guidelines about timing of delivery with COVID-19, our patient began to clinically recover postpartum. In cases of severe respiratory distress from COVID-19 pneumonia, patients may experience a reversal in poor respiratory status after the physiological changes of pregnancy are removed. Because we cannot exclude that the patient's recovery was due to other factors, this finding needs to be confirmed in larger studies.

While previous retrospective studies have shown successful trials of labour in patients with COVID-19 and mild respiratory symptoms, our patient presented with worsening pulmonary status and likely did not have the reserve to tolerate labour. In patients who are heavily dependent on oxygen supplementation for adequate saturation, caesarean delivery without trial of labour may be prudent to expedite delivery and avoid fetal distress.[1 12] In our case, after an interdisciplinary discussion, we opted for neuraxial anaesthesia rather than perioperative general anaesthesia with intubation, which our patient was able to successfully tolerate. We believe this is a safer method of anaesthesia for both obstetric COVID-19 patients and neonates if maternal respiratory status allows, and has the added benefit of decreasing viral exposure to medical staff. Our patient was also given hydroxychloroquine, azithromycin and tocilizumab antepartum, as there has been off-label investigational use of these medications in patients with COVID-19.[13]

To our knowledge, this is the first case to describe the use of tocilizumab for COVID-19 infection in a pregnant patient. Tocilizumab is an IL-6 inhibitor and is thought to interfere with the cytokine storm phase of COVID-19. It has been shown to rapidly improve outcomes in patients with moderate to severe COVID-19 infection in a small cohort of patients in China.[14] Tocilizumab exposure during pregnancy has mostly been studied in patients with severe rheumatologic diseases.[11 15] Tocilizumab has not been shown to increase congenital abnormalities or spontaneous abortions, but has been associated with preterm birth and low birthweight neonates, which may be a reflection of this patient population having a higher incidence of these outcomes, regardless of treatment. As in the small cohort studied,[14] the CRP improved in our patient after one dose of tocilizumab. Although it is difficult to attribute her clinical improvement solely to the medication, her respiratory status did not further decompensate after receipt of tocilizumab and improved tremendously after caesarean delivery. In cases of severe respiratory compromise with COVID-19, it may be reasonable to use experimental medications, such as hydroxychloroquine, azithromycin and tocilizumab, as they may improve outcomes.

While research has shown that diabetes mellitus is a predisposing risk factor for COVID-19,[16] an association with GDM has not been confirmed in obstetric research. Because some physiological consequences of GDM are similar to pregestational diabetes, it is possible that our patient was also at higher risk of COVID-19. Further research is needed to confirm whether the proinflammatory state and relative immunosupression of GDM makes these patients more susceptible to COVID-19.

Many studies have demonstrated the benefits of antenatal corticosteroids in improving fetal lung maturity and neonatal outcomes in preterm infants, particularly in those at 24–34 weeks gestation.[17] Similar to influenza and MERS, COVID-19 pneumonia may worsen with immunosuppressive steroids, and this possibility must be weighed against the fetal benefits. We decided

to administer betamethasone because of the fetus's early gestational age, but limited it to a single dose to reduce total exposure and potential immunosuppressive effects on the mother. Magnesium sulfate administration for fetal neuroprotection was also considered. Previous data on magnesium show promising results with decreased rates of cerebral palsy in neonates before 30 weeks gestation, but the data are less convincing from 30 to 32 weeks.[18] Because of the risk of respiratory depression and indeterminate benefit after 30 weeks gestation, magnesium sulfate was not given to our patient to reduce the likelihood of intubation.

The possibility of vertical transmission of COVID-19 from a seropositive mother to fetus in utero remains unknown. Similar to other studies, we did not find that the neonate was affected when tested immediately after delivery and at a few days of life.[2–6 8 9]

This case reviews the antenatal course of a patient with severe COVID-19 pneumonia and the maternal and neonatal outcomes after preterm delivery. Our patient experienced significant improvement in respiratory status postpartum, and the neonate similarly recuperated well without COVID-19 seropositivity. Future studies clarifying whether delivery improves clinical status and the appropriate timing and dosage of medications, including antiviral medication, betamethasone and magnesium, would be beneficial for obstetric providers.

Learning points

- Expedited delivery may improve the clinical status of gravid patients with severe COVID-19 pneumonia. Caesarean delivery should be the preferred mode of delivery when a patient does not have the respiratory reserve to tolerate a trial of labour and vaginal delivery.
- Investigational medications, like tocilizumab, may be vital to improving patient outcomes, as seen in this case, and should be considered in patients with severe COVID-19 pneumonia.
- Transmission of COVID-19 from a seropositive mother to fetus did not occur in this case, with negative COVID-19 nasopharyngeal PCR testing in the neonate immediately after delivery.

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