

Case Report

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Cytokine storm secondary to coronavirus disease-19 pneumonia in a preterm pregnancy: A management and bioethical dilemma

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Abstract:

A 27-year-old primigravida at 26 weeks' age of gestation presented with difficulty of breathing, nonproductive cough, and generalized body malaise. Coronavirus disease-19 (COVID-19) infection was confirmed by a positive reverse transcription-polymerase chain reaction. She was diagnosed with severe COVID-19 pneumonia with progressive oxygen desaturation requiring intubation and intensive care unit admission. The management and bioethical dilemma involved the use of investigational therapeutic interventions for compassionate use, with unknown effects to the fetus, namely remdesivir, tocilizumab, dexamethasone, and hemoperfusion to manage the cytokine storm and prolong pregnancy or to terminate the pregnancy hoping that it might improve the deteriorating condition of the patient. A multidisciplinary approach and family conference to solve the dilemma resulted in a successful outcome.

Keywords:

Coronavirus disease-19, hemoperfusion, remdesivir, tocilizumab

Introduction

Severe coronavirus disease-19 (COVID-19) pneumonia is defined as the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, confirmed by reverse transcription-polymerase chain reaction (RT-PCR) assay, and either oxygen saturation of $\leq 94\%$ while breathing ambient air or need for oxygen support.^[1,2]

Cytokine storm is a complication of severe COVID-19 infection marked with an aggressive inflammatory response with the release of a large amount of pro-inflammatory cytokines, including Interleukin-6 (IL-6), IL-1, tumor necrosis factor-alpha (TNF- α), and Interferon which causes influx of various immune cells such

as macrophages, neutrophils, and T-cells from the circulation, thereby causing lung injury, multi-organ failure, and unfavorable prognosis. Cytokine storm is managed by instituting hydration, nutrition, medical, and respiratory intervention. As COVID-19 infection is considered a new and emerging infection, there is a paucity of strong data regarding the treatment of cytokine storm in preterm pregnancy. Investigational therapies such as the use of remdesivir, tocilizumab, dexamethasone, and hemoperfusion are being used for compassionate use among patients with moderate-to-severe COVID-19 pneumonia in pregnancy.

The blood profile of patients with COVID-19 usually exhibits lymphopenia with or without total leukopenia. A lymphocyte count $< 1.0 \times 10^9/L$ indicates severe disease.

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Platelet count is usually normal or mildly decreased. C-reactive protein (CRP) and erythrocyte sedimentation rate are usually increased. Procalcitonin levels are usually normal. An elevation of procalcitonin indicates secondary bacterial infection. Increased levels of lactate dehydrogenase, ferritin, D-dimer, and creatine kinase elevation are seen in those with severe disease. Elevation in creatinine or liver enzyme levels, alanine transaminase (ALT), and aspartate transaminase (AST) occurs in complicated cases, progressing to multi-organ failure.^[3,4]

Remdesivir, previously known as GS-5734, is a nucleotide analog that reduces SARS-CoV-2 replication *in vitro* through selective inhibition of viral ribonucleic acid (RNA)-dependent, RNA polymerase, which SARS-CoV-2 utilizes for replication within host cells.^[3] A 10-day treatment course is usually administered with a loading dose of 200 mg intravenously on day 1 and 100 mg given intravenously on days 2–10.^[2] Suggested clearance is via renal and hepatic routes. It is usually not associated with renal toxicity. Remdesivir has been reported as well tolerated, with a low incidence of serious adverse events. Some of the adverse effects include anemia, constipation, deep venous thrombosis, dysphagia, unspecified hypertension, hypoxia, nausea, and pleural effusion in pregnant women.^[2]

Pregnant women with confirmed SARS-CoV-2 infection develop severe or critical illness in 9%–14% of cases.^[4] There are limited data regarding the treatment of COVID-19 in pregnant women. Reports mostly come from small case series and case reports. In one cohort study of pregnant women requiring mechanical ventilation and treated with remdesivir, the median time to recovery was approximately 13 days.^[2]

Tocilizumab is a recombinant humanized anti-human IL-6 receptor monoclonal antibody that specifically binds to IL-6, thereby inhibiting its pro-inflammatory effect. This prevents cell injury in patients with COVID-19 by inhibiting vessel permeability, vascular endothelial growth factor expression, and T-cell maturation.^[5] It is given as a single dose of 400 mg in a small case series of severe COVID-19 with good results. Suggested clearance is via renal and hepatic routes. Adverse reactions to tocilizumab include hypertension, diarrhea, abdominal pain, increase in ALT/AST, dizziness, headache, pharyngitis thrombocytopenia, neutropenia, gastrointestinal perforation, pancreatitis, hepatotoxicity, and anaphylaxis. It has been demonstrated that treatment with tocilizumab in 21 patients with either severe or critical COVID-19 resulted in clinical improvement in 75% of the cases.^[6] However, there is insufficient evidence to recommend the routine use of tocilizumab for severe COVID-19 patients suspected to be in cytokine

storm except in the context of a clinical trial or for compassionate use.^[7]

Dexamethasone is recommended as an adjunctive treatment for patients requiring oxygen support and for patients on mechanical ventilation, usually with an intravenous dose of 6 mg/day for 10 days. Dexamethasone is a known anti-inflammatory agent resulting in decreased edema, capillary leakage, and migration of inflammatory cells. However Dexamethasone also has limited data with regard to treatment of COVID-19 in pregnant women, but it is used in the context of a clinical trial or for compassionate use.^[7]

Hemoperfusion devices or extracorporeal blood purification has been proven to effectively remove released inflammatory cytokines seen in cytokine storm. It has been reported that a cytokine filter can buy extra time for hemodynamic and metabolic stabilization in a pregnant patient with COVID-19 infection. However, there is insufficient evidence to recommend the routine use of hemoperfusion as an adjunctive treatment for COVID-19.^[7]

It has been reported that most of the women with COVID-19 delivered preterm (<32 weeks age of gestation) and via cesarean section driven by the severity of maternal COVID-19 illness and with no obstetric indications. There were no reports of spontaneous preterm labor, placental abruption, or preeclampsia.^[2] Mechanical ventilation was not an indication for delivery. In women <32 weeks' age of gestation with severe hypoxemia, other options are considered before delivery, including prone positioning, extracorporeal membrane oxygenation, and other advanced ventilator methods.^[8]

Case Report

This is a case of a 27-year-old primigravida, on her 26 weeks and 4 days' age of gestation, single, Filipino, Roman Catholic, from Quezon City who presented at the emergency room with the difficulty of breathing.

The patient was apparently well until 6 days before admission when she experienced a sore throat accompanied by a fever of 39°C and generalized body malaise. There was neither difficulty of breathing nor shortness of breath noted at that time. She self-medicated with paracetamol 500 mg which afforded temporary relief. COVID-19 infection was suspected; hence, an RT-PCR swab test was done at that time, revealing a positive result. Four days before admission, the patient noted the persistence of symptoms now associated with shortness of breath on exertion. Few hours before admission, progressive difficulty of breathing prompted consult at the emergency room and subsequent admission.

The patient is nonhypertensive, nondiabetic with no history of other comorbidities such as bronchial asthma and thyroid disease. She denies allergies to any food and medications. She had her regular prenatal check-ups with her attending physician.

At the emergency room, the patient's blood pressure was 98/62 mm Mercury (mmHg), heart rate, 78 beats/min (bpm), respiratory rate, 28 cycles/min, temperature, 37°C, O₂ saturation, 88%, improved to 97% at 6 L/min through nasal cannula with difficulty of breathing, associated with nonproductive cough and generalized body malaise. There was neither vaginal bleeding nor hypogastric pain noted, with good fetal movement. There were bibasal rales on chest auscultation. She was maintained on oxygen support at 6 L/min through nasal cannula and started on Budesonide + Formoterol 2 puffs twice a day.

On the 2nd hospital day, chest X-ray was done, revealing bilateral pneumonia, more on the left. Pleural effusion could not be totally ruled out. Arterial blood gas revealed partially compensated respiratory alkalosis. Azithromycin, ceftriaxone, montelukast, paracetamol, enoxaparin, and dexamethasone were started.

On the 3rd hospital day, there was oxygen desaturation at 83%. Oxygen supplementation at high-flow rate and remdesivir was started. She was then transferred to the intensive care unit with oxygen support at high-flow nasal cannula [Figure 1] with fractional inspired oxygen at 100% at 30 L/min (lpm).

On the 4th hospital day, potassium and magnesium decreased, and troponin I was elevated. COVID-19 myocarditis was considered. Electrolyte correction with potassium chloride and magnesium was done. Episodes

of desaturation at 89%–93% persisted. Then, oxygen support was adjusted using high-flow nasal cannula, fractional inspired oxygen at 100% at 50 lpm. There was elevation of CRP and D-dimer. Pelvic ultrasound was done [Figure 2]. Magnesium sulfate drip at 1 g/h for 24 h for fetal neuroprotection was started.

On the 5th hospital day, desaturation as low as 87% was noted which prompted intubation of the patient [Figure 5]. Hypotensive episodes were noted. Dexmedetomidine and norepinephrine were added to her medications. Enoxaparin was shifted to heparin 5000 units, and single-dose tocilizumab 400 mg was given intravenously. A repeat chest X-ray demonstrated progressive bilateral pneumonia with consolidation with consideration for minimal pleural effusion at the left lung.

On the 6th hospital day, the patient's blood pressure became stable, but she remained tachycardic and tachypneic. Hemoperfusion was started. Oxygen saturation from the 7th to 10th day of hospitalization showed improvement with gradual weaning from mechanical ventilator. Single dose of furosemide 40 mg and novorapid 6 units to treat the steroid-induced dysglycemia were given. The patient underwent three sessions of hemoperfusion. Nonstress test was reactive. Chest X-ray revealed decrease in bilateral pneumonia [Figure 3].

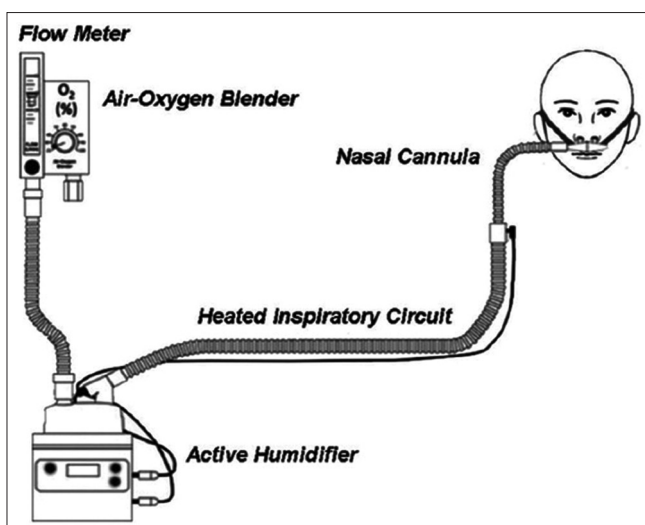


Figure 1: High flow rate machine illustration

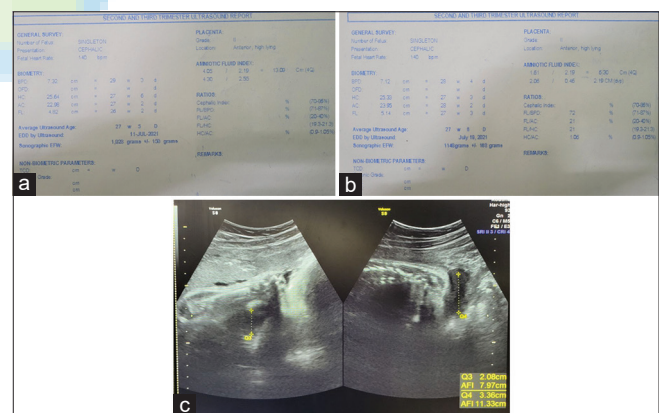


Figure 2: (a) Pelvic ultrasound (April 16, 2021): Pregnancy uterine 27 weeks and 5 days age of gestation, cephalic, with good cardiac and somatic activities, Normohydramnios, AFI: 13.9, placenta anterior Grade 2 high lying with visualization of subplacental sonolucency, estimated fetal weight 1028 ± 150 g Appropriate for gestational age. (b) Pelvic Ultrasound (April 23, 2021): Pregnancy uterine 27 and 6 weeks by average fetal biometry. Live, singleton in cephalic presentation with good cardiac and somatic activities. Placenta anterior, Grade 2, high lying, with visualization of subplacental sonolucency. Amniotic fluid index is below the 5th percentile for age of gestation at 6.3 centimeters. Estimated fetal weight is appropriate for gestational age at 1148 ± 168 g. (c) Biophysical Score (May 25, 2021): Pregnancy uterine 32 weeks and 1 day by average fetal biometry. Live singleton, in cephalic presentation with good cardiac and somatic activities. Placenta anterior, Grade 2, high lying, with visualization of subplacental sonolucency. Normohydramnios at 11.33 centimeters by deepest vertical pocket. Estimated fetal weight is appropriate for gestational age at 1734 ± 253 g. Biophysical score 8/8. AFI: Amniotic fluid index

On the 11th hospital day, after 5 days of intubation, the patient was extubated. She tolerated oxygen support via nasal cannula at 3 lpm. Pelvic ultrasound was done [Figure 2]. The fourth hemoperfusion was completed.

On the 12th–13th day of hospitalization, vital signs remained stable without episodes of desaturation [Figure 4]. The patient was cleared for discharge, given prenatal medications, instructed to continue Enoxaparin 0.4 ml subcutaneously for 2 weeks and Budesonide + Formoterol at 2 puffs daily.

On discharge, on her 28th week age of gestation, another pelvic ultrasound was done [Figure 2]. The patient was advised oral rehydration of 2–3 l of electrolyte drink. Subsequently, the patient had regular follow-up with her attending physician with close antenatal to monitor amniotic fluid.

The patient was readmitted at 37 5/7 weeks' age of gestation due to labor pains. She had stable vital signs on admission. Fetal heart tone was 140 bpm. On internal examination, the cervix was dilated to 6 cm, 80% effaced, cephalic, intact bag of waters, and station-2. On the

4th h of labor, patient delivered to a term, cephalic, live, female with a birth weight of 2778 g, APGAR score 8, 9, Ballard score 37 weeks, appropriate for gestational age via normal spontaneous delivery under epidural anesthesia [Figure 6]. The postpartum course was uneventful, and both mother and baby were discharged 24 h after delivery.

Discussion

A normal pregnancy by itself is a pro-inflammatory condition with elevated cytokines, IL-6, and TNF- α . For this reason, a pregnant woman is vulnerable to COVID-19 infection and is considered to belong to a high-risk population. Cytokine storm was diagnosed in this case, as evidenced by the elevated IL-6 and CRP.

The management dilemma, in this case, arises from the fact that COVID-19 is a new and emerging infection, and all the available interventions are investigational and only allowed for compassionate use. There are insufficient data on their efficacy and safety, especially in this case of a preterm pregnancy. Given this scenario, what choice do the physicians have? Will the investigational interventions for compassionate use do more harm than good? Is the maxim of first do no harm being violated by administering these interventions? Since pregnancy is a pro-inflammatory state and, in this case, further compounded by another pro-inflammatory condition, COVID-19, aggravated by cytokine storm, will it benefit the patient to just terminate the preterm pregnancy in the hope of saving the life of the mother? Herein lies the bioethical dilemma.

“At the heart of moral dilemmas in medicine are recurrent ethical principles that need to be examined, drawn from a considerable body of literature that guides the health care provider. While we could argue from a basis of practical consequences, a basis of proper motives and of discharge of duties, or of ideal personal virtues, the ethically relevant facts need analysis based on principles. This case study focuses on four major principles, namely to respect patients, promote benefit and to avoid or minimize harm, and to act justly.”^[9]

In this case, the mother’s condition deteriorated with the progression of the disease. Respect to the patient prompted

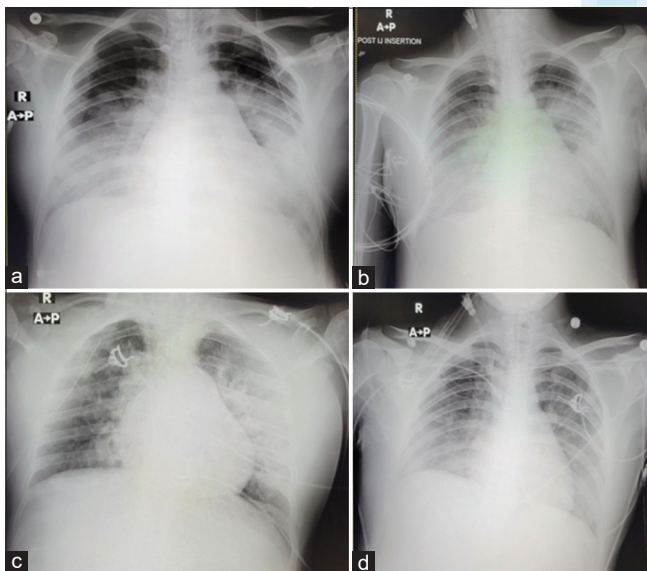


Figure 3: (a) Progressing bilateral pneumonia with consolidation. Consider minimal pleural effusion, left. (b) Progressing bilateral consolidation pneumonia. (c) Bilateral pneumonia with regression on the right. (d) Bilateral pneumonia with minimal resolution

Figure 4: Patient’s vital signs throughout the course of admission

Vital signs	4/13	4/14	4/15	4/16	4/17	4/18	4/19	4/20	4/21	4/22	4/23	4/24	4/25	4/26
Blood pressure	98/62	100/70	100/56	90/75	110/70	100/60	117/78	118/85	114/87	96/60	100/60	90/60	119/76	100/60
Heart rate	78	80	125	127	118	80	80	90	65	79	85	70	97	80
Respiratory rate	28	25	24	35	35	25	22	20	19	19	21	20	20	21
Temperature	37°C	36.7°C	38.9°C	37.7°C	37.5	36.6	36.9	36.5	36.7	36.5	36.8	36.6	36.9	36.5
Oxygen saturation (%)	88	83	87	98	95	100	100	100	100	100	100	99	100	100
											CPAP mode	Extubated		

CPAP: Continuous positive airway pressure



Figure 5: Patient intubated at the intensive care unit

family conference, investigational interventions were administered to promote benefit, prolonging the pregnancy avoided the harm of delivering a premature baby, and by doing so, the family and the physicians acted justly.

After a multidisciplinary meeting and a family conference, it was decided not to deliver the fetus due to prematurity. The decision to prolong the pregnancy and administer investigational interventions, with unknown effects to the fetus, was made by the family after the management plans were presented by the multidisciplinary team of infectious disease, cardiology, pulmonology, and perinatology specialists.

Summary

We report a case of cytokine storm secondary to COVID-19 pneumonia in a preterm pregnancy. The management and bioethical dilemma were resolved by a multidisciplinary team of specialists and the involvement of the family in the decision-making process. The successful outcome of this case further underscores the importance of teamwork and family involvement to attain a decision regarding the administration of investigational treatment in a timely manner. The outcome would not have been successful had the family refused the management presented to them.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.



Figure 6: Baby at day 1 postdelivery via normal spontaneous delivery, with no noted complications

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Conflicts of interest

There are no conflicts of interest.

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