Case Report

JHSMR Journal of Health Science and Medical Research

Life-Saving Extracorporeal Membrane Oxygenation Combined with Hemoperfusion for a Pregnant Woman with COVID-19 Severe Acute Respiratory Distress Syndrome

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Received 26 December 2023 ● Revised 11 March 2024 ● Accepted 11 March 2024 ● Published online 6 August 2024

Abstract

The pandemic of the novel coronavirus (COVID-19) affected millions of people worldwide, causing high mortality and morbidity, especially in pregnancy. The management of COVID-19, which progresses to severe acute respiratory distress syndrome during pregnancy, is very challenging. Herein we report a 35-year-old pregnant woman in her second trimester (16 weeks of gestational age) who presented with a productive cough and progressive dyspnea. She was diagnosed with a severe COVID-19 infection, confirmed by PCR testing. During hospitalization, she developed severe acute respiratory distress syndrome (ARDS) and was referred to a tertiary hospital. Despite the use of antiviral therapy, steroids, mechanical ventilators, and muscle relaxants, she still had significant hypoxemia. Thus, she underwent veno-venous extracorporeal membrane oxygenation (VV-ECMO). Due to the limitations of immunomodulatory therapy in pregnancy, our team decided to perform extracorporeal cytokine removal therapy with HA330 adsorbent hemoperfusion to remove circulatory cytokines and proinflammatory mediators and suppress the hyperinflammatory response. After 3 consecutive days of hemoperfusion, her C-reactive protein and interleukin-6 were controlled. On the 13th day of ICU admission, her clinical conditions, including pulmonary function, were improving, and she was successfully weaned off the VV-ECMO. A chest X-ray showed she was completely free of ARDs. The patient left the hospital with good clinical

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J Health Sci Med Res 2025;43(2):e20241077
doi: 10.31584/jhsmr.20241077
www.jhsmr.org

status and a viable fetus. We conclude that pregnant women infected with COVID-19 who develop refractory hypoxemia with cytokine storm syndrome may benefit from combined VV-ECMO and hemoperfusion as a rescue therapy.

Keywords: COVID-19, hemoperfusion, pregnancy, veno-venous extracorporeal membrane oxygenation

Introduction

Among those with severe COVID-19-infections, obstetric patients are especially challenging to manage due to physiological changes of immunomodulators during pregnancy that can lead to severe clinical illness features[1]. A cytokine storm syndrome is one presentation that can lead to significant organ dysfunction, including severe acute respiratory distress syndrome (ARDS)[2].

Veno-venous extracorporeal membrane oxygenation (VV-ECMO) has become an important invasive treatment in ICU patients with refractory hypoxemia in severe ARDS. It offers strong efficacy in critically ill pregnancy patients[3] Embase, and The cumulative index of nursing and allied health literature (CINAHL) were searched for case reports, case series, and studies reporting cases of Extracorporeal life support (ECLS) during the peripartum period that reported one or more of the following outcomes: maternal survival, maternal complications, fetal survival, and/or fetal complications. Qualitative assessment of 221 publications evaluated the number of cases, clinical details, and maternal and fetal outcomes of ECLS during the peripartum period. There were 358 women included and 68 reported fetal outcomes in cases where the mother was pregnant at the time of cannulation. The aggregate maternal survival at 30 days was 270 (75.4%. A previous study reported the successful saving of both a mother and a fetus using VV-ECMO during a severe COVID-19 infection[4]. However, the real cause of ARDs is hyperinflammatory cytokines, which cannot be removed via VV-ECMO. Thus, hemoperfusion plays an essential role in the cytokine storm syndrome, due to its proven properties of cytokine clearance[5]. Currently, there are no case reports of VV-ECMO combined with hemoperfusion treatment in pregnant COVID-19 patients. We present our experience of successful treatment using VV-ECMO combined with hemoperfusion in a 35-years-old critically ill pregnant woman.

Case report

A 35-year-old pregnant woman at 21 weeks of gestation with no underlying disease presented to the emergency service at a private hospital with a 1-day history of productive cough and progressive dyspnea. This was her first pregnancy, and she had attended no antenatal visits before her presentation. Prior to admission, she had been in close contact with a COVID-19 patient for 5 days. Her body temperature was 38.3°C, her oxygen saturation was 93% in room air, and her body mass index (BMI) was 24.9 kg/m^2. A nasopharyngeal swab showed a positive result on a COVID-19 nuclear acid polymerase chain reaction (PCR) test. The patient was admitted and received both antiviral therapy (remdesivir loading dose of 200 mg IV, followed by a maintenance dose of 100 mg once daily for a total of 5 days) and steroids (dexamethasone 8 mg IV once daily, adjusted according to clinical condition and tapered over 2 weeks) upon admission. 2 days after admission, she developed progressive dyspnea, and high-flow nasal cannula therapy (HFNC) was initiated. She needed maximum fractional oxygenation up to 100%. She was subsequently transferred by ambulance to our university hospital.

At the COVID-19 intensive care unit (ICU), she was tachypneic with a respiratory rate of 40 breaths/min and became progressively hypoxemic with an oxygen

saturation of 79%. A chest X-ray revealed bilateral patchy consolidation on both lungs (Figure 1). Thus, the patient was intubated and started on invasive mechanical ventilation. Her ventilator setting was pressure-controlled with a respiratory rate of 30 breaths/min, inspiration pressure (IP) of 30 mmHg, positive end-expiratory pressure (PEEP) of 15 mmHg, and a fraction of inspired oxygen (FiO2) of 100%. A blood gas examination after her ventilator was set showed a pH of 7.24, PaCO2 of 49 mmHg, PaO2 of 58 mmHg, and PaO2/FiO2 ratio of 58. Despite the high ventilator setting, the patient could not maintain oxygenation. Her heart function was evaluated by echocardiogram, which showed good contraction of both the right and left ventricles, with no valvular abnormalities and no evidence of pulmonary edema. Therefore, the intensivist diagnosed her with acute respiratory distress syndrome (ARDS). After the patient's family was advised about the risks and benefits, VV-ECMO was initiated.

A cardiothoracic surgeon inserted the VV-ECMO cannulae at the patient's bedside. Both common femoral veins (CFV) were punctured, and a passing guidewire was inserted using the Seldinger technique. Heparinization (1 mg/kg) was given during the operation. After the surgeon cannulated both CFVs, the VV-ECMO was begun. The VV-ECMO circuit started with an initial flow rate of 4.0 L/min, sweep gas of 3 L/min, and fractional oxygen in the sweep gas (FdO2) of 0.8. Arterial blood gas showed improvement with a PaO2/FiO2 ratio of 109 mmHg with this ECMO setting within 60 minutes. The mechanical ventilator was changed to a lung-protective ventilation strategy by decreasing the PEEP to 8 mmHg and setting the tidal volume to 200 ml. A few hours later, when the patient had stabilized,

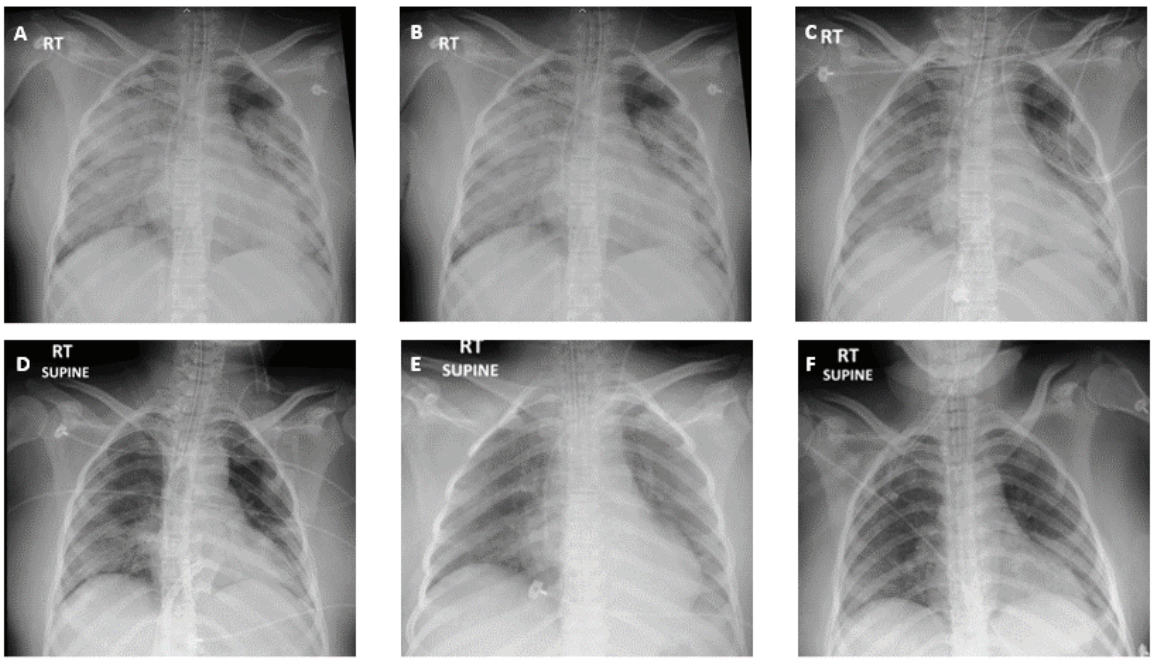

Figure 1 Chest X-ray images of the COVID-19 patient

A=Day 1 of admission, B=Day 2 of admission, C=Day 5 of admission, D=Day 10 of admission, E=Day 11 of admission, F Day 13 of admission

obstetricians evaluated transvaginal ultrasonography and identified a single viable fetus (SVF) weighing 483 gm with an amniotic fluid index (AFI) of 3.35 cm. There were no growth abnormalities detected, but the fetus was borderline small for the gestational age. They planned close monitoring of the fetus during the patient's gestation.

Considering that the patient's respiratory symptoms were severe and her inflammatory markers were still rising significantly (Table 1), the cytokine storm needed to be eliminated as soon as possible before it lead to further organ failure or lung fibrosis. Anti-interleukin 6 (Tocilizumab) was contraindicated due to lack of sufficient evidence justifying its use. Thus, our team decided to provide cytokine removal therapy in our setting with hemoperfusion (HA330 cartridge, Jafron©), aiming to reduce the systemic hyperinflammatory response. The HA 330 cartridge was integrated with the VV-ECMO in a passive setting. The patient received hemoperfusion for 3 hours per session, one session per day, totaling 3 days, using a double lumen bicaval cannula, with a blood flow rate of 200 mL/min. The hemoperfusion protocol used in this patient was modified from a previous study by Kaçar et al[6], which described the use of HA330 hemoperfusion for 2 hours daily over 3 consecutive days in septic shock patients. This previous study demonstrated effective reductions in inflammatory cytokine levels, such as CRP and improvements in heart rate. After completing

Table 1 Patients, ventilator and ECMO characteristics

Parameter	1st day	2nd day	3rd day	4th day	5th day	13th day	14th day
BT (c)	36.5	36.1	37.0	37.2	37.5	36.6	37.2
Vasopressor use	+	+	+	+	+	–	–
Hemoperfusion	–	+	+	+	–	–	–
VV-ECMO							
BF (LPM)	4	2.5	3	2.8	2.8	1.0	
Sweep gas	3	1.5	2.5	2.5	2.5	0	off
FdO2	0.8	0.7	0.7	0.5	0.5	0.4	–
Ventilator setting							
RR	30	12	12	12	12	24	24
IP or TV	30 (PCV)	200 (VCV)	200 (VCV)	200 (VCV)	200 (VCV)	280 (VCV)	280 (VCV)
Ti	1.2	0.95	0.95	0.95	0.95	0.85	0.85
PEEP	15	10	8	8	8	8	8
Ventilator FiO2	1.0	0.4	0.4	0.4	0.4	0.4	0.4
SpO2 (mmHg)	86	100	98	96	96	99	97
Laboratory result							
WBC (x10^3 µmol/L)	6.76	15.88	9.59	9.48	11.75	15.96	14.55
Lymphocyte (%)	10	1	5	3	2	3	5
Platelet (x10^6 µmol/L)	210	233	186	183	209	139	129
AST (U/L)	77	123	89	–	–	–	79
ALT (U/L)	49	66	72	–	–	–	79
Albumin (g/L)	2.6	2.1	1.9	1.9	2.3	2.6	3.2
CRP (mg/L)	6.88	42.09	12.65	–	13.36	2.86	–
IL-6 (pg/ml)	6.39	223	7.6	–	2.22	<1.5	–

BT=body temperature, VV-ECMO=venovenous extracorporeal membrane oxygenation, BF=blood flow, LPM=liter(s) per minute, FdO2=fraction of oxygen delivery, RR=respiratory rate, IP=inspiratory pressure, TV=tidal volume, Ti=inspiratory time, SpO2=oxygen saturation, WBC=white blood cell, AST=aspartate aminotransferase, U=unit, ALT=alanine aminotransferase, CRP=C-reactive protein, IL=interleukin, L=liter, pg=picogram, ml=milliliter, PCV=pressure controlled ventilation, VCV=volume controlled ventilation, µmol=micromole

the hemoperfusion, we tapered down the VV-ECMO, the respiratory parameters showed a recovery trend, and we discontinued the VV-ECMO at day 13 post-admission (Table 1). At that time, her lung symptoms and CXR showed great improvement (Figure 1), and she was extubated. The patient recovered and was discharged from the hospital a few weeks later. At the discharge date, the patient was approximately 23 weeks pregnant and had no abnormal respiratory symptoms. After that, she received regular follow-up antenatal care, and her newborn was delivered via cesarean section at approximately 39 weeks. The infant's birth weight was 2450 grams, and no abnormal features were observed.

Discussion

The COVID-19 viral infection is a new pandemic disease that can result in infections of the respiratory tract characterized by acute respiratory distress and severe pneumonia, often leading to respiratory failure7. Previous studies found that a severe COVID-19 infection in pregnancy had a mortality rate as high as 13% and an ICU hospitalization rate of 4%, and approximately 3% of pregnant COVID-19 patients required mechanical ventilation[8]. The factors associated with severe manifestations in pregnant patients include age, high body weight, hypertension, and diabetes. Furthermore, pregnant women with COVID-19 tend to exhibit increased production of various cytokines, such as ESR, CRP, IL-2, IL-6, and IFN-γ. The elevated levels of these cytokines in pregnant women contribute to the increased severity of COVID-19 infections. Thus, removing cytokines is beneficial in this patient group[2].

Hemoperfusion is a blood purification process designed to eliminate various substances, such as toxins, medications, and cytokines, from the body. Following the COVID-19 outbreak, it has become evident that hemoperfusion plays a significant role in cytokine removal[9-11]. Based on evidence of hemoperfusion in severe COVID-19 infection, numerous studies have demonstrated improvements in inflammatory markers, respiratory parameters, and SOFA scores, with no reports of life-threatening side effects[12]. There is a limited number of well-designed studies evaluating the efficacy and safety of using hemoperfusion in pregnant women infected with severe COVID-19. Nevertheless, earlier case reports have demonstrated successful outcomes following treatment with hemoperfusion in this population, with no significant adverse events reported[13,14]. There is only one previous case report on a COVID-19 infection with severe ARDS in a 22-year-old pregnant woman at 32 weeks of gestation who received hemoperfusion that resulted in survival of both mother and fetus[15]. Due to limited evidence, each patient should be carefully evaluated and the potential risks and benefits weighed for both the mother and the fetus before hemoperfusion is applied.

ECLS is a medical procedure that involves the use of an ECMO machine in patients experiencing circulatory or respiratory failure. Its use in pregnant women has been associated with reports of increased bleeding in both the mother and the fetus3. A collection of case reports includes 67 pregnant women who received extracorporeal life support. The survival rate among these women was approximately 80%, with a survival rate of approximately 70% for their infants. In the context of COVID-19, there are limited reports of pregnant women receiving extracorporeal life support[16,17].

Currently, there are no reported cases or studies on the combination of hemoperfusion and extracorporeal life support in pregnant women with COVID-19 infection. However, immunopathological data shows that pregnant women with COVID-19 tend to have significantly higher levels of inflammatory cytokines compared to non-pregnant COVID-19 patients. Given this observation, hemoperfusion is a potential therapeutic option for reducing inflammatory cytokines, and thus, disease severity. We

suggest considering the combination of hemoperfusion with extracorporeal life support in pregnant women with COVID-19 who present with refractory ARDS and have failed conventional therapies, and particularly indicated in cases of high severity scores caused by systemic inflammation driven by inflammatory cytokines. This treatment could result in improved oxygenation and attenuation of the cytokine storm and potentially preserve fetal well-being through enhanced maternal oxygenation and hemodynamics. However, certain concerns must be considered, including an elevated risk of bleeding and potential fetal complications. This treatment option should be approached with caution due to these potential risks.

Conclusion

Pregnant women who contract COVID-19 and experience a cytokine storm may not show improvement with standard treatments such as steroids and antiviral medications, especially when there are limitations in using the medications. Hemoperfusion presents another viable option. Since there are currently no randomized controlled trials or sample case reports available, our team presents a report on a pregnant woman with COVID-19 who underwent hemoperfusion using the HA-330 filter over the course of 3 days in conjunction with extracorporeal life support. Our study demonstrates that this combined treatment resulted in clinical improvement, allowing our patient to be discharged from the hospital and carry her infant to term.

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