International Journal of Obstetric Anesthesia 53 (2023) 103625

Contents lists available at ScienceDirect

International Journal of Obstetric Anesthesia

journal homepage: www.elsevier.com/locate/ijoa

Original Article

Challenges and pitfalls of extracorporeal membrane oxygenation in critically-ill pregnant and peripartum women with COVID-19: a retrospective case series

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ARTICLE INFO

Keywords:
Acute respiratory distress syndrome
Anticoagulation
COVID-19
Extracorporeal membrane oxygenation
Pregnancy

ABSTRACT

Background: Available data identify pregnancy as a strong determinant of a severe course of COVID-19 with increased mortality. Extracorporeal membrane oxygenation (ECMO) remains the last resort treatment in the critical course of COVID-19 yet may increase the risk of excessive bleeding, especially in the immediate post-cesarean section period. One in five patients receiving ECMO during the COVID-19 pandemic were women who were pregnant or postpartum. While the risk of critical respiratory failure in the peripartum period is high, in an early survey only 52% of pregnant patients intended to receive the COVID-19 vaccine.
Methods: Our study aimed to evaluate clinical characteristics and treatment modalities in a series of five pregnant and peripartum women supported with ECMO and anticoagulated with anti-Xa-guided nadroparin therapy in our center. We reviewed the full treatment courses; inflammatory, hemodynamic, and coagulation variables; and maternal and neonatal outcomes. We identified adverse events during the therapy.
Results: All five patients developed acute respiratory distress syndrome due to COVID-19 in the third trimester of pregnancy. Termination of pregnancy occurred between 28 and 36 gestational weeks. While four of five newborns survived to hospital discharge, only two of the five mothers survived to leave hospital.
Conclusions: ECMO is feasible in the third trimester but not devoid of complications. The severity of respiratory failure during COVID-19 and extracorporeal support may not adversely impact neonatal outcomes.

Introduction

According to the World Health Organization, pregnancy is a strong determinant of a severe course of COVID-19 when compared with non-pregnant women. An observational study on 1219 pregnant women with SARS-CoV-2 infection has confirmed a severe course of the disease in 8% of women and a critical course in 4%.[1] In the national registry study on the issue, when the delta variant predominated in the UK, 16% of symptomatic pregnant women admitted to hospital required intensive care admission.[2] Although available data identify pregnancy as a strong determinant of a severe course of COVID-19 and increased mortality, an international survey on COVID-19 vaccine acceptance indicated that only 52% of pregnant responders intended to receive the vaccine.[3] Therefore the risk associated with severe and critical COVID-19 in pregnant women may remain high. Extracorporeal membrane oxygenation (ECMO) is the last resort treatment in the critical course of COVID-19. According to registry data, one in five patients receiving ECMO during the COVID-19 pandemic were women who were pregnant or postpartum.[4] However, ECMO therapy is associated with multiple adverse events, and unfractionated heparin used routinely during the procedure increases the risk of excessive bleeding, especially in the direct post-cesarean period.

We present the clinical characteristics and treatment modalities in a series of five pregnant and peripartum women supported with ECMO and anticoagulated with anti-Xa guided nadroparin in our center.

Methods and materials

This retrospective observational study was approved by the Ethical Committee of the Medical University of Lublin, Poland (approval no.

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https://doi.org/10.1016/j.ijoa.2023.103625
Accepted 30 December 2022

KE-0254/59/2020). The study adhered to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for collecting and interpreting observational data. Only adult patients treated with veno-venous (VV) ECMO were included in the study. Each woman or her representative gave written consent to present the data. We reviewed the medical records of pregnant and peripartum women supported with ECMO in our center in whom polymerase chain reaction testing confirmed the SARS-CoV-2 virus. All patients were treated in a tertiary academic hospital in Lublin, Poland, between November 2020 and October 2021. We collected patient characteristics, including demographics; pre-ECMO medical status; ECMO settings; full treatment course; inflammatory, hemodynamic, and coagulation variables; and maternal and neonatal outcomes. We identified adverse events during the therapy. Descriptive statistical analysis included medians (minimum and maximum ranges) and frequencies (n [%]).

Results

Our study included five peripartum patients with acute respiratory distress syndrome (ARDS) caused by COVID-19. One patient was pregnant, while the remaining four were postpartum (one to seven days post-delivery). All had developed COVID-19 symptoms during the third trimester and required mechanical ventilation. All patients were treated with high positive end-expiratory pressure and low driving pressure, neuromuscular blockade, and prone positioning, before referral for ECMO support. The median PaO_2/FiO_2 ratio was 93 mmHg (67–98 mmHg), and the median Respiratory ECMO Survival Prediction (RESP) score was 5 (4–7) on the day of cannulation. In four cases, ECMO was inserted outside of our clinic, and transportation was performed by helicopter. Detailed information about each patient can be found in Table 1.

In all cases, VV ECMO was used. Three patients had the returning cannula placed in the right internal jugular vein and the draining cannula in the right femoral vein; one had the returning cannula in the left internal jugular vein; and one had the drainage cannula in the left femoral vein. In all parturients, subcutaneous doses of nadroparin were given every 12 h for anticoagulation during ECMO. The dosing of nadroparin was dependent on lean body mass and guided by the anti-Xa activity levels, measured twice daily and kept between 0.3 and 0.5 IU/mL. To prevent clotting in the circuit, blood flow <3.5 L/min in the circuit was not allowed. We monitored the pressure difference across the oxygenator and routinely inspected the deep veins of the lower limbs. The daily changes in D-dimer levels are presented in Fig. 1. The transfusion trigger for red blood cells was 100 g/L. The median duration of ECMO support was 11 (4–19) days. Only three patients were weaned off ECMO successfully, and two of those patients were discharged from the hospital alive. All patients required treatment with blood products. Further details of the ECMO support are outlined in Supplements 1 and 2.

All patients had the Pulse Index Continuous Cardiac Output monitoring system inserted (PULSION, Feldkirchen, Germany), and received a continuous norepinephrine infusion. Two patients also received dobutamine infusions. Daily hemodynamic measurements and catecholamine doses are presented in Supplement 3. The changes in the levels of C-reactive protein (CRP) and the median Sequential Organ Failure Assessment (SOFA) score throughout the treatment period are presented in Figs. 2 and 3.

The majority of newborns were delivered prematurely by cesarean section. Four of the five parturients delivered before ECMO was initiated and one delivered at term two months after ECMO was ceased. Detailed information about newborn status is shown in Table 2.

Discussion

We report a case series of respiratory failure associated with severe COVID-19 in pregnant and peripartum women who were treated with VV ECMO. Termination of pregnancy occurred between 28 and 36 gestational weeks. While four out of five newborns survived to hospital discharge, only two of five parturients survived. In comparison with an observational and a retrospective study that focused mainly on outcomes and complications of ECMO in a population of parturients, this series elucidates full treatment courses, hemodynamic status, and ECMO settings as well as inflammatory and coagulation variables during the patients' ICU stays.[5–6]

Ventilatory and ECMO management and organ failure

Ventilatory, circulatory, and extracorporeal circuit management remain a challenge in obstetric patients. According to observational studies, Barbaro et al. reported successful outcomes in 22 pregnant women among 1035 patients with COVID-19 on ECMO support, and Barrantes et al. described positive treatment outcomes in nine parturients.[5,7] O'Neil compared peripartum COVID-19 patients on ECMO support with a propensity-score matched non-pregnant female cohort and found an increased survival rate and fewer ECMO-related renal complications.[6] It is recommended that critically-ill pregnant women should be referred early for ECMO.[8] In contrast to previous descriptions of ECMO in pregnant women, the present case series elucidates the full treatment courses of five peripartum women with severe COVID-19. In our cohort, the median day of ECMO implementation

Table 1
Maternal factors

Patient/Hospital	1/A	2/B	3/B	4/C	5/D
Maternal factors					
Age (years)	35	30	35	27	39
Weight (kg)	70	74	56	80	130
Comorbidities	No	Asthma		Type I diabetes, obesity	Hypothyroidism, obesity
Maternal COVID-19					
Symptom onset (days)	12	14	6	8	9
Procalcitonin level (ng/mL)	0,39	0.33	53.08	13.72	6.15
PEEP/Plateau (cm H_2O)	12/27	14/29	12/27	12/32	18/31
PF ratio prior to cannulation (mmHg)	93	80	67	120	96
Prone positioning	Yes	Yes	Yes	Yes	Yes
Systemic steroids	Yes	Yes	Yes	Yes	Yes
Gestational age (weeks)	24	33	30	36	28
Delivery	CS	CS	CS	CS	CS
Time from CS to ECMO therapy (days)	ECMO during pregnancy	0	1	7	4
Maternal survival to hospital discharge	Yes	Yes	No	No	No

PEEP: positive end-expiratory pressure. PF ratio: PaO2/FiO2 ratio. CS: cesarean section. ECMO: extracorporeal membrane oxygenation.

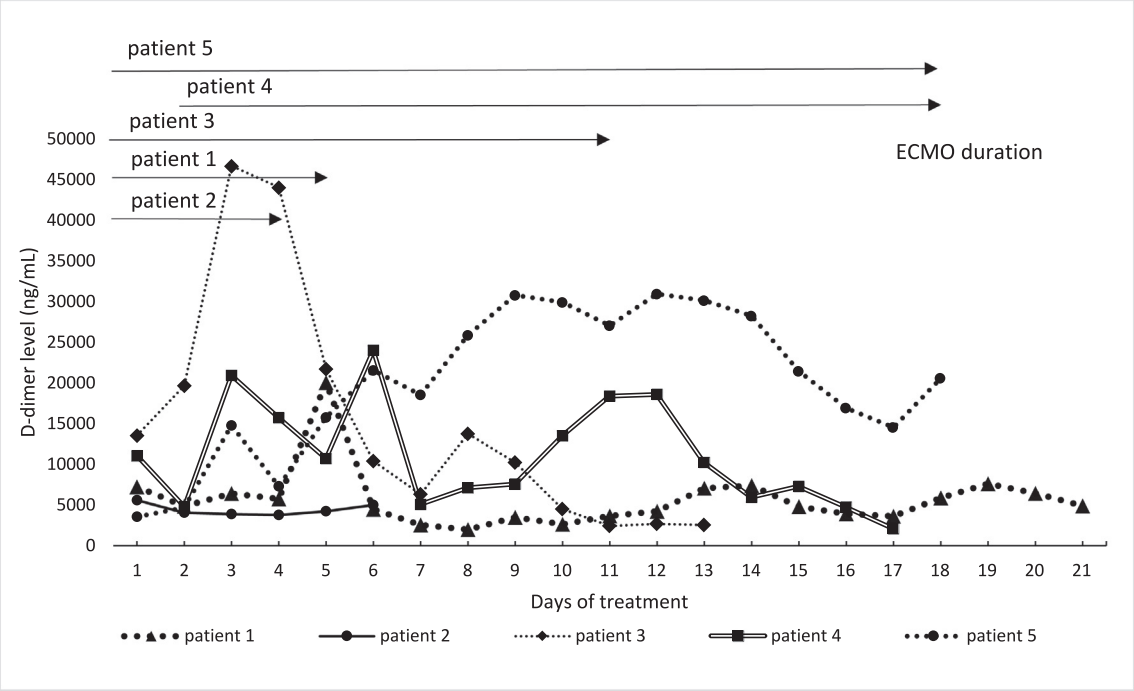

Fig. 1. D-dimers level during the treatment. D-dimer levels (mg/L) during critical care in particular patients. Patients 1 and 2 were successfully weaned off extracorporeal membrane oxygenation (ECMO) and discharged from hospital. Patient 3 was weaned off ECMO but did not survive until discharge from the intensive care unit. Patients 4 and 5 died during ECMO. Arrows denote ECMO duration in days in particular patients.

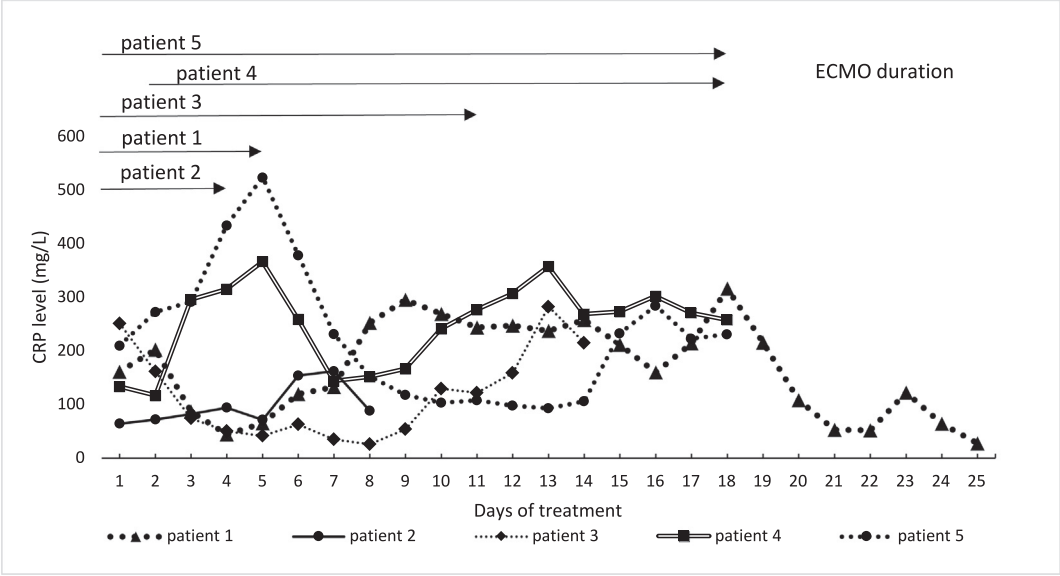

Fig. 2. C-reactive protein level during the intensive care unit treatment. C-reactive protein levels (mg/L) during the intensive care unit (ICU) treatment in particular patients. Patients 1 and 2 were successfully weaned off extracorporeal membrane oxygenation (ECMO) and discharged from hospital. Patient 3 was weaned off ECMO but didn't survive until discharge from ICU. Patients 4 and 5 died during ECMO. Arrows denote ECMO duration in days in particular patients. CRP: C-reactive protein.

was the ninth day after the onset of symptoms (6–14 days). In the study by Barrantes et al., ECMO was initiated at 6.5 days.[7] Complications including pneumothorax and subcutaneous emphysema were usually present at the start of ECMO therapy. Two patients required renal replacement therapy. Our findings on the prevalence of acute kidney injury in the study population correspond with its prevalence in patients supported with ECMO before the COVID-19 pandemic (47%) and in patients during the critical course of COVID-19 (44%).[5,9] The cause of death in two patients was respiratory failure, and one patient developed hemorrhagic shock that led to multi-organ failure.

Anticoagulation, bleeding, and thrombotic complications

Anticoagulation in critically-ill parturients during ECMO is particularly difficult. The triad of factors that strongly influence the coagula-

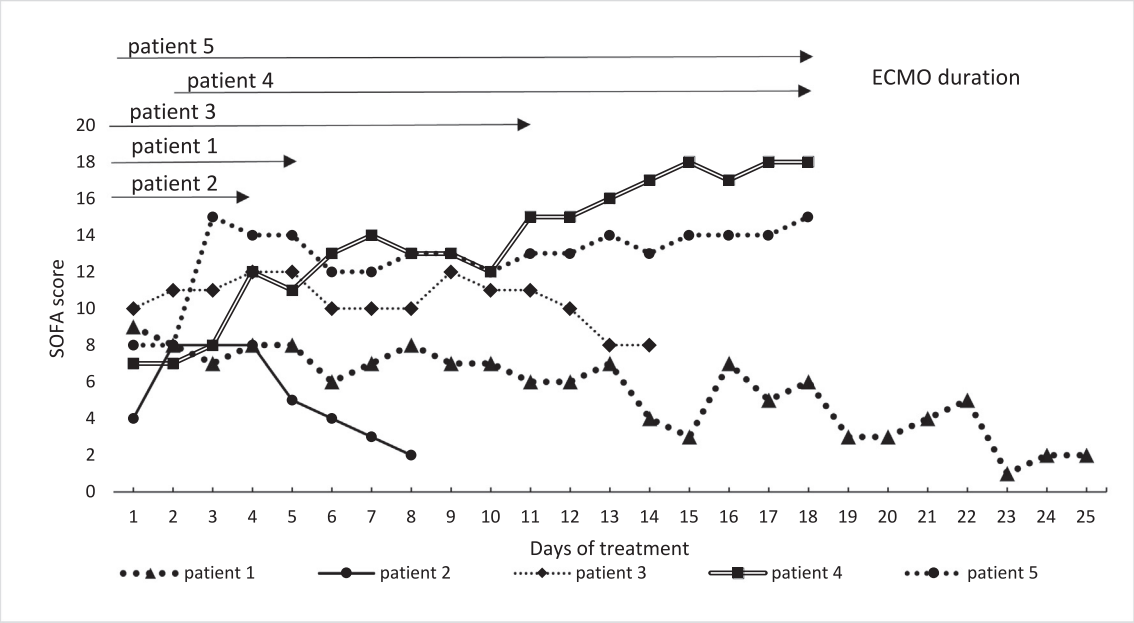

Fig. 3. The sequential organ failure assessment (SOFA) score during the intensive care unit (ICU) treatment in particular patients. Patients 1 and 2 were successfully weaned off ECMO and discharged from hospital. Patient 3 was weaned off ECMO but did not survive until discharge from ICU. Patients 4 and 5 died during ECMO. Arrows denote ECMO duration in days in particular patients.

Table 2
Newborn/fetal characteristics

Patient	1	2	3	4	5
Fetal monitoring during ECMO (CTG/US/other/none)	US	US	US	US	US
Apgar score (1/5 min)	10/10	9/10	3/4	10/10	4/6
Gestational age (weeks)	(24)/36	33	29	36	28
Admission to NICU	No	No	Yes	No	Yes
COVID status	Negative	Negative	Negative	Negative	Negative
Congenital abnormalities	None	None	Hydrocephalus	None	RDS
Mechanical ventilation	No	No	Yes	No	Yes
Catecholamines	No	No	Yes	No	No
Newborn survival to hospital discharge	Yes	Yes	No	Yes	Yes

CTG: cardiotocography. US: ultrasound. NICU: neonatal intensive care unit. RDS: respiratory distress syndrome. ECMO: extracorporeal membrane oxygenation (gestational age of fetus at the time of ECMO initiation in patient 1).

tion cascade involve contact with the extracorporeal circuit and the prothrombotic state present during pregnancy and critical courses of COVID-19.[10,11] In comparison with the case series that reported 22% cases of circuit/oxygenator thrombosis, we did not observe signs of this complication in our study group.[7] Clotting was not detected during routine ultrasonographic inspections of the deep veins of the lower limbs of our patients. The other commonly reported adverse event in parturients during ECMO in critical courses of COVID-19 is bleeding, present in 18.4% to 22.2%.[7,12,14] Bleeding requiring transfusion was present in three patients from our study group; in one case, although timely treatment with blood products and fibrinogen concentrate was initiated, the patient developed hemorrhagic shock and died. According to our center's experience before the COVID-19 pandemic, anti-Xa-guided subcutaneous nadroparin was used for anticoagulation during ECMO support.[13] This mode of anticoagulation during ECMO, although performed by less than 4% of centers, has been reported to be feasible and safe in observational trials and case series.[14–15]

Obstetric complications

In the present case series, all five pregnancies were terminated with cesarean delivery, and two newborns required neonatal ICU because of prematurity. Systematic reviews and cohort studies on the complications in this population show that the rate of delivery before 30 weeks of gestation increased from 10% prior to the pandemic to 15% in parturients infected with COVID-19.[16–17] If COVID-19 infection occurs in the third trimester of pregnancy, the rate of preterm delivery may be as high as 43%.[16] A systematic review performed on 435 parturients with COVID-19 found that although only eight women (1.8%) required ICU care, the rate of cesarean delivery reached 85%.[18] Thus, any attempts to seek an association or causal relationship between the severity of the infection and preterm labor is associated with treatment bias, as many clinicians decide to perform cesarean delivery for fear of unknown complications in the mother and the fetus.

Interpretation of this study is limited by its small sample size and retrospective nature. In light of the scarce information on the management of critically-ill pregnant and peripartum SARS-CoV-2-infected patients, the case series may add to the knowledge on this issue and aid the decision-making process at the bedside. Although the maternal survival rate in the present cohort was lower than in previous series, our study elucidates the patients' full treatment courses, including hemodynamic and laboratory variables.[5]

Pregnancy should not be considered a contraindication for initiation of ECMO during a critical course of COVID-19. The use of ECMO

is feasible in the third trimester of pregnancy but not devoid of complications. The severity of respiratory failure during COVID-19 and extracorporeal support may not adversely impact neonatal outcomes.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijoa.2023.103625.

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