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Case Report

Venovenous Extracorporeal Membrane Oxygenation for COVID-19 in Postpartum Patients: 1-Year Outcome

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DURING THE PANDEMIC, a significant number of patients with severe coronavirus disease 2019 (COVID-19) pneumonia required intensive care. Among these, peripartum women were particularly susceptible to severe respiratory symptoms. This complex pathophysiology involves mechanical and hormonal pathways, including the presence of lung restriction,[1] modulation of the immune system by pregnancy,[2] and increased oxygen demand.[3] Additionally, a high level of vaccine hesitancy in this population meant that most pregnant women were not vaccinated during the COVID-19 pandemic.[4] Furthermore, the usual measures to improve alveolar ventilation are limited in these patients, such as increasing ventilatory pressures to optimize invasive mechanical ventilation, prone positioning, and the administration of muscle relaxants. Consequently, a considerable cohort of pregnant women with COVID-19 develops severe hypoxemic respiratory failure.[5] When severe hypoxemia and/or severe hypercapnia with uncompensated respiratory acidosis persist despite conventional intensive therapies, extracorporeal respiratory support may be considered, according to the revised guidelines of the Extracorporeal Life Support Organization.[6,7]

Despite the considerable complex medical challenges with emotional and social impact, there are only a limited number of case reports,[8] case series,[9,10] registry analyses[5,11] and a retrospective multicenter cohort study[12] presenting the management and outcomes of peripartum women supported by venovenous extracorporeal membrane oxygenation (V-V ECMO) during the COVID-19 pandemic. In this case series, we describe the clinical course of 3 postpartum women who required V-V ECMO support immediately after their urgent caesarean sections.

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Table 1
Demography and Clinical Parameters

	Patient 1	Patient 2	Patient 3
Demographics			
Age (years)	26	28	30
Height (cm)	160	153	170
Weight (kg)	108	81	70
Gestational age at CS (weeks)	34	27	38
Severity scores (points)			
APACHE II	9	14	13
LISS	3.3	3.5	3.25
RESP	7	7	7
Pre-ECMO time (days)			
Positive SARS CoV-2 PCR	16	4	10
Hospital admission	4	4	10
Time NIV	1	1	8
From intubation	2	3	1
Pre-ECMO ventilation			
Mode	PCV	PRVC	PCV
F_iO_2 (%)	100	100	100
$P_{driving}$ (cmH_2O)	15	19	26
PEEP (cmH_2O)	10	12	8
Prone position	Yes	Yes	Yes
Pre-ECMO blood gas parameters			
PaO_2 (mmHg)	70	81	65
$PaCO_2$ (mmHg)	70	57	55
pH	7.20	7.28	7.31
ECMO management			
Duration on ECMO (days)	25	10	70
No. of oxygenators	1	1	4
Prone position	No	No	Yes
Pneumothorax	No	No	Yes
Post-ECMO outcomes			
Duration of IMV (days)	35	11	73
ICU LOS (days)	38	29	91
Hospital LOS (days)	41	34	97
Pneumothorax	No	No	Yes

Abbreviations: APACHE II, Acute physiology and chronic health evaluation; CS, cesarian section; ECMO, extracorporeal membrane oxygenation; F_iO_2, fraction of inspired oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; LISS, Lung Injury Severity Score; LOS, length of stay; NIV, noninvasive ventilation; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PCR, polymerase chain reaction; $P_{driving}$, driving pressure; PEEP, positive end expiratory pressure; RESP, respiratory ECMO survival prediction; SARS CoV-2, severe acute respiratory syndrome coronavirus-2.

Methods

Demographic and clinical characteristics of the patients are presented in Table 1. All women already had 2 older children, and this was their third child delivered by cesarean section.

The management of the 3 patients was identical in various aspects of the ECMO support. For all patients, the femorojugular configuration was applied with percutaneous cannulation, guided by vascular ultrasound examination and transesophageal echocardiography. Extracorporeal blood flow and sweep gas flow were adjusted to maintain arterial oxygen saturation of >90% and a normal pH. During the ECMO run (Maquet Cardiohelp, Getinge AB, Sweden), mechanical ventilation was used with rest parameters by applying a fraction of inspired oxygen (F_iO_2) of 40%, a ventilation rate of 10/min, driving pressure of 10 cmH_2O, and a positive end-expiratory pressure of 10 to 14 cmH_2O. These settings ensured optimal respiratory mechanics and prevented the deleterious effects of prolonged exposure to high oxygen concentrations.

In all patients, anticoagulation was achieved by administering unfractionated heparin to target an activated clotting time of 160 to 180 seconds. Patients received the recommended dose of remdesivir (100 mg, intravenously [IV], once daily), methylprednisolone (40 mg, IV, twice daily), and vitamin D_3 (3,000 IU, enteral route, daily) according to the current Hungarian national guidelines available.[13] A gynecologist performed regular postpartum assessments. bromocriptine was administered (2.5 mg tablets, enteral route, twice a day) to suppress lactation. They were sedated with infusion of propofol (2−3 mg/kg/h), sufentanil (10 μg/h) or fentanyl (100 μg/h), and midazolam (0.5−5.0 mg/h) targeting Richmond Agitation and Sedation Score of −5. During the initiation of ECMO, a muscle relaxant (rocuronium bromide, 0.6−1.0 mg/kg, IV bolus and maintenance as needed) was administered.

The weaning process from ECMO began once lung compliance approached the normal range (0.5−0.8 mL/cmH_2O/kg) during ventilation. Subsequently, extracorporeal blood flow was gradually decreased to 2.5 to 3.0 L/min, along with a simultaneous and gradual decrease in sweep gas flow to zero. The ECMO cannulas were removed after maintaining a partial pressure of arterial oxygen (PaO_2)/ F_iO_2 ratio of 300 for a minimum of 5 hours without sweep gas. Sedation was then progressively decreased, and the patients were weaned from mechanical ventilation. The tracheostomy cannula was removed once the patients regained consciousness and muscle strength, and they were able to sustain physiological gas exchange and clear airway secretions.

A follow-up assessment was performed 6 months and 12 months after hospital discharge. We determined the modified Rankin score and health-related quality of life assessment.[14,15] These assessments revealed that all 3 women resumed normal physical activities, and their babies demonstrated normal physical and cognitive development. Furthermore, these patients participated in a follow-up respiratory assessment in a larger cohort[16]; the data from these 3 individual patients underwent secondary analyses and are reported in the present case series accordingly. Within these assessments, spirometry was performed to measure forced expiratory volume in the first second of expiration (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF), and forced expiratory flow between 25% and 75% of expired volume. Diffusing capacity of carbon monoxide (DLCO), carbon monoxide transfer coefficient (KCO), and alveolar volume (VA) were determined using a single-breath method. Whole-body plethysmography was used to assess functional residual capacity (FRC) and expiratory reserve volume (ERV). The forced oscillation technique was applied to measure total respiratory system resistance at 5 and 19 Hz (R_5, R_{19}) to characterize total and central airway resistances, respectively. Additionally, the area under the reactance curve (AX_5) was also evaluated to assess respiratory tissue stiffness. Small airway function was assessed by calculating the difference between the R5 and R19 ($R_5−R_{19}$). Parameters related to

Table 2
Parameters Related to Respiratory Function

	6-Month Follow-up			12-Month Follow-up		
	Case 1	Case 2	Case 3	Case 1	Case 2	Case 3
Spirometry						
FEV_1 (% predicted)	94.6	102.2	73.7	104.4	109.6	88.7
FVC (% predicted)	86.8	92.0	71.7	97.7	110.3	94.0
FEF_{25-75} (% predicted)	178.5	113.0	87.3	184.4	124.5	109.1
PEF (% predicted)	120.4	97.0	109.9	147.1	126.8	114.9
Diffusion capacity						
DLCO (% predicted)	82.0	70.6	60.3	83.5	87.1	64.7
VA (% predicted)	88.3	93.7	74.7	85.8	99.5	84.2
KCO (% predicted)	95.9	77.8	83.0	105.0	90.3	79.1
Plethysmography						
FRC (% predicted)	70.1	87.7	80.0	71.4	79.8	90.4
ERV (% predicted)	68.7	79.6	72.1	67.5	75.9	96.7
Forced oscillations						
R_5 (% predicted)	64.5	75.7	108.8	72.6	82.7	120.5
AX_5 (% predicted)	106.7	68.4	253.0	103.6	59.7	214.8
R_{19} (% predicted)	59.7	74.8	97.4	73.8	83.7	103.7
R_5-R_{19} ($cmH_2O.s/L$)	0.76	0.26	0.20	0.82	0.32	0.43
Body weight (kg)	110	82	70	120	85	72
Rankin score	0	0	1	0	0	0

NOTE. Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), forced expiratory flow between 25% and 75% of the volume expired (FEF_{25-75}), and peak expiratory flow (PEF) were measured by spirometry. Diffusing capacity of carbon monoxide (DLCO), alveolar volume (VA) and carbon monoxide transfer coefficient (KCO) were assessed by gas diffusion test. Functional residual capacity (FRC) and expiratory reserve volume (ERV) were measured by whole body plethysmography. Respiratory system resistance at 5 and 19 Hz (R_5, R_{19}), and the area under the reactance curve (AX_5) was evaluated using respiratory oscillometry characterizing total and central airway resistances, and tissue elasticity, respectively. The difference between R_5 and R_{19} reflecting small airway function was also calculated ($R_5 - R_{19}$). Rankin score is based on a 6-min walk test and health-related quality of life assessment.

the respiratory function of the three patients are summarized in Table 2.

Case Reports

Case 1

A 26-year-old pregnant woman presented with upper airway symptoms and was tested positive for severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) at the 32nd week of gestation. Ten days later, she was admitted to the emergency department with an oxygen saturation of 60% on room air. A chest radiograph revealed bilateral patchy infiltrates indicative of COVID-19 pneumonia. Despite oxygen therapy, her condition worsened, necessitating an urgent caesarean section under regional anesthesia with noninvasive ventilation (NIV) at 100% F_iO_2. After delivery, she was admitted to the intensive care unit (ICU), intubated, and mechanically ventilated on the first postpartum day due to severe respiratory failure. Prone positioning was also performed for better oxygenation. On the following day, she was referred to the regional tertiary center's ECMO service. An expert team from this center was mobilized to initiate ECMO support at the county hospital in Gyula, Hungary. Subsequently, she was transferred to our center with ongoing mobile ECMO support. Standard ECMO support continued, as detailed above. Alongside ongoing COVID-19−specific treatment, ceftriaxone (1 g, IV twice daily) was added due to suspected bacterial superinfection. Owing to insufficient improvement in respiratory mechanics and gas exchange, as estimated by a 100% oxygen test, a percutaneous tracheostomy was performed on the day 12 of ECMO support. On day 20 of ECMO support, she developed a fever, and her serum procalcitonin level increased. Microbiological sampling confirmed catheter-related bloodstream infection and ventilator-associated pneumonia caused by multidrug-resistant *Acinetobacter baumannii*, leading to the initiation of colistin therapy (3 million IU, IV 3 times daily). Additionally, she developed purulent sinusitis and corneal ulceration with purulent keratitis in her right eye, caused by *Pseudomonas aeruginosa*. These conditions were treated with specific nasal drops of oxymetazoline hydrochloride (2 drops into each nasal opening, 4 times daily) and topical antibiotics (neomycin and dexamethasone/tobramycin 5−7 times daily) along with a cycloplegic solution (cicloplegicedol drops locally, 4 times daily). On day 25 of ECMO, after a 5-hour period without the sweep gas, she was successfully weaned from ECMO. However, an additional 10 days of mechanical ventilation was needed to wean from the ventilator. Two days after ventilator weaning, her tracheostomy cannula was removed. She left the ICU for a rehabilitation facility 38 days after ECMO initiation.

After 6 months, there were no signs of abnormalities in the central conductive airways as indicated by the spirometric (FEV_1, FEF_{25-75}, and PEF) and forced oscillometry (R_5 and R_{19}) outcomes. However, small airway dysfunction was detectable from the $R_5−R_{19}$ data, which was associated with moderate lung restriction indicated by the diminished

FVC, FRC, VA, and ERV. The decreased DLCO without alterations in the KCO suggests loss of alveolar surface, with maintained ventilation and perfusion in the working lung compartments. These mild respiratory symptoms allowed her to perform daily activities and care for her family without exhaustion, although she continued receiving treatment for her eye injury. After 12 months, there was a mild improvement in the mechanical properties of the conducting airways in KCO. However, no improvement was observed in small airway function or lung volumes, which can be attributed to the opposing effect of respiratory regeneration and increase in body mass.

Case 2

A 28-year-old woman with no history for major diseases tested positive for SARS CoV-2 at the 26th gestational week of pregnancy. She was admitted to the ICU at the county hospital in Kecskemét, Hungary. She received close monitoring and high-flow nasal cannula therapy. Her respiratory failure rapidly deteriorated, necessitating the imitation of NIV. An urgent caesarean section was performed under general anesthesia and invasive ventilation. After surgery, ventilation in the prone position was applied due to severe hypoxemia, with a PaO_2 of 60 mmHg while maintaining an F_iO_2 of 100% and high positive end-expiratory pressure of 12 cmH_2O. Although a temporary improvement in PaO_2/F_iO_2 was observed under this condition, her oxygenation worsened again after supine repositioning. This led to a referral for V-V ECMO support. Our mobile ECMO team initiated the extracorporeal life support, and she was subsequently transferred to our tertiary center to continue standard ECMO support, as detailed elsewhere in this article. We continued invasive mechanical ventilation on rest settings under deep sedation, and she also received her COVID-19–specific therapy, as detailed elsewhere in this article. After 10 days of extracorporeal support, the tidal volume on rest ventilation setting normalized, allowing weaning from ECMO and decannulation. On the next day, the level of sedation was decreased, and she was successfully weaned from the ventilator and extubated. As a part of the postdecannulation routine examination, Doppler ultrasound examination revealed mural thrombi at both cannulation sites, prompting the initiation of enoxaparine in a therapeutic dose (80 mg, subcutaneously, twice daily). On day 14 of her ICU stay, she became febrile without elevation in the procalcitonin level (0.10 ng/mL). Samples for microbiological examination were collected. Abdominal ultrasound examination confirmed the presence of a hematoma anterior to the uterus. Ultrasound-guided drainage was performed, and amoxicillin/clavulanic acid (1.2 g, IV, 3 times daily) was started IV. Meanwhile, her oxygen demand increased, necessitating the start of intermittent NIV therapy, alternating with high-flow nasal cannula administration. As the overall status of the patient deteriorated and hemodynamic instability occurred, we empirically escalated the antimicrobial therapy to imipenem/cilastatin (1 g, IV, 4 times daily), despite previous cultures still being negative. A few days later, her gas exchange improved, the fever resolved, and the procalcitonin level returned to the normal range. Control abdominal ultrasound examination showed no residual hematoma, allowing for the discontinuation of antibiotic therapy. After mobilization, she was discharged on day 29 to a rehabilitation facility and was able to return home in good general condition 5 days later.

At the 6-month follow-up, this patient showed no evidence of airway abnormalities, either in the central conductive airways as indicated by the normal spirometric (FEV_1, FEF_{25-75}, and PEF) or forced oscillometry outcomes (R_5 and R_{19}, and R_5-R_{19}). The mild lung restriction affected the expiratory lung volumes only (FRC and ERV). The decreased DLCO was associated with diminished KCO, suggesting gas diffusion abnormalities through the alveolo-capillary barrier. However, the Rankin score demonstrated the maintenance of normal daily activities. After 12 months, the patient exhibited no obvious change in her lung function outcomes. The slight further decreases in FRC and ERV could be explained by the slight gain in body mass.

Case 3

A 30-year-old woman at the 38th week of her pregnancy tested positive for SARS-CoV-2 and was presented to the emergency department 2 days later due to fever and mild dyspnea. She had no earlier medical history for major diseases. She underwent an uncomplicated caesarean section under spinal anesthesia while receiving 3 L/min oxygen through a nasal cannula. A postpartum chest computed tomography (CT) scan showed a pneumonia severity index of 3 to 4, reflecting lung involvement of approximately 50%.[17] She was admitted to the ICU, where her respiratory failure rapidly progressed, necessitating immediate NIV. NIV therapy with an F_iO_2 of 100% was continued for the next 8 days. Repeated chest CT scan revealed radiological progression to pneumonia severity index of 5 (ie, >75% lung involvement[17]) accompanied by segmental pulmonary embolism and pneumomediastinum with subcutaneous emphysema. On postpartum day 10, her hypoxemic respiratory failure worsened, necessitating urgent endotracheal intubation and prone positioning. Subsequently, she was referred to and accepted for ECMO support and transferred to our ICU. ECMO was initiated as detailed elsewhere in this article, and she was ventilated with rest settings. From day 6 on ECMO, the respiratory system compliance deteriorated to 2 to 5 mL/cmH_2O, and the patient became completely ECMO dependent. Prone positioning was applied to facilitate lung aeration. From day 9 of ECMO, asystolic periods occurred frequently, requiring the administration of 0.5 mg atropine IV and occasionally chest compressions. However, echocardiography revealed no cardiac dysfunction, leading to the assumption of a vasovagal mechanism. During the second week of ECMO, there was an increase in the amount of the purulent tracheal secretion and inflammatory markers, with procalcitonin levels increasing from <0.06 ng/mL to 0.27 ng/mL and C-reactive protein increasing from 140 mg/L to 331 mg/L in 24 hours. After microbiological sampling, empiric antibiotic therapy with meropenem was initiated (1 g, IV, 3 times daily). *Klebsiella*

pneumoniae and *Streptococcus pneumoniae* were isolated from the tracheal secretions. Based on their sensitivities, we were able to de-escalate to ceftriaxone (1 g, IV twice daily). Although the procalcitonin level decreased below 0.5 ng/mL by day 7 of administration, her gas exchange remained completely dependent on ECMO. Consequently, a chest CT scan performed on day 13 revealed progression of the lung injury. In the next 2 days, the patient was repeatedly placed in the prone position for 16 to 20 hours per day. Percutaneous tracheostomy was performed on day 20, and the subsequent chest radiography revealed a complete left-sided pneumothorax. After chest drain insertion, an air leak comprising 70% to 80% of inspiratory minute volume was observed, mechanical ventilation was completely ceased for the next 14 days. Sedation was deepened to decrease her oxygen consumption administering additional 0.4% to 0.6% v/v sevoflurane through the oxygenator and continuous IV administration of thiopental (maximum 200 mg/h), in addition to the IV fentanyl (200 μg/h), propofol (200 mg/h), midazolam (30 mg/h), and clonidine (225 μg/h), along with the application of mild hypothermia (36°C). The patient was subsequently referred to the National Institute of Oncology, Budapest, Hungary for consideration for lung transplantation. However, she remained SARS CoV-2 positive and exhibited high levels of anti-human leukocyte antigen antibodies (>5,000 mean fluorescent intensity), which precluded lung transplantation. After 11 days, it became feasible to restart invasive mechanical ventilation, allowing for gradual increases in respiratory support. On day 42 of ECMO, the patient developed septic shock, necessitating high doses of vasopressors (norepinephrine 40 μg/min and vasopressin 2.4 IU/h). Broad-spectrum empiric antibiotic therapy was initiated with meropenem (1 g, IV, 3 times daily) and IV linezolid (600 mg, IV, twice daily). Subsequently, *Klebsiella pneumoniae* was isolated from blood cultures. Oxygen balance was inadequate due to high cardiac output and increased oxygen consumption, necessitating the use of β-blocker therapy with bisoprolol (5 mg, enteral route, twice daily) and heart rate control with ivabradine (15 mg, enteral route, twice daily). After resolving the nosocomial bloodstream infection, respiratory system compliance slowly improved, allowing a decrease in the level of sedation. She regained consciousness, but suffered from severe critical illness polyneuromyopathy. With the assistance of physiotherapists and a psychologist, her condition gradually improved. After 70 days of ECMO support, she was weaned successfully from the extracorporeal circulation and decannulated. She was weaned finally from the ventilator on day 83, and the tracheostomy cannula was removed 2 days later. The patient was discharged to a rehabilitation facility on day 91 and eventually sent home with minimal need for oxygen supplementation.

Lung function assessment 6 months after discharge showed marked lung restriction, as evidenced by markedly elevated AX_5 and deteriorated FVC, VA, FRC, and ERV. This resulted in a mild elevation in the tone of the central conducting airways. Persistent gas diffusion abnormalities through the alveolocapillary barrier were indicated by the decreased DLCO and diminished KCO. This decrease in lung function was also reflected in her Rankin score. After 12 months, there was an improvement in lung restriction, as shown by improvements in AX_5, spirometric parameters, DLCO, and plethysmographic measures. Accordingly, the improved Rankin score parallelled these beneficial pulmonary changes.

Discussion

In this case series, we present 3 postpartum patients who required V-V ECMO support due to life-threatening COVID-19 pneumonia. Extracorporeal life support durations were 25 and 10 days for cases 1 and 2, respectively; the third patient required an extended 70-day ECMO course, including an interim 2-week period without mechanical ventilation. Life support was successful for all 3 women. At the 6-month follow-up, the patients exhibited good general physical condition, characterized by Rankin scores of 0 to 1, and moderately impaired lung function, primarily restrictive in nature. At the 12-month follow-up, improvements in both physical condition and lung function were observed for all 3 patients, as evidenced by uniform Rankin scores of 0 and only mild restrictive lung function impairment.

Application of V-V ECMO during pregnancy was considered even before the COVID-19 era, particularly in cases of severe respiratory failure. From 1997 to 2017, the Extracorporeal Life Support Organization Registry recorded 280 peripartum women.[11] In this report, the overall maternal survival rate was 70%, with a noticeable decrease in the mortality among these patients over the 21-year period. Subsequently, numerous case reports and small case series documented the benefits of V-V ECMO support during the H1N1 influenza pandemic, including for pregnant and peripartum patients.[18-20] Furthermore, a previous review and meta-analysis, which included all available case reports and case series of extracorporeal life support in pregnancy, identified 177 cases of acute respiratory distress syndrome as the most common indication in the study. This analysis reported a survival rate of 79.7%.[21] These findings have contributed to the global promotion of the ECMO use, and our small cohort of peripartum cases reaffirms the particular value of this life-saving modality during the peripartum period.

Pregnant women were affected by the COVID-19 pandemic, with concerns about increased vulnerability due to characteristic metabolic and immunological changes, alongside restrictive lung disorder. Indeed, the UK Obstetric Surveillance System reported an increased risk of hospitalization and ICU admission for pregnant women with symptomatic SARS-CoV-2 infection.[22] Although the absolute risk for a poor outcome was low, there was an increase in caesarean deliveries and neonatal unit admissions.[22] Nevertheless, ECMO support in pregnant or postpartum patients with COVID-19 is often required in cases of severe pneumonia, and there is a considerable survival from the acute phase of the respiratory distress.[9,10] Similar outcomes were reported recently in the Extracorporeal Life Support Organization Registry, which included 100 pregnant or peripartum women with severe SARS-CoV-2 infection. This registry documented an 84% in-hospital survival rate,

with no excessive ECMO-related complications during the hospitalization period.[5]

Although outcomes after ECMO support in postpartum women have been documented in a few previous studies,[9,10] there have been no earlier reports detailing the postdischarge period for this patient population. Our results in this case series indicate no major airway abnormalities, even 6 months after hospital discharge. However, moderate lung volume loss is evident, as reflected by the peripheral airway resistance in case 1, and in the diminished static lung volumes and gas diffusion indices observed in all 3 patients. At the 1-year follow-up, beneficial changes in lung function parameters were observed in all 3 patients, aligning with those observed in nonpregnant population who received ECMO support for COVID-19 pneumonia.[23-25] However, the weight gain of >10% in case 1 may have masked the intrinsic improvements in lung function outcomes. This finding underscores the importance of lifestyle counseling in post-COVID care. The lack of severe lung function defects is in accordance with the fairly normal Rankin scores obtained during the 1-year follow-up period.

In conclusion, all peripartum patients who received ECMO support for their COVID-19 pneumonia experienced favorable outcomes. They maintained good health-related quality of life during the 6- to 12-month follow-up period, despite undergoing prolonged, complex, and complicated life support therapy. This case series contributes to the understanding of the potential benefits of early and optimal consideration of ECMO support, even in the peripartum period.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

CRediT authorship contribution statement

Alexandra Pálfi: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Éva Zöllei:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Zoltán Varga:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation. **László B. Tomozi:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation. **Domonkos Schulcz:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation. **Gábor Bari:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation. **Ferenc Peták:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Fruzsina Kun-Szabó:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Kristóf Baráth:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation. **László Rudas:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Ádám L. Balogh:** Writing – review & editing, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Barna Babik:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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