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Extracorporeal membrane oxygenation for severe ARDS in pregnant and postpartum women during the 2009 H1N1 pandemic

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Abstract *Purpose:* To describe the technical challenges, efficacy, complications and maternal and infant outcomes associated with extracorporeal membrane oxygenation (ECMO) for severe adult respiratory distress syndrome (ARDS) in pregnant or postpartum patients during the 2009 H1N1 pandemic. *Methods:* Twelve critically ill pregnant and postpartum women were included in this retrospective observational study on the application of ECMO for the treatment of severe ARDS refractory to standard treatment. The study was conducted at seven tertiary hospitals in Australia and New Zealand. *Results:* Of the 12 patients treated with ECMO, 7 (58%) were pregnant and 5 (42%) were postpartum. Their median (interquartile range [IQR]) age was 29 (26–33) years, 6 (50%) were obese. Two patients were initially treated with veno-arterial (VA) ECMO. All others received veno-venous (VV) ECMO with one or two drainage cannulae. ECMO circuit-related complications were rare, circuit change was needed in only two cases and there was no sudden circuit failure. On the other hand, bleeding was common, leading to relatively large volumes of packed red blood cell transfusion (median [IQR] volume transfused was 3,499 [1,451–4,874] ml) and was the main cause of death (three cases). Eight (66%) patients survived to discharge and seven were ambulant, with normal oxygen saturations. The survival rate of infants whose mothers

received ECMO was 71% and surviving infants were discharged home with no sequelae. *Conclusions:* The use of ECMO for severe ARDS in pregnant and postpartum women was associated with a 66% survival rate. The most common cause of death was bleeding. Infants delivered of mothers who had received ECMO had a 71% survival rate and, like their mothers, had no permanent sequelae at hospital discharge.

Keywords Extracorporeal membrane oxygenation · Pregnancy · H1N1 influenza pandemic · ARDS

Introduction

Extracorporeal membrane oxygenation (ECMO) is a method for supporting patients with severe adult respiratory distress syndrome (ARDS) refractory to mechanical ventilation [1–3]. ECMO has been used in neonates and children with satisfactory outcomes [4, 5]. More recently, technical advances have enabled its safer application in adults [3, 6]. Among such adults, occasional patients have been supported with ECMO while pregnant or in the postpartum period. Such treatments have led to individual case reports only [7–15]. This lack of information makes it difficult to assess the safety and efficacy of this procedure in pregnant women and to estimate how it might affect maternal and/or infant outcome.

In the winter of 2009, 760 patients were admitted to intensive care units (ICUs) in Australia and New Zealand with the pandemic swine-origin (H1N1) influenza [16]. ECMO was used in 68 adult patients who had either H1N1 influenza or strongly suspected H1N1 influenza [17]. Of these, 10 were pregnant or postpartum, which were described as part of the published cohort [17]. Two patients presented immediately subsequent and were added to aggregate to a series of 12, thereby providing the largest source of information to date on the safety and efficacy of ECMO during pregnancy. Accordingly, we now report on the various technical aspects and challenges of ECMO therapy in this cohort of pregnant and postpartum women with severe respiratory failure and describe maternal and infant outcomes.

Methods

Study design

Data collection was approved by the relevant human research ethics committees. We collected information on all pregnant and postpartum women (within 28 days of delivery) treated with ECMO for confirmed or strongly suspected 2009 H1N1 influenza-associated respiratory failure during the 2009 winter period (June 1st through September 30th) in the ICUs that provided ECMO support in Australia and New Zealand.

Women who were postpartum at the time of ECMO commencement, but pregnant at the onset of influenza were included as they still had the anatomical, physiological and immunological alterations associated with pregnancy.

Data collection

Please see the electronic supplementary material (ESM) for details of data collection and statistical analysis.

Results

Patient characteristics at the time of ECMO commencement

Of the 12 patients treated with ECMO, 7 (58%) were pregnant and 5 (42%) were postpartum. The median (IQR) age was 29 (26–33) years. The associated comorbidities are summarized in Table 1. A diagnosis of H1N1 infection was confirmed in 10 (83%) patients, 1 had positive serology for influenza A and 1 had clinical features highly suggestive of influenza during a pandemic. Details regarding the severity of ARDS and the ECMO technical characteristics are described in the ESM and Table 1.

Details of ICU support

The median (IQR) duration of mechanical ventilation was 25 (18–32) days. Seven (58%) patients required a tracheostomy to facilitate weaning from ventilation. All 12 patients received packed red blood cell transfusion during ECMO therapy. The median (IQR) volume of blood transfused per patient during ECMO therapy was 3,499 (1,451–4,874) ml. Five patients required platelet transfusions, 3 of who also required fresh frozen plasma. All patients received vasoactive drug infusions at some time during ECMO therapy.

The median (IQR) duration of ECMO support was 14 (9–19) days. The length of ICU stay and hospital stay is reported in Table 3.

Table 1 Patient characteristics prior to initiation of ECMO therapy

Patient number	Gestation/ postpartum	Age (years)	Comorbidities	Duration of MV prior to ECMO (days)	SpO_2 (%)	PaO_2/FiO_2 ratio	$PaCO_2$ (mmHg)	Max PEEP (cm)	Rescue therapies	Other organ support
1	26 weeks	34	Obesity	<1	55	27	68	20	RM	
2	13 weeks	22	Asthma	10	88	65	99	14	PGI_2 RM	
3	21 weeks	23	Asthma Obesity	1	84	51	50	13	iNO RM	Vasoactive
4	23 weeks	33	Obesity	1	82	31	62	20	PGI_2 RM	Vasoactive
5	20 weeks	42		16	93	71	50	15	Prone iNO, RM	
6	26 weeks	39	Asthma	<1	N/A	42	54	20	iNO RM	CRRT vasoactive
7	30 weeks	29		10	90	72	102	15	Prone	Vasoactive
8	Postpartum	27	Obesity	8	81	53	60	20	Prone iNO, RM	CRRT vasoactive
9	Postpartum	29		2	92	49	38	18	Prone iNO, RM	Vasoactive
10	Postpartum	23	Diabetes	9	83	50	30	15	RM	
11	Postpartum	27	Obesity	5	91	33	60	27	RM	
12	Postpartum	32	Obesity Corrected TOF	1	92	56	89	24	iNO RM	CRRT vasoactive

Gestation was documented at time of ICU admission

BMI body mass index, *iNO* inhaled nitric oxide, *RM* recruitment manouevres, *MV* mechanical ventilation, *PGI_2* nebulised prostacyclin, *TOF* tetralogy of Fallot, *$PaCO_2$* partial pressure of carbon dioxide in arterial blood, *PEEP* positive end-expiratory pressure, *CRRT* continuous renal replacement therapy, *vasoactive* vasoactive drug infusions, *N/A* not available

Technical details

Ten (83%) patients initially received VV ECMO and 2 (17%) received VA ECMO (Table 2). VA ECMO was the initial choice in the two patients due to the finding of moderate or severe left ventricular dysfunction on echocardiography. All patients had vascular cannulae inserted peripherally by a percutaneous Seldinger technique. Six (50%) patients received an additional venous drainage line (2 drainage lines and 1 return line) as blood flow rates through the circuit were deemed inadequate for effective therapy (Table 2).

All circuits used a Quadrox D oxygenator (Maquet, Rastatt, Germany) and in 11 (92%) patients, a Jostra pump head (Maquet, Rastatt, Germany). All patients received therapeutic anticoagulation (Table 2). In 10 (83%) patients, a single circuit was utilized for the duration of the entire treatment, whereas two patients required a circuit change due to progressive failure of the initial circuit. Blood flow through the ECMO circuit at 4 and 24 h is reported in Table 2.

Outcomes

Eight (66%) patients were successfully weaned from ECMO, all of who survived to hospital discharge (Table 3). Of these, 7 (88%) were discharged home and 1 patient was discharged to a rehabilitation facility. All eight patients were ambulant at discharge with a median room air oxygen saturation of 95% (95–97). Six of the eight survivors were assessed for quality of life between 12 and 18 months after hospital discharge using the Short Form 36 (SF36v2®) tool. Their summary scores in both the physical health and mental health components were found to be similar to the Australian norms for an age- and sex-matched population. Two non-survivors were pregnant and two were postpartum. Of the four non-survivors, two died of bleeding (other than intracranial; one pulmonary and one from multiple sites), one died from intracranial haemorrhage and one of overwhelming fungal infection. Details of bleeding complications are included in Table 4.

Table 5 shows comparative outcomes between this cohort of patients and the non-pregnant cohort of 18 women of childbearing age (15–45 years) who received ECMO support during the same time period.

Complications

Eight (67%) patients suffered from bleeding complications (requiring transfusion) during ECMO support (Table 4). Seven (58%) patients acquired one or more nosocomial infection. Of the infections encountered, one was bloodstream, four were respiratory, one was urinary tract, one was line-related and five were wound infections. One maternal death was attributed to infection.

Table 2 Technical details of ECMO support

Patient number	ECMO configuration	No. of sites	Site and size of access cannula/e	Site and size of return cannula	Flow at 4 h (L/min)	Flow at 24 h (L/min)
1	V-V	2 drainage 1 return	RIJ 19, LF 23	RF 23	7.3	7.2
2	V-V	1 drainage 1 return	RF 23	LF 21	3.1	3.1
3	V-V	1 drainage 1 return	RF 21	RIJ 17	5.1	4
4	V-V	1 drainage 1 return	RF 21	LF 23	5.0	4.1
5	V-V	1 drainage 1 return	RF 23	RIJ 19	5.4	6.4
6	V-V	1 drainage 1 return	RF 22	LF 18	N/A	N/A
7	V-V	2 drainage 1 return	LF 25, RF 23	RIJ 19	3.9	4
8	V-A to V-V	2 drainage 1 return	LF 25, RIJ 21	RF 19	9.1	6.5
9	V-V	1 drainage 1 return	RF 21	RIJ 18	3	2.9
10	V-V	2 drainage 1 return	RF 23 RIJ 17	LF 21	3.4	3.9
11	V-V	2 drainage 1 return	RF 23, RIJ 17	LF 21	4.9	5.2
12	V-A to V-V	2 drainage 1 return	RF 25, RIJ 17	LF 19	6.1	6

Cannula size in French
V-V venovenous, *V-A* veno-arterial, *RF* right femoral, *LF* left femoral, *RIJ* right internal jugular, *N/A* not available

Table 3 Maternal and infant outcomes

Patient no.	Pregnant/ postpartum	ECMO duration (days)	MV duration (days)	ICU LOS (days)	Hospital LOS (days)	Maternal outcome	Infant outcome
1	Pregnant	18	34	40	43	Survived	Survived
2	Pregnant	2	17	22	27	Survived	Survived
3	Pregnant	11	22	28	42	Survived	Survived
4	Pregnant	5	16	17	26	Survived	Stillborn
5	Pregnant	20	78	83	112	Survived	Stillborn
6	Pregnant	<1	4	4	7	Died	Survived
7	Pregnant	20	30	33	33	Died	Survived
8	Postpartum	17	25	25	28	Died	Survived
9	Postpartum	10	18	20	24	Survived	Survived
10	Postpartum	27	36	35	43	Died	Survived
11	Postpartum	15	32	38	53	Survived	Survived
12	Postpartum	12	31	42	75	Survived	Survived

LOS length of stay, *MV* mechanical ventilation

Other significant complications noted were limb ischaemia in two cases in patients receiving VA ECMO (neither of which required amputation or embolectomy), and venous thromboembolism (1). No technical difficulties, such as accidental decannulation, disconnection, oxygenator failure, pump failure, haemolysis, air embolism or other circuit complications, were noted in this cohort of patients. There were no thrombotic complications.

Pregnancy and delivery details

Three patients (25%) were primigravida. The median (IQR) gestational age at the time of ICU admission for the seven pregnant patients was 24 (21–27) weeks. None of the pregnant patients were in the first trimester of pregnancy. Of the five postpartum patients, all received ECMO therapy within a week of delivery. Three of the pregnancies (38%) were complicated by pre-eclampsia

Table 4 Anticoagulation and bleeding complications

Patient number	Anticoagulation	APTT mean[a] (SD)	Bleeding site	Maternal outcome
1	Heparin	76 (23)	Nil	Survived
2	Heparin	61 (22)	Nil	Survived
3	Heparin	112 (37)	Nil	Survived
4	Heparin	152 (66)	Uterine	Survived
5	Heparin	152 (59)	Pulmonary	Survived
6	Heparin	N/A	Multiple	Died
7	Heparin	70 (12)	Intracranial	Died
8	Heparin	69 (12)	ECMO cannula	Died
9	Heparin	95 (66)	Nil	Survived
10	Heparin	54 (19)	Pulmonary	Died
11	Heparin	72 (14)	ECMO cannula	Survived
12	Heparin	76 (8)	Fasciotomy	Survived

APPT activated partial thromboplastin time, *SD* standard deviation, *N/A* not available
[a] Mean of highest daily APTT value (in seconds) achieved during ECMO therapy

Table 5 Comparison of pregnant/postpartum patient cohort with other women of childbearing age (15–45 years) who received ECMO during the same time period

Variable	Pregnant/postpartum cohort ($N = 12$)	Other women of childbearing age ($N = 18$)	p Value
Median age (IQR) (years)	28 (24–32)	34 (27–37)	0.62
Median duration of MV (IQR) (days)	24 (17–32)	22 (12–30)	0.25
Median duration on ECMO (IQR) (days)	12 (6–17)	10 (7–13)	0.32
Bleeding rate (%)	67	50	0.45
Infection rate (%)	58	67	0.71
Median ICU length of stay (IQR) (days)	27 (21–37)	21 (13–32)	0.34
Median hospital length of stay (IQR) (days)	35 (24–43)	25 (15–33)	0.51
Mortality (%)	33	28	1.0

and one patient had a placenta praevia. There were no multiple pregnancies. Three patients (25%) had a preterm operative delivery due to the severity of the maternal illness. Of the 12 patients, 5 delivered spontaneously, 2 had vacuum-assisted delivery and 5 had caesarean sections (3 patients after ECMO therapy was completed, 1 just after ECMO was commenced due to extreme severity of maternal illness and 1 prior to the commencement of ECMO therapy).

Details of infants born to mothers following ECMO therapy ($n = 7$)

Five of the 7 (71%) infants delivered after commencement of ECMO were live births (Table 3). Of the two stillborn infants, pregnancy was terminated due to the severity of maternal illness in one case and in the second, there was a spontaneous birth of a stillborn infant shortly after commencing ECMO treatment. The median gestational age at birth was 31 (25–36) weeks. The median birth weight was 1,570 (972–3,015) g. Two of the live-born infants had a low Apgar score (between 0 and 6) 5 min after birth. Four of 5 live-born infants were admitted to a special care unit for respiratory support. No congenital abnormalities were noted. All the live-born infants survived.

Discussion

Summary of principal findings

We studied the technical challenges, efficacy, complications and maternal and infant outcomes in a cohort of critically ill pregnant and postpartum patients with severe, hypoxic respiratory failure secondary to ARDS during the 2009 H1N1 pandemic who were treated with ECMO. We found that obesity (pre-pregnancy BMI >30) was common and that, despite significant right ventricular dysfunction in four patients, only two were initially treated with VA ECMO and that adequate gas exchange was achieved in all cases. Circuit-related complications were rare; circuit change was needed in only two cases and there was no sudden circuit failure. On the other hand, bleeding was common and responsible for the transfusion of large volumes of packed red blood cells and significantly contributed to three of the four deaths. Eight (66%) patients survived and seven were ambulant and

discharged with normal oxygen saturations. The survival of normal infants delivered while the mother was on ECMO was 71%.

Comparison with previous studies

Publications regarding the use of ECMO in pregnancy have, so far, only been single case reports. Of the five patients described with respiratory failure [7–11], four survived and of the five infants, three survived.

In the recent CESAR study [6], a multi-centre randomized control trial comparing transfer to an ECMO centre for ECMO therapy to conventional mechanical ventilation alone in severe ARDS (but not pregnant patients), the survival rate for ECMO therapy was 63% overall. The Australian and New Zealand observational study [17] of 68 adult patients treated with ECMO for severe respiratory failure during the winter of 2009 (of which some the patients reported in this study are a subset) reported an overall survival of 75% (95% CI 60–82%) [12].

Significance of study findings

Our study suggests that ECMO is an appropriate life supportive option in pregnant and postpartum patients with severe respiratory failure and extreme levels of hypoxia, and that when utilized in this setting, it can deliver acceptable maternal and infant outcomes. Such outcomes may be related to the very early use of ECMO, thereby limiting the duration of maternal hypoxia, hypercarbia and acidosis as well as limiting the duration of ventilator-associated lung injury. Bleeding was the most common complication of therapy and it was the major contributing factor in three deaths. This finding, the concurrent observations that no patient experienced thrombotic complications, that only two circuits required change and that none failed suddenly all indicate that these patients were likely relatively over-anticoagulated during ECMO. This may suggest the need for a conservative approach to anticoagulation during ECMO treatment in pregnant women.

Also, of clinical relevance is the observation that the presence of right ventricular dysfunction does not necessarily require VA ECMO support and that once mechanical ventilation is minimized and the right heart decompressed, the systemic circulation remains stable.

Study strengths and limitations

Our study is a retrospective case series, with the associated inherent shortcomings, including the lack of randomization of treatment to ECMO or standard care. Patient selection for ECMO and subsequent management of these challenging cases was determined by clinicians based on experience, limited current literature and local guidelines. However, equipment, policies and practices remained relatively homogenous owing to integrated intensive care services and training in our two countries. Our study does not report on the long-term pulmonary function tests of the mothers or the long-term neurological sequelae in the infants. Consequently, these results may not be generalisable to pregnant and postpartum patients who receive ECMO for other conditions. To our knowledge, however, this is the largest published series of pregnant and/or postpartum patients treated with ECMO. It includes the complete experience from our two countries during the 2009 pandemic. The propensity of the H1N1 virus to cause severe respiratory failure in young adults with an increased risk in pregnant and postpartum women [18, 19] enabled us to study a number of patients with similar lung pathology over a relatively short time span. The findings of our study have relevance to the treatment of future patients who may present with severe 2009 H1N1 ARDS in subsequent outbreaks.

Conclusions

ECMO support for severe respiratory failure is technically feasible in pregnant and postpartum patients—femoral vascular cannulation and prolonged circuit life are possible and adequate oxygenation is achievable despite the recognised augmented cardiac output. ECMO is effective, with outcomes comparable to those of non-pregnant patients, and acceptable infant outcomes. Although ECMO was relatively safe, with complication rates similar to other groups, major bleeding contributed to significant morbidity and mortality suggesting that a low anticoagulation or anticoagulation-free approach in future patients may be prudent.

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Conflict of interest None reported.

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