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Review

Veno-venous Extracorporeal Membrane Oxygenation for pregnant women with Acute Respiratory Distress Syndrome: a narrative review

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Abstract

Acute respiratory distress syndrome remains an uncommon condition during pregnancy. In patients with severe acute respiratory distress syndrome, when oxygenation or ventilation cannot be supported sufficiently using best practice conventional mechanical ventilation and additional therapies, veno-venous extracorporeal membrane oxygenation may be considered. In the past two decades, there has been increasing adoption of this technique to support adult patients with refractory acute respiratory distress syndrome. However, its use for the management of pregnant women is rare and remains a challenge. This narrative review addresses acute respiratory distress syndrome and its management during pregnancy, and then focuses on indications, contraindications, challenges, potential complications, and outcomes of the use of veno-venous extracorporeal membrane oxygenation for acute respiratory distress syndrome in the pregnant patient.

Keywords: **Acute Respiratory Distress Syndrome, Veno-venous Extracorporeal Membrane Oxygenation.**

Introduction

Acute respiratory distress syndrome (ARDS) corresponds to the rapid onset of hypoxemic respiratory failure with bilateral radiographic opacities in the absence of congestive heart failure. Fortunately, it remains an uncommon condition during pregnancy. The range of reported prevalence for ARDS in gravid patients suggests regional variation as well as concerns regarding diagnostic precision[1]. In an American cohort of 2,808 pregnant patients with ARDS who underwent mechanical ventilation, the occurrence rate of this syndrome increased from 36.5 cases per 100,000 live births in 2006 to 59.6 cases per 100,000 live births in 2012[2].Whether ARDS is more or less common in the obstetric population remains unclear[3]. ARDS in pregnancy is complicated by prolonged maternal ventilation and high rates of perinatal asphyxia, fetal heart rate abnormalities and spontaneous preterm births[4,5]. Maternal mortality associated with ARDS is elevated and ranges from 10 to more than 50%,[4] while fetal perinatal mortality rates are estimated around 20-25%[5]. Therefore, improving the management of ARDS during pregnancy to reduce complications and maternal-fetal mortality is of critical importance.

In 2012, an international group of experts in the field of critical care medicine developed a new definition of ARDS, called the Berlin definition. This newer classification provides greater clarity to this syndrome and a classification of disease severity for the purposes of research and clinical practice[6]. The Berlin definition for ARDS includes the following[6]:

1) Timing of onset occurs within 1 week of a known insult or worsening respiratory symptoms.

2) Chest imaging revealing bilateral infiltrates not fully explained by effusions, lobar collapse, or

nodules as observed on chest radiograph or chest tomography.

3) Origin of the radiographic opacities producing respiratory failure not fully explained by cardiac failure or volume overload.

4) Oxygenation deficits:

Mild: PaO_2/FiO_2 range 201 to 300 mmHg with Positive End Expiratory Pressure (PEEP) or Continuous Positive Airway Pressure ≥ 5 cm H_2O

Moderate: PaO_2/FiO_2 range 101 to 200 mmHg with PEEP ≥ 5 cm H_2O

Severe: PaO_2/FiO_2 ≤ 100 mmHg with PEEP ≥ 5 cm H_2O

In 2021, Matthay et al. suggested that the Berlin definition be widened to include patients supported with high-flow nasal oxygen (HFNO) of at least 30 L/min, who otherwise meet the other criteria for the Berlin definition of ARDS[7]. HFNO has become extensively used to support critically ill patients with hypoxemic respiratory failure, especially during the COVID-19 pandemic. This expanded definition would make the diagnosis of ARDS more largely applicable and independent of the need for tracheal intubation or positive-pressure ventilation[7]. However, it still has to be accepted on a global scale by the medical community.

Different definitions have been used for obstetric-related ARDS. A functional definition, proposed by Cole et al., describes that ARDS during pregnancy results either from an obstetrical cause, and/or is modified by an obstetric-related factor[3]. Triggers for ARDS in pregnant patients are thus divided into obstetric (unique to pregnancy) and non-obstetric causes (not unique to pregnancy) and are described in Table I[8]. ARDS complicating pregnancy is more frequent during the third trimester. It might be more severe than ARDS in non-pregnant females, even though outcomes in the two populations are probably similar[9].

In patients with severe ARDS, when oxygenation or ventilation cannot be supported sufficiently using conventional mechanical ventilation and additional therapies, veno-venous extracorporeal membrane oxygenation (VV ECMO) may be considered. During full-flow VV ECMO, blood is typically drained from the inferior vena cava through a canula inserted in the femoral vein, pumped through a semipermeable membrane that enables diffusion of oxygen and carbon dioxide, and then reinjected through another cannula introduced in the jugular or the contralateral femoral vein[10]. Dual-lumen jugular VV ECMO is another option. This technique was initially regarded as encouraging because there is a single jugular cannulation site. Nevertheless, the reinfusion port must be perfectly placed to ensure its efficacy and the diameter of the shared lumen for drainage restricts ECMO blood flow rate[10]. In a recent large multicenter study, it was only adopted in 7% of patients as a primary ECMO approach in ARDS[11]. When patients with ARDS require combined cardiorespiratory support, other cannulation options may be implemented. These include veno-arterial ECMO (VA ECMO) and triple cannulation techniques such as veno-veno-arterial or veno-arterio-venous ECMO[12]. These ECMO modalities are outside the scope of this

Table I. — Causes of ARDS in pregnancy.

Causes unique to pregnancy	Causes not unique to pregnancy
Tocolytic-induced pulmonary edema	Aspiration
Chorioamnionitis	Sepsis: pneumonia, urosepsis, …
Amniotic fluid embolism	2009 Influenza A(H1N1), SARS-CoV-2
Trophoblastic embolism	Varicella pneumonia
Pre-eclampsia, eclampsia	Air embolism
Placental abruption	Fat emboli
Ovarian hyperstimulation syndrome §	TRALI, multiple transfusions
Endometritis	Severe trauma +/- pulmonary contusion
Retained products of conception	Inhalation injury, chemical pneumonitis
Septic abortion	Near drowning
Obstetric hemorrhage-related cause	Pancreatitis
	Drug overdose
	Cutaneous burn
	Rare infections modified by pregnancy: listeria, malaria, blastomycosis, coccidioidomycosis, …

Legend: TRALI = transfusion-related acute lung injury; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; § May also rarely occur in non-pregnant women undergoing treatment of infertility; Table reproduced and modified from Guntupalli et al.[8] with permission from Elsevier.

review, which will specifically focus on VV ECMO for pregnant patients with ARDS. However, some studies and recommendations on the use of ECMO during pregnancy include patients supported with VV and VA ECMO and will be considered in our analysis.

Historically, ECMO implantation in adults with refractory ARDS was fraught with complications[10]. In the past 15 years, improvements in equipment (cannulas, tubings, oxygenators) have made VV ECMO simpler and safer[13]. Its expansion has also been boosted by the last pandemics (2009 H1N1 influenza and COVID-19) and the results of clinical trials[14-16]. However, its use for the management of pregnant women is rare and remains a challenge.

This narrative review will first address the management of ARDS during pregnancy. It will then focus on the use of VV ECMO as a potential support for pregnant patients with severe ARDS and will describe its indications, contraindications, challenges, complications and outcomes.

Methods

We identified articles and other pertinent information by performing a manual search of electronic databases PubMed, the Cochrane Library and Google Scholar for English and French language articles, with a last update on July 25, 2022. We carried out an extensive search using different combinations of Mesh terms including "pregnancy", "Acute Respiratory Distress Syndrome", "ARDS", "treatment", "management", "complications", "Extracorporeal Membrane Oxygenation", "ECMO", and "veno-venous". We supplemented data by exploring reference lists from previously found relevant articles, and considered available guidelines published by scientific societies.

Even though we undertook a large search of the literature, it has some limitations. Publications on the subject of veno-venous ECMO support for pregnant patients with ARDS are rare and restricted to case reports, case series, a few reviews including these cases, and expert opinions and guidelines. Our research was not conceived as a systematic review and some elements might have been omitted not purposefully.

Management of ARDS during pregnancy

Randomized control trials specifically evaluating ventilation strategies and other supportive options for ARDS in the obstetric population are lacking. However, several guidelines regarding the management of ARDS in the general population have been published in the past few years[17-19]. The global approach to ARDS during pregnancy should be based on the same principles[3,20]. Some minor adaptations are warranted considering the specific characteristics of the gravid patient[3]. Additionally, experts suggest that the safety and efficacy of all ventilator settings and other therapeutics implemented in the management of ARDS should be reviewed at least daily[19].

a) General measures and fluid management

Standard critical care measures, if appropriate, should not be forgotten in the gravid patient, such as adequate sedation, nutritional support, antimicrobial drugs, prevention of stress ulcers and venous thromboembolism…[21]. Concomitantly, the underlying cause of ARDS should be identified and treated. The pregnant patient after 20 weeks of gestation should be placed as much as possible in a 15° left-lateral tilt position when supine, to avoid aortocaval compression and decrease in uteroplacental flow[22].

Fluid resuscitation to optimize oxygen delivery and cardiac output is often indicated in the initial management of many severe conditions associated with ARDS (burns, septic shock…). However, non-cardiogenic pulmonary edema is, by definition, an important element of ARDS[6]. Fluid overload, by increasing hydrostatic pressure, might worsen pre-existing alveolar edema. Therefore, after the resuscitation phase, many clinicians prefer a more conservative fluid management strategy in ARDS[23].

A conservative fluid strategy uses fluid restriction, diuretics and possibly hyperoncotic albumin to prevent a positive fluid balance, as opposed to a liberal fluid strategy. The British guidelines on the management of ARDS suggest it may have some benefits in ARDS patients without evidence of harm[18]. Nevertheless, this statement is based mainly on a single trial[24] and there is low quality of evidence for the majority of outcomes. In the absence of specific data, fluid management in pregnant women with ARDS should follow the same assumption[20].

b) Non-invasive ventilation

Both HFNO and non-invasive positive pressure ventilation have been successfully used in pregnant patients with ARDS[25,26]. It avoids the potential complications of endotracheal intubation and the side effects of sedative drugs. However, non-invasive ventilation should only be considered early in the treatment of mild ARDS in pregnant patients who are conscious, have protective airway reflexes and are hemodynamically stable[1]. Besides, the use of non-invasive ventilation should not

delay intubation when needed, as this may lead to worse outcomes in the adult population with acute respiratory failure[27].

c) Intubation

Inability to maintain PaO_2 > 70 mmHg and/or arterial oxygen saturation (SaO_2) > 95% on supplemental oxygen, non-invasive ventilation or a clinical deterioration should trigger endotracheal intubation and ventilation using a lung protective strategy in pregnant patients with ARDS[28]. An altered mental status (Glasgow Coma Scale of less than 8) with the inability to protect the airway should prompt intubation as well[20]. Nonetheless, timing of intubation must be personalized and is influenced by several other factors, such as presence of multi-organ failure, previous comorbidities and need for transfer to another facility with higher level of care.

Airway management can be challenging in the gravid patient with ARDS. Weight gain, large breasts and airway edema might increase the risk of difficult tracheal intubation in parturients[22]. The modifications of respiratory physiology related to pregnancy and the pre-existing hypoxemia caused by ARDS also shorten the time before desaturation[22]. Finally, delayed gastric emptying and a reduced tone of the lower gastroesophageal sphincter put the gravid patient at higher risk of gastric aspiration during intubation and altered mental status[25]. Therefore, a rapid sequence induction is recommended in these patients and any airway intervention should ideally involve an experienced physician with skills in difficult airway management[22,29].

d) Mechanical ventilation

The main goals of ventilation support in ARDS are to rest the respiratory muscles, while providing suitable gas exchange and avoiding ventilator-associated lung injury (VILI)[1]. Recommended ventilation strategies in ARDS during pregnancy are similar to those applied to the general adult patients,[1,17-19] with consideration of the modified physiology of the gravid patient and the effects of hypercapnia, hypoxia and acidosis on the fetus[29]. Current guidelines about mechanical ventilation in pregnant and non-pregnant patients with ARDS recommend the use of lung protective ventilation strategy with low tidal volumes (TV) and limited plateau pressure (plateau pressure being the pressure measured after a 0.2-0.5 s end-inspiratory pause)[1,17-20]. A tidal volume around 6 mL/Kg of predicted body weight should be used as a first approach, while trying to maintain a plateau pressure ≤ 30 cmH2O and using a PEEP above 5 cmH_2O[30]. Neither pressure-controlled nor volume-controlled ventilation has proved its superiority over the other[31]. A relatively high respiratory rate (between 25 and 30 cycles/min) should be initially employed to avoid potentially harmful rises in $PaCO_2$, especially during pregnancy. Respiratory rate can be increased up to 35 breaths/min, but too high a rate creates a risk of dynamic hyperinflation[19].

Controlling plateau pressure is paramount and this parameter must be monitored continuously[19]. The decreased chest wall and diaphragmatic compliance encountered in later pregnancy can impede the possibility to use a lung protective strategy and the usual plateau pressure target of < 30 cm H_2O may be difficult to obtain[32]. In patients with modified compliance of the chest wall (including pregnant patients), the relationship between plateau pressure and the risk of barotrauma or mortality is less obvious[33]. Therefore, a plateau pressure slightly above 30 cmH_2O might be tolerated in such patients, as long as the TV is reduced to minimize VILI[19]. Monitoring transpulmonary pressure might help in modifying ventilatory parameters[8].

PEEP settings should be individualized: experts suggest using higher level of PEEP (> 12 cmH_2O) in patients with moderate or severe ARDS, provided that it improves oxygenation without important deterioration in hemodynamic stability or respiratory compliance[19]. Most patients with ARDS require a high concentration of inspired oxygen to maintain acceptable oxygenation. However, oxygen itself has a potential toxicity and can induce lung injury. Oxygen toxicity is increased in patients receiving FiO_2 > 0.6, especially for a long period of time[27]. Therefore, PEEP should be titrated to optimize oxygenation while reducing the amount of oxygen delivered by the ventilator[30].

Maternal PaO_2 is the best indicator of fetal oxygenation and should be above 70 mmHg to maintain acceptable fetal acid-base balance. During pregnancy, progesterone-mediated rise in TV lead to increased minute volume, respiratory alkalosis and decreased $PaCO_2$[25]. The normal maternal PaCO2 is 28-32 mmHg with a maternal-fetal $PaCO_2$ gradient of 10 mmHg. Permissive hypercapnia, which is usually tolerated in non-pregnant patients, may be detrimental to the fetus. Indeed, although mild hypercapnia increases uterine blood flow, a $PaCO_2$ > 60-70 mmHg decreases this flow and increases fetal intracranial pressure. On the other hand, severe maternal hypocapnia, by reducing utero-placental blood flow and creating fetal alkalosis with a leftward shift of the oxygen dissociation curve, may also cause fetal hypoxia[8]. Cerebral vessels are particularly

sensitive to modifications in $PaCO_2$ and this mechanism is also present in the fetus at the end of gestation and in neonates. Hypercapnia causes cerebral vasodilation, while hypocapnia results in cerebrovascular constriction[34].

When conventional lung-protective mechanical ventilation is unable to maintain arterial blood gas targets, alternative strategies such as continuous muscle paralysis, lung recruitment maneuvers, inhaled nitrous oxide and prone positioning may be needed[8].

e) Recruitment maneuvers

Recruitment maneuvers (RM) are the transient application of a high airway pressure, intended to expand the collapsed lung and increase the alveolar surface available for gas exchange[21]. Several different maneuvers are used in ARDS. Basically, the procedure should not last longer than 10-20 s, and the airway pressure should not go over 30-40 cm H_2O. RM should be interrupted if hemodynamic stability is compromised[19].

Guidelines offer different recommendations on RM[17-19]. They should probably not be used systematically in pregnant and non-pregnant patients with ARDS. In situations of clear de-recruitment (intubation, breathing circuit disconnection…) or if hypoxia is refractory ($PaO_2/FiO_2 < 100$ mmHg), a careful RM can be considered in the absence of contraindication[19].

f) Prone positioning

Prone positioning requires moving a patient from the supine or left-lateral tilt position, while preserving the integrity of the patient-ventilator circuit and the different lines and catheters. It is thought to improve ventilation-perfusion matching in ARDS by reducing lung compression by mediastinal structures and increasing aeration of the dorsal lung[21]. It is inexpensive but time-consuming. To optimize its safety, each department should implement written procedures and specific staff training[19].

In most recent guidelines, prone positioning is recommended for patients in moderate to severe ARDS, with a PaO_2/FiO_2 ratio of less than 150 mmHg. To be effective, the position should be maintained for at least 12 to 16 hours per day[17-19].

Prone positioning is technically more difficult to implement in late pregnancy and concerns were raised in the past about its effect on the uterus, fetus and intra-abdominal pressure. However, there has been regained interest for prone positioning during the COVID-19 pandemic. Some authors and scientific societies now consider it safe and reliable in the management of pregnant women, if measures to avoid compression of the uterus are taken[20,35,36]. Prone positioning is not advisable in the presence of an acutely non-reassuring fetal heart rate tracing, and external fetal monitoring should be continued during proning sessions[36].

g) Neuromuscular blockade

Current guidelines suggest considering the use of a neuromuscular blocking agents (NMBA) in patients suffering early moderate or severe ARDS with a PaO_2/FiO_2 ratio of less than 150 mmHg[18-19]. The NMBA, usually cisatracurium besylate, should be administered through a continuous infusion within 48 hours after the start of ARDS, and for no more than 48 hours[19]. Daily evaluation of this treatment is needed. Similar suggestions have been made in the obstetric population[1,20].

h) Inhaled nitric oxide (NO)

Inhaled nitric oxide (NO) is not considered standard therapy in ARDS management. Acute and transient increases in oxygenation have been demonstrated in patients with ARDS treated with inhaled NO. However, this has not led to a reduction in ventilator-free days, severe morbidity, or mortality[37,38]. Some experts suggest that inhaled NO might be used temporarily in ARDS patients, when the implementation of protective ventilation measures and prone positioning has failed to avoid deep hypoxemia[19]. In these situations, long-term rescue therapies, such as VV ECMO, should be considered[18].

The data on the effects of inhaled NO during pregnancy are limited. Inhaled NO is not contraindicated in gravid women because it is instantly metabolized and avoids placental metabolism[20]. It has been utilized in the treatment of severe pulmonary hypertension in pregnant patients and was not associated with teratogenicity[39,40]. If inhaled NO is considered to treat a pregnant ARDS patient, it should not be maintained in the absence of response and the minimum effective concentration should be used[19].

i) Corticosteroids

Concerns remain about the use of steroids in ARDS due to associated adverse effects including immunosuppression, psychosis, gastrointestinal bleeding, and muscle-weakness acquired in the Intensive Care Unit (ICU). In addition, it is not clear if they would be of benefit in ARDS of any cause in the general population[23]. Current evidence suggests that low-dose steroids (for example betamethasone 12 mg given in two doses 12–24 hours apart) to promote fetal lung maturity are unlikely to cause significant maternal damage[41]. Fluorinated steroids

(such as betamethasone and dexamethasone) cross the placental barrier and repeated doses during pregnancy have been associated with neurosensory and cognitive disorders in childhood[42]. Therefore, use of fluorinated glucocorticoids should be reserved to fetal lung maturation only. Even though corticosteroids are recommended in both pregnant and non-pregnant patients with COVID-19 and receiving oxygen,[43] dexamethasone must be replaced by more appropriate choices during pregnancy. Alternatives include oral prednisolone 40 mg once daily or intravenous hydrocortisone 80 mg twice daily. Oral methylprednisolone 32 mg once daily or an intravenous dose of 1 mg/Kg twice daily may also be administered, especially if the pregnant patient is in an ICU setting[44].

Indications and contraindications of VV ECMO in ARDS during pregnancy

In cases of refractory respiratory failure during pregnancy, VV ECMO may be considered as a strategy to improve maternal condition and to preserve the viability of the preterm fetus. Such strategy can be supported by expected improvement in fetal well-being through better maternal PaO_2 and $PaCO_2$ levels, but needs to be balanced with the risk of maternal and fetal mortality and morbidity[36]. Important clinical and ethical decisions must be made by a multidisciplinary group composed of senior members of the ICU, obstetric, neonatal and anesthesia teams (in accordance with the patient's/next of kin's wishes, and local practice and laws)[36,45]. Defining expectations early on during an ECMO course is essential and discontinuing VV ECMO should be considered if there is no rational hope for meaningful survival or bridge to transplant[45].

Until recently, guidelines regarding the use of ECMO during or after pregnancy were scarce. The Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries United Kingdom (MBRRACE-UK) Maternal Mortality report published in 2014 recommended early VV ECMO referral for pregnant women and new mothers in severe respiratory failure who had failed conventional ventilation[46]. Since the beginning of the COVID-19 pandemic, clinicians and scientific societies have had a renewed interest in the management of ARDS and the use of VV ECMO. The Society for Maternal-Fetal Medicine (SMFM) states that pregnancy is not a contraindication to the use of ECMO in women severely affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and that despite some challenges, this modality should not be withheld from a pregnant patient for whom it may potentially benefit if the patient is otherwise a candidate[20].

In 2020, Combes et al. proposed an update on indications and contraindications to VV ECMO for ARDS in the general adult population[10]. In 2021, these criteria were slightly modified by Wong et al. to be applied to the obstetric population and meet maternal-fetal specific physiological needs (criteria described in Table II and III)[36]. The hypercarbia threshold triggering VV ECMO implantation has been reduced from 60 mmHg in non-pregnant patients to 50 mmHg during pregnancy[10,36]. Indeed, a prolonged period of maternal permissive hypercapnia and acidosis created by lung protective ventilatory strategies in ARDS might be detrimental to fetal well-being and survival[47]. It is well established that there is improved survival for patients who are started on VV ECMO within 5 days of mechanical ventilation, both in the general and peripartum population[48,49]. Additionally, initiating ECMO early in the course of deteriorating ARDS during pregnancy might improve both maternal and fetal outcomes, compared with mechanical ventilation alone[47]. Finally, early recognition of VV ECMO candidates and timely consultation with an ECMO center is important to improve outcomes[45].

Challenges in the management of VV ECMO during pregnancy

a) ECMO cannulation

Correct insertion and position of the VV ECMO cannulas are paramount and may be a technical challenge in the obstetric population. Maintaining adequate utero-placental perfusion during cannulation is also important and monitoring fetal heart rate throughout this procedure may provide early indication of reduced uterine blood flow[36].

Table II. — Proposed indications to VV ECMO for ARDS during pregnancy.

Indications: EOLIA entry criteria [a] modified by Wong et al.[36]
PaO_2/FiO_2 < 50 mmHg for > 3 h
PaO_2/FiO_2 < 80 mmHg for > 6 h
pH < 7.25 and/or $PaCO_2$ > 50 mmHg for > 6 h [b]
Legend: a After proven conventional management (including lung protective mechanical ventilation, prone positioning and possibly neuromuscular blockade) for severe ARDS have been applied and failed. Less frequently, rescue ECMO may be deployed when a patient is too unstable for prone positioning, or when this is the only way to facilitate safe transport from a non-expert center that is unable to apply evidence-based conventional practices b With respiratory rate increased to 35 breaths per minute and mechanical ventilation settings adjusted to keep a plateau airway pressure of ≤ 32 cm H_2O Table reproduced from Combes et al.[10], as modified by Wong et al.[36], with permission from Springer Nature.

Table III. — Proposed contraindications to VV ECMO for ARDS during pregnancy.

Relative contraindications	Absolute contraindications
Invasive mechanical ventilation for more than 7–10 days	Moribund state with established multiple organ failure
Contraindication to anticoagulation	Prolonged cardiac arrest
Severe coagulopathy	Severe anoxic brain injury
Advanced age (not applicable to pregnancy)	Massive intracranial hemorrhage
Salvage ECMO (referred to as "rescue" in EOLIA), i.e., employing ECMO when severe right heart failure, or other severe decompensation occurs	Severe chronic respiratory failure with no possibility of lung transplantation
	Metastatic malignancy or hematological disease with poor short-term prognosis
	Other advanced comorbidities with poor short-term prognosis
Table reproduced and modified from Combes et al.[10] with permission from Springer Nature.	

In 2022, Wong et al. recommended using a 25-French drainage cannula in the right femoral vein and a 23-French return cannula in the right internal jugular vein in order to obtain adequate flow rates in the pregnant patient[36]. A less-invasive percutaneous cannulation technique is usually performed in adult patients and the use of fluoroscopy or echocardiography (transthoracic or more frequently transesophageal) can help with cannula positioning[45]. The gravid uterus may complicate insertion of the femoral cannula. Ngatchou et al. overcame this hurdle by placing the gravid patient at a 15°-30° left lateral tilt to help reduce aortocaval compression and advance the venous cannula from the right femoral vein into the inferior vena cava[50].

b) ECMO settings

Specific ECMO targets for PaO_2 and $PaCO_2$ during pregnancy have not been clearly established. Permissive hypercapnia, which is accepted in non-pregnant patients, is poorly tolerated by the fetus due to altered transplacental diffusion of CO_2[49]. Furthermore, $SaO_2 > 80\%$ is considered an adequate degree of oxygenation during VV ECMO in non-pregnant adults but is unacceptable during pregnancy[36]. Lankford et al. recently proposed the following objectives: to adjust ECMO blood flow rates to achieve a maternal $SpO_2 \geq 92\%$ or a maternal $SaO_2 > 95\%$, and to adjust the sweep gas flow rate to avoid hypercapnia and gradually reach a $PaCO_2 \leq 35$ mmHg[49]. Upon initiation of ECMO, sweep gas flow rate and blood flow should be started at around 2 L/min and then modified frequently to achieve a controlled slow variation of pH and $PaCO_2$[45]. An initial rapid drop in $PaCO_2$, by causing cerebral vasoconstriction and impairing brain tissue perfusion, is associated with an increased incidence of neurological complications in patients supported with VV ECMO[51].

The higher cardiac output observed during pregnancy (an increase by 30% to 50% from 8 to 28 weeks of gestation)[25] may impede correct oxygenation during VV ECMO, as more venous blood bypasses the drainage cannula. Therefore, in the gravid patient, higher initial VV ECMO flows than in the global adult population are often necessary to improve oxygenation (5-6 L/m²/min)[36]. A further increase in ECMO flow may lead to increased recirculation between drainage and return cannulas, hemolysis and thrombocytopenia[52]. Fortunately, other options to counteract ineffective VV ECMO blood flows are acceptable during pregnancy, including the use of beta blockers[52] (to reduce cardiac output) and the placement of an additional venous drainage cannula[53].

c) Ventilator settings

The main goal of VV ECMO in ARDS is to provide adequate gas exchanges while minimizing VILI. The use of a large venous drainage cannula enables high ECMO flow and adequate oxygenation while applying "ultra-protective lung ventilation". How much the intensity of mechanical ventilation should be decreased, and whether the lungs should be maintained open to avoid complete atelectasis are still a matter of debate[10]. Some teams suggest to achieve lung rest for both pregnant and non-pregnant patients on VV ECMO by using pressure control ventilation with a peak inspiratory pressure of 20 to 25 cmH_2O, PEEP of 10 to 15 cmH_2O, respiratory rate of 10 breaths/min, and fraction of inspired oxygen of 0.3 to 0.4[36]. They also recommend monitoring driving pressure regularly to maintain it under 15 to 20 cmH_2O,36 as elevated driving pressure seems to be associated with increased mortality during ARDS[54,55]. Readiness for ECMO weaning should be assessed daily and when the patient is stabilized, preventing diaphragm atrophy by introducing spontaneous breathing activity may be desirable[10].

d) Fetal monitoring

Currently, there are no consensus guidelines on the frequency of fetal monitoring for pregnant women

on VV ECMO. Some centers perform continuous external fetal monitoring (cardio-tocography) as soon as 24 weeks of gestation to quickly identify reversible causes of fetal distress (aorto-caval compression, maternal hypoxemia or hypotension, inadequate ECMO settings, circuit thrombosis, cannula malposition…) and correct them[36]. Persistent maternal cardiovascular instability or fetal abnormal tracings often triggers urgent delivery. Other methods of assessment, such as fetal ultrasound and biophysical profiles, may be used to detect fetal non-reassuring status.

e) Timing of delivery

Both the timing of delivery during VV ECMO support and whether the pregnancy should be interrupted or not before ECMO initiation remain uncertain. These decisions are influenced by several key factors including gestational age, anticipated ECMO duration, receipt of antenatal corticosteroids, the likelihood of maternal improvement and delivery urgency[49].

Delivery of the fetus can be extremely challenging when the mother's homeostasis is severely impaired. In addition, cesarean section is a major surgery associated with important maternal inflammation and risks of infection, hemorrhage or hemodynamic instability[36]. Even if fetal delivery has several theoretical physiologic advantages in the long term (reduced aorto-caval compression, improved oxygen delivery to maternal tissues and redistribution of blood flow away from the uterus to vital organs),[56] these benefits may occur at the expense of neonatal prematurity and there is no clear proof that delivery improves maternal outcomes[57,58]. Previous reports have also shown that continuing pregnancy for several weeks during ECMO support is feasible[49,59].

Neonatal mortality following delivery is 0.2% at 32 weeks of gestation and stays at this level or lower for each additional week. Major neonatal morbidity is also acceptable at these gestational ages[60]. Therefore, in case of refractory hypoxemia despite optimal medical treatment in ventilated COVID-19 gravid patients, the recent SMFM COVID-19 guidelines suggest different management based on gestational age: controlled delivery should be considered after 32 weeks of gestation and VV ECMO support before 32 weeks[20]. However, the severity of maternal illness may trigger earlier delivery. The SMFM also states that the use of ECMO is not necessarily an indication for delivery, and that ECMO implantation should not be delayed to perform a delivery if the mother or fetus are not in immediate life-threatening conditions[20]. Finally, other experts reserve preterm delivery on ECMO for usual obstetric indications[49].

Decisions about delivery timing should be addressed in a multidisciplinary discussion involving senior physicians, with respect to the patient's or next of kin's wishes if possible[36].

f) Mode and place of delivery

Cesarean section is the principal mode of fetal delivery on VV ECMO, even if cases of vaginal deliveries have been described[59,61]. The choice of delivery mode should be influenced by maternal status, indication for delivery and the potential complications of cesarean section. Nevertheless, the duration of labor is unpredictable during vaginal birth and it is not suitable in most emergency indications[25].

There are no formal recommendations about the best place of delivery for pregnant women with ARDS on VV ECMO (ICU, operating room, delivery suite). This depends on maternal and fetal instability, level of emergency of the delivery and local practices. Instruments for delivery should be readily available in the ICU and facilities treating these patients must have in-house high-risk obstetrics coverage[36].

Complications of VV ECMO during pregnancy

The main complications of VV ECMO, which are common to the obstetrical and global adult populations, are thrombotic events, bleeding, cannulation-related complications, hemolysis and nosocomial infections. The principal fetal complications include preterm delivery and neonatal intensive care admission. Other technical challenges of the use of VV ECMO during pregnancy have been described in the previous section.

a) Thrombotic events and anticoagulation

One of the important complications related to VV ECMO is thrombotic events, happening in the ECMO circuit and to the patient as well. Thrombosis in the ECMO circuit can subsequently lead to oxygenator and pump failure. Even though pregnancy is a hypercoagulable state, there is little evidence that pregnant women are at higher risk of oxygenator or ECMO circuit thrombosis[53]. Menaker et al. evaluated the incidence of cannula-associated deep vein thrombosis after VV ECMO removal in an adult population at 85%. This number was independent of anticoagulation regimen or ECMO run time[62]. Performing duplex ultrasound of cannula sites after decannulation might be prudent in pregnant patients, given their thrombophilic profile[36].

Systemic anticoagulation is routinely used to prevent these thrombotic issues. This should be done after

assessing the risk of hemorrhage, particularly in the peripartum population. Unfractionated heparin is the most frequently used anticoagulant, but protocols are highly variable. Guidelines about anticoagulation and its monitoring in pregnant women on VV ECMO are again lacking. In the general adult population, the Extracorporeal Life Support Organization (ELSO) recommends giving heparin as an IV bolus (50-100 units/Kg) at the time of cannulation, and by continuous infusion during VV ECMO support[63]. ELSO recommendations regarding monitoring of anticoagulation are vaguer. Roughly, heparin infusion should be regulated to keep the whole blood activated clotting time or the activated partial thromboplastin time (aPTT) at around 1.5 times normal values. Heparin concentration can also be measured indirectly as anti-Xa activity, aiming at a value around 0.5 units/mL[63]. During VV ECMO, other teams have an aPTT goal of 45 to 55 seconds for both pregnant and non-pregnant patients, with a higher goal of 60 to 80 seconds in the presence of COVID-19[36]. The literature regarding the use of viscoelastic hemostatic assays (TEG or ROTEM) in ECMO is growing and these tests might be useful as predictors of clotting and bleeding during ECMO support[63].

Modern management of VV ECMO with high ECMO flows and heparin-coated surfaces have allowed for a substantial decrease in systemic anticoagulation. In VV ECMO, the current trend is towards less anticoagulation, as several retrospective studies have demonstrated the safety and feasibility of either lower or no anticoagulation[64,65]. Further research is needed to confirm this hypothesis and extend this new practice safely to the obstetrical population.

b) Bleeding

Hemorrhage is the most common complication reported on VV ECMO and is caused by a combination of platelet dysfunction, thrombocytopenia, loss of large von Willebrand factor multimers and anticoagulation. In a study including twelve pregnant or postpartum patients treated with VV or VA ECMO for severe ARDS during the 2009 H1N1 pandemic, two-thirds of patients suffered from bleeding complications, several required transfusion of large volumes of red blood cells, and bleeding was an important contributing factor in 3 deaths[53]. More recently, Ramanathan et al. described hemorrhagic complications in 37.3% of obstetric patients on VV or VA ECMO[4]. These rates are similar to the ones observed in the non-pregnant ECMO population (30 to 70%)[66].

Common sources of bleeding comprise cannulation sites, as well as uterine, gastrointestinal, pulmonary and intracranial sources[67]. Although relatively infrequent, intracranial hemorrhage is associated with poor outcome[10].

Temporary suspension or reversal of systemic anticoagulation before fetal delivery must be personalized. Some centers stop systemic heparin for at least 2 hours before a planned cesarean section on ECMO and if adequate hemostasis is acquired, consider restarting it after 24 to 48 hours[36]. After fetal delivery, obstetric causes of hemorrhage should be ruled out (traumatic delivery, uterine atony, retained placenta…).

c) Cannulation-related complications

In a recent systematic review including large studies on the utilization of VV ECMO in the adult population, cannulation-related complications occurred in 7% of patients[68]. Their incidence has been reduced by the increased use of ultrasound guidance during cannula insertion and has not been clearly determined in pregnant patients[69].

d) Nosocomial infections

Nosocomial infections during VV ECMO in pregnancy has not been specifically studied. The adult ECMO population may be more prone to nosocomial infections because of concomitant indwelling catheters, critical illness, and prolonged ventilation and hospital stay[10]. In addition to typical ICU-related nosocomial infections, patients on VV ECMO may develop ECMO-specific infections (infection at peripheral cannula insertion sites)[70]. In a recent analysis of the ELSO registry data documenting positive cultures during ECMO support, the group in which ECMO was implanted for respiratory failure had the highest rate of positive blood cultures during ECMO (64.9%)[70]. These data should be interpreted with caution, as positive cultures may not indicate true infection and individual patients may have more than one positive culture. Although there seems to be a correlation between nosocomial infection on ECMO and increased mortality, further investigations are needed to confirm this hypothesis.

The pharmacokinetics and pharmacodynamics of medications, including antimicrobials, is modified by the presence of the extracorporeal circuit and by pregnancy, making the treatment of infections more challenging[10].

e) Hemolysis

Technical-induced hemolysis is a mechanical injury to red blood cells (RBCs) caused by excessive

high shear stress force, which is increased in the presence of blood pumps and intravascular cannulas. Small cannulas and high ECMO blood flows may reinforce this phenomenon. Free hemoglobin, released into the plasma by damaged RBCs, may lead to severe complications such as renal dysfunction or multiple organ failure[71]. Hemolysis is a frequent cause of anemia during VV ECMO and ranges from minimal to severe[66]. Severe hemolysis is characterized by a plasma free hemoglobin level > 500 mg/L and is encountered in approximately 2% of patients on VV ECMO, while a large majority of VV ECMO patients have a plasma free hemoglobin level < 100 mg/L[66,71]. Lactate dehydrogenase levels can also be measured to monitor hemolysis but are less specific. There is a correlation between hemolysis and thrombosis during VV ECMO and patients with severe hemolysis should be screened for ECMO-circuit and patient thrombosis, particularly pump head thrombosis[66,71]. No specific data on hemolysis during VV ECMO support in pregnancy can currently be found in the literature.

f) Fetal complications

In a recent case series of nine pregnant or peripartum women with severe COVID-19 ARDS supported with VV ECMO, Barrantes et al. reported that the majority of the newborns were premature and required admission to intensive care. 71% of those infants required mechanical ventilation[72]. In 2020, Naoum et al. performed a systematic review and meta-analysis of published reports on the use of VA and VV ECMO during pregnancy and the peripartum period. The most commonly described fetal complications were again preterm delivery (48.5%) and neonatal intensive care admission (27.9%)[59]. However, these complications may not only be related to the use of ECMO, but also to the severity of maternal instability.

Maternal and fetal outcome after VV ECMO

In 2020, Combes et al. published an individual participant data meta-analysis of patients with severe ARDS included in two recent randomized trials, CESAR[14] and EOLIA[15,16]. There was strong evidence to suggest that early recourse to VV ECMO lead to a reduction in 90-day mortality and less treatment failure compared with conventional ventilation support[16]. Unfortunately, no patients with obstetric ARDS were recruited in the CESAR trial[14] (even if it was not an exclusion criterion) and pregnant women were excluded from the EOLIA trial[15].

The published data concerning the use of ECMO for severe ARDS during pregnancy is confounding. Several case-reports, small case-series and systematic reviews on the use of ECMO in the obstetric population have been published[4,52,59,61,73-80]. However, these studies were retrospective and could be affected by several biases, especially positive publication bias. In addition, they differed in population (pregnant and/or postpartum women), type of ECMO used (veno-venous and/or veno-arterial) and the indications for ECMO (respiratory or cardiovascular indications, obstetrical or non-obstetrical reasons). The lack of well-designed prospective studies with control groups can be explained by the rarity of these conditions among the obstetric population and by the ethical problems such studies would raise.

Nonetheless, published reports show that overall maternal survival with all types of ECMO in the obstetric population is higher than in the general adult population at approximately 80%. Fetal survival rates were evaluated at around 70%[61,73,74]. Concomitantly, survival for all adult patients treated with VV ECMO is 58% and only 42% with VA ECMO[81]. A retrospective cross-sectional study published in 2022 analyzed the utilization rate and outcomes of VV or VA ECMO in obstetric and non-obstetric patients from 1999 to 2014 in the United States[79]. Between 1999-2002 and 2011-2014, obstetric ECMO utilization significantly rose from 1 to 11 per million obstetric discharges and in-hospital mortality was significantly reduced from 74 to 32 per 100 women. During the study period, there was an adjusted 22% (95% confidence interval [CI], 7-34%) decreased risk of all-cause in-hospital mortality for obstetric ECMO compared to non-obstetric ECMO[79]. The increased survival in peripartum patients could be explained by a younger age and the more reversible nature of their initial pathologies. In 2016, Saad et al. published a systematic review and meta-analysis about the use of ECMO in pregnant and postpartum women with H1N1-related ARDS[75]. The pooled estimate of the survival rate was 74.6% (95% CI, 60.7-88.6%) and the rate of live birth was 70%. Whether these outcomes were better than those achieved with standard of care lung protective mechanical ventilation could not be answered[75].

Long-term consequences of the use of ECMO have been reported both in the general and obstetric populations. Luyt et al. compared the 1-year outcomes of survivors of H1N1 influenza A-associated ARDS in the general population, according to the use or no use of ECMO. A majority of survivors had minor lung disabilities with diminished diffusion capacities, and most had psychological impairment and poorer health-related quality of life than a sex- and age-matched general population group. ECMO and no-ECMO group patients had similar

outcomes[82]. In a cohort of obstetric patients treated with ECMO reported by Lankford et al., pulmonary functions tests were performed in 5 patients up to 36 months after ECMO removal. All 5 patients had abnormal spirometry. DLCO was assessed in 3 patients and was reduced in all of them, with 2 of 3 patients (66%) experiencing severe gas transfer alteration[49].

Currently, there are no available reports or studies on long-term outcomes of children who have been exposed to ECMO during intrauterine life.

Conclusion

VV ECMO is feasible to support a gravid patient suffering from severe ARDS and to prolong pregnancy. Maternal survival with VV ECMO seems to be higher than in the general adult population and pregnancy should not be a deterrent to its use. In addition, clinicians should perhaps have a lower threshold to opt for this treatment option in pregnant patients with ARDS than in non-pregnant patients. Critical care support should be well planned, and important medical and ethical decisions taken by a multidisciplinary team with expertise in ECMO management. In future years, the creation of a prospective international registry including all women who require ECMO during pregnancy and data about their children's follow-up would be a valuable tool to help clinicians and families make decisions.

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