Chapter 16
Extracorporeal Membrane Oxygenation in Pregnancy

Tal E. Sandler and Shaun L. Thompson

Introduction

Since its inception in the 1950s by John Gibbon, extracorporeal membrane oxygenation has improved our ability to facilitate and augment oxygenation, ventilation, and cardiac support in critically ill patients [1]. Technological advancements improved ECMO utilization and are now considered to play a major role in acute respiratory failure, cardiac arrest, and shock states. Additionally, pre-hospital applications have successfully been implemented, to include management of cardiovascular collapse secondary to pulmonary embolism, airway obstruction leading to refractory hypoxemia, overdoses, and hypothermia, to name a few [3]. The combination of ECMO technology and advancements in critical care has allowed for favorable survivability with decrease in morbidity [4]. As access to ECMO services has increased worldwide and with improvements in cannulation methods and equipment, early use has been well defined in the literature. Specialty population whom may benefit from ECMO, such as obstetric patients, have little evidence in regard to overall utilization and favorability [2]. This chapter will focus on describing disease processes in pregnancy and peripartum period that may benefit from ECMO. In addition, considerations regarding pharmacology, physiology, and complications that the pregnant patient may pose while utilizing ECMO will be discussed.

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Basics of ECMO

Extracorporeal membrane oxygenation is defined as extravascular cardiopulmonary life support. Blood is drained from the venous system, circulated by a mechanical pump through an oxygenator (also known as membrane lung), and returned back into systemic circulation (venous versus arterial). Oxygenation and carbon dioxide elimination is accomplished through passive diffusion and determined by flow rate and rate of countercurrent flow (sweep), respectively [3]. Depending on the indication for ECMO, there are two types of ECMO that are utilized. First is veno-venous (VV) ECMO, and this is utilized in order to replace lung function in states of refractory respiratory failure. The other variant is veno-arterial (VA) ECMO and is implemented in states of cardiogenic shock or combined cardiopulmonary failure. The nomenclature of VV or VA ECMO indicates which vessels are cannulated in order to drain blood from the patient to the membrane lung and then back into the patient into either the venous (VV) or arterial (VA) system. Indications for VV ECMO include refractory hypoxia and hypercarbia despite maximal medical and ventilator support, status asthmaticus, pneumonia, anterior mediastinal masses, and most commonly acute respiratory distress syndrome [5]. Indications for VA ECMO include cardiac failure following myocardial infarction, acute chronic heart failure, acute heart failure including postpartum cardiomyopathy, pulmonary embolism, amniotic fluid embolism, and refractory ventricular tachycardia [5].

Circuit Design

The ECMO circuit is based on the cardiopulmonary bypass circuit utilized in the operating room for open heart surgical procedures. Large bore cannulas, typically 19–25 French, are placed in either the femoral vein or artery via percutaneous approach. This site is typically chosen due to need for rapid placement and also due to favorable size of vessels to accommodate the large cannula. Other configurations that can be utilized are femoral/internal jugular access for both VV and VA ECMO and use of a dual lumen cannula for VV ECMO which is placed in the internal jugular vein.

Once cannulas are in place, they are attached to large bore polyvinylchloride (PVC) tubing that is typically 3/16 to ½ inch in diameter. Large bore cannulas and tubing are utilized in order to reduce resistance to flow based on the Law of Laplace [5]. This tubing will bring blood to the membrane oxygenator, or membrane lung, via a centrifugal pump. The first half of the membrane lung is utilized for temperature regulation in order to maintain the body temperature at 37° C. The second stage of the membrane lung allows for oxygenation and carbon dioxide removal via passive diffusion as stated above. Figure 16.1 is a cross section of a membrane lung and shows the separation of these two halves.

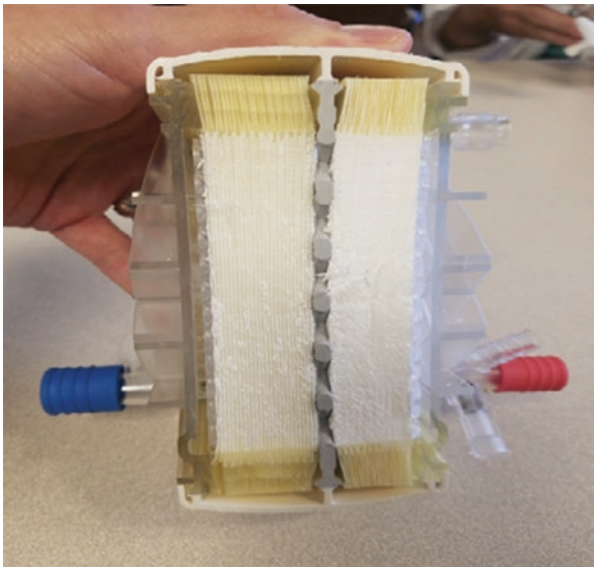

Fig. 16.1 Cross section of the membrane lung. The first half of the membrane lung is utilized for temperature management to maintain normothermia. The second half is where diffusion of gases occurs across concentration gradients. Blood enters the left side of the membrane lung, denoted by the blue plug. Blood exits the membrane lung and back to the patient on the right side, denoted by the red plug. (Image courtesy of Shaun Thompson, MD)

Centers have the ability to customize the ECMO circuit according to the intended patient population. Additional components of modern ECMO circuits include pressure monitors, hemoglobin and oxyhemoglobin saturation monitors, and pump speed monitoring. Circuit bridge/access connectors are available for the ability to conduct lab draws and give the ability to add inline renal replacement therapy [6, 7]. Figure 16.2 shows a photograph of an ECMO circuit in use.

Type of Pumps

Newly designed ECMO circuits utilize centrifugal pumps to provide suction away from the patient and return blood following gas exchange in the membrane lung. Centrifugal pumps have largely replaced previous utilized roller pumps due to their smaller size, durability, and ability to be used for prolonged circulation while avoiding complications such as mechanical hemolysis [6, 7]. The centrifugal pumps used in modern ECMO machines are magnetically levitated and driven which help to reduce mechanical shear forces on red blood cells to minimize damage and hemolysis [8]. Use of magnetically driven pumps also decreases friction and reduces the production of heat [9]. Because of these technical improvements, these pumps have been shown to be safely used for long periods of time allowing extended runs on ECMO if necessary [8, 9].

Fig. 16.2 ECMO circuit: components of the ECMO circuit are seen in this photo. The membrane lung is encased in plastic that is red in color in this picture. Drainage and return cannula are marked with blue and red tape, respectively, on the left side of the photo. (Photo courtesy of Dan Johnson, MD and used with permission)

Membrane Oxygenator (Membrane Lung)

As noted, the ECMO circuit provides gas exchange, independent of the patient's lung, through an oxygenator membrane. Through the years, oxygenators were composed of different types of biomaterials including silicone rubber and polypropylene hollow fibers. Newer membranes surfaces are often made from polymethylpentene, polyvinylchloride, or polyurethane which provide efficient gas exchange with low resistance to flow. Polymethylpentene (PMP) membranes are more commonly used currently because of their low resistance to flow, optimal gas exchange with a smaller needed surface area, and minimization of plasma leakage that decreases efficiency of the membrane lung [8]. The surface area of the oxygenator membrane and the path of blood mixing determine the capacity for gas exchange. Ultimately, blood and gas flow occur in counter-current direction allowing for the gas exchange to happen by passive diffusion through the membrane against concentration gradients [6, 7].

Cannulas

Multiple cannulas are available that can be selectively chosen for the individual patient, based on body size, with sizes ranging from 6Fr to 51Fr. In order to avoid luminal occlusion, cannulas are manufactured with wire reinforcements. Fenestrations are added to the flexible tip of jugular and femoral venous drainage cannulas to maximize flow, while return cannulas have either a single port or a short fenestrated tip.

Many cannulas are coated with heparin in order to limit the potential development of thrombus in the cannula. Systemic heparin is also given during cannulation, and these steps are vital to perform as thrombosis of the cannula can be life-threatening and possibly fatal if the patient is completely reliant upon ECMO for survival [5].

It is imperative to properly choose the correct size and configuration to ensure efficient and optimal performance of the circuit [6].

Veno-Venous ECMO

VV ECMO is utilized for respiratory support when cardiac function is preserved. Cannulation can be performed in a few ways and depends on the urgency of the situation at the time of implementation of ECMO. For rapid deployment, percutaneous insertion of cannulas into the femoral veins bilaterally can be performed [5]. Other orientations that can be utilized include a drainage cannula in the femoral vein with a return cannula in the internal jugular vein and dual lumen cannulas which are placed in the internal jugular vein. In all cannulation scenarios, blood is removed via the vena cava and returned to the right atrium [3]. Figure 16.3 shows schematic examples of ECMO cannulation positions for VV ECMO.

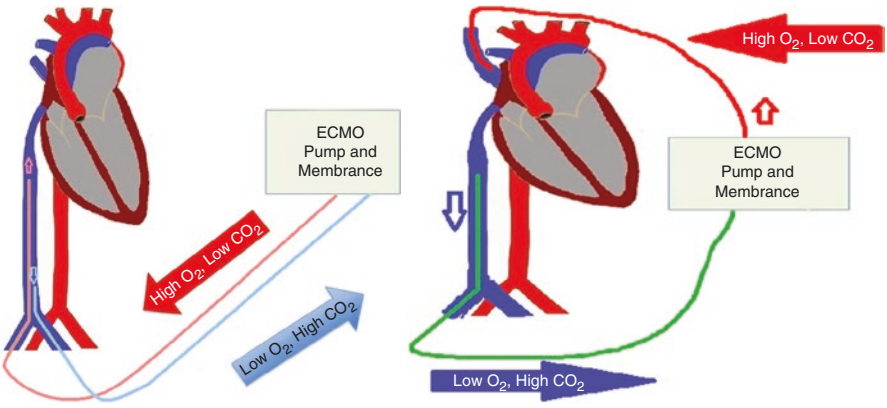

Fig. 16.3 Configurations of veno-venous extracorporeal membrane oxygenation. Drainage cannula is positioned in the distal portion of the IVC with the return cannula positioned in the proximal portion of the IVC close to the right atrium. Another configuration would be if the return cannula was introduced through the internal jugular vein with the cannula terminating in the right atrium (B). (Image courtesy of Walker Thomas, MHPTT, FASE, RDCS and used with permission)

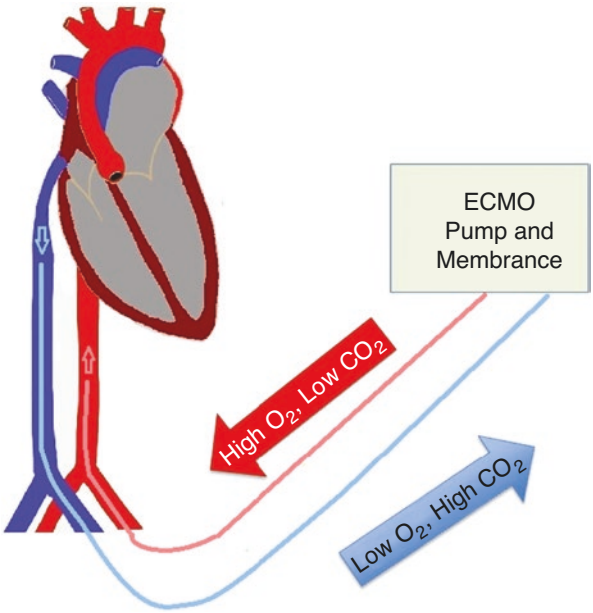

Fig. 16.4 Configuration of veno-arterial extracorporeal membrane oxygenation. Drainage cannula is positioned in the proximal portion of the IVC close to the cavo-atrial junction with the return cannula positioned in the abdominal aorta. (Image courtesy of Walker Thomas, MHPTT, FASE, RDCS and used with permission)

Veno-Arterial ECMO

VA ECMO is utilized in situations of cardiac failure or combined cardiorespiratory failure. The circuit is configured parallel to the heart and lung. Similar to VV ECMO, cannula placement is performed with percutaneous access and advancement of cannulas over guidewires into the respective vessels. Blood is drained from the venous system and returned to the arterial system bypassing the heart and lung. Cannulation strategy includes access of the femoral vein (most common) with return via the femoral, axillary, or carotid arteries [3]. The most common cannulation scenario in adults requiring VA ECMO support is femoral vein/femoral artery access due to the emergent nature that is typically required if this form of support is necessary [5]. Figure 16.4 shows a schematic of cannulation strategy for VA ECMO if the femoral arteries were utilized for cannulation.

Ultrasound Guidance for Cannulation

Echocardiography has been successfully utilized as a tool to aid in cannulation [10–14]. Both transthoracic and transesophageal echocardiography allow for guidewire visualization within the inferior vena cava (IVC) and aorta [10, 11]. This ensures and reduces the chances of extravascular cannula placement [14]. Moreover, cannula position can be verified prior to initiating and also during ECMO support for optimal results [10–14]. Echocardiography of the heart should also occur prior to

placement onto ECMO in order to verify or exclude cardiac dysfunction as failure to do so may result in improper implementation of VV ECMO if cardiac failure exists [10–14].

Contraindications to Implementation of ECMO

Absolute contraindications include futility of care in cases where an exit strategy is unlikely such as patients not candidates for durable mechanical support or transplantation. Other examples of contraindications include metastatic cancer, severe brain injury, unrepaired aortic dissection, chronic severe organ dysfunction, and unwitnessed cardiac arrest [5]. Relative contraindications include advance age, severe obesity, severe peripheral vascular disease, morbid obesity, and contraindication for anticoagulation [5]. Multidiscipline consultation with intensivist, cardiologist, cardiac surgeon, and pulmonologist is recommended prior to initiating support [5].

Pregnancy and Peripartum Complications

Acute Respiratory Failure

Pregnancy is associated with multiple physiological and anatomical changes that affect the respiratory system. The parturient experiences decrease in functional residual capacity and an increase in minute ventilation secondary to increase in respiratory rate, leading to overall increase in PaO2 (~105 mmHg) and a lower PaCO2 (~30 mmHg) compared to the nonpregnant state of health. Compensatory metabolic acidosis (HCO3 ~18) occurs in response to the respiratory alkalosis. The overall affect causes a right shift of the hemoglobin-dissociated curve reducing the affinity of maternal hemoglobin to oxygen and enabling transfer of oxygen to the fetus. While these changes are crucial to the survivability of the fetus, they can be deleterious to the parturient as they are predisposed to states of acidosis such as in respiratory failure [15].

Etiology of respiratory failure is similar to the non-obstetric patient; these include reactive airway disease, pulmonary infections, and ARDS secondary to sepsis, trauma, pancreatitis, and multiple blood transfusions [16]. The risk of pulmonary infection is increased in the parturient secondary to changes in immunity. Downregulation of cell-mediated immunity occurs in response to allow tolerance of the paternal-derived fetal antigens predisposing the pregnant woman to increased complications [17]. Viral infections such as the previously reported influenza outbreak in the late 2000s proved that pregnancy is an independent risk factor for respiratory complications such as ARDS. Other pregnancy-related causes of ARDS are illustrated in Table 16.1 [17].

Table 16.1 Disease states in pregnancy that can cause ARDS [2, 16, 20]

Acute respiratory failure cause in the obstetric population
Preeclampsia-induced pulmonary edema
Chorioamnionitis
Acute fatty liver of pregnancy
Obstetric hemorrhage
Tocolytic-induced pulmonary edema
Amniotic fluid embolism
Septic abortion
Retained products of conception
Aspiration

While respiratory failure is uncommon, mortality associated with ARDS is increased compared to the non-obstetric patient (24–39%) [16]. Therefore it is crucial that the clinician has an understanding of the physiological respiratory changes in order to manage these patients appropriately.

Initial management includes identification of cause, maternal supportive care, and fetal monitoring for signs of distress, although conservative management approaches, such as invasive mechanical ventilation, should be utilized promptly, if needed. The 2009 influenza pandemic paved the way for the application of ECMO in refractory hypoxemic states. Multiple case reports have been published in the successful use of ECMO in both pregnant and postpartum patients. Multicentered reports from France, Australia, and New Zealand have described the use of ECMO with favorable survival rate similar to general population [16].

Massive Pulmonary Embolism

The hypercoagulable state of pregnancy increases the risk of thromboembolic complications. It is reported that pulmonary embolism has an incidence of 1 in 3000 and is considered to be the most common cause of maternal mortality in the developing world [18]. Treatment for hemodynamically stable pulmonary embolism has been well described, while that of massive and unstable pulmonary embolism is not well defined in pregnancy. Current guidelines indicate that thrombolytic therapy is a relative contraindication in the obstetric patient but has been described [19]. The use of ECMO is not fully supported given limited evidence. Review of the literature illustrates a limited number of utilizations of ECMO in hemodynamically unstable patients (pregnant and postpartum) with favorable maternal and fetal survivability [20].

Cardiac Arrest

Cardiac arrest is a rare event in pregnancy. The reported incidence is 1 in 12,000 admission for delivery in the United States. Outcomes are dependent on etiology,

with a relatively good prognosis as survival rate has been reported up to 58% [21]. Pregnancy is associated with cardiovascular changes as early as 6 weeks, which needs to be well understood in order to manage cardiac arrest. Heart rate increases 20–30% with an associated increase in cardiac output by 30–50%. Plasma volume expansion is noted up to 50% at term. These physiological changes are adaptive to supply oxygen and nutrition to the growing fetus. As the uterus enlarges, aorto-cava compression can occur, decreasing preload, leading to relative hypotension and bradycardia [21].

Management of cardiac arrest differs in the obstetric population. While standard ACLS is implemented, the obstetric team should promote left uterine displacement, remove all fetal monitors, and prepare for emergency caesarean delivery within 4 min of resuscitative efforts if return of spontaneous circulation (ROSC) is not successful [21]. If ROSC is achieved, then the reported survivability is favorable. ECMO utilization as a bridge to recovery has been utilized post ROSC, but data is limited into overall benefit [20].

Cardiomyopathy

Peripartum cardiomyopathy is described as the development of heart failure, of undetermined etiology, during the last month of pregnancy or within 5 months postpartum. Incidence is very low, affecting less than 0.1% of the obstetric population. Risk factors include advanced age, preeclampsia, gestational hypertension, multiparity, substance abuse, and cardiovascular comorbidities [22]. As described in the cardiac arrest section, multiple physiological changes occur during pregnancy that affect the cardiovascular system. The overall increase in intravascular volume and cardiac output causes a transient but reversible left ventricular hypertrophy (LVH) [21, 22]. Although not completely understood, this increase in LVH and inflammation, autoimmune response, and/or genetic predisposition to peripartum cardiomyopathy are believed to be contributing factors. Outcomes can vary, with mortality rates varying from 4% to 80% [22]. While medical treatments include standard heart failure therapy, ECMO has been described in case reports as bridge to recovery versus advance therapies such as assist devices/transplant [22].

ECMO in the Obstetrical Patient

Initiating ECMO support for cardiopulmonary failure in the obstetric patient is rare and uncommon. To date, evidence in the overall benefit and utility of ECMO is based on individual case reports. Comprehensive literature review focusing on ECMO utilization and pregnancy, albeit limited, concludes that ECMO can be relatively safe and effective as a bridge to recovery of the mother with limited adverse consequence to the fetus [23]. Survivability has been reported up to 77% for mothers and 65% for fetuses [23]. Multiple centers are successfully implementing ECMO

in this special population with positive results, although research and analysis need to be completed in order to implement pregnancy-related guidelines for ECMO administration.

Cannulation Strategy

Strategy for cannulation should be individualized for each patient. Currently, no defined protocol is described in the literature for the obstetric population. Cannulation in the femoral vessels may prove to be difficult secondary to the gravid uterus [24]. Additionally, flow limitation can occur secondary to aorto-caval compression. The procedure list must take these factors into account when planning the ECMO configuration and cannulation sites. Placing the patient in a slight left lateral decubitus in order to displace the gravid uterus off the inferior vena cava may be of benefit as it will maintain venous return.

Ultrasound and echocardiography have important roles in the cannulation of any patient onto ECMO support. To evaluate the vessels to be cannulated, ultrasound can be performed to estimate size of the vessels in order to verify that the cannulas to be used will be accommodated and are the appropriate size for the vessels to be used for cannulation [10].

Echocardiography can then be employed to verify guidewire placement into the IVC and SVC for VV ECMO and into the IVC and aorta for VA ECMO [10, 11, 14]. Once guidewire placement is verified to be correct, the cannulas can be placed. Appropriate positioning of the cannulas is paramount in order to supply proper support to the patient. For VV and VA ECMO, the multistage drainage cannula should lie in the IVC below the level of the right atrium [10, 11, 25]. Figure 16.5 shows a transthoracic echocardiographic image of a drainage cannula in proper position below the level of the right atrium.

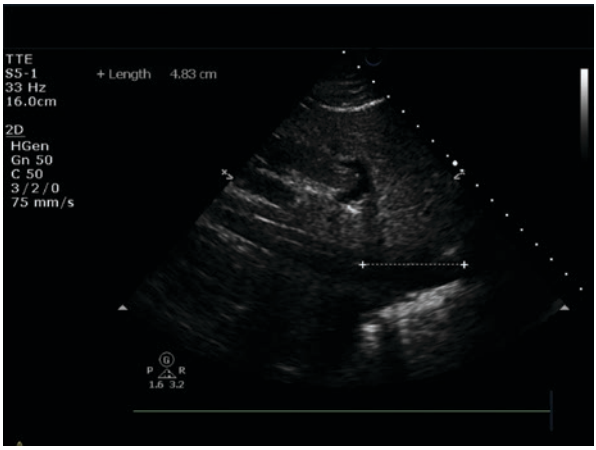

Fig. 16.5 Echocardiographic visualization of cannula/wire: the tip of the cannula shown 4.8 cm from the right atrium in proper position

The return cannula for VV ECMO should terminate at the level of the right atrium with flow directed toward the tricuspid valve [10, 11, 25]. Color Doppler can be used to verify proper flow of both the drainage and return cannula [11, 25]. The return cannula can be difficult to visualize with ultrasound as the tip of the cannula terminates in the distal aorta or proximal iliac artery.

Anticoagulation

Once ECMO has been initiated, anticoagulation needs to be started in order to avoid clot formation in the membrane, circuit, or patient. Given the artificial nature of the cannula, upregulation of the coagulation cascade and immune response occurs once blood contacts the non-endothelialized surface of the circuit [26]. The effect may be compounded secondary to the prothrombotic state of pregnancy. Approaching anticoagulation choice for the obstetric population requires balancing type of anticoagulant and benefit versus risk to the mother and fetus. In non-obstetric patients, unfractionated heparin is the most commonly used anticoagulant given the rapid onset and reversal and ease of monitoring effect [26]. This can be translated to the obstetric population. Unfractionated heparin is noted to be a large molecule that does not cross the placenta [27]. Maternal adverse effects include osteoporosis, if used long term, and heparin-induced thrombocytopenia. Although uncommon, low-molecular-weight heparin, well tolerated in the pregnancy, has been described in case reports as an agent to prevent thrombosis while on ECMO [26, 27]. Both unfractionated heparin and low-molecular-weight heparin can be safely used while breastfeeding [28]. Novel agents, such as direct thrombin inhibitors (argatroban and bivalirudin), have little data available into their safety profile during pregnancy. Case reports have been published with use, without adverse effects [29].

Sedation

While sedation may be required to facilitate cannulation, once ECMO has been initiated, sedation is not essential to tolerate the circuit. If the use of sedation is necessary, choice of sedative requires a balance of benefit versus risk to the mother and fetus, as noted in the anticoagulation section. Recent studies suggest that the use of opioids, hypnotics, anxiolytic, and sedatives does not have deleterious effects on fetal development [22] with the exception of benzodiazepines [30]. Conversely, meta-analysis review shows conflicting results in overall teratogenicity of benzodiazepine; overall consensus suggest to avoid use in the first trimester secondary to the potential cause of cleft lip or palate [30, 31].

Complications

The most common complication related to ECMO utilization is hemorrhage, estimated in 20–33% of patients [26]. One study of pregnant patient and ARDS, during the 2000s N1H1 pandemic, concluded that there is no significant difference in bleeding in pregnant or postpartum patients who require ECMO compared to women of similar age. Another potential concern is the development of thrombi and thromboembolic events given the hypercoagulable state of pregnancy, warranting the use of anticoagulation [32, 33]. Associated complications may occur during cannulation, as noted previously, secondary to the gravid uterus. Late pregnancy may cause aorto-cava compression, affect pre-load and limiting flow, and therefore require more aggressive fluid administration resulting in possible fluid overload [24].

Hypoxemia can still occur in patients requiring VV or VA ECMO and in a pregnant patient can cause serious issues not only for the mother but also for the fetus [20]. Recirculation is a phenomenon unique to VV ECMO and occurs when oxygenated blood returned to the patient is taken back immediately by the drainage cannula prior to entering the patient's circulation [34–36]. This is typically remedied by repositioning the cannulas in order to allow adequate distance between the cannulas [36]. Other things that can increase recirculation include high intrathoracic pressures, intracardiac pressures, or intra-abdominal pressures [34, 36]. If pathology exists that results in these situations, it should be addressed and treated immediately. In the case of pregnancy, the gravid uterus may not allow adequate venous return, so left uterine displacement may be needed in order to allow adequate drainage to allow proper flow to support the patient [20].

Other causes of hypoxemia besides recirculation on VV ECMO include anemia, improper flow settings to meet patient demands, and increased oxygen consumption by the patient not only due to critical illness but also due to the extraction by the fetus [5, 20, 34, 35]. Treatment of this includes increasing flow on the ECMO circuit, blood transfusion to increase oxygen-carrying capacity, deepening of sedation, and possible paralysis. Worst case scenario would be a transition from VV to VA ECMO to provide systemic delivery of oxygenated blood to the patient [5, 20, 34–36].

Hypoxia can occur on VA ECMO as well and is caused when oxygenated blood from the ECMO circuit mixes with deoxygenated coming from the patient's lungs that may not be fully participating in gas exchange [35]. This is known as "North-South syndrome" or "Harlequin syndrome." Treatment of this is typically accomplished by increasing flow on the ECMO circuit in order to move the "mixing zone" between oxygenated blood from the circuit and deoxygenated blood from the patient in the aorta closer to the innominate artery on the right side in order to assure that oxygenated blood is being distributed to all areas [5, 35].

Lastly, equipment failure should be ruled out if hypoxia persists despite optimization of the cannulas and patient parameters. The membrane lung performance can be measured by looking at pre- and post-membrane blood oxygenation [5]. If the pre- and post-membrane oxygenation values are similar, then the membrane lung may need to be replaced.

Despite the aforementioned complications, ECMO can be considered as a safe treatment option for the obstetric population that suffer from respiratory and/or cardiac failure [20].

Conclusion

Rescue modality for pulmonary or cardiopulmonary failure in the obstetric population is emerging in practice. Multiple case reports have been published in regard to the safe and successful use of ECMO in both pregnancy and the peripartum period. Despite no consensus on guidelines or treatment protocols, centers of excellence who are well versed in ECMO should continue to pave the way in research, thereby promoting ECMO as a practical option for the obstetric population.

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