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RESEARCH **REVIEW ARTICLE**

Veno-Arterial Extracorporeal Membrane Oxygenation in Pregnancy: A Literature Review

Waheed F. Hammad [2], Hala Almajali [3], Zaineh M. Alfreahat [4], Salem Alsalman [5], Yasmeen Jamal Alabdallat [6], Moustafa Younis [1]

ABSTRACT

Veno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO) is a very important circulatory support system, and its use has increased over the years, especially in pregnancy and its related consequences on the mother and the fetus. This article aims to review all the important aspects of VA-ECMO in pregnancy. Further, it discusses the findings that VA-ECMO is less commonly used during pregnancy and does not disregard maternal, neonatal, or long-term outcomes, as the survival rate is relatively good compared to the general population. A description of what VA-ECMO is, protocols, usually targeted goals, preferred sites of access, indications, and contraindications, the use of anticoagulation and its side effects, specific complications, including bleeding from multiple sites, and the incidence of thromboembolic complications are all explored. Moreover, a thorough discussion is intended to address some of the special considerations and technical challenges in pregnancy due to uterine compression, maternal susceptibility to thrombosis and infections, the status of the fetus, and the mode of delivery.

KEYWORDS - Veno-arterial Extracorporeal Membrane Oxygenation; Pregnancy; Respiratory Failure; Peri-partum

[1] MD, Pulmonary, Critical care and Sleep Medicine, University of Florida, Gainesville, Florida

[2] MD, Al Hussain New Salt Hospital, Ministry of Health, Amman, Jordan

[3] Medical student, Faculty of medicine, University of Jordan, Amman, Jordan

[4] Medical student, faculty of medicine, Yarmouk university, Irbid, Jordan

[5] MD, Internal medicine/Intensivist; Critical Care Department; king Hussein Medical Center, Royal Medical Services, Amman, Jordan

[6] Medical student, Faculty of medicine, Hashemite University, 13133, Zarqa, Jordan.

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Corresponding Author:
Moustafa Younis, M.D.
Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Florida, Gainesville, Fl USA

Email: Myounis@ufl.edu

BACKGROUND

In recent years, the utilization of extracorporeal membrane oxygenation (ECMO) as a critical care intervention has seen a rise due to advancements in intensive care technology(1). ECMO, a specialized technique of cardiopulmonary bypass, provides temporary support for respiratory and/or cardiac functions in critical situations, and its application in obstetrics is becoming increasingly common(2–5). Several causes, including the aging of the maternal population and the rise in chronic illnesses like obesity and heart disease, are responsible for this trend (6). Consequently, there is a potential for a notable increase in maternal morbidity and mortality rates, including cases of refractory cardiogenic shock where ECMO may be utilized as a salvage therapy (1,2,6–9).

While venoarterial ECMO (VA-ECMO) offers the potential for improved survival, the outcomes may vary, emphasizing the significance of selecting the appropriate indications for each obstetric patient (10). This article will offer a comprehensive exploration of VA-ECMO in obstetric patients, including a detailed examination of its prevalence, incidence, maternal and neonatal outcomes, indications, contraindications, anti-coagulation strategies utilized, complications, and special considerations unique to this group of patients.

PREVALENCE AND INCIDENCE

The prevalence and utilization of VA-ECMO in pregnancy is relatively low, as it is typically reserved for highly complex cases (11,12). Due to the infrequent use of VA-ECMO in pregnancy and the variation in medical practices among different healthcare centers, there is limited data on the frequency of its use. However, estimates suggest that around 1 in 10,000 pregnancies may require VA ECMO support, depending on factors such as regional practices, the presence of specialized medical centers, and the underlying conditions that may necessitate its use (1,13)

A recent meta-analysis reported the distribution of delivery methods among the VA-ECMO cases studied. Vaginal delivery comprised 18.7% (67 cases), cesarean section constituted 44.1% (158 cases), and dilation and extraction were employed in 1.4% (5 cases). It is essential to highlight that the mode of delivery was not reported in 35.8% (128 cases). This breakdown offers valuable insights into the prevalence of different delivery methods in the context of VA-ECMO utilization during the peripartum period (13).

VA-ECMO OUTCOMES

Maternal outcomes with VA-ECMO depend on factors like gestational age and comorbidities. Survival rates for mothers undergoing VA-ECMO during pregnancy were approximately 80% (1,12), but differences in ICU discharge rates did not reach statistical significance ($p = 0.44$ and 0.47) (12,13). Maternal survival rates at hospital discharge were slightly lower, with 73% for patients started on VA-ECMO during pregnancy and 85% for patients initiated on VA-ECMO after delivery (12). Long-term outcomes were insufficiently documented.

Concerning neonates, Aissi et al.'s study reported that 28% lost their lives during ECMO support, with an additional 7% dying following ECMO (14). The overall neonatal survival rate was 65%, which was consistently maintained across different study periods (14).

Published statistics suggest that maternal and fetal survival with ECMO generally surpasses that in the overall adult population, standing at approximately 80% and 70%, respectively (15–17).

Comparatively, the current survival rate for adult patients undergoing venovenous ECMO (VV-ECMO) is 59%, whereas the rate for VA-ECMO is only 43% (18). This might be due to the relatively lower number of pregnant patients undergoing VA-ECMO; thus, the results are not absolute, but a trend can be interpreted from it (19).

In contrast, the literature regarding long-term follow-up assessments for infants undergoing ECMO seems less comprehensive. The potential challenges in tracking and assessing these neonates' developmental, cognitive, and health outcomes as they grow could contribute to the limited availability of long-term data.

A 2016 meta-analysis exploring VA-ECMO in pregnant and postpartum patients with H1N1-related ARDS reported maternal and fetal survival rates exceeding 60% (2). Additional studies showed pregnant and peripartum patients on VA-ECMO exhibited survival rates between 70% and 80%, surpassing general population rates. Iatrogenic complications mirrored those in the general population (15,17,20,21).

A recent meta-analysis on peripartum outcomes for mothers and fetuses undergoing VA-ECMO revealed a 30-day survival rate of 75.4% for mothers and 64.7% for fetuses (13). Complications associated with VA-ECMO were in line

with general population trends. Timing of ECLS relative to delivery was linked to variations in survival, suggesting better outcomes for peripartum patients due to potentially more reversible conditions.

In a recent case report, successful ECMO use was highlighted in a 37-year-old pregnant woman with severe COVID-19 respiratory failure. Despite challenges, ECMO led to rapid improvement, facilitating a successful cesarean delivery on day 3. Nursing-administered breast-pumping on ECMO and performing the cesarean section without interrupting anticoagulation were notable aspects. The patient's discharge on day 49 underscores ECMO's efficacy in managing refractory respiratory failure during pregnancy, especially in COVID-19 cases (22).

In a decade-long study, 20% of women of reproductive age undergoing ECMO were either pregnant or within six weeks postpartum. The initiation of ECMO during pregnancy or intrapartum yielded a 60% survival rate for both mothers and fetuses (12). Since peripartum patients have special features in some respects, as they are generally younger and more likely to be in good physical condition, they are less likely to have chronic illnesses such as diabetes, renal diseases, and chronic pulmonary disease. Their root need for ECMO is most likely reversible due to pregnancy status (like shock), which all contribute to better post-ECMO outcomes and superior survival rates (19).

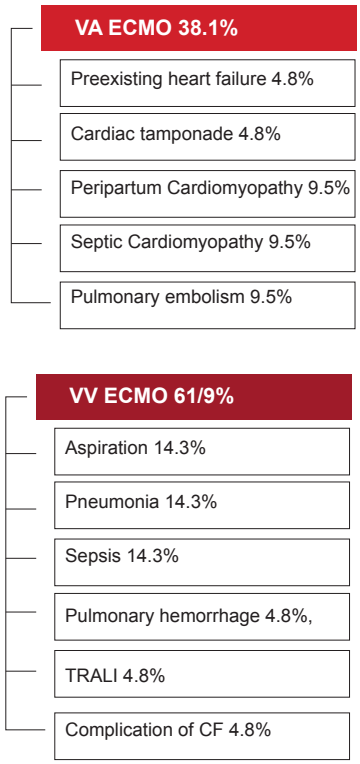
The timing and mode of delivery for ECMO patients, which necessitates a multidisciplinary strategy, are important considerations. Birth time and manner are influenced by several important factors, including gestational age, antenatal steroid use, predicted ECMO duration, chance of improvement in the mother's cardiopulmonary function, and birth urgency (19).

VA ECMO INDICATIONS

The most common VA-ECMO indications during pregnancy and peripartum include cardiac failure secondary to preeclampsia or eclampsia (after stabilization), either directly due to severe hypertension or indirectly in severe cases resulting in diffuse multiorgan dysfunction. Other indications include high-risk pulmonary embolism, cardiac arrest (extracorporeal cardiopulmonary resuscitation), septic abortion resulting in septic shock, peripartum cardiomyopathy, decompensated congenital heart disease (as VSD, PDA complicated to Eisenmenger syndrome), prosthetic valve failure, and amniotic fluid embolism (AFE) (12,14,19,23)

The distribution of the several indications for both VA and VV-ECMO are listed below (Figure 1). The most common indication of VV-ECMO in pregnancy is ARDS, which can be attributed to various causes, as listed in Figure 1.

Figure 1. Represents different Indications for both VV and VA ECMO support in pregnancy. CF, cystic fibrosis; ECMO, extracorporeal membrane oxygenation; TRALI, transfusion-related acute lung injury; VA, venoarterial; VV, venovenous [14].



CONTRAINDICATIONS

While critically unstable pregnant or postpartum patients may benefit greatly from VA-ECMO, there are both definite and relative limitations that must be considered before utilization. Restrictions that are both absolute and relative are noted in Table 1 below. Absolute contraindications are few and are considered rare in pregnancy or postpartum age (24).

Relative contraindications include the need for an urgent delivery, eclampsia (a seizure), or active bleeding. Previous aortic dissection that wasn't repaired because the retrograde high-velocity flow could spread the dissection flap further is also a contraindication, as is aortic regurgitation because it could cause progressive left ventricular enlargement (24). While they do not disqualify the patient from VA-ECMO, these conditions need maternal stabilization and further evaluation before VA-ECMO is considered (25).

Additionally, before cannulation, a recovery or transplant from VA-ECMO support ought to be constantly considered as an exit strategy. The absence of such a plan may be regarded as a warning against cannulation (24).

Additionally, patients who have had a previous replacement of the mitral valve should be extremely cautious when it comes to coagulability and bleeding because VA-ECMO can significantly reduce trans-mitral flow, raising the risk of thrombus development. Nevertheless, results support that high bleeding risk should not be considered an absolute contraindication for ECMO (14,24).

Table 1. Represents different absolute and relative contraindications of va-ecmo in pregnancy.

Certainty	Criteria
Possible	• short life expectancy • acute or any preexisting status that is incompatible with restoration and VA-ECMO weaning (such as neurological injury, disseminated malignancy) • if the patient's goals-of-care are not suitable with such level of cardiorespiratory support • end-stage cardiac failure when recovery or transplant is not possible. • having an exit strategy
Relative Contraindications	• Previous aortic dissection that isn't repaired • Advanced peripheral vascular disease when peripheral cannulation is considered • Aortic regurgitation [16] • Contraindications to systemic anticoagulation • Prolonged mechanical ventilation before ECMO • Advanced age • Cardiac arrest with extra-pulmonary organ failure [18] • Urgent need for delivery, eclampsia (seizure), or active bleeding

ANTI-COAGULATION

Coagulation status must be monitored accurately during VA-ECMO support, and a variety of laboratory tests can be used depending on institutional protocols and the anticoagulant selected, such as activated clotting time (ACT), heparin anti-Xa level, activated partial thromboplastin time (aPTT), global thromboelastography, and prothrombin time. Maintaining the platelet count above 50,000/mm3 and replacing coagulation factors as needed are measures used to reduce bleeding risk significantly (24).

The ECMO circuit lacks an endothelial surface, increasing the risk of clotting both in the circuit and the patient. This significantly increases the risk of embolic events that can be dramatic on the arterial side. Examples of such include embolic strokes, mesenteric ischemia, and limb ischemia. Therefore, the use of continuous systemic anticoagulation is of utmost importance. The most used and preferred agent is intravenous heparin drip for the whole duration of VA-ECMO support. This is secondary to heparin's short half-life, the ability to monitor closely, and ease of dose adjustment (24,25). The heparin drip can be titrated to a goal (aPTT) of 60–80 seconds, ACT, or factor Xa level(19). The targets vary based on the patient's bleeding risk profile and institution policies. Due to the overall rapid rate of antithrombin depletion with chronic IV heparin dose, a concern for heparin resistance can rise. Furthermore, IV heparin increases the risk of heparin-induced thrombocytopenia. Hence, some institutions institute protocols that include the use of direct thrombin inhibitors such as bivalirudin or Argatroban (23).

Literature updates on anticoagulation strategies, specifically comparing heparin and bivalirudin in non-pregnant patients undergoing ECMO, indicate that bivalirudin may provide survival benefits and reduce thrombosis in a subgroup of adult ECMO patients (26,27).

As discussed in recent literature, two emerging anticoagulation strategies, Nafamostat Mesilate (NM) and Bivalirudin, are being explored to mitigate the risk of bleeding during ECMO treatment. In a retrospective review by Lee JH et al., the research team analyzed aPTT values in 16 ECMO patients. Among these patients, 44% initially received heparin before switching to NM, while 56% were administered NM exclusively. The study's statistically significant results indicate that the aPTT values in the NM group were lower than those at the ECMO site. These findings apply to all ECMO patients studied and do not specifically address pregnant individuals, as testing new anticoagulation strategies during pregnancy could pose unknown short- and long-term risks to the fetus (28).

A study by Wood et al. focused on patients requiring ECMO intervention and found a significant reduction in overall complication rates for those not systemically anticoagulated while on VA-ECMO. These patients needed fewer packed red blood cells (PRBC) and platelet transfusions. More than half of the non-anticoagulated patients did not need any PRBC transfusions. Addition-

ally, these patients experienced a lower incidence of hemorrhagic complications requiring intervention and unexpectedly fewer thrombotic complications. The absence of systemic anticoagulation did not increase thrombotic events within the ECMO circuit, with no cases of circuit clots or heparin-induced thrombocytopenia (HIT). In contrast, about 7% of anticoagulated patients developed HIT. Consequently, it was concluded that routine systemic anticoagulation for patients on VA-ECMO is not necessary to prevent higher mortality or thrombotic complications (29). Previous research on VA-ECMO with low or no anticoagulation has similarly shown reduced major bleeding events and blood product transfusions without a significant rise in thrombotic complications (30,31). Though these results were observed in non-pregnant women, it does provide insight into how much anticoagulation should be given only if needed in pregnant patients to avoid the complications mentioned above.

In patients with major bleeding, such as intracranial hemorrhage or perioperative patients, anticoagulation can be paused in patients on VA ECMO. However, these patients must run on higher VA-ECMO flows to decrease the risk of stasis and clotting. The risk of hemorrhagic and thrombotic consequences must be balanced in the right therapeutic setting (24,25).

COMPLICATIONS

A systematic review by Naoum et al. highlighted that when the overall most commonly used cannulation method was venoarterial, the most prevalent complications were mild to moderate bleeding 66 (18.4%), severe bleeding that necessitated surgical intervention 48 (13.4%) and new morbid neurological states 48 (13.4%), as a result when measuring the 30-day survival rate, of the 270 (75.4%) mothers who survived, 245(68.4%) survived without a residual neurological state excluding those who had peripheral neurological deficits or needed rehabilitation. Based on the periodic sequence of pregnancy, reporting the outcomes of fetuses was possible just from 68 (84%) of the antepartum group; the most common fetal complications were preterm birth 33 (48.5%), admission into NICU 19 (27.9%) and intracranial complications 5 (5.9%) such as intracranial bleeding, ventriculomegaly, ventriculomegaly with cerebral ischemia and therapeutic hypothermia associated asphyxia (20).

Furthermore, given the hypercoagulable state induced by pregnancy, thrombo-embolic complications are also more common. As previously mentioned, patients are at risk of embolic strokes, limb ischemia, intra-coronary thrombi due to stasis from increased afterload in a failing heart (more common in central VA-ECMO), and mesenteric ischemia, which is associated with a mortality rate of almost 100% (23). Uterine compression on the IVC late in pregnancy reduces flow rate and, consequently maternal cardiac output and fetal oxygenation (25)

Regarding deep vein thrombosis and vascular complications in pregnancy, a systematic review (13) showed that those complications were less common at 2.8% and 3.9%, respectively, compared to limb ischemia in the general adult population at 2% to 14%. After conducting thorough research, we found no studies that address the relation between the gravid uterus and an increased risk of limb ischemia in peripheral cannulation. As such, further research is required to explore this possibility. Figure 2 lists complications in pregnancy for both the mother and fetus.

CONCLUSION

VA-ECMO is considered a lifesaving intervention for the general population of patients who have any condition leading to cardiac failure; studies show it has been used in pregnant patients with the potential benefit of improving survival rates among both mothers and fetuses successfully. However, after all, VA ECMO still has limited data on pregnancy and needs more trials and investigations to reach a good understanding of the long-term outcomes and complications. Given the lack of documented guidelines targeting pregnant patients, it's still a high-risk procedure that needs a multi-disciplinary team with specialized centers to ensure the safest and most optimum approach and results.

It is crucial to have a comprehensive and organized database for all pregnant patients treated with VA-ECMO to gather accurate information on their outcomes and long-term fetal outcomes. This will help in future research and development of optimal anticoagulation strategies, fetal monitoring, and methods and timing of delivery. It will also aid in identifying potential complications and addressing them accordingly. A well-structured database will improve our understanding of VA-ECMO in pregnancy and help provide better care to obstetric patients.

AUTHORS' CONTRIBUTION

Moustafa Younis was involved in conceptualization, overall supervision, and manuscript revision. All authors approved this version of the manuscript for submission. Waheed F. Hammad, Hala Almajali, Zaineh M. Alfreahat, and Yasmeen Jamal Alabdallat were involved in manuscript writing, editing and revision. Salem Alsalman was involved in overall supervision and manuscript revision.

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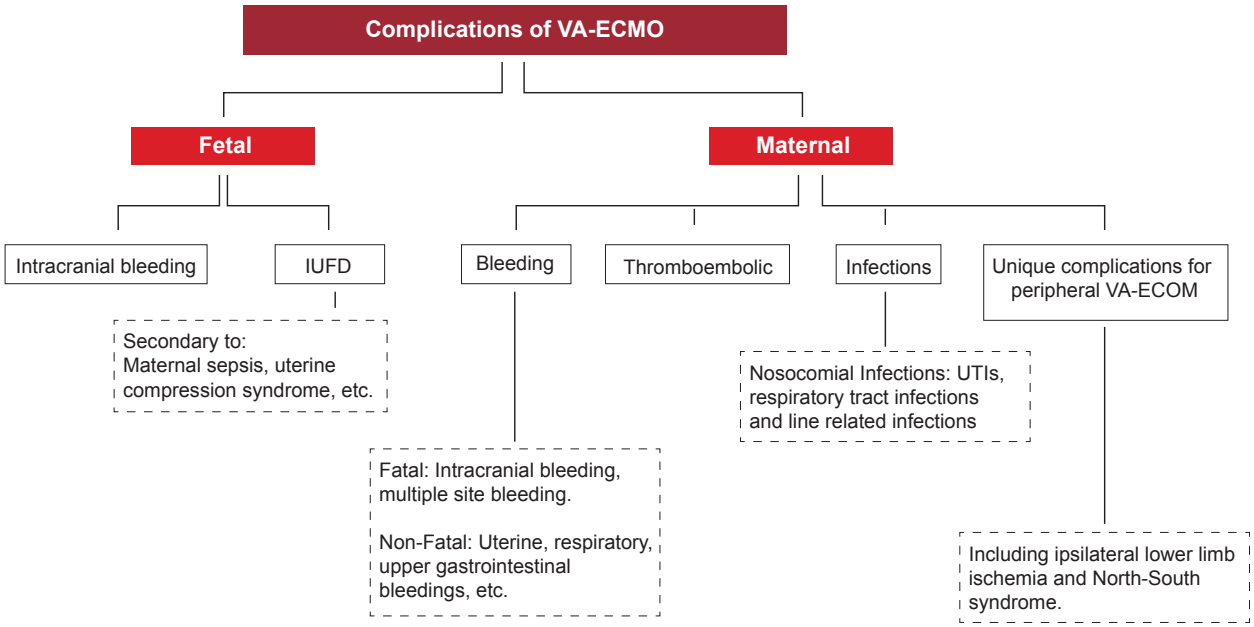
SUPPLEMENTAL MATERIALS

Figure 2. Shows different complications of VA-ECMO both for the mother and the fetus.



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