# Updates in Neonatal Extracorporeal Membrane Oxygenation and the Artificial Placenta

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**KEYWORDS**

• ECLS • Neonatal ECMO • Preemie ECMO • Artificial placenta

**KEY POINTS**

- Extracorporeal life support is a lifesaving technique for neonates with respiratory and/or cardiac failure.
- Technological and medical advances have paved the way for applying the benefits of ECMO to support premature infants.
- Recreation of the fetal environment with an artificial placenta/womb is promising for improving morbidity and mortality of extremely premature infants.

## INTRODUCTION

Extracorporeal life support (ECLS), initially performed in neonates, is now commonly used for both pediatric and adult patients requiring pulmonary and/or cardiac support.[1] ECLS can provide hemodynamic stability and gas exchange. Although it is not curative, it serves as a bridge to organ recovery or definitive therapy. Originally developed for term and near-term infants, there is experience with "preemie ECMO" (29–33 weeks estimated gestational age [EGA]) that demonstrates clinical feasibility.[2] For extremely premature infants less than 28 weeks EGA, an artificial placenta (AP) has been developed, which recreates the fetal environment, preserves fetal circulation, and provides protection and the milieu for normal organ development. This approach is currently investigational but clinical translation is promising. In this article, we discuss the status and advances in neonatal and "preemie ECMO" and the development of an AP and its potential use in extremely premature infants.

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Clin Perinatol 49 (2022) 873–891
https://doi.org/10.1016/j.clp.2022.07.002
perinatology.theclinics.com

## NEONATAL EXTRACORPOREAL LIFE SUPPORT

### *Indications*

ECLS has specific indications in the neonatal population, and this review focuses on neonatal patients with respiratory and combined respiratory/cardiac failure. Patients with congenital heart disease are beyond the scope of this review. Patients with severe respiratory and/or cardiac failure with high likelihood of mortality, as well as an etiology that is reversible are considered for neonatal ECMO.[3] Common neonatal indications for ECMO include congenital diaphragmatic hernia (CDH), meconium aspiration syndrome, pulmonary hypertension, and sepsis. CDH, meconium aspiration, and persistent pulmonary hypertension encompass approximately 75% of respiratory ECMO cases.[3] Neonates typically meet the following criteria: (1) inadequate oxygen delivery to tissues with maximal therapy, (2) severe hypoxic respiratory failure, (3) elevated oxygenation index (OI), and/or (4) severe pulmonary hypertension.[3] For patients in respiratory failure, the most common metric is OI.[4] An OI greater than 40 correlates with an 80% mortality and ECMO should be considered for neonates with an OI greater than 25.[5,6] Additionally, neonates with hypercapnic respiratory failure, sustaining a pH from 7 to 7.25 may benefit from ECMO (**Table 1**).[7] It should be noted that sudden hypercapnic respiratory failure with preserved oxygenation should prompt consideration of a distal ETT mucous occlusion that behaves physiologically like a one-way valve.

### *Contraindications*

Contraindications to neonatal ECMO include the following: (1) no expectation of recovery from organ failure, (2) chromosomal abnormality not compatible with life, (3) uncontrolled bleeding, (4) vessel size too small for cannulation, and (5) severe brain bleeding/damage. Relative contraindications include EGA less than 34 weeks and weight less than 2.0 kg given early clinical experience with poor outcomes[8] (see **Table 1**). More recent advances have established the feasibility of "preemie ECMO" for infants 29 to 33 weeks EGA.[2] Typically, patients requiring ECLS need prolonged high ventilator settings, which can be associated with ventilator-induced lung injury and mortality. Extended ventilation greater than 7 days was initially a contraindication to ECLS but this has been extended to 14 days with no change in survival rates.[9–12] These guidelines may be further modified depending on specific ventilatory strategies used. Many infants treated by "gentle ventilation" strategies for longer than 2 weeks should still be considered for ECLS on a case-by-case basis selecting patients anticipated to have lung recovery.

**Table 1**
**Indications and contraindications of neonatal ECMO**

| Indications | Contraindications |
|---|---|
| Oxygenation index >25 | Lethal chromosomes or another anomaly |
| $Pao_2$ to $Fio_2$ ration <60 | Poor predicted neurologic outcome/irreversible brain injury |
| pH < 7.25 | Uncontrolled bleeding |
| Shock | ICH > Grade III |
| A-a DO2 > 500 mm Hg | Advanced multiorgan system failure |
| Pplat > 30 cm $H_2O$ | Ventilation > 40 d |
| | Weight < 1.5 kg |
| | EGA < 29 wk |

*Adapted from* Fallon BP, Gadepalli SK, Hirschl RB. Pediatric and neonatal extracorporeal life support: current state and continuing evolution. Pediatr Surg Int. 2021 Jan;37(1):17-35.

### *ECMO Outcomes*

In the 2020 ELSO registry, the overall survival for neonatal patients who received ECMO for respiratory disease is 73%.[3] However, survival rates vary by diagnosis as follows: meconium aspiration (92%), persistent pulmonary hypertension (73%), sepsis (60%), CDH (50%), and prematurity (50%).[3]

Neonates who survive ECMO are at risk for several long-term health issues

Neurologic complications are common secondary to preexisting risk of bleeding, systemic anticoagulation, carotid and/or internal jugular (IJ) ligation, and physiologic perturbations.[13] Twenty-five percent of neonates requiring ECMO develop neurophysiologic deficits.[14] Not surprisingly, patients with neurologic complications have an increased mortality rate.[13] At 7 years of age, half of the neonatal ECMO survivors sustained some form of disability that persisted over time. One study of 135 patients found that although the patients' intelligence level fell within the normal range, they had increased behavioral problems in school.[15] Neonates requiring ECMO for CDH experience a spectrum of long-term health problems including respiratory, gastrointestinal, and neurologic complications. These complications correlate with the severity of CDH and duration of critical illness in the newborn period.

### *Mode of Support*

#### *Veno-arterial ECMO*

The earliest mode of ECLS support was veno-arterial (VA) ECMO. VA ECMO was performed by open cut-down cannulation of the carotid artery and the IJ vein,[16,17] and it remains the most common method of cannulation for neonatal patients (**Fig. 1**). VA-ECMO provides both cardiac and pulmonary support and offloads the right side of the heart, which is particularly beneficial in patients with severe pulmonary hypertension. A major concern with VA ECMO is related to stroke risk and neurologic complications due to carotid artery ligation. Interestingly, differences in rates of neurologic complications and stroke related to age or cannulation site were not apparent after adjusting for other factors such as age, support type, severity of illness, in a study by Johnson and colleagues.[18] In a large study of 140 patients, Duggan found no difference in neurologic outcomes comparing carotid artery reconstruction versus ligation at the time of decannulation.[19] In a review of the ELSO registry in 2014, 21% neonates cannulated with VA ECMO sustained neurologic injuries. It is unclear if cerebral venous hypertension contributes to this neurologic injury after jugular cannulation.[20] In a retrospective review of 81 neonates treated with ECLS, 46% sustained frontal and temporoparietal white matter injury based on MRI.[21] Although the pattern of injury was similar between VA and VV modes, the frequency may be higher with VA ECMO. Finally, it should be noted that not all patients with MRI abnormalities develop significant clinical sequelae.

#### *Veno-venous ECMO*

Veno-venous (VV) ECMO provides respiratory support but does not provide direct cardiac support. Potential advantages to this cannulation method include preservation of the carotid artery, pulsatile blood flow and oxygenated coronary blood flow. There is a neurologic complication rate of 20% with neonatal VA ECMO, and these rates have been found to be lower with VV ECMO.[22] Ligation of the right carotid artery and jugular vein in VA ECMO may increase the risk of stroke.[23] Loss of pulsatile cerebral blood flow, decreased cerebral autoregulation, and circuit-associated emboli, or severe cardiorespiratory dysfunction during VA ECMO may explain the increased neurologic

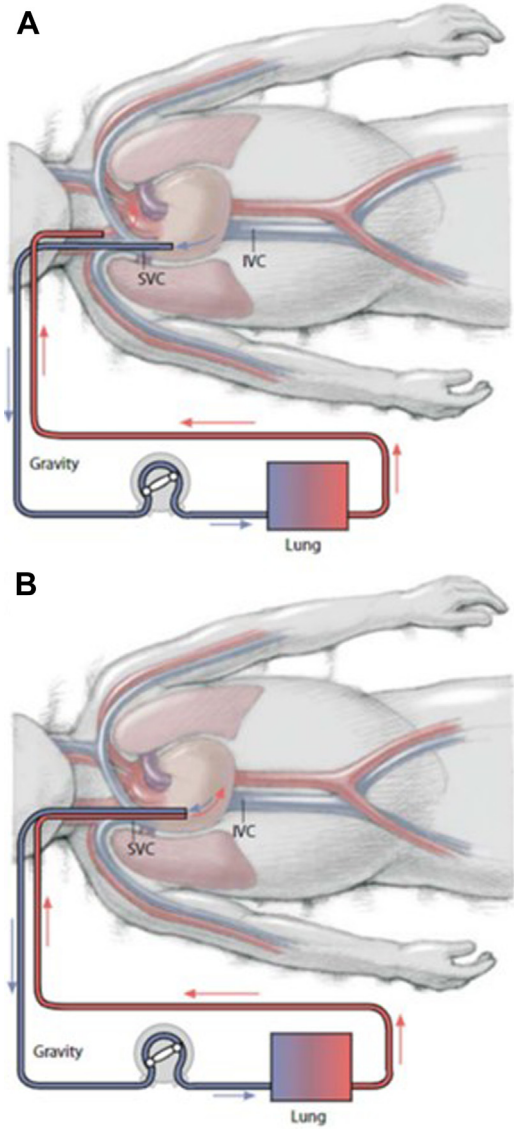


**Fig. 1.** (*A*) A VA ECMO versus (*B*) B double-lumen VV ECMO. (Frischer J.S., Stolar C.J.H., Hirschl R.B. (2020) Extracorporeal Membrane Oxygenation for Neonatal Respiratory Failure. In: Puri P. (eds) Pediatric Surgery. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-662-43588-5_58.)

complications compared with VV ECMO neonatal patients. In general, VV ECMO cannulation can be performed with 1 double-lumen cannula or 2 single-lumen cannulae (see **Fig. 1**). In neonates, dual-site cannulation was abandoned in the 1980s due to the small size of the femoral vein and concerns about limb morbidity. Placement of a right IJ double-lumen cannula avoids a second vessel access, and because the oxygenated blood enters the pulmonary vasculature, pulmonary artery vascular resistance is decreased.[24–26] The Origen double-lumen cannula was initially developed for

VV ECMO in the neonatal population. The Origen cannula was simple to insert via the right IJ cut-down technique without the need for fluoroscopy or echocardiography. However, a postoperative echocardiography was recommended to confirm position in the mid-right atrium with flow directed toward the tricuspid valve. Although effective, problems with this cannula included recirculation related, in part, to cannula design. In 2019, the Origen right atrial cannula was no longer produced.

### *Catheter Advances*

In 2008, the Avalon dual-lumen bicaval cannula was developed as a single-site VV ECMO cannula. This cannula effectively drains blood from the inferior vena cava and superior vena cava and delivers oxygenated blood into the right atrium (**Fig. 2**B). This wire-reinforced cannula ranges in size from 13 to 31 French.[27] Because the distal catheter needs to land in the IVC, real-time imaging with fluoroscopy and echocardiography is required for safe and effective insertion. The Crescent cannula is a wire-enforced, bicaval cannula. The insertion site for the Crescent cannula is also in the RIJ (**Fig. 2**A). There are titanium markers along the cannula to allow for visualization with imaging. This is placed under fluoroscopy as well.[28] This catheter shows promise in the continued development of double-lumen cannulae for ECMO.[29]

Initial enthusiasm for the 13F Avalon catheter in neonates waned in light of safety and efficacy concerns. There is a short distance between the ICV/SVC holes and the right atrial infusion hole. As such, small changes in catheter position affect performance.[30] Although successfully performed in neonates by several groups,[31] several investigators expressed safety concerns, which eventually limited widespread adoption for neonates.[32]

Given safety concerns about the 13F Avalon cannula and the unavailability of the Origen cannula, ECMO centers transitioned to VA cannulation for most neonates in 2019. Due to this shift, there was resurgence in interest in the 2-cannula approach. This approach was studied in 11 patients from 2015 to 2019 with femoral vein and jugular access points. Because the femoral vein is small and ECMO flow rates are largely dependent on adequate drainage, they used the femoral vein for inflow and the jugular for drainage, which could accommodate a larger cannula. Nine out of 11 patients survived to home discharge, and although there was common femoral vein

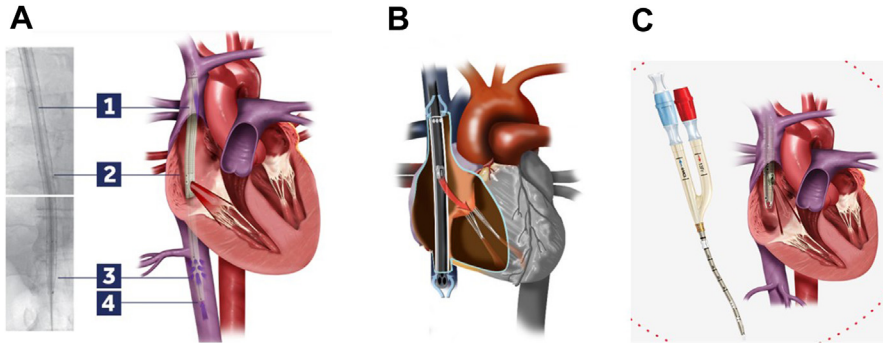


**Fig. 2.** (*A*) Crescent bicaval cannula. (*B*) Avalon cannula. (*C*) Crescent atrial cannula. ([*A*] Reproduced with permission of Medtronic, Inc., Minneapolis, MN; [*B*] *From* Hirose H, Yamane K, Marhefka G, Cavarocchi N. Right ventricular rupture and tamponade caused by malposition of the Avalon cannula for venovenous extracorporeal membrane oxygenation. J Cardiothorac Surg. 2012 Apr 20;7:36; and [*C*] *Courtesy of* MC3 Cardiopulmonary, Dexter, MI.)

occlusion, no clinical or functional deficit was noted in the cannulated limb at follow-up.[33]

In 2021, the Crescent* right atrial, jugular dual-lumen (13, 15, and 19 Fr) catheter was launched for clinical application (Fig. 2C). The 13 Fr catheter was designed for neonatal VV ECMO and is supplied with an introducer to facilitate wire-guided placement via Seldinger technique or cut down with an obturator. The design features include radiopaque markers to aid in positioning and axial orientation. The reinfusion port size, shape, and location were designed to optimize flow performance and minimize recirculation. Given the recent launch of this catheter, published data on safety and efficacy are not available but it is anticipated to increase the application of VV ECMO in neonates.

### *Anticoagulation: Monitoring and Treatment*

Bleeding and thrombosis remain unsolved problems in the management of ECLS patients. The most common method of anticoagulation for neonatal ECMO remains continuous heparin infusion. There are many institutional protocols for regulating heparin levels in this population.[34] ATIII is required for heparin functionality, and in some institutions, it is monitored and replaced but should be used judiciously.[35] The main methods for monitoring anticoagulation are activated clotting time (ACT), prothrombin time (PTT) anti-Xa levels, and thromboelastography. ACT is most commonly used and can be performed at the bedside but there remain concerns about the accuracy and reliability of ACT in many clinical scenarios. As such, there has been an interest in other monitoring approaches. PTT measures intrinsic coagulation pathway and is a more specific measurement of heparin effect on the patient. Anti-Xa is the most specific, measuring the inhibition of Xa by heparin ATIII complexes. A retrospective review comparing ACT versus anti-Xa levels did not demonstrate any major differences between 2 groups or any increased complications.[36] Our center and others have adopted a hybrid approach adding anti-Xa measurements to routine ACT measurements in patients with complex coagulation scenarios. Although anti-Xa measurements seem promising, there is currently no consensus on which measurement is best.[37]

Alternative anticoagulants to heparin are currently being evaluated, including bivalirudin and argatroban. Because they are direct thrombin inhibitors, do not depend on ATIII and do not have the risk of HIT, they may provide more stable anticoagulation compared with heparin.[38] A literature review comparing bivalirudin to heparin overall demonstrated more stable coagulation profiles with similar thromboembolic events.[39–41] In one of the largest series of neonatal and pediatric patients on ECLS studying with bivalirudin, it was found to be a feasible anticoagulation option for patients who could not receive heparin.[42] Current data, primarily in the pediatric population, support the safety of bivalirudin, and many centers are adopting this approach.[43] Preliminary data in neonatal CDH patients suggest safety and efficacy[44] but further data are required in the neonatal population in order to make a definitive transition in practice.

Although there are new advances in improving anticoagulation with ECMO, all anticoagulation poses a bleeding risk especially in neonatal and “preemie” ECMO. The ECLS laboratory at the University of Michigan (UM) has developed a nitric oxide surface-based anticoagulation system to obviate systemic anticoagulation while on ECMO. The surface coating is based on S-nitroso-N-acetyl-l, L-penicillamine (SNAP). Nitric oxide is released from the SNAP-based polymer coatings for as long as 20 days and has been shown to prevent thrombosis.[45–48] Additionally, we found that adding argatroban to the coating reduces fibrin formation.[49] This technology

will be essential for providing extracorporeal support to extremely premature infants for whom the risk of systemic anticoagulation is prohibitive.

### *Preemie ECMO*

The application of ECMO in premature infants is limited by the increased risk for intracranial hemorrhage (ICH). The risk of ICH in premature infants on ECMO is high given the baseline ICH risks and requirement for systemic anticoagulation. Early studies with premature infants on ECMO found the risk of morbidity and mortality to be high[8]; however, recent experience demonstrates lower risks and clinical feasibility.[2,50,51] It was initially thought that neonates with weight less than 2 kg had significantly decreased survival due in part because of prematurity and size constraints to maintain adequate flows with small cannulas. Multiple studies have shown reasonable survival, as high as 40% in infants as small as 1.6 kg.[52,53]

The outcomes of all neonates with gestational ages 29 to 34 weeks on ECMO from 1976 to 2008 were evaluated by Church and colleagues. The survival of the 29 to 33-week EGA cohort was 48% compared with the clinically established 34-week EGA cohort at 58%. There was no significant difference in ICH rate but a statistically significant difference in the incidence of cerebral infarct (22% vs 16%). Although the rates of survival and cerebral infarction were worse for the more premature cohort, these differences were modest and clinically acceptable.[2]

### *Clinical Outcomes for Extremely Low Gestational Age Newborns*

One in 10 infants in the United States is born prematurely (defined by less than 37 weeks EGA).[54] There is increasing risk of morbidity and mortality with extremely low gestational age newborns (ELGANs) defined as neonates born at less than 28 weeks EGA. This mortality risk is up to 38.4% for ELGANs, compared with 0.2% for full-term infants.[54] Prematurity remains an unsolved problem and a great opportunity exists to improve outcomes in this vulnerable population.

The poor outcomes for this patient population stem from 2 interrelated factors: organ immaturity and the unintended iatrogenic consequences of conventional medical treatments. The positive-pressure ventilation required by many of these infants has been associated with negative physiologic effects on the lung, including decreased surfactant production,[55] increased pulmonary vascular resistance, and activation of local and systemic inflammatory responses.[55] Cardiac output is also negatively affected due to the decreased pulmonary blood flow.[56] The associated elevation in intrathoracic and thus intracranial pressure has been associated with an increased risk of intraventricular hemorrhage.[57] Finally, the high fraction of inspired oxygen ($Fio_2$) that these patients require is a major contributor to retinopathy of prematurity (ROP).[58] Other predictable complications of ELGANs include sepsis and necrotizing enterocolitis (NEC).

A greater appreciation for the deleterious effects of these supportive measures has stimulated many clinical advances and improved survival of premature neonates. Understanding that premature lungs are in the canalicular stage of development and that positive pressure ventilation is deleterious, the ventilatory approach has shifted to less invasive and gentler respiratory strategies. This approach has resulted in improvements in overall and BPD-specific outcomes. This strategy avoids endotracheal intubation in favor of nasal continuous positive airway pressure to the extent possible.[59–61] The use of nasal intermittent positive pressure ventilation may further help prevent intubation, although effects of this ventilation strategy on overall survival and long-term outcomes are not yet known.[62] When endotracheal intubation is necessary, gentler ventilation strategies have been associated with improved outcomes. These

include using the lowest possible ventilator settings, permissive hypercapnia ($Paco_2$ 45–60 mm Hg), and early extubation when possible.[63–68] A restrictive oxygen strategy has been associated with lower rates of ROP[69,70] and lower need for supplemental oxygen at 36 weeks postconceptual age.[70] This is counterbalanced by evidence of higher rates of mortality,[69–71] NEC, and patent ductus arteriosus requiring surgical ligation with the restrictive oxygen target.

A variety of ventilation modes has been evaluated to limit ventilator-induced lung injury for ELGANs. Volume targeted ventilation, which may limit the overdistension of the lung (volutrauma), has been associated with a lower incidence of BPD and decreased mortality compared with pressure-limited ventilation.[72] High-frequency oscillatory ventilation (HFOV) has been frequently studied as an alternative to conventional ventilation for premature neonates with respiratory distress syndrome. These trials consistently show no benefit of HFOV over conventional ventilation in terms of mortality or neurologic outcomes.[73] However, some trials have shown a decrease in the rate of chronic lung disease in those patients managed with HFOV.[74]

### *Artificial Placenta*

Despite advances and refinements in the care of ELGANs, the mortality and morbidity remain high especially at the earliest gestational ages compatible with life. A radical paradigm shift in the treatment of prematurity would be to recreate the intrauterine environment using an AP or artificial womb. This pioneering approach was initiated more than 50 years ago,[75] and several investigators refined the approach as technology improved and our understanding of fetal physiology matured. In the past 15 years, there has been a renewed interest by several research groups, which have accelerated the technology to the point of clinical translation. Two similar but distinct approaches have emerged: the transumbilical AV-ECLS "artificial womb" and the VV-ECLS "artificial placenta" approach. Both approaches maintain fetal circulation, a low oxygen fetal environment with no mechanical ventilation and fluid filled lungs. In addition, both approaches have demonstrated multiorgan protection and ongoing development during extracorporeal support. We will highlight the similarities/differences, recent advances, and remaining milestones necessary for clinical translation.

### *Pumpless Arteriovenous-Extracorporeal Life Support*

The ECLS Laboratory at the UM began study on the development of an AP in the early 2000s with an evaluation of the relationship between flow through an AV circuit and gas exchange in a rabbit model.[76] This paved the way for the development of an AP using pumpless AV ECLS with a custom low-resistance oxygenator using transumbilical cannulation. Five of 7 near-term lambs survived the 4-hour study period.[77] However, all animals developed progressive decline in cardiac function that resulted in hypotension, hypoxia, and a decrease in flows by 54% during the study period. This led the authors to conclude that a pumpless system, even when used with a low-resistance oxygenator, would be limited by cannula resistance and umbilical arterial spasm resulting in diminished flows and cardiac failure. Although a pumpless transumbilical AV mode is simple and attractive, it is in series with the systemic circulation, which puts additional strain on the heart that worsens in the presence of any degree of vasospasm.

More recently, significant advances have been made in the pumpless AV-ECLS AP approach by the research team at Children's Hospital of Philadelphia. They have developed the Extra-uterine Environment for Neonatal Development (EXTEND) system using a pumpless AV circuit. They found that the UA/UV approach resulted in successful placement of larger cannulae, longer circuit runs, higher weight-adjusted circuit

flows, and fewer flow interruptions.[78] A subsequent study used echocardiography to identify increased heart strain in the first 2 weeks of support on EXTEND with return to baseline by the third week.[79] They demonstrated 4 weeks of support with hemodynamic stability, maintenance of fetal circulation, adequate gas exchange, and evidence of fetal growth.[80] They have made significant progress in mitigating umbilical vessel spasm by topical papaverine administration, atraumatic operative technique during cannulation, maintaining warmth, physiologic oxygen saturation of the umbilical venous inflow when initiating circuit flow and immediate transfer from the womb to their Biobag device. Although an advance, the potential for vascular spasm was not entirely ameliorated and one study demonstrated 30% of animals died due to vascular spasm limiting flows.[79]

A collaborative Western Australian-based program involving researchers from the Women and Infants Research Foundation, the University of Western Australia, and Tohoku University Hospital in Japan have developed a similar pumpless AV-ECLS AP platform called the ex vivo intrauterine environment (EVE) system. This system began development with the goal of addressing 2 problems that hampered previous attempts at a pumpless AP. First, they decreased the volume and resistance of the circuit by including a smaller, lower-resistance oxygenator. Second, they administered vasodilators to the fetus to maintain adequate organ circulation. With this system, they were able to support 5 premature lambs for $18.2 \pm 3.2$ hours.[81] Placing a second oxygenator in parallel reduced circuit resistance and prolonged survival to 60 hours.[82] The EVE system includes a "biobag" filled with artificial amniotic fluid, which had early issues with bacteremia.[83] They have subsequently achieved support up to 1 week in 5 of 6 preterm lambs without bacteremia.[84] Pumpless support using AV-ECLS (EXTEND and EVE platforms) requires 8 to 12 Fr cannulas and the absence of umbilical vessel spasm to maintain adequate flows (**Fig. 3**). Therefore, this approach is predicated on immediate transfer of the fetus from the womb to an "artificial womb."

### *Pump-Driven Veno-Venous Extracorporeal Life Support*

We hypothesized that VV ECLS with right atrial drainage and umbilical vein reinfusion would surmount the challenges of an AV approach while still maintaining fetal circulation, hemodynamic stability, and adequate gas exchange. Using VV-ECLS with a pump, right atrial drainage, and umbilical vein reinfusion places the circuit in parallel with the systemic circulation, thereby adding little to no increased afterload on the patient's heart. With the goal of clinical translation for a premature infant after delivery,

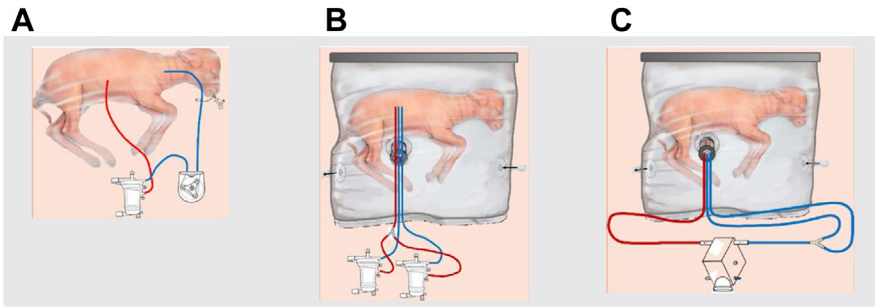


**Fig. 3.** Depiction of AP circuit. (*A*) AP University of Michigan. (*B*) Artificial womb (Perth, Aus, Japan). (*C*) Artificial womb (Philadelphia, PA). (*Adapted from* De Bie FR, Davey MG, Larson AC, Deprest J, Flake AW. Artificial placenta and womb technology: Past, current, and future challenges towards clinical translation. Prenat Diagn. 2021 Jan;41(1):145-158.)

we posited this cannulation strategy would allow for an adequately sized drainage cannula in the right atrium via the IJ vein and a smaller but acceptably sized umbilical vein cannula without limiting flows. White and colleagues supported 3 premature infants with VV-ECLS using the umbilical vein for reinfusion.[85] These babies lived for 10, 3, and 2 days with good gas-exchange parameters but all died of bleeding complications. Subsequently, this approach has been used clinically in 4-term or near-term neonates with good outcomes substantiating the feasibility of this approach.[86]

We developed a large animal model for an AP based on pump-driven VV-ECLS in 2012.[87] We supported 5 premature lambs (EGA 130–135 days; term = 145) using jugular vein drainage and umbilical vein reinfusion for more than 24 hours with stable hemodynamics and appropriate fetal gas exchange. Mean AP flow was 94 ± 20 mL/kg/min. Necropsy revealed a patent ductus arteriosus, foramen ovale, and sinus venosus. There was no difference in lung histology between the AP animals and controls, and there was no gross or microscopic ICH.

After establishing feasibility of VV-ECLS support, we sought to extend the duration of AP support and determine if premature lambs could be rescued by the AP and fetal circulation reinitiated, thus recreating a likely clinical scenario. To test this hypothesis, 7 premature sheep were delivered, intubated, and started on pressure-control ventilation. All sheep failed (persistent $P_{O_2}$ or $P_{CO_2}$<60 mm Hg and >100 mm Hg or hemodynamic instability) within 80 minutes and were transitioned to VV-ECLS AP support. Within an hour, arterial $P_{O_2}$ and $P_{CO_2}$ returned to target range; lactate normalized within 13 hours. Necropsy after 70 hours of support revealed a patent ductus arteriosus, foramen ovale, and sinus venosus in all sheep.[88] This study demonstrated that the AP can serve as a rescue therapy after failure of mechanical ventilation and fetal circulation can be reinitiated.

### *Airway Management*

Although all AP systems maintain fluid-filled lungs and avoid gas ventilation, there are 2 distinct approaches based in part on the vascular access strategy. The pumpless AV ECLS EXTEND and EVE systems both use a fluid-filled Biobag as an "artificial womb." This is a closed environment with continuous fluid exchange. They have made substantial advances in reducing the infections that had previously plagued this approach.[84,89] This approach is necessary, in part, to prevent the umbilical vasospasm in a transumbilical AV-ECLS system. Proponents of this approach point out that it recreates the intrauterine environment and allows for normal glottic resistance required for maintenance of normal airway pressures and lung growth (**Table 2**).

An alternative approach is to recreate critical fetal physiology, and not necessarily replicate the entire womb. Our laboratory has developed an alternative approach to lung management (see **Fig. 3**). After delivery, we intubate the fetal lamb and fill its lungs with liquid perfluorocarbon—an inert liquid that is not absorbed by the lungs and thus will not cause tissue edema or fluid and electrolyte shifts—to a level of 5 to 8 $cmH_2O$ which allows for fetal breathing movements. We then maintain the baby in a standard incubator. This approach resulted in lung development similar to gestational-age-matched controls and reduced lung injury compared with alternative management strategies.[90] This has become our standard airway-management strategy and has continued to provide evidence of lung development in later studies.[91] This strategy could be modified to accelerate lung growth,[92] and transition from the AP to liquid ventilation before air breathing.[93]

Some of the potential benefits of our approach include relative simplicity of implementation and easier access to the infant by the care team and family members.

**Table 2**
**Artificial placenta/artificial womb at different institutions**

| | Artificial Placenta Model | Artificial Womb Model | |
|---|---|---|---|
| Model Name | AP | EVE | EXTEND |
| Year of most recent update | 2022 | 2017 | 2022 |
| Species | Lamb | Lamb | Lamb |
| Configuration | VV | VA | VA |
| Pump | Yes | No | No |
| Cannulation | JV/UV (10–12Fr) | UV/UA (10/8) | UV/UA (12/12) |
| Amniotic fluid management | Fluid filled ETT | Sterile, complete sunmersion (6L) | Sterile, complete sunmersion (2–4L) |
| Issues leading to mortality | • Cannula related<br>• Arythmia<br>• Tamponade<br>• Arrest | • Equipment failure<br>• Thrombo-embolism<br>• Cannula | • Equipment failure<br>• Cannula related<br>• Umbilical spasm<br>• Circuit clotting |
| Clinical issues | Newborn at predicted high risk of mortality, rescue therapy | Continuation of physiologic environment of fetus, could delay birth | Continuation of physiologic environment of fetus, could delay birth |
| Advantages | Recreates essential fetal physiology<br>Enhanced newborn risk stratification | Mimic natural feta physiology<br>Avoids barotrauma | Mimic natural fetal physiology<br>Avoids barotrauma |
| Disadvantages | • Varying degrees of barotrauma before clinical application<br>• Fetal circulation may not be reinitiated if applied late as rescue therapy | • Need for EXIT procedure for cannulation/maternal risks<br>• Limited fetal risk stratification<br>• Complicated fetal care with placental barrier<br>• Corticosteroid use | • Need for EXIT procedure for cannulation/maternal risks<br>• Limited fetal risk stratification<br>• Complicated fetal care with placental barrier |

*Adapted from* De Bie FR, Davey MG, Larson AC, Deprest J, Flake AW. Artificial placenta and womb technology: Past, current, and future challenges towards clinical translation. Prenat Diagn. 2021 Jan;41(1):145-158.

### *Cannulation Challenges and Miniaturization*

Current versions of the AP use some form of umbilical access. Cannulation of these vessels is straightforward in animal models in which access can be secured in a controlled fashion while the animal is still connected to the mother's placenta, before the onset of vasospasm or desiccation of the cord. Translation of this technique to clinical use would require an ex utero intrapartum treatment (EXIT) procedure or modified cesarean delivery with the AV-ECLS approach. Alternatively, cannulation can be performed after delivery but spasm of the umbilical vessels could limit cannula size with the VV-ECLS approach.

To address this challenge, surgeons must develop techniques for limiting postdelivery vasospasm of the umbilical vessels or identify an alternative cannulation strategy. Peng and colleagues performed ex vivo dilation of segments of umbilical vessels immediately after delivery to determine the extent to which these vessels could be dilated postdelivery to facilitate cannulation. They found a dilation threshold of 7 mm for the umbilical vein and 6 mm for the umbilical artery,[94] suggesting that large-bore cannulation of these vessels may be feasible.

Another approach is the use of a single cannula in the IJ vein, obviating umbilical access altogether. This cannulation strategy is commonly used in ECMO through a dual-lumen cannula; however, a dual-lumen cannula would not provide adequate flows when miniaturized to 5 to 6 Fr. An alternative single-vessel, trans-jugular approach was developed more than 30 years ago at the University of Michigan.[95] This system uses tidal flow perfusion through a single-lumen cannula. It is currently being evaluated as a potential perfusion strategy for the AP. A major benefit of this system is that it allows for maximization of the diameter of the drainage cannula—the limiting variable in extracorporeal support. The primary limitation of this system is recirculation—occurring with each transition between drainage and reinfusion—which decreases the efficiency of the oxygen delivery. Longer occluder cycle times reduce the degree of recirculation but are also associated with larger volume and pressure fluctuations for the patient, which can result in hemodynamic instability and hemolysis. In our most recent study on the tidal-flow system, we have supported 3 premature sheep (EGA 118–124 days) for 24 hours, maintaining adequate gas exchange and hemodynamics.[96]

Premature infants born at 23 to 27 weeks typically weigh 500 to 800 grams. Most premature sheep models used for AP development use 110 to 120 days EGA sheep because they are equivalent to the lung development of 23 to 24 weeks human infants. However, they weigh 2 to 4 kg, which greatly exceeds the weight of the target patient population. Preliminary studies using a sheep model at 115 days gestation (1.8 kg) demonstrated adequacy of support for 18 hours with 6 Fr infusion and drainage catheters (unpublished results). Future research will focus on smaller lambs and longer duration of support.

Technical and physiologic feasibility of miniaturizing the pumpless AV-ECLS approach has been reported. In the animal models, 8 to 12 F cannulas were placed during an EXIT procedure obviating size limitations from umbilical vessel spasm. Using EXTEND, 5 extremely preterm (EGA 85–96 days) lambs weighing 480 to 850 grams were cannulated via the umbilical artery and umbilical vein and supported for 4 to 7 days with mean circuit flows of 213 mL/kg/min and stable gas exchange and hemodynamics.[78] However, all lambs developed hydrops leading to demise. The researchers speculate this was due to cardiac immaturity and inability to accommodate high postmembrane pressures. In a similar miniaturization study using the EVE platform, 7 out of 8 lambs (EGA 95 days) survived for 5 days on support with good gas exchange, stable hemodynamics, and normal echocardiographic parameters. Interestingly, despite

circuit flows well above 200 mL/kg/min in all animals, there was no evidence of high output cardiac failure or hydrops.[84]

In the last decade, the AP has progressed into a well-developed technology poised for clinical translation in the near future. Several key milestones including miniaturization and development of nonthrombogenic circuits must be accomplished before it can be trialed in humans.

### *Clinical Application*

Although the pumpless AV-ECLS platforms more closely recreate intrauterine physiology, clinical application may require an EXIT procedure or a modified cesarean section with a classic incision. The incidence of maternal intraoperative adverse events associated with cesarean deliveries at 24 to 25 weeks was 63.5% compared with 30.8% at 26 to 27 weeks[97]; an emergent EXIT procedure would likely further increase these risks. Because it relates to the fetus, this approach would lack any risk stratification for the infant apart from gestational age and thus would limit initial clinical application to the patients on the cusp of viability. Further research is required to mitigate these potential maternal risks and refine patient selection.

The approach to patient selection for a postnatal VV-ECLS AP is 2-fold. Similar to inclusion criteria for ECMO, it could be applied to critically ill premature infants after failing maximal medical therapy (see **Table 2**). This cohort would be expected to have suffered significant barotrauma and may not reap all the lung protective and developmental benefits of an AP. It could also be applied before respiratory failure in a cohort of ELGANs anticipated to have high mortality and morbidity according to risk stratification metrics. The Score of Neonatal Acute Physiology Perinatal Extension and the Clinical Risk Index for Babies II have been developed to estimate mortality risk in premature neonates. Recent studies suggest these markers may be useful in predicting high mortality in premature infants in the early newborn period.[98–100] This will serve as good starting points but will need to be validated for their use as predictive models to identify the best candidates for AP support. In order to have the greatest impact on morbidity and mortality of premature infants, the AP should be widely available and easily implemented at any neonatal ECMO center. When patient selection criteria are refined, there may be a hybrid approach to clinical application based on careful consideration of risks and benefits. Fetuses at the border of viability may benefit from a preemptive AV-ECLS approach, whereas fetuses precipitously delivered or older ELGANs may benefit from a postnatal VV-ECLS approach after risk stratification.

## SUMMARY

ECLS remains an effective lifesaving technique for neonates with respiratory and/or cardiac failure. Technological and medical advances have paved the way for applying the benefits of extracorporeal support to premature infants. Recreation of the fetal environment with an AP/womb holds the promise of improving the mortality and morbidity of extremely premature infants.

## DISCLOSURE

The authors do not have any commercial or financial conflicts of interest to disclose.

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