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A Paradigm Shift in the Treatment of Extreme Prematurity: The Artificial Placenta

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Abstract

Purpose of Review—Extremely low gestational age newborns (ELGANs), born at <28 weeks estimated gestational age, suffer the greatest consequences of prematurity. There have been significant advances in their care over the last several decades, but the prospects for major advances within traditional treatment modalities appear limited. An artificial placenta (AP) using extracorporeal life support (ECLS) has been investigated in the laboratory as a new advance in the treatment of ELGANs. We review the concept of an AP, the purported benefits, and the most recent research efforts in this area.

Recent Findings—For fifty years, researchers have attempted to develop an AP based on ECLS. Traditional AP strategies have been based on arteriovenous ECLS (AV-ECLS) using the umbilical vessels with moderate success. Recently, the use of venovenous ECLS (VV-ECLS) and miniaturization of ECLS components have shown potential for creating a next-generation AP.

Summary—ELGANs suffer the greatest morbidity and mortality of prematurity, and are poised to benefit from a paradigm shift in treatment. While challenges remain, the AP is feasible. An AP would not only protect ELGANs from the complications of mechanical ventilation, but support their development until a stage of greater maturity, preparing them for a life free of the sequelae of prematurity.

Keywords

Artificial Placenta; ELGANs; ECMO; Prematurity; ECLS

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Introduction: A Brave New World- The Artificial Placenta

For the past century, science fiction writers have imagined the possibility of an artificial placenta; a device which would allow humans to be “manufactured” outside the womb, developing from a single cell to a viable, healthy infant. Aldous Huxley's *Brave New World* and the Wachowskis' *The Matrix* famously portrayed fluid-filled pods used for extrauterine gestation as a marvel of technical progress but also as a method of authoritarian control over the individual. An artificial placenta may appear far beyond the reach of modern science, but the idea of creating a life support system to maintain growing fetuses in a womb-like environment with extracorporeal support was first investigated 60 years ago. The motivation for developing a real-life artificial placenta is to radically improve the treatment of extreme prematurity by recreating the intrauterine environment.

Complications of Prematurity: Predictable and Intransigent

Preterm birth (birth before 37 weeks EGA) occurs in approximately 11% of births in the United States. It is the leading cause of neonatal morbidity and mortality in industrialized nations, accounting for 60-80% of deaths in infants without congenital anomalies.[1] Premature birth and the sudden transition to postnatal life is disruptive to premature infants who are in a period of rapid growth and maturation. While all premature infants are at risk for complications, extremely low gestational age newborns (ELGANs) defined as estimated gestational age (EGA)<28weeks, suffer the greatest mortality and morbidity.

Prematurity leads to complications that involve a wide range of physiologic systems and have both short- and long-term effects. Short-term complications include persistent patent ductus arteriosus, intraventricular hemorrhage, periventricular leukomalacia, sepsis, retinopathy of prematurity, necrotizing enterocolitis and respiratory distress syndrome (RDS). Long-term morbidities include neurodevelopmental sequelae (cerebral palsy, cognitive delay, blindness and deafness), chronic lung disease, failure to thrive, and feeding difficulties. [2]

Acute respiratory failure is by far the most significant cause of morbidity and mortality in prematurity. This can be due to the failure of the lungs to fully develop, persistent pulmonary hypertension of the newborn, parenchymal lung disease, or a combination of these. Bronchopulmonary dysplasia (BPD) remains the most common long-term complication, affecting at least 40% of ELGANs with severity proportional to the degree of prematurity. [3, 4]

Advances in the Treatment of Prematurity: Revolutionary Treatments now Plateaued

Over the past century, many advances have been made in the treatment of preterm infants which have significantly improved patient outcomes. Prior to the 1940s, neonatal care for premature babies was barely existent as few infants below 1500g survived. [5] Dr. Hess published some of the earliest outcomes data on premature infants in 1953, demonstrating that more than half of the surviving infants survived without handicap with only 15% of

survivors showing severe handicap. [6] Although these outcomes were skewed due to selection bias, this and other reports led to the establishment of premature nurseries in the 1950s and 1960s.

Revolutionary advances in the treatment of prematurity were made in the subsequent decades with administration of steroids to mothers before premature delivery, advanced mechanical ventilation, and exogenous surfactant. In the 1970s, there was growing evidence that giving mothers glucocorticoids prior to preterm delivery resulted in a decreased incidence of RDS by promoting lung maturation. [7, 8] The benefits of maternal steroids in accelerating lung maturity has been confirmed in recent studies [9] and is now the standard of care. Also during the 1970s, new ventilator strategies including intermittent mandatory ventilation (IMV) and continuous positive airway pressure (CPAP) were adopted for the care of RDS in neonates.[10] These led to improved survival and a decreased incidence of BPD. Further technological advances followed, including high frequency oscillator ventilation (HFOV) in 1980 after being demonstrated in a canine model by Bohn et al. [11] and being proven safe in humans the same year.[12] HFOV, along with high-frequency jet ventilation, have been used increasingly in the care of neonates with RDS after evidence that it is at least equivalent to conventional ventilation. [13] In the 1980s, intratrachealexogenous surfactant was introduced. Strong evidence demonstrated the efficacy of surfactant in the prevention and treatment of RDS with improved survival in very premature infants.[14-16]

Over the last few decades, the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) have reported trends in the morbidity and mortality among very low birth weight (VLBW) infants, demonstrating that increased improvements in prenatal, obstetric, and neonatal care have translated to increased survival. [2, 3] However, recent evidence suggests that a plateau has occurred and there has been no significant increase in survival rates of VLBW infants without long-term morbidity. [17] Furthermore, the transition of pulmonary parenchyma from the canalicular to the saccular stage of development occurs between 22 and 24 weeks' gestation, marking the earliest time the lungs can effectively exchange gas, and therefore a significant barrier for the effectiveness of mechanical ventilation.

Paradigm Shift: Extracorporeal Support

Over the last 60 years, many novel strategies have been proposed to improve the survival of premature infants physiologically and developmentally unprepared to thrive outside the womb. After Gibbon developed the “heart-lung machine” in the 1950s, researchers began work on extracorporeal support for premature infants and called their system the “artificial placenta” (AP). Although premature infants appeared ideally suited for extracorporeal support, this technology was new and the physiology and complications of extreme prematurity were poorly understood. It was a brilliant idea that could not be realized at the time: the possibility of using ECLS to recreate the intrauterine environment and preserve fetal circulation to allow more time for fetal development became an overarching goal for research.

History of ECMO: Extracorporeal Support for Near-Term and Term Infants Flourishes

Given the morbidity and mortality associated with neonatal respiratory failure, alternative approaches to current treatment modalities were considered in the 1970s. Prolonged extracorporeal circulation and gas exchange was first demonstrated in 1975.[18] Due to concerns regarding the risks of bleeding in premature infants, its use was focused on full- and near-term neonates with respiratory failure.[19] Given the risks of bleeding and circuit requirements, empiric ECMO inclusion criteria remain EGA $\geq$ 34 weeks and weight $\geq$ 2kg. A series of neonatal ECMO patient outcomes was published in 1982 and reported 45 cases with a survival rate of 50%[20]. Subsequently two randomized controlled trials of ECMO for neonates with neonatal respiratory failure were published, showing high survival rates of 100%[21] and 98%. [22] As ECMO continued to improve, inclusion criteria expanded.

The terminology describing extracorporeal life support (ECLS) in infants has been partitioned depending on the patient's gestational age at initiation of ECMO (Table 1). For infants $\geq$ 34 weeks EGA, ECLS is generally called ECMO, is similar to ECMO used in adults or children, and is the standard of care for refractory respiratory and cardiac failure. Between 29 and 33 weeks EGA, ECLS is referred to as “preemie ECMO;” it has been proven clinically feasible, albeit with reduced survival rates and increased rates of IVH. “Preemie ECMO” has been selectively used for severe respiratory failure in premature infants down to 29 weeks gestational age, with birth weights as low as 1.1kg.[23] Before 28 weeks EGA, ECLS is termed an “artificial placenta” and currently remains in the realm of laboratory research.

ECLS Definitions

ECMO in children and adults is used in one of two modes, either venoarterial (VA) or venovenous (VV). VA ECMO has traditionally been used for patients with cardiac or cardiopulmonary failure, while VV ECMO is used in cases of isolated respiratory failure. [24] The first generation of ECMO devices were used from 1975 to 2008. The new generation of ECMO devices, marked by the advent of centrifugal pumps, polymethylpentene oxygenators, and specialized cannulas, is termed “ECMO II.” [25] In an artificial placenta, the umbilical vessels are used, which changes the ECMO configurations and nomenclature. The umbilical vein is always used for inflow. Blood can be pumped from the patient by his or her own heart via the umbilical artery (AV-ECLS), or augmented with a pump. Alternatively, an external pump can support drainage of blood from the jugular vein (VV-ECLS).

An artificial placenta is generally defined by four characteristics: 1) maintenance of fetal circulation and recreation of the intrauterine environment including a low partial pressure of oxygen, 2) lack of mechanical ventilation, 3) simulated fetal breathing with fluid-filled lungs, and 4) incorporation of either AV or VV-ECLS. [26] The major obstacle to current use of extracorporeal support in premature babies, the elevated risk of intracranial hemorrhage with heparinization, will need to be addressed with a fifth element of the AP, nonthrombogenic surfaces requiring little to no heparin.

Patient Selection for the Artificial Placenta

The patients most likely to benefit from AP support are ELGANs (<28 weeks EGA). Identification of those infants at highest risk for mortality will be critical for application of the AP in phase I clinical trials, likely using a pairs-matched study design. Infants at high risk for mortality can be identified within the first hour of life or the first 12 hours of life using the Clinical Risk Index for Babies (CRIB II) or the Score for Neonatal Acute Physiology- Perinatal Extension II (SNAPPE II), respectively. [27, 28] The overall mortality and morbidity of ELGANs has remained substantial; infants at 22-25 weeks EGA are reported to have 49% mortality by 18 to 22 months, 61% mortality or profound impairment, and 73% mortality or impairment.[29]

The Artificial Placenta: Early History

In the 1950s, extracorporeal circulation was proposed as a way to treat prematurity related lung failure. In 1958, Westin and colleagues described a watertight arteriovenous perfusion system on human fetuses. [30] These experiments were followed in 1965 by Callaghan et al [31] who attempted to connect a gas exchanger to the umbilical vessels in an arteriovenous (AV) circuit in 9 lambs. This method met with little success. In 1969, Zapol et al.[32] had more success keeping an exteriorized fetal sheep alive for 55 hours. Interest in this work decreased when the aforementioned advances in steroid administration, ventilation and surfactant use were made in perinatal care.

The AP was not truly revisited until 1979 when Griffith et al.[33] demonstrated the feasibility of the AP in mechanically-ventilated animals and showed an inverse relationship between arterial oxygenation and pulmonary vascular resistance. During the 1980s, a group headed by Dr. Yoshinori Kuwabara began an impressive body of research on the AP. They initially described their experience with ex-utero support of 50 fetal goats using AV-ECL Scircuit with a pump. During this study they refined their model, including using an arterial reservoir, to improve survival time up to 165 hrs. [34] Further modifications of the incubation system lead to improved survival in subsequent studies with a mean of 146hrs and as long as 236h.[35] Unno and colleagues made further modifications using AV-ECLS with the implementation of a sedative (diazepam) and muscle relaxant (pancuronium) achieving survival in two sheep of 494 and 534 hrs followed by successful transition to a ventilator for 1 week.[36] This group went on to demonstrate that ongoing fetal lung growth and maturation was possible with AP support.[37] In subsequent studies this group shifted their focus and investigated fetal metabolic and endocrine responses to changes in ambient temperature [38], using a closed circuit ring centrifugal pump with pulsatile flow with survival up to 234 h [39], and the behavior cycles that normally exist late in fetal life. [40] These studies served as the initial building blocks towards the goal of an artificial placenta and are the foundation for recent AP research.

The Artificial Placenta: Recent Advances

Two of the technical difficulties with earlier AP circuits were high priming volumes and high-resistance oxygenators. This led to research into the use of a pumpless AV-ECLS system to avoid these issues which have met with limited success. [41-43] Although short

term fetal circulation and adequate gas exchange was maintained, our experience with pumpless AV-ECLS revealed umbilical artery vasospasm, high circuit resistance, and cardiac failure. [42] Two groups recently pursued this type of circuit. Arens et al. [43] described the development of the NeonatOx oxygenator with a more than fourfold reduction in size of the oxygenator with good gas exchange properties, and Miura et al. [44**] described their experience with a pumpless AV-ECLS circuit which supported a lamb for $18.2\text{h} \pm 3.2\text{h}$ survival. Both utilized the umbilical vessels, no pump, and a prototype oxygenator with a small priming volume. Despite adding a pump to the AV-ECLS system, we encountered refractory hypotension. (Mychaliska GB, unpublished results). Although the simplicity is appealing, the clinical utility of a pumpless AV-ECLS circuit in humans seems technically infeasible due to the small size of the human umbilical artery, its tortuous anatomy, and the need for prolonged support with hemodynamic stability.

We hypothesized that an altered mode of extracorporeal support with inflow via the umbilical vein and outflow via the right jugular vein would solve the problem of hypotension by eliminating the variable of vasoreactivity of the umbilical arteries, and still maintain fetal circulation and stable gas exchange. Furthermore, VV-ECLS has the following translational advantages: 1) passive drainage from the right atrium via the right IJ using a 6-8F cannula which decreases negative pressure and blood trauma; 2) eliminating the need for an external reservoir; and 3) the VV-ECLS circuit works in parallel to the fetal circulation, creating little increase in resistance and afterload. In AV-ECLS, because the circuit and oxygenator are placed in series, there is increased resistance which can contribute to cardiac failure.[45]

We have created a sheep model of VV-ECLS and have demonstrated long-term support ($>24\text{hr}$, $n=5$) with stable gas exchange and hemodynamics (Figure 1). [46**] During these experiments sheep were delivered prematurely by Caesarean section and cannulated while on native placental support. Initially they were maintained in an artificial amniotic bath, but it was noted to become easily infected causing sepsis in sheep who lived $>24\text{hrs}$. This led us to maintain the sheep in an incubator, with an endotracheal tube filled with amniotic fluid and capped.

Next, we hypothesized that the AP could be applied after a trial of mechanical ventilation (MV), and fetal circulation would be reinitiated. In premature lambs, mechanical ventilation failed within one hour and subsequently 6 of 7 lambs were then successfully transitioned to the AP and survived for 24 hours. [47**] Subsequent work has focused on sheep models of extreme prematurity (equivalent to a 24 week human), lung development, brain function, development of nonthrombogenic surfaces, and survival after weaning from the AP. While much progress has been made, many challenges remain to model development and clinical translation (Table 2).

Conclusion

Aldous Huxley's "decanting bottles" used to gestate the fetuses of a dystopian London remain science fiction, but the development of a real artificial placenta is feasible and holds the promise of changing the paradigm in the treatment of extreme prematurity. Sixty years

ago, enlightened researchers recognized that ELGANs are the ideal patients for extracorporeal support. Today, we have many elements of the necessary technology, and conceptual understanding of the physiology of extreme prematurity, to recreate the intrauterine environment. In the near future we expect to be able to use an artificial placenta to allow premature babies to further develop, preparing them to thrive in a new world.

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Bullet Points

- The artificial placenta is the ideal life support system for premature infants as it has the potential to recreate the intrauterine environment and maintain fetal circulation.
- ELGANs suffer the most severe consequences of prematurity and represent the population most likely to benefit from the AP.
- VV-ECLS represents an advance in the AP with the potential to overcome a number of historic limitations to AP support.
- While great strides have been made in ECLS and AP technology, challenges remain in the development of an AP prior to clinical translation.

Figure 1.

Artificial Placenta Circuit using Venovenous extracorporeal life support (VV ECLS): Venous drainage is accomplished by jugular vein drainage cannula. Blood is pumped by M-Pump (MC3, Ann Arbor, MI), a collapsible-tubing rotary pump. Blood is then oxygenated (Terumo, Ann Arbor, MI) and warmed prior to being returned to the sheep via an umbilical vein reinfusion cannula.

Table 1
ECLS Modality Based on Gestational Age Group

ECLS Modality Based on Gestational Age			
Estimated Weeks Gestation	24 – 28	29 - 33	34 - 40
Type of ECLS	Artificial Placenta	“Premie ECMO”	ECMO
Stage of Clinical Use	Laboratory Research	Clinically Feasible	Standard of Care

ECLS, Extracorporeal Life Support; ECMO, Extracorporeal Membrane Oxygenation.

Table 2
Challenges to Clinical Implementation of an Artificial Placenta

Development of an Artificial Placenta: Future Challenges	
Neurologic	<ul style="list-style-type: none"> • Avoiding trauma and bleeding • Demonstrating normal function and development
Cardiovascular	<ul style="list-style-type: none"> • Maintaining fetal circulation long-term
Pulmonary	<ul style="list-style-type: none"> • Avoiding trauma and demonstrating lung development • Weaning off AP support to conventional ventilation and air breathing
Nutrition	<ul style="list-style-type: none"> • Optimizing nutrition with enteral feeds
Gastrointestinal	<ul style="list-style-type: none"> • Ensuring adequate intestinal perfusion
Renal	<ul style="list-style-type: none"> • Maintaining renal function and electrolyte balance
Infections Disease	<ul style="list-style-type: none"> • Maintaining sterility • Preventing and treating sepsis
Hematologic	<ul style="list-style-type: none"> • Eliminating anticoagulation
Circuit	<ul style="list-style-type: none"> • Optimize and automate AP circuit. • Miniaturize pump, oxygenator, and cannulas • Enhance biocompatibility
Clinical	<ul style="list-style-type: none"> • Develop clinical criteria to determine which infants will benefit from AP support • Develop phase I clinical trial using pairs-matched study design