

## Artificial Placenta: Intrigue-Interest and Future Challenges

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### Abstract

Surge in research on artificial placenta have been due to greater understanding about embryological development and placental function coupled with technological advancements in extracorporeal life support that has augmented the interest and translation into practice many research options that holds an exciting armamentarium to support the survival of the extremely low gestational age neonates (ELGAN). Nitric oxide surface based anticoagulation (NOSA) has now paved way for ex utero intra partum treatment (EXIT) and nascent extracorporeal life support technologies with NOSA concept. Future of artificially placenta suddenly has turned intriguing, interesting and challenging.

Over 50 years ago, visionary researchers began work on an extracorporeal artificial placenta to support premature infants. Despite rudimentary technology and incomplete understanding of fetal physiology, these pioneering scientists laid the foundation for future work. The research was episodic, as medical advances improved outcomes of premature infants and extracorporeal life support (ECLS) was introduced for the treatment of term and near-term infants with respiratory or cardiac failure. Despite ongoing medical advances, extremely premature infants continue to suffer a disproportionate burden of mortality and morbidity due to organ immaturity and unintended iatrogenic consequences of medical treatment. With advancing technology and innovative approaches, there has been a resurgence of interest in developing an artificial placenta to further diminish the mortality and morbidity of prematurity. Two related but distinct platforms have emerged to support premature infants by recreating fetal physiology: a system based on arteriovenous (AV) ECLS and one based on veno-venous (VV) ECLS. The AV-ECLS approach utilizes only the umbilical vessels for cannulation. It requires immediate transition of the infant at the time of birth to a fluid-filled artificial womb to prevent umbilical vessel spasm and avoid gas ventilation. In contradistinction, the VV-ECLS approach utilizes the umbilical vein and the internal jugular vein. It would be applied after birth to infants failing maximal medical therapy or pre-emptively if risk stratified for high mortality and morbidity. Animal studies are promising, demonstrating prolonged support and ongoing organ development in both systems. The milestones for clinical translation are currently being evaluated.

**Keywords:** Artificial Placenta; ELGAN; NOSA; EXIT

### Abbreviations

AP: Artificial Placenta; AUE: Artificial Uterine Environment; ECMO: Extracorporeal Membrane Oxygenation; ECLS: Extra Corporeal Life Support; EPI: Extremely Preterm Infants; ELGAN: Extremely Low Gestational Age Neonates; PROM: Premature Rupture of Membranes;

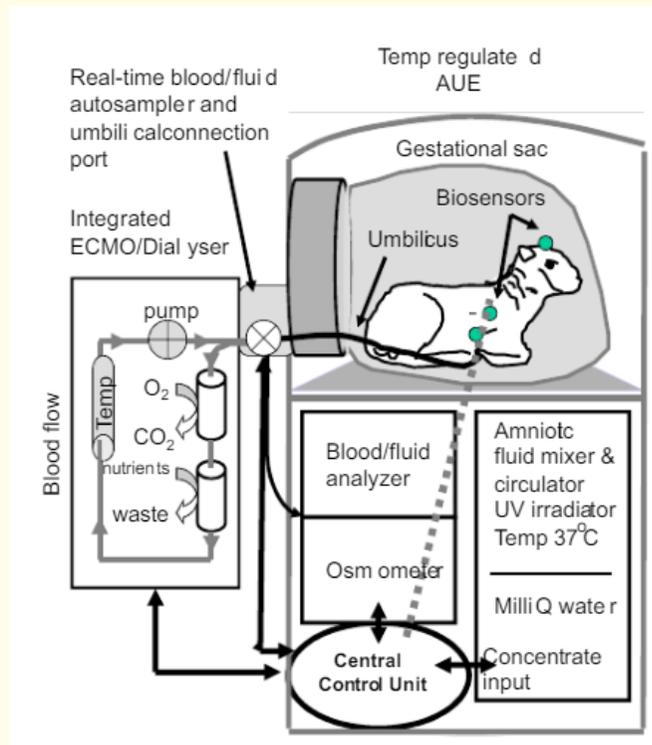
ELBW: Extremely Low Birth Weight; NAVA: Neurally Adjusted Ventilator Assistance; APUE: Artificial Placenta Uterine Environment; EXTEND: Extra Uterine Environment for Neonatal Development; AV-AP: Arteriovenous Artificial Placenta; VV-AP: Venovenous Artificial Placenta; EXIT: Ex Utero Intra Partum Treatment; NOSA: Nitric Oxide Surface Based Anticoagulation

**Introduction**

Extremely Preterm Infants account for 0.34% of live births on a global scale [1]. An artificial uterine environment (AUE) has been a subject of fiction as envisioned in *The Matrix* and *The Brave New World*. Initial work that commenced in this area 75 years ago lost momentum in between but is now regaining significant attention with the concept of treating extremely preterm along fetal management lines [10]. Westin and Callaghan adapted the use of ECMO (extra corporeal membrane oxygenation) into design of artificial placenta (AP) [11,12]. Rochow had summarised the development of synthetic amniotic fluid and pumping chambers [13]. Pak, *et al.* emphasised the importance of hemodialyser in the circuit to eliminate oedema [14]. The last decade has again witnessed resurgence in research in this area.

**Discussion**

When you look at extremely preterm infants (EPI) or ELGAN - extremely low gestational age newborns as a foetus rather than as a neonate the success of management makes one rethink the options of artificial placenta (AP). 23 - 25 weeks represents the grey zone where traditional methods have not been successful enforcing new research techniques that strive to better the existing clinical outcomes. Sheep models have been used in multiple centres to create successful evaluation trials with significant success. Life pod concept is depicted in figure 1.



**Figure 1:** Life pod concept.

Prematurity is the second highest cause of infant mortality globally [2]. Half are idiopathic and around 40% is due to premature rupture of membranes (PROM) [3]. Advanced maternal age is associated with increased likelihood of conditions like preeclampsia that leads to preterm labour. Lower end of the prematurity spectrum is the higher end for mortality and morbidity-the extremely pre term (EPI less than 28 weeks) and extremely low birth weight (ELBW) less than 1000 gm. Ultra extremely preterm (22 - 24.9) is currently classified in the nonviable group. Vital organ development to sustain life is the major cause of concern for these “micro-preemies” [4].

See table 1 for classification of preterm categories in relation to gestational age and birth weight.

Degree of prematurity	Age range (weeks of gestation)	Birthweight (g)
Preterm	< 37	
Moderately preterm	32 - 37	1500 - 2500
Very preterm	28 - <32	1000 - 1500
Extremely preterm	22 - <28	< 1000
Ultra extremely preterm “Greyzone”	22 - 24.9	< 600

**Table 1:** Classification of preterm categories in relation to gestational age and birth weight.

System morbidity associated includes bronchopulmonary dysplasia, persistent patent ductus arteriosus, respiratory distress syndrome, chronic obstructive pulmonary disease, intraventricular haemorrhage, periventricular leukomalacia, cerebral palsy, developmental delay mainly due to high pressure mechanical ventilation. Necrotising enterocolitis, retinopathy of prematurity, acute microbial infection, sepsis involving gastrointestinal and immune system is mainly due to infection and high oxygen saturation.

The current standard of care centres on high frequency nasal oxygen, intermittent mandatory ventilation, continuous positive airway pressure, high frequency oscillator ventilation, high frequency jet ventilation, steroids to accelerate lung maturation, surfactant therapy are still not adequate for the grey zone infants [5,6]. NAVA - neurally adjusted ventilator assistance is one of the methods to deal with these issues [18,19]. The developmental phase corresponding to grey zone infants (24 weeks) corresponds to transition from canalicular to saccular stage [7]. Breathing efforts are weak and uncoordinated due to immature neural control and ineffective gas exchange [8]. To understand the requirements of APUE (Artificial Placenta Uterine environment) or AP (artificial placenta) how the natural placenta works needs to be understood. The deoxygenated blood in umbilical arteries branch out into villi. Maternal blood percolates around the villi reaching there via the spiral arteries [9]. Gas exchange, supply of nutrients and elimination of waste are important functions of natural placenta. Hormones cytokines growth factors and antioxidants are the chemical milieu supplied by the placenta for fetal growth. Therefore, it is clear that circulatory, respiratory, renal, fluid electrolyte and endocrine balance has to be supported by any concept that would have to succeed as an artificial placenta with hemocompatibility to limit thrombogenesis and inflammation.

**Evolution of techniques**

The circuits in artificial placenta (AP) have now nearly switched over to veno venous (VV) technique with internal jugular cannula being the source of blood and return via the umbilical vein (Figure 2). Comparison of the two techniques is given in table 2. The umbilical artery (UA) umbilical vein (UV) technique being termed as AV-AP (arteriovenous artificial placenta) is the older method. In AP-VV method the drainage is controlled by a pump from the jugular. A parallel circuit with fetal circulation is created. The concept of nutritional supplemental advances the concept of artificial placental support. Another concept is the use of peristaltic pump outflow to counter hypotension. Non sterile environment predisposes to infection. Umbilical artery vasospasm issues are avoided when adopting the AP VV method. An important area of research advances has been negotiating consumption coagulopathy in relation to ECMO support [15-17]. Life pod concept is detailed in figure 1. Other research efforts include Extra uterine environment for neonatal development (EXTEND) which uses a pump less AV circuit.

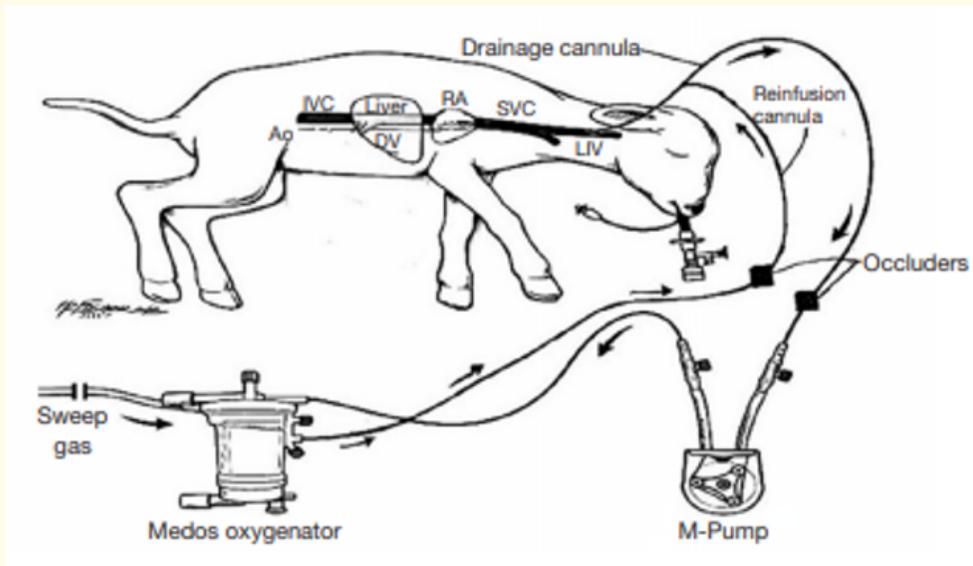


Figure 2: VV-AP with nonocclusive M Pump (Kadling 2019-Ref 21).

Characteristic	AV-ECLS	VV-ECLS
Target population	EGA 22 - 24 weeks	EGA < 28 weeks
Cannulation	During delivery	After failing ventilation
Drainage cannula	Umbilical artery (1 or 2)	Internal jugular vein
Reinfusion cannula	Umbilical vein	Umbilical vein
Circuit pump	Fetal heart	Mechanical pump
Airway management	Fluid-filled biobag	Intubated, fluid-filled lungs

Table 2: Comparison of AV-AP/ECLS and VV-AP/ECLS is given below.  
AV-AP or ECLS, VV-AP or ECLS (AP-Artificial Placenta).

### Future

Translation to practice would involve ex utero intra partum treatment (EXIT) or modified caesarean by using AV -AP or ECLS. NOSA nitric oxide surface based anticoagulation as a local rather than systemic anticoagulation is indeed a great step into future research. Older ELGANS or those delivered precipitously may benefit from VV AP with AV AP being reserved for those with borderline viability.

### Conclusion

Pump driven VV AP with NOSA seems to lead the way to future, with nutritional and endocrine concepts would ultimately provide total AP with growth factors and antioxidant supplementation in the correct dose. NOSA would soon find applications in other extracorporeal life support roles together with better coating material would soon make local anticoagulation a better option.

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