Chapter 9

Advancing Medical Frontiers: Unveiling the Potential of Artificial Placenta in Perinatal Medicine

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Abstract

Advancements in medical technology have led to the development of artificial placenta systems, which aim to support the survival and development of extremely premature infants. The placenta plays a vital role in fetal development by facilitating nutrient exchange and waste removal. Premature birth poses significant challenges in neonatal care, with preterm infants facing increased risks of morbidity and mortality. Respiratory failure is a major concern due to the underdeveloped lungs of preterm infants. Artificial placenta models have been designed to mimic fetal and utero-placental physiology, offering potential solutions to these challenges.

This abstract reviews the history and components of artificial placenta systems, highlighting the importance of pumpless arterio-venous (AV) circuits, low-resistance oxygenators, umbilical access, and immersion in sterile fluid. The development of these components has led to improved survival rates and stability in experimental models. However, challenges such as cardiac afterload, optimization of circuit design, and prevention of infection and inflammation remain to be addressed.

Promising artificial placenta models have been developed by research groups at the University of Michigan, Tohoku University (Sendai, Japan), and the University of Western Australia (Perth). These models have demonstrated

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increased survival times, stable hemodynamics, and successful organ maturation. The Philadelphia Children's Hospital model, known as EXTEND AW, has shown particular success, with lambs surviving up to 28 days and exhibiting normal organ development and neurological maturation.

Despite these advancements, there are still challenges to overcome before artificial placenta technology can be implemented in clinical practice. These include reducing oxygenator surface area, improving hemocompatibility, optimizing nutrition and amniotic fluid composition, standardizing patient selection criteria, and developing efficient cannulation techniques.

In conclusion, artificial placenta technology is a promising field with the potential to revolutionize neonatal care. With further advancements and research, artificial placenta systems may offer a solution to the challenges faced by extremely premature infants, improving their chances of survival and long-term health outcomes.

Fetal and placental anatomy

The human gestation period, ranging approximately 266 days or thirty-eight weeks from fertilization to delivery, is a remarkable process of prenatal development. During the early stages of pregnancy, the embryonic period unfolds, encompassing the formation of crucial organ systems that lay the foundation for the growing individual. This period concludes at the end of the eighth week, marking the transition into the fetal period. Throughout the remainder of pregnancy, the focus shifts towards the maturation of organ systems and overall growth (Fig 1). The placenta, a complex and highly specialized organ composed of both embryonic/fetal and maternal components, plays a pivotal role in supporting the developing fetus. It serves as a nexus for nutrient exchange, providing essential sustenance for fetal development, while also facilitating the removal of metabolic waste products. The intricate interplay between the embryo/fetus and the maternal organism through the placenta ensures the survival and thriving of the growing life within the womb (1).

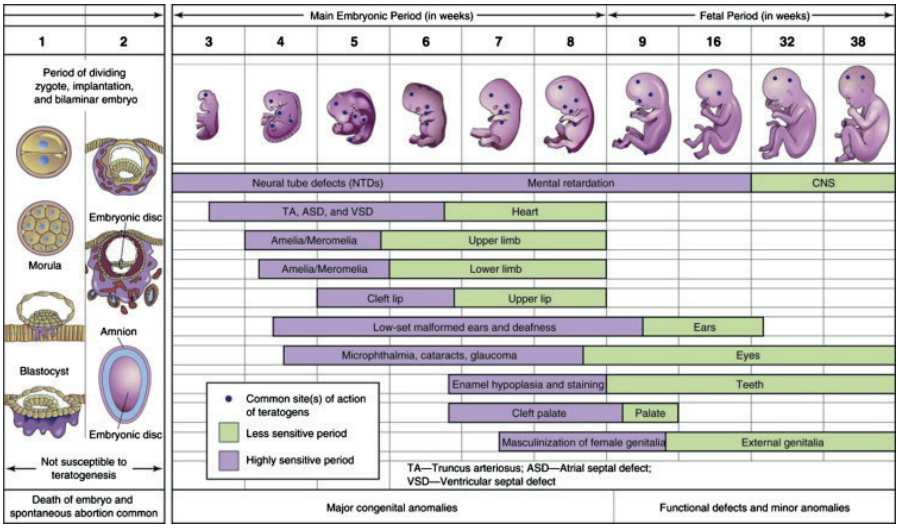

Figure 1. A depiction of the various embryonic and fetal stages during intrauterine development (2).

Placenta

The placenta is a remarkable fetomaternal organ that plays a critical role in supporting the developing fetus throughout pregnancy. It consists of two distinct components: the fetal part, which originates from the chorionic sac (chorion frondosum), and the maternal part, derived from the endometrium (decidua basalis). Together, the placenta and the umbilical cord form a sophisticated transport system, facilitating the exchange of substances between the mother and the fetus (3).

The placenta serves multiple essential functions, ensuring the well-being and development of the growing fetus:

Protection: The placenta acts as a protective barrier, shielding the fetus from potentially harmful substances and pathogens present in the maternal circulation.

Nutrition: It plays a crucial role in providing the fetus with vital nutrients, including oxygen, glucose, amino acids, and lipids, necessary for its growth and development.

Respiration: The placenta facilitates the exchange of respiratory gases, allowing the transfer of oxygen from the maternal bloodstream to the fetal circulation, while carbon dioxide and other waste products are eliminated.

Excretion: Metabolic waste products produced by the fetus, such as urea and bilirubin, are eliminated through the placenta, preventing their accumulation and ensuring a stable internal environment.

Hormone, Cytokine, and Growth Factor Production: The placenta is a remarkable endocrine organ, producing a variety of hormones, cytokines, and growth factors essential for maintaining pregnancy, regulating maternal physiological adaptations, and supporting fetal development.

The intricate functions of the placenta make it a vital interface between the mother and the developing fetus, enabling the exchange of substances necessary for growth, metabolism, and overall well-being. Its role extends far beyond simple nutrient transfer, highlighting its significance in ensuring a successful and healthy pregnancy (Fig 2).

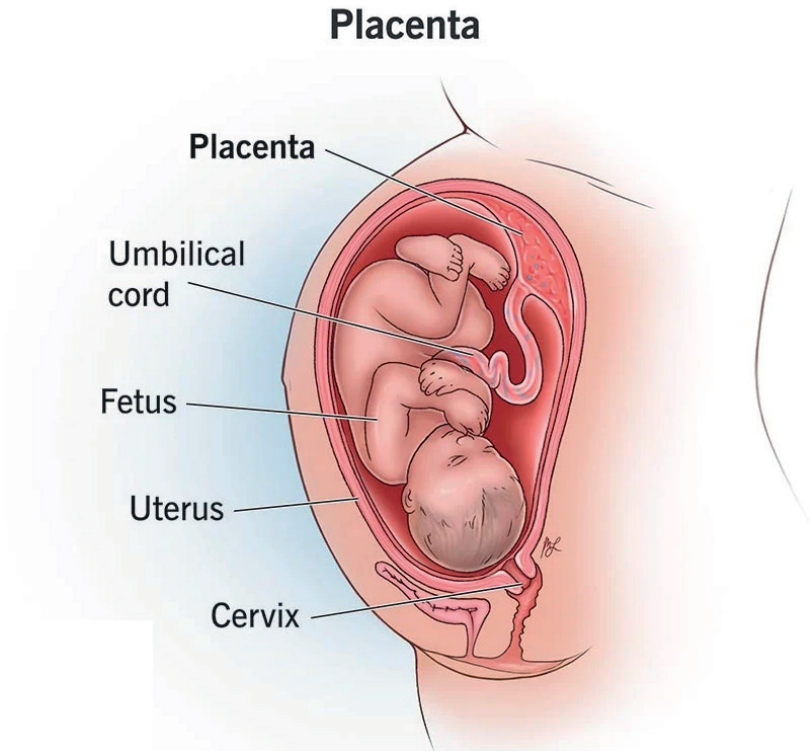

Figure 2. An illustrative depiction showcasing the fetus, placenta, and adjacent anatomical structures (4).

Amniotic Fluid: Unveiling Its Significance in Embryonic Development and Maternal-Fetal Interactions

Amniotic fluid, a clear and yellowish fluid that surrounds and protects the fetus within the uterus, plays a crucial role in supporting fetal growth, movement, and development (Fig 3). It serves multiple functions, including creating space for fetal growth, facilitating absorption of nutrients for growth and maturation, providing a protective barrier against external trauma, and exhibiting antibacterial properties due to the presence of cytokines, antibacterial peptides, and chemokines. Furthermore, amniotic fluid aids in the dilation of the cervix during delivery, contributing to the birthing process (5).

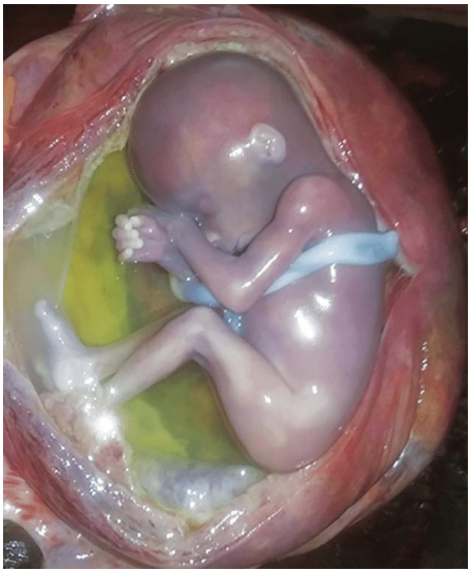

Figure 3. The fetal development stage characterized by the presence of amniotic fluid surrounding the fetus (6).

Preterm birth

Preterm birth, which occurs before 37 weeks of gestation, presents significant challenges in neonatal care. The nine-month gestation period is commonly divided into trimesters for convenience. However, current technology does not support the viability of fetuses born before approximately 22 weeks of gestation. Survival rates for infants born between 22 and 28 weeks of gestation have improved, but a substantial proportion still experience significant morbidity that affects their long-term survival. For instance, mortality rates for infants born at 23-25 weeks of gestation range from 74% to 28%, while morbidity rates range from 92% to 80% (7).

Prematurity, encompassing all newborn babies born before 37 weeks of gestation, represents a major concern in neonatal health. It is the leading cause of neonatal death and the most common cause of prenatal hospitalization, accounting for more than one-third of all infant deaths (7). Prematurity is associated with a range of complications, including acute respiratory distress syndrome (RDS), bronchopulmonary dysplasia, periventricular and intraventricular bleeding, cerebral palsy, retinopathy of prematurity (ROP), and necrotizing enterocolitis (7).

Prematurity- Respiratory stress

Respiratory failure poses a significant challenge in the care of very early preterm newborns due to the impaired gas exchange resulting from the structural and functional immaturity of their lungs (8).

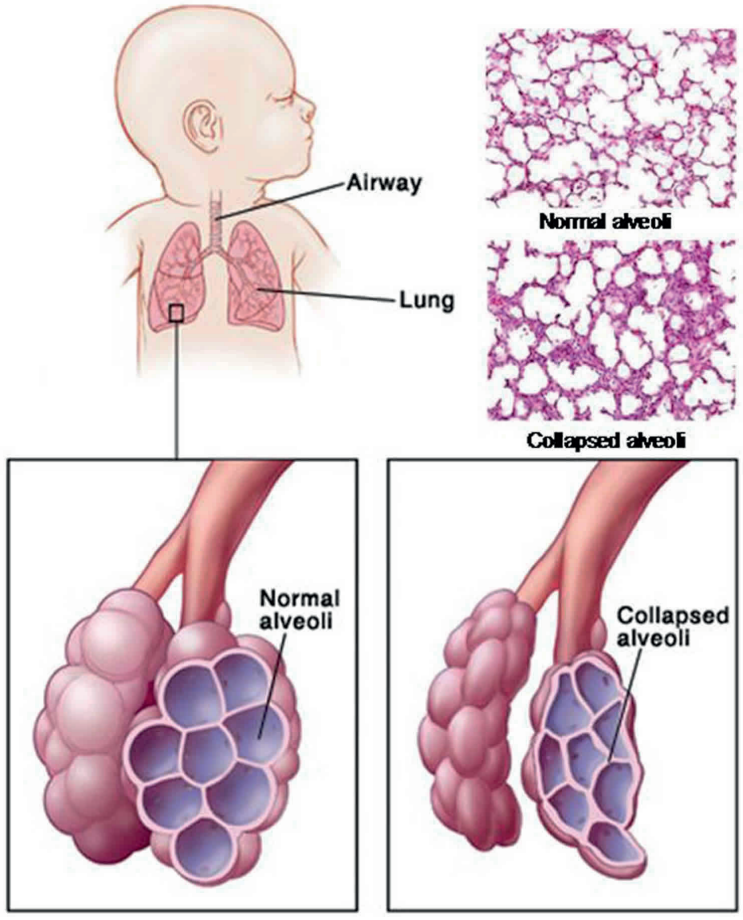

Figure 4. A schematic representation depicting the normal and collapsed alveoli within the lung of an infant (9).

The premature initiation of gas ventilation in the lungs hinders lung development. Extremely premature infants at the limit of viability (22-24 weeks) have lungs in the late canalicular phase of pulmonary development, characterized by a limited number of fully formed alveoli and a thick alveolar/capillary interface (Fig 4). At this stage, the underdeveloped lungs are ill-equipped for efficient gas exchange, leading to respiratory failure. Additionally, the immaturity of the premature lungs makes them more susceptible to oxidative stress, infection, and inflammatory damage, further compromising oxygenation and contributing to the development of bronchopulmonary dysplasia, a chronic respiratory disease associated with iatrogenic damage. It is worth noting that despite advancements in neonatal care, such as minimally invasive neonatal ventilation, exogenous surfactant administration, and prenatal corticosteroid therapy, these interventions cannot fully prevent severe respiratory failure due to the structural and functional immaturity of the premature lungs (10).

Understanding the challenges posed by the immature lungs of very early preterm newborns and their susceptibility to respiratory failure and related complications is crucial for healthcare professionals in providing optimal care and developing innovative strategies to improve outcomes for these vulnerable infants.

Artificial Placenta – History and Components

The concept of an artificial placenta, which can support the survival and development of extremely premature infants, has been a topic of fascination and inspiration in both scientific and fictional Works (Fig 5). Extracorporeal life support (ECLS) refers to the preservation of life through an external assist device, while extracorporeal membrane oxygenation (ECMO) involves the direct transfer of air or oxygen into the blood via a gas-permeable membrane. The idea of using extracorporeal oxygenation to treat respiratory failure in severely premature infants emerged shortly after the development of primitive oxygenator technology in the 1950s (11).

Early experiments in the field of artificial placenta research date back to 1958 when Westin et al. cannulated the umbilical vessels of previable human fetuses and connected them to a heated perfusion chamber with an oxygenator, extending their survival for up to 12 hours (12). Subsequent studies in fetal lambs by Callaghan and colleagues further advanced the understanding of artificial placenta technology. Over the years, various research groups have explored different models of artificial placenta, refining circuit configurations, pumps, oxygenators, vascular access methods, and fluid containers to improve oxygen delivery and enhance survival rates (13).

During the 1970s, advancements in neonatal care, including positive pressure mechanical ventilation, prenatal maternal steroids, and exogenous surfactant administration, reduced the focus on artificial placenta research (14,15). However, the recognition of the limitations of these treatments, advancements in oxygenator technology in the 1990s, and increased interest in fetal and utero-placental physiology reignited the exploration of artificial placenta technology. The research shifted from solely emphasizing long-term survival to also evaluating safety, fetal well-being, and specific organ maturation, with the aim of eventual clinical implementation (16).

An artificial placenta should encompass several key components to effectively support fetal development and function. These include:

• Maintenance of fetal circulation configuration and open major fetal shunts to prevent neonatal transmission.

• Blood oxygenation and maintenance of correct hemoglobin saturation without lung aeration.

• Hemodynamic stability, including appropriate heart rate and blood pressure responses to fetal conditions.

• Proper hydration and elimination of excess fluid to maintain fluid balance and electrolyte composition.

• Adequate kidney function for the elimination of metabolic nitrogenous wastes.

• Endocrine support to ensure the appropriate hormonal environment for fetal development (17).

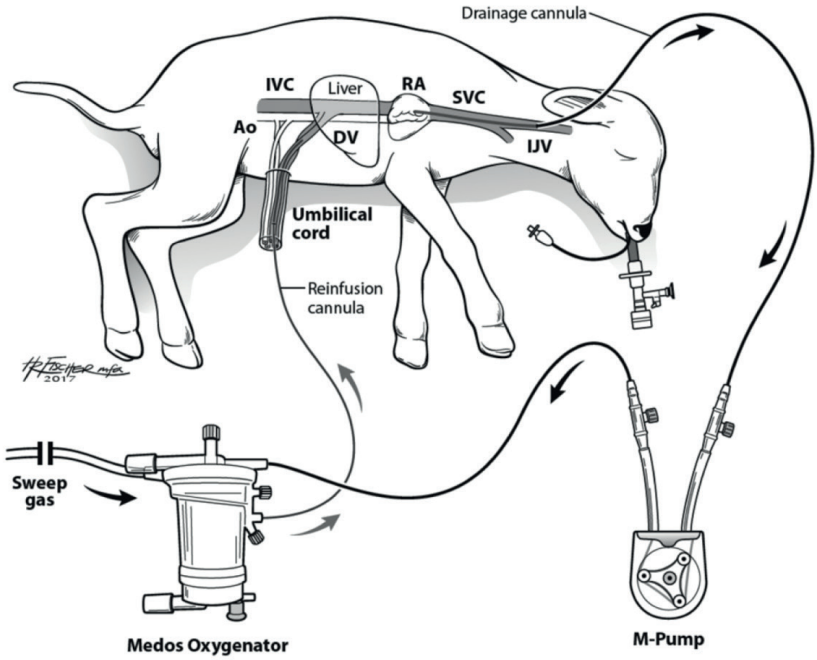

Figure 5. Artificial placenta setup: Blood is drained from the right jugular vein using a collapsible-tubing roller pump and directed to an oxygenator/heat exchanger, after which it is returned through the umbilical vein. The second umbilical vein is used for intravenous fluid and medication administration, while an umbilical arterial line is inserted for hemodynamic monitoring and blood gas sampling. The lamb's lungs are kept filled with amniotic fluid by clamping the endotracheal tube. Key anatomical landmarks include the aorta (Ao), ductus venosus (DV), internal jugular vein (IJV), inferior vena cava (IVC), right atrium (RA), and superior vena cava (SVC) (18).

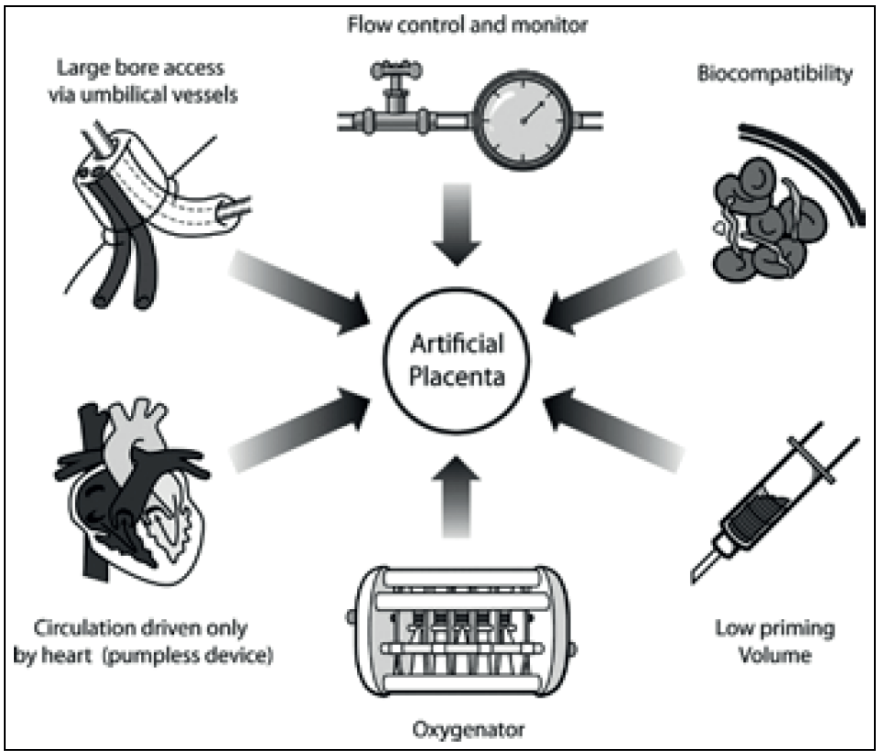

Figure 6. The essential components and key features necessary for the development of an artificial placenta device (19).

Pumpless arterio-venous circuit

An ideal artificial placental circuit, designed to mimic fetal and utero-placental physiology, should feature a "pumpless" arterio-venous (AV) configuration that allows for autoregulation and blood flow driven by the fetal cardiac beat and arterial pressure as the driving force through the oxygenator. Early development of artificial placenta technology focused on AV configurations (20-22).

However, early models required the inclusion of pumps to overcome the high resistance of the oxygenator and achieve physiological fetal flows (Fig 6). Survival rates in pump-assisted models were systematically limited due to cardiac decompensation, resulting in circulatory depression and fetal hydrops. Both centrifugal and roller pumps caused suction that impeded the natural pumping function of the fetal heart, leading to imbalances in preload and afterload that strained the cardiac function. The fetal heart is highly

sensitive to such imbalances, especially in the presence of high-resistance oxygenators and pumped circuits (23).

The umbilical artery (UA) and umbilical vein (UV) configuration presents challenges due to spasm, and preserving vascular integrity is crucial in this model. Two main configurations were utilized to connect the fetal blood vessels to the artificial placental circuit. The arteriovenous (AV) configuration simulated the natural placenta by using the umbilical vessels, with fetal blood being pumped by the heart from the umbilical arteries (UA) to the umbilical vein (UV). The venovenous (VV) configuration involved connecting the artificial placenta to an oxygenator with the exit through a catheterized jugular vein and return via the UV. To address load imbalances, open-top reservoirs were incorporated into the circuit to convert pulsatile flow to laminar flow and regulate pressure and flows back to the right heart. The addition of reservoirs improved neonatal survival rates in the circuit but introduced risks of air-blood interaction, increased initial volume, and did not effectively prevent progressive cardiac decompensation. The inclusion of a hemodialyzer improved fluid and electrolyte balance and circuit survival but failed to prevent progressive circulatory failure and was subsequently disregarded in later versions of the model (24). In pumpless systems, increased cardiac afterload remained the limiting factor due to supraphysiological resistance resulting from limitations in oxygenator technology and other circuit components (25).

Further advancements in artificial placenta technology are necessary to overcome the challenges associated with cardiac afterload and optimize the circuit's performance. These advancements require improvements in oxygenator technology and other circuit components to achieve physiological resistance levels and ensure adequate blood flow, while also addressing issues related to fluid and electrolyte balance, air-blood interaction, and circuit stability. Overcoming these challenges will bring us closer to the development of a functional and effective artificial placenta for supporting the survival and development of extremely premature infants.

Low resistance oxygenators

In the early models of artificial placenta, film oxygenators with high surface area, large feed volume, and high resistance were utilized. These oxygenators allowed for effective oxygenation through direct blood-air contact but posed challenges in terms of biological compatibility and increased the risk of infection (26). To address these concerns, membrane oxygenators became the new standard in the 1970s. These oxygenators employed flat and

helical gas-permeable membranes for gas exchange, eliminating the need for direct blood-air contact. In recent artificial placenta models, hollow fiber oxygenators with resistances equivalent to physiological placental resistances have been implemented, significantly reducing the cardiac afterload required for pumpless circulation (27).

Continuous efforts are being made to further optimize the design of oxygenators in artificial placenta systems. One approach is to reduce the surface area and initial volume of the oxygenators. Decreasing the surface area helps minimize platelet and complement activation, improving biocompatibility (28). Additionally, researchers are exploring the use of alternative microfluidic oxygenators, which have the potential to further reduce feed volumes and enhance the efficiency of gas exchange. These microfluidic oxygenators hold promise for improving the performance and compactness of artificial placenta systems (29).

By advancing oxygenator technology and exploring innovative designs, researchers aim to optimize gas exchange efficiency, minimize adverse reactions, and improve overall compatibility in artificial placenta models. These advancements are crucial for the development of a functional and safe artificial placenta that can effectively support the survival and development of extremely premature infants (Fig 7).

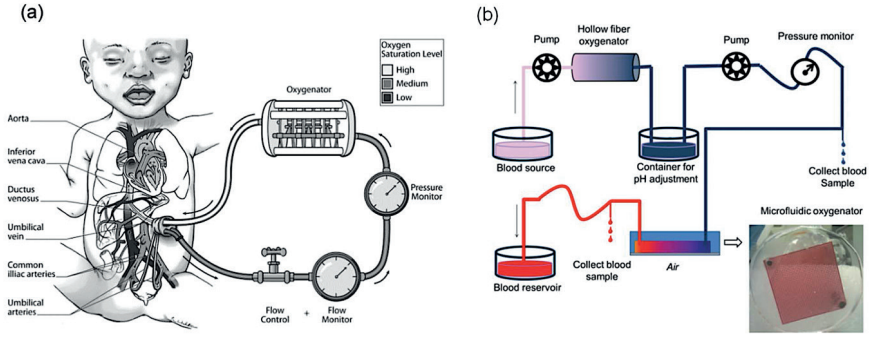

Figure 7. The implementation of a microfluidic oxygenator for the artificial placentaconcept, and the arrangement of the experimental setup for in vitro gas exchange testing (29).

Umbilical access

In the pursuit of an ideal artificial placenta model that closely mimics fetal and utero-placental physiology, the use of umbilical vessels for vascular

access has been extensively explored. Various configurations utilizing cervical, femoral, and umbilical vessels have been tested over time. Comparisons have shown that cannulation of the umbilical artery and umbilical vein (UA/UV) provides superior flow distribution, particularly to vital organs such as the heart and brain (30).

To optimize flow dynamics, the principles of the Hagen-Poiseuille law are considered. By using short end-to-end cannulas (approximately 2 cm) and larger umbilical arteries, the resistance within the circuit can be minimized, allowing for physiological flows in animal models with UA/UV cannulation (31). The avoidance of cervical vessel cannulation offers additional advantages, including the protection of important vessels, reduced risk of embolic events in the brain, and decreased likelihood of complications related to decannulation, thereby minimizing the need for fetal sedation or paralysis. However, one of the challenges associated with umbilical vascular access is vasospasm, which, if severe, can result in circulatory arrest and subsequent fetal demise (32). To mitigate this risk, humidification of the umbilical vessels and the administration of vasodilators such as papaverine, both topically and intravenously, have been proposed (33).

To ensure the integrity of the umbilical vessels and prevent trauma, erosion, turbulence, and obstruction, the use of very short umbilical cannulas that do not extend deep into the vessels has been recommended. The curvature of human umbilical vessels makes intra-abdominal advancement of cannulas impractical (34).

In summary, optimizing the vascular access in artificial placenta models is crucial for ensuring adequate and physiological blood flow distribution. Cannulation of the umbilical artery and umbilical vein has shown promising results, although challenges such as vasospasm need to be addressed for successful implementation. By refining the cannulation technique and addressing associated complications, researchers aim to develop an artificial placenta model that effectively supports fetal circulation and development.

Immersion in sterile fluid

An important aspect of artificial placental models is the immersion of the fetus in a sterile and warm liquid environment, typically maintained at around 39.0°C. This immersion serves several crucial purposes in supporting fetal development and well-being. Firstly, it provides insulation, protecting the fetus from external factors such as sound, mechanical pressure, infection, and injury. Additionally, the presence of amniotic fluid helps regulate the

fetus's body temperature, preventing excessive heat loss or fluid imbalance. It also plays a role in moistening the umbilical vessels and creating a space that allows for normal fetal breathing and swallowing movements.

One significant advantage of keeping the fetal lungs fluid-filled is that it delays the neonatal hemodynamic transition caused by ventilation. This helps maintain the integrity of the fetal circulation and supports ongoing pulmonary development. Ventilation of immature lungs can lead to complications such as oxygen toxicity, inflammatory damage to delicate lung tissue, and arrest of lung development. On the other hand, the presence of fluid in the airways and glottic resistance stimulates pulmonary maturation. Similarly, the presence of amniotic fluid in the gastrointestinal tract has been shown to enhance the development of the intestinal mucosa and support overall growth.

While the benefits of a liquid immersion environment are evident, researchers have also acknowledged the potential risks associated with fetal sepsis in open or semi-closed bath models. Due to their immature immune systems, fetuses are more vulnerable to bacterial invasion through the lungs or skin. Infection can trigger a systemic inflammatory response that affects brain and lung development and often leads to fetal death. To mitigate this risk, the transition to a closed and sterile environment with continuous amniotic fluid exchange has been implemented. This approach helps eliminate pneumonia and reduces the risk of amniotic fluid contamination and fetal bacteremia, while also minimizing the need for prophylactic antimicrobials.

However, it is important to consider the potential drawbacks of fetal immersion, such as the physical and potential psychological barrier it may create between the fetus and prospective parents. The impact of this distance on parent-fetal bonds is a significant question that requires further investigation. Understanding whether prospective parents are accepting of this separation and how it may influence their emotional connection with the fetus is crucial in the development and implementation of artificial placental models.

In summary, the immersion of the fetus in a sterile and warm liquid environment has numerous advantages in supporting fetal development, including insulation, temperature regulation, maintenance of lung and gastrointestinal tract development, and prevention of infection. Balancing the benefits and potential drawbacks of fetal immersion is essential to optimize the design and acceptance of artificial placental models (Fig 8).

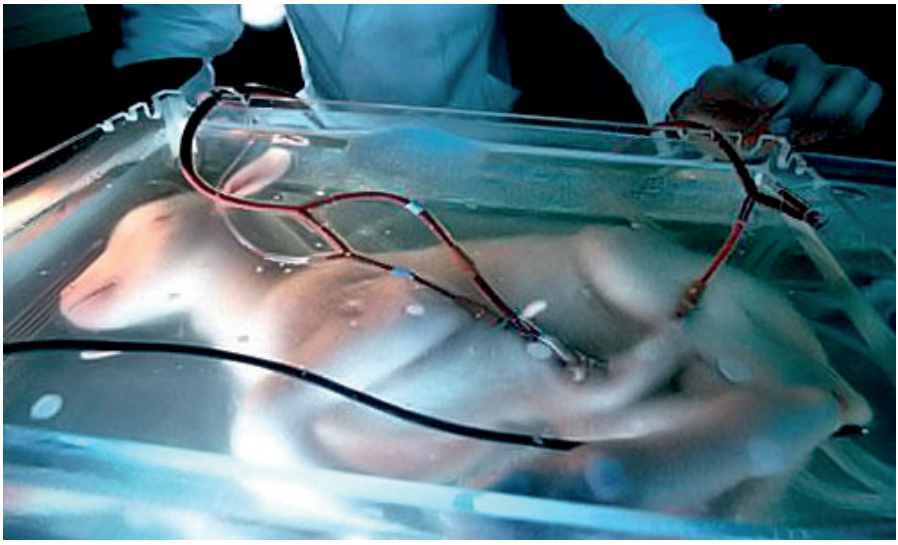

Figure 8. A fetal lamb supported by an artificial placenta system, receiving support and immersed in an amniotic fluid bath (40).

Feeding and medication

As the focus shifted towards long-term survival in artificial placental circuits, the need for improved nutrition became apparent. Dextrose or glucose infusions alone were insufficient, leading to the addition of amino acids, lipids, and vitamins to provide a total calorie target of 70-80 kcal/kg/day. This comprehensive nutritional approach aims to support optimal growth and organ maturation in the fetus (41).

Maintaining ductal patency is crucial for fetal circulation, and the continuous infusion of prostaglandins (PGE1/PGE2) has become a standard practice in all artificial placenta models. This helps prevent fatal ductal narrowing caused by increased oxygen tension (42). To counteract the thrombogenicity associated with the tubing and oxygenator, heparin is also continuously infused. However, compared to extracorporeal life support (ECLS) circuits, the heparinization requirements in artificial placental models may be reduced due to factors such as decreased surface area, priming volume, and the systemic inflammatory response (43).

In previous studies, intermittent sedation with midazolam and pentobarbital was utilized to manage periods of fetal agitation and reduce the risk of traumatic decannulation events. However, recent studies have questioned the effect of sedatives on fetal neurodevelopment, leading to

a cautious approach in their use. Additionally, the use of umbilical cord cannulation without direct contact to the fetus has decreased the need for sedation in some cases. It is crucial to avoid prolonged paralysis as it can negatively impact fetal muscle development and hinder spontaneous breathing after discontinuation of extracorporeal life support (44).

Repetitive phlebotomy for monitoring fetal well-being can lead to progressive anemia. Daily administration of erythropoietin has been shown to prevent this anemia, ensuring adequate oxygen-carrying capacity while minimizing the need for excessive blood sampling. To prevent bacteremia, prophylactic intravenous broad-spectrum antibiotics and antifungals are commonly administered in many artificial placenta models, and in some cases, they may be added to synthetic amniotic fluid. However, in sterile closed circuits, the need for these interventions is reduced unless contamination occurs (45).

Current and Successful Artificial Placenta Models: Design and Outcomes

The quest to replicate fetal and utero-placental physiology has driven the progress in artificial placenta development, aided by advancements in technology. Various models have emerged, each employing distinct approaches to recreate the intricate dynamics of fetal and utero-placental interactions. Over the past decade, the Michigan, Sendai-Perth, and Philadelphia groups have spearheaded research and analysis of three prominent artificial placenta models, each with its own level of success.

University of Michigan (USA): Veno-Venous Preterm Extracorporeal Life Support

In the pump-assisted veno-venous (VV) circuit with jugular vein/umbilical vein (JV/UV) cannulation, the use of a fluid-filled endotracheal tube replaced immersion in amniotic fluid to address concerns related to sepsis. This modification extended the mean survival of fetuses from 1 day to nearly 2 weeks, with the maximum reported survival reaching 17 days. Hemodynamic stability was achieved through the administration of vasopressors, while supraphysiological partial pressures of oxygen were necessary to ensure adequate oxygenation. However, the maintenance of ductal patency through prostaglandin E1 (PGE1) infusion proved to be inconsistent.

Although this artificial placenta model successfully rescued late premature lambs that had previously failed on postpartum mechanical ventilation, it does not fully align with the primary objective of artificial placental technology,

which is to delay lung ventilation and thereby preserve lung maturation. The fetal lambs used in the study were predominantly at the 118- and 130-day stages of gestation, corresponding to the early and late saccular phases of lung development, respectively. It is worth noting that borderline human fetuses at 22-24 weeks of gestation are in the late canalicular phase, which corresponds to approximately 100 to 110 days of gestation in lambs (46).

This discrepancy in lung development stages between the animal model and human fetuses highlights the need for further research and refinement in artificial placenta models to better emulate human fetal physiology. Adjustments and adaptations specific to the developmental stage of human fetuses will be crucial to optimize outcomes and fulfill the goal of preserving lung maturation in extremely premature infants.

Tohoku University, Sendai (Jap) and University of Western Australia, Perth (Aus): Ex-vivo Uterine Environment (EVE)

In 2012, a Japanese team made significant advancements in optimizing the pumpless arterio-venous (AV) circuit initially developed by the Michigan group. They achieved this by reducing the priming volume and introducing milrinone, an inotropic vasodilator drug. These modifications led to an increase in survival time from 4 hours to 30 hours. However, the model still faced limitations due to progressive circulatory failure caused by high circuit resistance .To address this issue, the researchers implemented a parallel configuration of two hollow fiber membrane oxygenators, effectively reducing the circuit resistance by half. This improvement resulted in a further increase in survival time to 1, 2, and eventually 7 days. External circuit flow regulators were necessary to stabilize hemodynamics and prevent high cardiac output failure. In order to mitigate the risks of bacteremia and systemic inflammatory response, the fluid bath was transformed into a closed, low-volume container, and continuous circulation of sterilized amniotic fluid was established. Prophylactic administration of meropenem and fluconazole was incorporated into the amniotic fluid, both intravenously and locally. Additionally, hydrocortisone was added to the artificial placenta model to suppress inflammatory responses, promote lung maturation, and prevent hypocortisolemic refractory hypotension. The use of corticosteroids successfully alleviated the inflammatory reaction, and the absence of infection was noted. However, analysis of the brains of the experimental subjects revealed evidence of brain white matter damage, likely attributed to systemic hypoperfusion or acute embolic events. These findings underscore the need for further optimization of the model in preparation for its potential clinical application. The maximum reported survival time achieved in this study was 7 days (47).

Further research and refinement are necessary to address the remaining challenges and ensure the safety and efficacy of the artificial placenta model. This includes developing strategies to enhance perfusion to vital organs and prevent adverse neurological outcomes, among other consideration

Philadelphia Children's Hospital (USA):

Extra-Uterine Environment for Neonatal Development (EXTEND)

In 2017, the Philadelphia team introduced the EXTEND AW model, which demonstrated promising outcomes in lambs aged 106 to 117 days. The lambs survived for up to 28 days within the artificial placenta model, followed by successful ventilation. The model utilized a pumpless, low-resistance, low-surface area heparin-coated arterio-venous (AV) circuit with umbilical artery/umbilical vein (UA/UV) cannulation. The circuit maintained stable hemodynamics without the need for external flow regulators, vasopressors, or corticosteroids. Refractory hypotension was effectively managed by providing physiological oxygen delivery and circuit flows.

The lambs were immersed in a closed, sterile fluid medium with continuous exchange of synthetic amniotic fluid, eliminating the need for prophylactic antimicrobials. Notably, the absence of bacteremia was observed throughout the study. The Philadelphia team reported long-term stable hemodynamics, somatic growth, and sustained organ maturation in the lambs. The lungs of the lambs in the EXTEND model progressed naturally from the canalicular to the saccular phase of lung development, without the use of corticosteroids or tracheal occlusion. Assessment of pulmonary function during mechanical ventilation showed comparable results to age-matched control lambs.

Brain analysis revealed normal cerebral maturation, with no evidence of white matter damage or intracranial hemorrhage. It is worth noting that fetal lambs are considered to be less prone to intracranial bleeding compared to human fetuses, as sheep experience earlier germinal matrix maturation. Neurodevelopmental maturation in the lambs within the artificial placenta model was demonstrated by the progressive consolidation of sleep/wake cycles, measured through ocular electromyography.

Transiently decreased cardiac contractility was observed during a one-week adaptation phase in the circuit, followed by normal cardiac function and contractility for the remainder of the study. No myocardial damage or inflammation was observed, and the heart development and structure in the circuit lambs were comparable to age-matched controls.

While specific assessments of liver and kidney function have not been reported yet, metabolic parameters reflecting kidney function remained stable. Mild increases in hepatic function tests and bilirubin levels were observed during the study period, which may be attributed to the absence of maternal elimination rather than indicating hepatic dysfunction (48)

The EXTEND AW model developed by the Philadelphia team demonstrates promising outcomes, including stable hemodynamics, normal organ development, and neurological maturation in lambs within the artificial placenta model. Further studies are needed to evaluate liver and kidney function, as well as to address any potential long-term effects and optimize the model for future clinical applications (Fig 9).

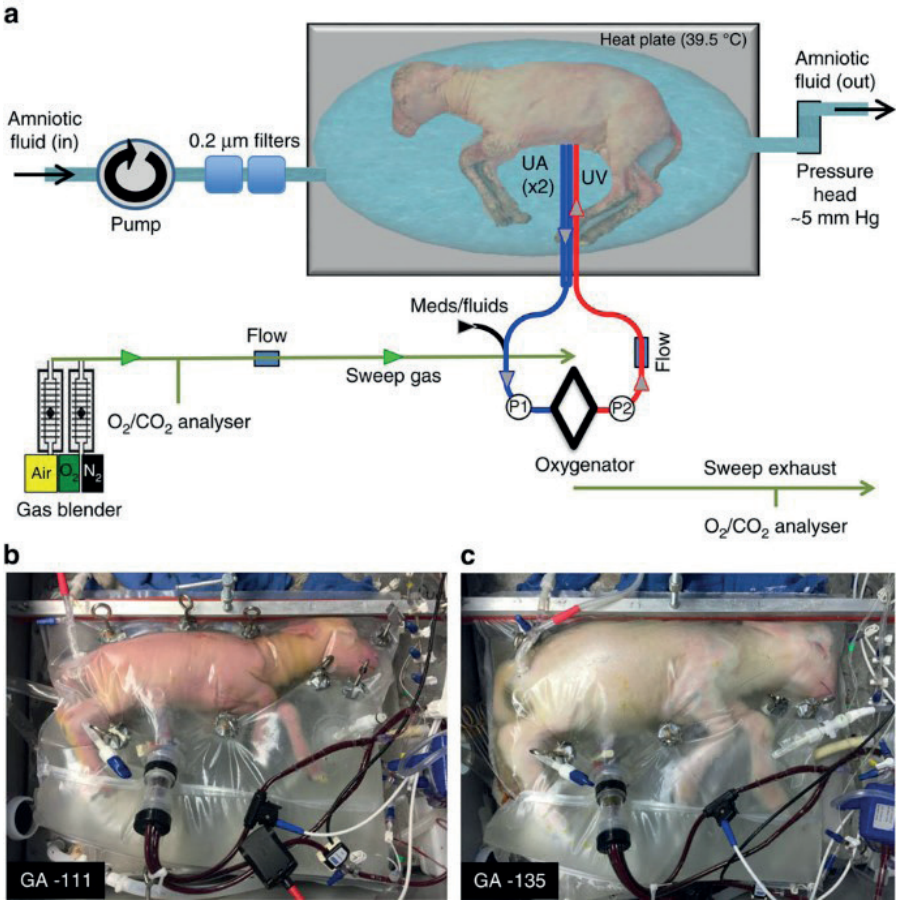

Figure 9.The UA/UV Biobag system design includes a pumpless, low-resistance oxygenator circuit, a closed fluid environment with continuous fluid exchange, and an umbilical vascular interface. The figure shows a representative lamb cannulated at 107 days of gestation and on day 4 of support, as well as the same lamb on day 28 of support, demonstrating somatic growth and maturation(49).

Challenges in clinical practice

Significant progress has been made in artificial placenta technology over the past decade, bringing it closer to clinical implementation. However, several challenges still need to be addressed.

One challenge is the reduction of oxygenator surface area and improvement of hemocompatibility through the use of new biomaterial coatings. This can help minimize the need for systemic anticoagulation, thereby reducing the risk of bleeding complications. Restoring placental alignment to allow for pulsatile flow from umbilical arteries to transition into laminar flow in the umbilical vein has not yet been achieved in recent artificial placenta models. Incorporating a closed, compliant pressure chamber into the system can prevent pulsatile flows from reaching the fetal right heart via the umbilical vein. Optimizing nutrition, growth factors, and amniotic fluid composition is essential for promoting proper somatic growth within the artificial placenta system. Exploring enteral nutrition strategies, as opposed to solely relying on parenteral nutrition (TPN), may be advantageous for the developing gut and reduce the risks associated with TPN-related cholestasis. Therefore, further investigation in this area is necessary. The widespread application of artificial placenta technology in emergency scenarios, such as premature rupture of membranes, requires standardized patient selection criteria and the development of a simple, fast, and effective cannulation technique. Advancements in these areas will contribute to the creation of an ideal artificial placenta model.

Conclusion

Artificial placenta technology is an evolving field of study that has captivated the scientific community for over six decades. Progress in circuit configuration, oxygenator technology, vascular access, fluid immersion, sterility, nutrition, and medical therapy has significantly advanced this technology, bringing it closer to mimicking utero-placental physiology. Recent experimental models have demonstrated improved survival rates and hemodynamic stability, allowing for safety assessments in preparation for future clinical applications. Despite these promising results, challenges remain along the path to clinical implementation. Furthermore, artificial placenta technology not only holds great clinical potential but also provides exciting opportunities for further research endeavors.

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