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The artificial placenta: sci-fi or reality?

La placenta artificial: ¿ciencia ficción o realidad?

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RESUMEN

Una placenta artificial es una plataforma de soporte vital para bebés prematuros o que tuvieron menos de 37 semanas de gestación completa. Aunque existe la posibilidad de utilizar esta plataforma para la reparación intraoperatoria de anomalías congénitas (p. ej., hernia diafragmática congénita) en bebés prematuros tardíos, o para el estudio del desarrollo fetal, el objetivo principal de esta tecnología es actualmente el tratamiento de bebés extremadamente prematuros, o aquellos nacidos durante el período peri-viable entre las 21-24 semanas de gestación completa.

Los bebés que nacen en este período peri-viable, generalmente tienen malos resultados debido a la necesidad de ventilar mecánicamente sus pulmones extremadamente inmaduros, a menudo a altas presiones máximas. Las plataformas de soporte vital basadas en placenta artificial están diseñadas para evitar la necesidad de ventilar como un medio para facilitar el intercambio de gases y así evitar lesiones en el pulmón prematuro inmaduro. En cambio, el intercambio de gases altamente eficiente y fácilmente regulado se realiza mediante dispositivos de intercambio de gases conectados a la vasculatura fetal. Dependiendo de la forma del sistema utilizado, se han probado diseños de circuitos venoso-venosos y arterio-venosos, con los prototipos arterio-venosos más recientes que utilizan el corazón fetal, en lugar de una bomba externa, para generar la presión del circuito.

A pesar de tener la apariencia de un concepto futurista, el trabajo de desarrollar una placenta artificial se ha llevado a cabo de forma intermitente desde al menos finales de los años 50. El hecho de que la tecnología aún no haya entrado en servicio clínico, a pesar de que han pasado más de 60 años, refleja los desafíos técnicos que rodean el desarrollo y uso de la placenta artificial. Esta demora en la introducción también refleja el panorama cambiante de la atención neonatal y, en particular, los avances en la ventilación mecánica y los modos de soporte respiratorio no invasivo, como la presión positiva continua en las vías respiratorias, la introducción de esteroides prenatales y la disponibilidad de terapia con surfactante exógeno.

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Como tal, es razonable argumentar que el grupo demográfico objetivo para la tecnología de placenta artificial ha cambiado significativamente desde que comenzó su desarrollo. Los bebés que antes se consideraban peri-viables y probables candidatos para la terapia con placenta artificial (es decir, los que nacieron antes de las 28 semanas de gestación) ahora tienen tasas mucho mejores de supervivencia libre de enfermedad con la tecnología disponible en la actualidad. El grupo demográfico con los peores resultados, y los posibles candidatos para la terapia de placenta artificial contemporánea, son aquellos nacidos de embarazos significativamente comprometidos (por ejemplo, infección intrauterina, sepsis, preeclampsia severa, insuficiencia placentaria severa) a las 21-24 semanas de gestación y con un peso de aprox. 300 gramos.

Este artículo proporcionará una revisión del historial de desarrollo de la placenta artificial, un resumen de la situación actual y concluirá discutiendo los desafíos restantes que deberán abordarse antes de que esta tecnología pueda introducirse en la práctica clínica.

SUMMARY

An artificial placenta is a life support platform for babies born preterm, or prior to 37 weeks' completed gestation. Although there is potential to use this platform for the intraoperative repair of congenital abnormalities (e.g. congenital diaphragmatic hernia) in late preterm babies, or for the study of fetal development, the primary target for this technology is currently treatment of extremely preterm infants, or those delivered during the peri-viable period between 21-24 weeks' completed gestation.

Babies born in this peri-viable period generally have poor outcomes due to the need to mechanically ventilate their extremely immature lungs - often at high peak pressures. Artificial placenta-based life support platforms are designed to obviate the need to ventilate as a means of facilitating gas exchange, and thus avoid injury to the immature preterm lung. Instead, highly efficient, and easily regulated gas exchange is performed by gas-exchange devices connected to the fetal vasculature. Depending on the form of the system used, venous-venous and arterio-venous circuit designs have been trialled, with the more recent arterio-venous prototypes using the fetal heart, rather than an external pump, to generate circuit pressure.

Despite having the appearance of a futuristic concept, work to develop an artificial placenta has been undertaken intermittently since at least the late 1950s. That the technology is yet to enter clinical service, despite 60-plus years of work, reflects the technical challenges surrounding the development and use of the artificial placenta. This delay in introduction also reflects the changing neonatal care landscape, and notably advances in mechanical ventilation and non-invasive respiratory support modes such as continuous positive airway pressure, the introduction of antenatal steroids, and the availability of exogenous surfactant therapy.

As such, it is reasonable to argue that the target demographic for artificial placenta technology has changed significantly since development first began. Babies once considered peri-viable and a probable candidate for artificial placenta therapy (i.e. those born below 28 weeks' gestation) now have much improved rates of disease-free survival using currently available technology. The demographic with the poorest outcomes, and the likely candidates for contemporary artificial placenta therapy, are those born from significantly compromised pregnancies (e.g. intrauterine infection, sepsis, severe pre-eclampsia, severe placental insufficiency) at 21-24 weeks' gestation and weighing as little as 300 grams.

This paper will provide a review of the development history of the artificial placenta, a summary of the current state-of-play, and conclude by discussing the remaining challenges that will need to be addressed before this technology might be introduced to clinical practice.

PRETERM BIRTH AND THE NEED FOR AN ARTIFICIAL PLACENTA

Preterm birth (PTB), being born before 37 weeks of completed gestation, is a leading cause of early childhood death, and is implicated in over one million deaths each year[1-3]. Worldwide, it is estimated that over 15 million babies are born premature each year, with the highest rates of prematurity and associated morbidity and mortality correlating strongly with socio-economic disadvantage. As such, parts of Asia, Sub-Saharan Africa, and regions in the United States report preterm birth rates above 13% of their total delivery populations. Conversely, Scandinavian countries, with highly developed and well-financed public health systems, report some of the lowest rates of prematurity, around 4-5%[4,5]. PTB is a complex syndrome, and although its sizable health-burden is clearly appreciated[6], the aetiology of prematurity is incompletely understood. Infection (notably in early, high-risk preterm deliveries)[7,8], inflammation, placental pathologies[2,3,9], environmental insults (smoking, alcohol consumption)[10], and a previous history of preterm labour[3] are all implicated in increasing the risk for delivering a baby preterm. Understandably, unpacking these often-interrelated factors and the role(s) that they play in increasing the risk of preterm delivery is difficult. Our incomplete understanding of these processes continues to hamper our ability to devise effective treatments and to diagnose mothers at risk of preterm delivery so as to facilitate timely and effective interventions.

We are now starting to make improvements, via public health initiatives, in our ability to identify women at risk and deliver interventions to lower the rate of preterm birth[11]. In contrast, our ability to care for preterm infants has steadily improved over the past fifty to sixty years[12]. Indeed, preterm babies once viewed as being unsuitable for resuscitation and unable to survive (or surviving only with significant, life-long disability) are now routinely discharged with few or no overt injuries relating to their preterm birth and subsequent treatment. Given the highly integrated nature of modern medicine, it is difficult to isolate the specific factors that underpin these improvements. However, three key pieces of technology, namely, mechanical ventilation (and advances in safety and efficacy therein), the introduction of antenatal steroid therapy, and the introduction of exogenous surfactant therapy based around the post-natal application of porcine- or bovine-surfactant preparations are clearly linked to improved outcomes. Together with broader improvements in obstetric and neonatal care, these technologies have contributed to significant improvements in both overall survival and in the disease-free discharge rates of preterm infants.

Despite the availability of an increasingly large and effective array of these and other preterm therapeutics, there remains a small rump of extremely preterm infants for whom key outcome measures (survival, disease-free at discharge) have stubbornly remained unchanged over the past several decades[13]. Setting aside the inherently high-risk nature of these cases, one may argue that an explanation for this distinct lack of improvement lies in the fact that key obstetric and neonatal interventions are broadly focussed on the provision and support of pulmonary respiration in the preterm infant. Mechanical ventilation, a key development, is quite clearly targeted at supporting pulmonary gas exchange. Setting aside the cardiovascular stability benefits associated with antenatal steroid administration, the primary target of these drugs is precocious functional maturation (increased surfactant production, alveolar development, septal thinning) of the preterm lung. And although it is increasingly clear that surfactant components play a host of distinct roles (including immune-modulation and protection from infection) the key benefit derived from exogenous surfactant therapy is an immediate improvement in pulmonary compliance facilitating improved gas exchange at lower ventilation pressures and thus greater protection from injury to the lung and to cardiovascular disruption.

A number of investigators have argued that these therapeutic interventions have reached an efficacy threshold when applied to peri-viable, extremely preterm infants born 21-24 weeks' gestation[14-16]. The primary reason for this assertion is that, at this extreme gestational age, the fetal lung is highly immature from a structural and functional perspective. At 21-24 weeks' gestation the fetal lung is transitioning from the canalicular to the saccular phase of development. From a histological perspective, the lung is characterised by the presence of respiratory bronchioles, and lacks extensively formed terminal alveolar sacs that begin to develop after 36 weeks' gestation in the human. The transitional canalicular / saccular lung enables limited perfusion of the gas exchange surfaces which are in turn extremely limited in surface area. A lack of pulmonary surfactant, combined with comparably thick septal walls combine to result in a lung that is highly non-compliant and ill-suited to function as a gas exchange organ. It is perhaps no surprise then, that therapies (ventilation, antenatal steroids, surfactant) that require at least some degree of functional lung maturation to be efficacious have failed to deliver the same significant improvements in outcomes that are now routinely observed in older preterm babies[13].

One approach to this problem is to view the extremely preterm infant not as a small baby, but as (at least from anatomical and physiological perspectives) a fetus, and in doing so attempt to devise a treatment modality that recognises and takes advantage of these characteristics.

At a most simple level, the concept of the artificial placenta for extremely preterm infants is based around the aim of obviating the need to use the immature lung for gas exchange. Instead, gas exchange is performed by oxygen / carbon dioxide exchange devices attached to the fetal circulation. Although not exclu-

sively the case, a significant number of studies in this area have sought to replicate the *in utero* environment more fully, and have devised a variety of means by which the developing fetus may be submerged in a bath of artificial amniotic fluid - protecting the fetus from the risks (skin tears / abrasions / dehydration) associated with the external environment and promoting an environment able to support normal lung maturation, including fluid swallowing/breathing reflexes.

This mini-review will provide an overview of the developmental history of the artificial placenta, discuss contemporary developments in the field over the past decade, and then move to a final discussion of the challenges that remain to be overcome before this technology could reasonably be considered for clinical application.

DEVELOPMENTAL HISTORY OF THE ARTIFICIAL PLACENTA

Initial studies to explore the potential to support preterm infants using non-pulmonary gas exchange were likely inspired by pioneering work undertaken by Dr John Gibbon in the field of cardiac bypass surgery. Dr Gibbon's work, beginning in the mid-1930s with a report of the successful provision of artificial lung and heart support to a cat with a deliberately occluded pulmonary artery, and culminating with the successful repair of a large atrial septal defect and left-to-right shunt in an 18 year-old girl hospitalised with recurrent right ventricular failure, is rightly regarded as one of the most important advances in medicine[17].

In 1958, a group of researchers at the Karolinska Institute represented by Westin, Nyberg and Enhöring reported a technique for the perfusion of peri-viable human fetuses weighing 375g, for periods of up to 12 hours. A number of proof-of-principle animal studies rapidly followed this landmark study; Lawn and McCance in Cambridge reported using pig fetuses at 60-70 days' gestation on an artificial placenta device[18]. Callaghan and colleagues in Canada used late-preterm sheep fetuses to execute short (~40 minute) pulmonary bypass protocols, followed by successful recovery and extended (> 6 month) survival[19].

Some of the most important early work in the field was that undertaken by Zapol and colleagues. Writing in the journal Science, Zapol *et al*. reported the successful maintenance of a male preterm lamb fetus (125 days gestational age, 3,05kg) for a period of 55 hours prior to the experiment concluding as a result of acute cardiac failure. Analyses revealed progressive anaemia, but with well controlled lactate, pH and pCO_2 values. Cultures of both fetal blood and the artificial amniotic bath in which the animal was submerged demonstrated the presence of klebsiella and aerobacter species[20].

A subsequent report, again by Zapol and colleagues, reinforced the need for artificial placenta-based systems to carefully replicate native fetal physiological conditions. In an elegant series of contrast angiography studies, it was demonstrated that the ductus arteriosus rapidly responded to increases in arterial PaO_2 by constricting. Indeed, an increase in PaO_2 from 13-20 mmHg to 40-60 mmHg saw nearly complete conversion of fetal circulatory distribution to a newborn configuration, consistent with marked occlusion of the ductus arteriosus. Most interestingly, and of additional importance in the management of fetuses on an artificial placenta platform, the authors also showed that a return of PaO_2 to normal low levels (i.e. 13-20 mmHg) was accompanied by a rapid return of a fetal circulatory configuration and dilation of the ductus arteriosus. Similarly, neither metabolic nor respiratory acidosis altered ductal patency[21]. This study in particular highlights the potential of the artificial placenta platform to serve as a means by which to dissect and study questions relating to fundamental fetal physiology, anatomy and development.

The next significant advances in the field came from studies undertaken in Japan and South Korea between 1989 and 2002. Kuwabara and colleges at the University of Tokyo reported the findings of a nine-animal study using goat fetuses between 112- and 136-days' gestational age (term is approximately 148 days' gestation). In this model, fetuses were submerged in a bath of artificial amniotic fluid with catheters introduced to the umbilical arteries and veins. The artificial placenta itself consisted of an arterial reservoir, roller pump, membranous oxygenator and heat exchanger. Six animals were successfully catheterised and were maintained in good physiological condition for an average period of 146,5±15 hours. The longest successful experiment was 231,18 hours in a 123-day gestational age fetus weighing 1,95kg. The primary cause of death in successfully catheterised animals was reported as being progressive circulatory depression and cardiac failure[22]. A follow-up paper by Kuwabara and Unno reported additional and highly impressive advances in the development of their platform. Using two goat fetuses (120d gestation, 1,6kg weight and 128d gestation, 2,4kg weight), the authors reported a successful artificial placenta maintenance period of 494 and 542 hours, respectively. In addition, both fetuses were successfully adapted from the artificial placenta onto pulmonary respiration and ventilated for an additional 704 and 169 hours, respectively - an achievement that remains a landmark success in the field[23]. Interestingly, the authors reported that they were unable to wean the goat fetuses off assisted ventilation. The cause(s) of this remain unclear, but may relate to iatrogenic injury deriving from the constant use of pancuronium bromide to immobilise the animals during the experimental period. Additional studies in sheep by Sakata and colleagues explored the use of centrifugal, high-flow pumps synchronised to the fetal heart; Pak and colleagues

also performed a number of experiments with fetal goats at 120-130d, achieving survival periods of around 24 hours using a roller-pump driven system[24].

Taken together, these studies demonstrated an incremental improvement in both survival times and significant advances in the quality of the maintenance (i.e. stability of key physiological variables within normal ranges, absence of life-threatening infection) able to be achieved with artificial placenta technology. Critically, in the case of the work by Callaghan *et al*., and by Unno and colleagues, this work clearly demonstrated that it was possible to maintain a fetus on an artificial placenta platform for an extended period of time and then successfully adapt it to pulmonary gas exchange - a fundamental requirement for the clinical translation of any such life support platform.

CONTEMPORARY DEVELOPMENTS – 2010 ONWARDS

The past decade has seen a rapid upswing in both the number of studies being published in the field of artificial placenta development, and the amount of interest shown by the scientific and lay media in the potential application of this technology in a clinical environment. Despite this, and the promising advances that have occurred of late, there still remains a sizable body of development work to be done before an artificial placenta could conceivably used in an attempt to treat an extremely preterm infant.

Efforts to develop an artificial placenta have evolved into two distinct model systems, demarcated broadly by three factors: i) the orientation of the fetal catheterisation being either an arterio-venous system employing the umbilical vessels, or a venous-venous system employing a cervical vessel (generally a fetal jugular vein) and an umbilical vein; ii) the use of either the fetal heart (in arterio-venous systems) or an external pump (in venous-venous systems) to pressurise the external gas exchange circuit; and iii) either the submersion of the fetus in a bath of artificial amniotic fluid (in arterio-venous systems dependent on maintenance of umbilical patency) or the maintenance of fetuses in a dry-air system with the lung artificially fluid-filled and occluded to establish the pressure necessary for normal pulmonary development to occur.

Much of the contemporary work in the field is derived from the efforts of three research groups. Two are based in the United States, one at the University of Michigan and a second at the Children's Hospital of Philadelphia. The third is a Japanese-Australian collaboration between researchers at the Women and Infants Research Foundation (Perth, Western Australia) and Tohoku University (Sendai, Miyagi Prefecture, Japan). More recently, a group in the Netherlands have announced their intention to rapidly develop a clinic-ready artificial placenta platform[25], and a further Canadian-Australian group have begun late-term artificial placenta experiments using pig fetuses[26].

The University of Michigan group has worked for a number of years to develop what might now be described as a 'ventilation-assist' artificial placenta model using a venous-venous return system, driven by an external pump. In the latest iterations of this work, the fetus is maintained in room air. In contrast, work undertaken in Philadelphia, and by the Japanese-Australian consortium, is based around studies employing an arterio-venous system, with the fetus submerged in an artificial amniotic fluid bath and the circuit pressurised by the fetal heart. Given the significant differences in these approaches, and in their potential utilisation, it is useful to discuss them separately.

PUMP-DRIVEN VENOUS-VENOUS RETURN SYSTEMS

Work published in 2012 by the team at the University of Michigan under Dr Mychaliska reported the use of a venous-venous return system to maintain late gestation preterm (130 days' gestation) fetuses. The artificial placenta design was based around a peristaltic roller pump-driven system that takes fetal blood from the right jugular vein, passes it through a gas exchange device (0,5m^2 hollow fibre oxygenator) before returning it to an umbilical vein. In these studies, fetuses were maintained in an amniotic fluid bath for up to 24 hours, with five out of nine animals surviving their treatments[27]. In a subsequent study that perhaps highlights one potential application of the system under development, the investigators reported using a similar but non-immersion system to explore the use of their artificial placenta platform to rescue late preterm (130 days' gestation) lambs from ventilatory failure. Animals were first ventilated for approximately one hour before the lung was deliberately filled with amniotic fluid and the animal transferred to artificial placenta support. Six out of seven animals survived a 70-hour procedure. $PaCO_2$ and PaO_2 were maintained within normal ranges and all animals were free of intraventricular haemorrhage[28]. In a follow-up study published in 2015, the authors reported the use of more preterm lambs (110-120 days' gestation) to test the performance of their apparatus over a seven-day treatment period. Four out of nine animals survived their seven-day protocols, with a further animal surviving six days[29]. More recently, the same group has demonstrated promising results from a comparative study of lung injury between animals either adapted to mechanical ventilation for 48 hours or venous-venous artificial placenta therapy incorporating a perflurocarbon-flooded lung for approximately seven days. As might be expected, animals in the artificial placenta group had lower lung injury scores than those exposed to mechanical ventilation[30]. Additional investigations regarding splenic and gastrointestinal development have also returned promising results[31,32].

FETAL HEART-DRIVEN ARTERIO-VENOUS RETURN SYSTEMS

One of the most important advances in arterio-venous system development came from work published by Reoma and colleagues, again at the University of Michigan. Using very late preterm fetuses (140 days' gestation) animals had catheters placed into umbilical vessels and were commenced on arterio-venous artificial placenta therapy lasting for a maximum of four hours in an immersion-based system. The authors reported that the major limitation of this approach was high cannula resistance and progressively deteriorating flow through the artificial placenta circuit[33]. At around the same time the Michigan group moved to report their initial findings with a pump-assisted venous-venous return system, Drs Miura and Matsuda at Tohoku University reported the findings of their work with a new, low-priming volume artificial placenta system. Advancing the work of Remoa and colleagues, Miura and colleagues incorporated a low-resistance, high-performance membranous oxygenator that allowed for a 40% reduction in circuit priming volume. Using preterm lambs (120-130 days' gestation) animals were maintained for an average of 18 hours[34]. In a further important advance, the same group hypothesised that the use of a parallelised circuit would allow a further reduction in circuit resistance, additionally reduce stress on the fetal heart, and achieve longer periods of healthy fetal maintenance. In this study, again using preterm lambs, survival was extended out to an average of 60,4 hours - a sizable advance over earlier work[35]. Additional studies, undertaken collaboratively with researchers at the Women and Infants Research Foundation in Western Australia, explored adapting progressively premature (115 days' gestation) fetal sheep to the parallelised pumpless system, and the inflammatory and microbial impacts deriving from the use of an open bath system[36,37]. Subsequent work by the same group, led by Dr Usuda, then incorporated progressively reduced priming volumes into their system and demonstrated stable, infection-free fetal maintenance for a period of one week[38]. Having achieved an extended (336 hr) period of artificial placenta maintenance using their platform (Dr Usuda, personal communication), the most recent focus of this group's work has been on modifying its artificial placenta platform to support extremely preterm ovine fetuses (95 days' gestation) and similarly aged extremely preterm fetuses compromised by intrauterine inflammation, similar to that commonly seen in periviable human preterm deliveries[15,16]. One key finding of this work - which highlights the importance of model selection - is that the maintenance of compromised fetuses is significantly more challenging, and that their growth parameters are inferior, relative to gestational age-matched fetuses from healthy or uncompromised pregnancies.

A significant body of work has been undertaken over the same period by a group at the Children's Hospital of Philadelphia. A landmark study published by Dr Flake's group in 2017 reported the findings of a number of years of iterative development work culminating in an arterio-venous artificial placenta platform. Commencing with late preterm sheep fetuses (125-140 days' gestation), Partridge and colleagues first described an initial system based around carotid artery and jugular vein catheterisation with lambs submerged in an open amniotic fluid bath. Lamb survival time was limited to between 23 and 108 hours due, in keeping with earlier reports by Miura *et al*., to sepsis and catheter positioning. A follow-up set of studies using slightly more immature lambs (120-132 days' gestation) reported a significant improvement in survival time (an average 346±93 hours) but with continued challenges in relation to microbial colonisation. The Philadelphia apparatus subsequently went through a series of further adaptations (a carotid artery - umbilical vein circuit orientation followed by an umbilical artery - umbilical vein circuit orientation) and the implementation of a closed bag system to house the fetus, with catheters externalised via a sealed port. Using a mature umbilical artery - umbilical vein circuit design, the investigators reported successful maintenance of normal physiological parameters and absence of infection in fetuses as young as 105 days' gestation for a period of up to four weeks[39]. More recent work by the same group has sought to address a significant gap in the literature, namely how fetal organ systems develop under the influence of artificial placenta therapy - with a particular focus on the brain[40,41].

FUTURE CHALLENGES AND CONCLUSIONS

As outlined above, the artificial placenta field has a long and iterative development history that is seemingly in contrast with the novel, somewhat futuristic manner in which it is frequently viewed today. Significant technical challenges and an evolving obstetric and neonatal care landscape have combined to greatly delay the clinical translation of what, in the late 1950s, likely seemed to be an imminent and much welcome advance in the care of extremely preterm infants. Today, some 60 years later, although progress towards the clinical translation of an artificial placenta for extremely preterm infants in certainly accelerating, significant technical and ethical hurdles remain to be overcome before one might expect to see an artificial placenta used to support an extremely preterm fetus. Perhaps paramount amongst challenges these is the relative lack of data to inform the maintenance of compromised, extremely preterm fetuses (as would be expected in a peri-viable delivery) on artificial placenta platforms. Although ontologically, the sheep lung at 110d may broadly align with the developmental status of a 24-week human fetus, a 110d sheep fetus is also in the region of 3-4 times the body weight, with a far greater circulatory volume, and likely with significantly better cardiac compensation capabilities.

Although the primary focus of artificial placenta development has been as a therapy for extremely preterm infants in lieu of ventilation, there is additionally good potential for using artificial

placenta technology as a modality for rescuing neonates suffering respiratory failure, or as a tool for the intraoperative support of neonates undergoing surgery to repair congenital abnormalities. Indeed, work undertaken by the Michigan group highlights this particular application very effectively. With the recent availability of platforms of maintaining extremely preterm fetuses in good health, there is now also the potential to meaningfully deploy this technology for the study of fetal development absent maternal and placenta *input*.

However, discussions around when one might introduce the artificial placenta as a replacement for ventilation support in extremely preterm infants remain a contentious topic. Perhaps the best guidance in when we might eventually consider applying this therapy for this purpose may be gained from the adaptation of heart-lung bypass technology, from which the artificial placenta paradigm is itself derived. Hill reported that, by 1953, Dr Gibbon's heart-lung machine had achieved a success rate of 78% in experimental trials before it was introduced to treat patients (i.e. those with massive pulmonary embolism otherwise undergoing Trendelenberg operations) with extremely limited chances of survival[41]. Today, extremely preterm fetuses at gestations as early as 23 weeks' gestation have a >60% chance of survival in some jurisdictions with currently available ventilator technology and advanced neonatal care. Thus, it is quite reasonable to conclude that although the artificial placenta has come a long way, there remains a very great deal of work to be done before one could responsibly advocate for its clinical application in even the most preterm of babies.

Declaración de conflicto de interés
The authors report no conflict of interest.

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