Artificial Uterus in Extremely Preterm Birth: Current Advances and Future Prospects. A Narrative Review

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ABSTRACT

Extreme prematurity remains one of the leading causes of neonatal morbidity and mortality and is associated with long-term respiratory, neurological, and neurodevelopmental complications. Although advances in neonatal intensive care have improved survival rates for these patients, conventional strategies, such as mechanical ventilation, force the immature fetal organism to undergo a premature transition to neonatal physiology, exposing the lungs, cardiovascular system, and brain to conditions for which they are not yet prepared. In this context, the artificial uterus and extrauterine fetal support systems have emerged as an experimental alternative aimed at temporarily preserving fetal physiology outside the maternal uterus.

The objective of this narrative review was to analyze the physiological basis, historical development, major contemporary models, experimental results, and transnational and ethical challenges related to these technologies. The available literature shows that platforms such as EXTEND/Biobag have succeeded in maintaining, in extremely preterm animal models, a closed liquid environment, functional umbilical circulation, extracorporeal gas exchange, and prolonged hemodynamic stability, thereby promoting lung maturation and partially preserving conditions associated with fetal neurodevelopment. Unlike conventional neonatal care, these systems do not aim to rapidly adapt the preterm infant to extrauterine life, but rather to prolong the fetal physiological state in a controlled manner during a critical stage of organ maturation. However, their clinical application in humans remains limited by challenges related to anticoagulation, circuit miniaturization, umbilical cannulation, infection control, neurological safety, candidate selection, and bioethical considerations regarding viability and medical intervention.

Overall, the artificial uterus represents a promising preclinical technology and a paradigm shift in the management of extreme prematurity, whose future value will depend not only on prolonging survival but also on improving functional survival and reducing long-term sequelae.

Keywords: artificial uterus, extreme prematurity, extrauterine fetal support, artificial placenta, ectogenesis.

INTRODUCTION

Extreme prematurity remains one of the leading causes of neonatal morbidity and mortality worldwide. It is estimated that approximately 15 million premature births occur each year, a significant proportion of which involve infants born before 28 weeks of gestation, classified as extremely preterm [1,2]. Despite advances in neonatal intensive care over the past decades, the survival of these patients continues to be associated with high rates of long-term respiratory, neurological, and neurodevelopmental complications.

The main pathophysiological problem lies in the fact that many of these patients are born during critical stages of organ maturation, particularly during the canalicular and early saccular phases of lung development. During this period, the lung exhibits significant structural immaturity, characterized by poor alveolar development, incomplete vascularization, and insufficient surfactant production, severely limiting the ability to perform effective gas exchange outside the intrauterine environment [2,3]. As a result, survival often depends on mechanical ventilation, oxygen therapy, and multiple invasive procedures that, although essential, contribute to the development of lung injury and multisystem damage.

In addition to pulmonary immaturity, premature birth forces the fetal body to undergo an abrupt physiological transition to neonatal life when multiple systems are not yet prepared to function outside the intrauterine environment. The shift from placenta-dependent circulation to a physiology based on pulmonary ventilation and independent postnatal circulation can trigger hemodynamic instability, systemic inflammation, oxidative stress, and alterations in cerebral perfusion, contributing to complications such as bronchopulmonary dysplasia, intraventricular hemorrhage, white matter lesions, and encephalopathy of prematurity [1,4].

Although contemporary neonatal strategies have improved survival, functional outcomes remain limited in patients at the threshold of viability, particularly due to the persistence of long-term pulmonary and neurological sequelae [2].

In this context, interest has resurfaced in recent decades in developing technologies capable of partially preserving fetal physiology outside the maternal uterus. Contemporary extrauterine fetal support systems, including artificial placenta and artificial uterus platforms, aim to maintain fetal circulation, extracorporeal gas exchange, and fluid-filled lungs, thereby partially preventing premature neonatal transition [3,5]. These devices are not intended to achieve complete ectogenesis, but rather to prevent the severe lung and brain damage that occurs when immature lungs are exposed to air prematurely, thereby prolonging the physical environment of the uterus (Figure 1).

Unlike conventional neonatal care, whose primary goal is to rapidly adapt the preterm infant to extrauterine life, these technologies aim to temporarily prolong the fetal physiological state to allow for organ maturation that more closely resembles normal intrauterine conditions.

The development of modern platforms such as EXTEND and Biobag has experimentally demonstrated the possibility of maintaining prolonged physiological support in extremely preterm animal models, including preservation of fetal circulation, hemodynamic stability, and progressive lung development [5,6]. These advances have transformed extrauterine fetal support from a historically theoretical concept into a potentially viable experimental strategy for the future management of extreme prematurity.

However, the eventual clinical application of these technologies in humans continues to face significant physiological, technical, obstetric, and ethical challenges. Limitations persist regarding the miniaturization of extracorporeal circuits, anticoagulation, umbilical cannulation, infection control, and long-term neurological safety, in addition to bioethical questions concerning fetal viability, informed consent, and the limits of medical intervention [7,8].

The objective of this narrative review is to analyze and synthesize the physiological basis of extrauterine fetal support, the evolution of the main contemporary models, the available experimental results, and the technical, physiological, and ethical barriers that will influence its future clinical application in humans.

METHODS

This work presents a narrative literature review focused on the development and current status of extrauterine fetal support technologies, artificial placenta, and artificial uterus applied to the management of extreme prematurity. The manuscript was prepared through a non-systematic review of contemporary scientific literature related to fetal physiology, extracorporeal fetal support, perinatal bioengineering, and experimental models of artificial gestational support.

The literature search was conducted using international biomedical databases, including PubMed, Scopus, and Google Scholar, covering the last 10 years. Relevant historical studies prior to this period, which were fundamental to understanding the conceptual and experimental evolution of the field of partial ectogenesis techniques, were also included.

Search terms related to “artificial uterus”, “artificial placenta”, “extrauterine fetal support”, “EXTEND”, “Biobag”, “ectogenesis”, “prematurity”, “fetal physiology”, “extracorporeal life support”, and “fetal circulation” were used. In addition, the bibliographic references of articles considered relevant were reviewed to identify further publications of physiological, historical, and translational interest.

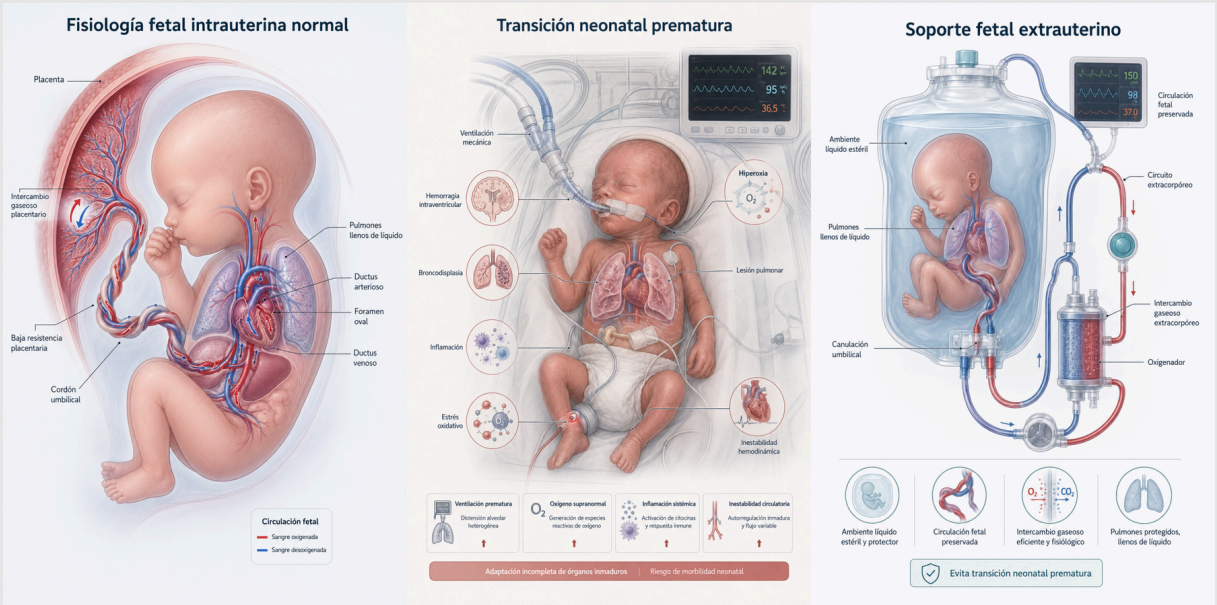


Figure 1. Pathophysiological basis of extrauterine fetal support. Comparative diagram illustrating normal intrauterine fetal physiology (left panel; labeled in the original image as “Fisiología fetal intrauterina normal”), premature neonatal transition (center panel; labeled as “Transición neonatal prematura”) in extremely preterm infants, and the physiological principle of extrauterine fetal support (right panel; labeled as “Soporte fetal extrauterino”), based on the preservation of fetal circulation and extracorporeal gas exchange. *Image created by the authors with the assistance of artificial intelligence tools. The original labels within the figure are presented in Spanish.*

Original articles, narrative reviews, experimental studies, and publications focused on fetal cardiovascular physiology, lung development, neurodevelopment, and contemporary artificial fetal support platforms were included. Priority was given to recent work and studies considered fundamental within the historical development of the field, particularly those related to modern extrauterine fetal support systems and their potential future clinical applications.

The information gathered was organized according to the main thematic areas of the review, including: physiological foundations of extrauterine fetal support, fetal-neonatal transition, historical evolution of the artificial placenta and artificial uterus, main contemporary experimental models, reported physiological outcomes, and translational challenges for their future clinical application in humans. The manuscript was prepared following the SANRA (Scale for the Assessment of Narrative Review Articles) guidelines, with an emphasis on thematic clarity, methodological transparency, and critical reasoning.

The selection and interpretation of the literature were based on the physiological, experimental, and translational relevance of each publication, as well as its contribution to the conceptual development of the field. Due to the narrative nature of this work, a formal systematic protocol, quantitative evaluation, and statistical analysis were not applied; therefore, the findings should be interpreted as a critical narrative synthesis and not as a quantitative estimate of the effect of these technologies.

PHYSIOLOGICAL BASIS OF EXTRAUTERINE FETAL SUPPORT

The development of extrauterine fetal support systems is based on the need to artificially preserve fetal physiology during critical stages of organ maturation. Unlike conventional neonatal intensive care, whose main objective is to rapidly adapt the premature newborn to extrauterine life, artificial placenta and artificial uterus technologies seek to temporarily maintain a fetal physiological state, preventing or delaying the premature transition to neonatal physiology [3,7].

During intrauterine life, the placenta is the primary organ for gas exchange, metabolic regulation, and fetal hemodynamic support. Fetal circulation is characterized by a specialized parallel system in which structures such as the ductus arteriosus, foramen ovale, and ductus venosus redistribute oxygenated blood to priority organs while the lungs remain functionally inactive and filled with fluid [3,5]. Under normal physiological conditions, the placenta also represents the vascular territory of least resistance within the fetal circulation, allowing for adequate cardiac preload and stable cardiac output with minimal ventricular afterload [9].

Unlike neonatal physiology, fetal gas exchange occurs exclusively at the placental level. As a consequence, the fetal lungs do not actively participate in blood oxygenation and remain filled with fluid throughout gestation. This fluid environment is essential for normal alveolar and pulmonary vascular development, while elevated pulmonary vascular resistance limits pulmonary blood flow and promotes the maintenance of physiological fetal shunts [7].

Normal birth triggers a complex physiological transition characterized by pulmonary aeration, elimination of fetal alveolar fluid, decreased pulmonary vascular resistance, and a progressive increase in pulmonary blood flow. Simultaneously, clamping of the umbilical cord eliminates placental circulation and forces a complete cardiovascular reorganization, with progressive closure of fetal shunts and establishment of independent neonatal circulation [3]. However, in extreme prematurity, this transition occurs when multiple organs remain structurally and functionally immature. In particular, the lung remains in early canalicular or saccular stages, characterized by incomplete alveolar development, immature vascularization, and insufficient surfactant production [2].

Early exposure of the immature lung to oxygen and positive pressures represents one of the main mechanisms of prematurity-induced lung injury. Several studies have shown that even brief periods of ventilation can trigger alveolar inflammation, oxidative stress, vascular alterations, and arrest of physiological lung development, significantly contributing to the development of bronchopulmonary dysplasia and chronic respiratory disease [1,3]. In this context, the pathophysiological problem lies not only in lung immaturity but also in the need to prematurely force the transition to a neonatal physiology for which the fetal organism is not yet prepared.

In addition to lung injury, premature neonatal transition significantly alters fetal cardiovascular physiology. Abrupt changes in intrathoracic pressure, vascular resistance, and blood flow can modify cerebral perfusion and promote serious neurological complications, such as intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL). The germinal matrix of the extremely premature infant has a particularly fragile vascularization and is susceptible to hemodynamic fluctuations, increasing the risk of intraventricular hemorrhage and cerebral white matter injury [4].

Extreme prematurity is also associated with relative hyperoxia, systemic inflammation, metabolic disturbances, and early exposure to environmental stimuli that exceed the neonate's physiological maturity. These conditions contribute to the development of necrotizing enterocolitis, sepsis, encephalopathy of prematurity, and long-term neurodevelopmental disorders [1]. Recent transcriptomic studies have further demonstrated activation of multiple inflammatory pathways and molecular alterations related to energy metabolism, mitochondrial function, and neuronal development in extremely premature infants [4].

In this pathophysiological scenario, the modern concept of extrauterine fetal support emerges. Unlike conventional neonatal therapy, which aims to rapidly adapt the premature infant to extrauterine life, artificial placenta and artificial uterus systems seek to prevent or delay this premature physiological

transition. The central principle consists of preserving functional fetal circulation, maintaining fluid-filled lungs, and providing extracorporeal gas exchange through low-resistance circuits that partially replicate the functions of the physiological placenta [3,5].

The most advanced contemporary models, such as EXTEND and Biobag, typically use pumpless arteriovenous circuits powered by the fetal heart itself, associated with closed, sterile liquid environments designed to recreate normal intrauterine conditions [6]. This strategy attempts to minimize hemodynamic disturbances, avoid premature air ventilation, and allow organ maturation to continue under physiological conditions closer to the fetal environment.

Overall, extrauterine fetal support proposes a paradigm shift: not to adapt an immature organism early to neonatal physiology, but to temporarily prolong fetal physiology while organic maturation continues.

HISTORICAL EVOLUTION AND CONTEMPORARY MODELS

The development of extrauterine fetal support technologies began shortly after the emergence of the first extracorporeal circulation systems in the mid-20th century. From the outset, the primary objective was to attempt to keep extremely immature fetuses alive by artificially replacing placental functions, particularly gas exchange and fetal hemodynamic support [2,5].

One of the most important precedents is the experiment conducted by Westin in 1958, who successfully cannulated previable human fetuses using rudimentary extracorporeal oxygenation systems, with limited survival times of a few hours [2]. Subsequently, during the 1960s and 1970s, several groups developed experimental models, primarily in ovine fetuses, using umbilical cannulation and arteriovenous circuits designed to partially reproduce fetal placental circulation.

However, most of these systems presented significant limitations related to thrombosis, hemolysis, fetal edema, umbilical vasospasm, and progressive hemodynamic instability. Many models used mechanical pumps that significantly increased extracorporeal vascular resistance, generating fetal cardiac overload and decreased umbilical flow. These findings led to the understanding that the fetal heart has a limited capacity to tolerate increases in afterload and that any successful system must reproduce the low-resistance characteristics of physiological placental circulation [6].

Subsequently, the development of prenatal corticosteroids, exogenous surfactant, and advanced neonatal ventilation partially shifted the focus away from conventional neonatal intensive care. However, as it became recognized that many of these interventions continued to be associated with significant pulmonary and neurological injury, interest in strategies to avoid premature neonatal transition resurfaced [1,3].

The major turning point occurred with the development of the EXTEND (EXTrauterine Environment for Neonatal Development) system by the group at the Children's Hospital of Philadelphia, described by Partridge *et al.* in 2017 [5,6]. This system introduced the modern concept of the "Biobag", a closed, sterile liquid environment designed to replicate intrauterine physiological conditions.

EXTEND uses a pumpless arteriovenous circuit powered directly by the fetal heart, connected to a low-resistance oxygenator and physiological umbilical cannulation. Unlike previous models, this strategy avoided the use of mechanical pumps and minimized hemodynamic alterations related to increased afterload and fetal cardiovascular dysfunction.

In the original study published in Nature Communications, Partridge and colleagues successfully maintained extremely premature lambs for up to four weeks with hemodynamic stability, progressive somatic growth, and continued lung maturation [6]. Furthermore, some animals subsequently achieved successful transition to conventional ventilation and prolonged survival after removal of the system.

From these advances, other relevant contemporary platforms began to emerge, whose main technical and physiological characteristics are summarized in Table 1. The EVE (Ex Vivo Uterine Environment) system, developed in Australia and Japan, shares multiple physiological principles with EXTEND, including pumpless arteriovenous circuits and closed liquid environments. The main difference between the models lies in the type of circuit and its limitations.

However, although it allowed successful support in smaller ovine fetuses, closer in weight to extremely premature human infants, the results showed greater difficulties related to somatic growth, fetal hydrops, and prolonged system stability [2,3]. These differences suggest that simply reproducing fetal gas exchange is not enough; sustained hemodynamic and metabolic stability remains one of the main determinants of the physiological success of extrauterine support.

Other models, such as those developed in Toronto and Michigan, explored alternative configurations using porcine fetuses and mechanically pumped systems. While these platforms provided important information on miniaturization, vascular accessibility, and prolonged extracorporeal support, they also highlighted one of the field's main limitations: the more complex and artificial the circulatory support becomes, the more difficult it is to preserve normal fetal physiology. Pump-assisted systems can stabilize extracorporeal flow, but they increase vascular resistance and hemodynamic alterations that deviate from physiological placental circulation, promoting thrombosis, umbilical vasospasm, and progressive cardiovascular instability [2,3].

Currently, EXTEND continues to be the experimental model with the most consistent physiological results, although its human application remains in the preclinical phase (Figure 2).

Table 1. Comparison of the main contemporary models of extrauterine fetal support.

Model	Type of extracorporeal circuit	Use of a mechanical pump	Experimental species	Main results	Main limitations	Development stage
Historical systems (1960–1990)	Extracorporeal arteriovenous (ECV)	Yes, in many models	Primarily sheep	Demonstrated initial viability of extrauterine fetal support.	Thrombosis, hemolysis, fetal edema, umbilical vasospasm, and hemodynamic instability.	Historical experimental
EXTEND (Biobag)	Low-resistance pumpless arteriovenous (PRAV)	No	Sheep	Support up to 4 weeks, hemodynamic stability, somatic growth, lung maturation, and subsequent transition to conventional ventilation.	Human application is still preclinical; challenges of miniaturization, anticoagulation, and umbilical catheterization.	Advanced preclinical
EVE (Ex Vivo Uterine Environment)	Pumpless arteriovenous (PRAV)	No	Sheep	Partial reproduction of intrauterine conditions in ovine models more closely resembling extreme human prematurity.	Fetal hydrops, reduced somatic growth, and limited prolonged stability.	Preclinical
Toronto Model	Assisted extracorporeal circuit.	Yes	Swine	Relevant information on miniaturization and prolonged support.	Increased vascular resistance and difficulty in preserving normal fetal physiology.	Experimental
Michigan Model	Assisted extracorporeal circuit.	Yes	Swine	Advances in vascular accessibility and extracorporeal fetal support.	Pump dependence, thrombosis, and cardiovascular instability.	Experimental

Comparison of the physiological and technical characteristics of modern artificial placenta and artificial uterus platforms, including type of extracorporeal circuit, use of mechanical pump, experimental species, main results and reported limitations.

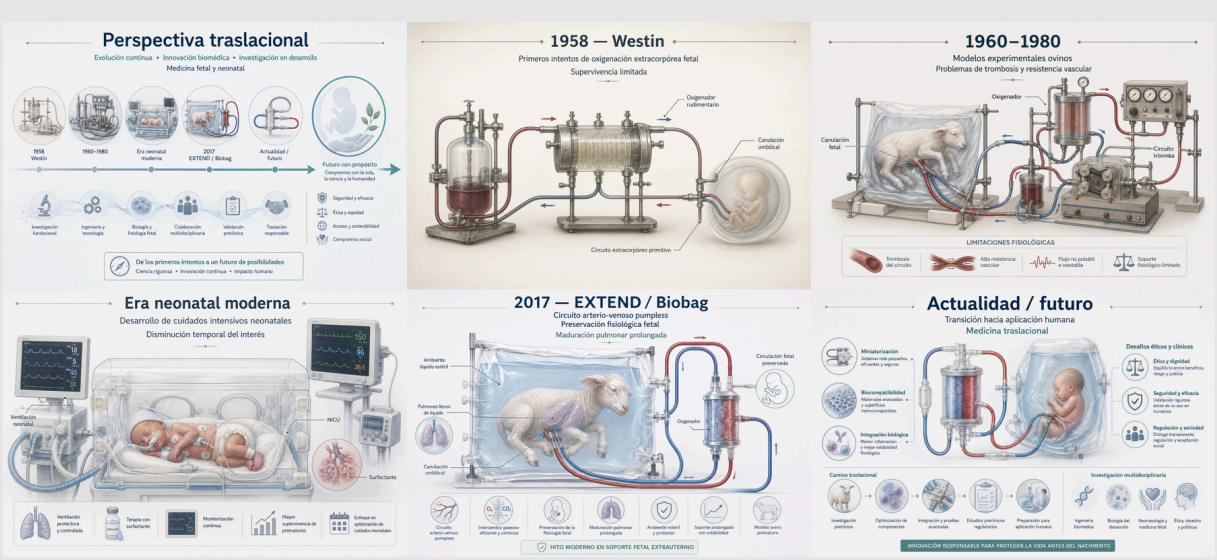


Figure 2. Historical evolution of extrauterine fetal support and artificial uterus technologies. Timeline illustrating the major milestones in the development of artificial placenta and artificial uterus technologies, including the first extracorporeal fetal oxygenation experiments by Westin (1958), experimental ovine models developed between 1960 and 1980, the emergence of modern neonatal intensive care, the development of the EXTEND/Biobag platform in 2017, and current translational perspectives toward clinical application. The figure also summarizes the main physiological advances, technological innovations, and ethical considerations associated with each stage. *Image created by the authors with the assistance of artificial intelligence tools. The original labels within the figure are presented in Spanish.*

PHYSIOLOGICAL COMPONENTS AND OUTCOMES

Contemporary extrauterine fetal support systems aim to temporarily preserve fetal physiology through extracorporeal support, an artificial fluid environment, and the maintenance of conditions similar to the intrauterine environment [3,7].

The central component of these platforms is the extracorporeal circuit, which replaces the placental functions of oxygenation and carbon dioxide elimination. The most physiological models, particularly EXTEND and EVE, utilize pumpless arteriovenous configurations powered directly by the fetal heart, avoiding mechanical pumps that have historically been associated with increased vascular resistance, hemolysis, and fetal hemodynamic instability [2,6].

The low resistance of the circuit is a critical aspect because the physiological placenta normally represents the vascular territory of lowest resistance within the fetal circulation. The fetal heart, especially the right ventricle, has a limited capacity to tolerate significant increases in afterload. Consequently, small variations in extracorporeal resistance can significantly alter cardiac output and compromise cerebral and systemic perfusion [9].

Studies using the EXTEND system demonstrated that progressive increases in resistance decrease combined cardiac output and alter fetal Doppler parameters; however, they also showed preservation of hemodynamic redistribution mechanisms aimed at maintaining cerebral and coronary perfusion, findings consistent with physiological fetal cardiovascular autoregulation [9]. These results suggest that extrauterine fetal support can preserve authentic fetal hemodynamic responses and not merely function as a passive platform for extracorporeal oxygenation.

Umbilical cannulation allows for partial replication of placental circulation through arterial drainage to the oxygenator and fetal venous reinfusion [5]. However, it remains a major technical limitation due to the risk of vasospasm, thrombosis, and progressive reduction of extracorporeal flow, especially in extremely small human fetuses. To reduce these complications, atraumatic microsurgical strategies, strict thermal control, preservation of cord-free segments, and the use of topical vasodilators have been proposed [3].

Another characteristic component of the modern artificial uterus is the artificial liquid environment. The “Biobag” system, developed by the Philadelphia group, introduced the concept of a closed, sterile liquid chamber where the fetus remains completely submerged during extracorporeal support [6]. The integration of these components can be schematically represented as a system composed of a liquid environment, umbilical cannulation, extracorporeal circuit, oxygenator, filtration, and continuous fetal monitoring (Figure 3).

Maintaining a fluid-filled environment has several important physiological implications. In addition to reducing ventilator-associated lung injury, it promotes thermal stability, musculoskeletal development, and a decrease in excessive environmental stimuli. It also helps preserve hemodynamic conditions closer to those found in utero [1].

Modern systems also incorporate filtration and infection control mechanisms designed to maintain prolonged sterility. Some models use continuous exchange of artificial amniotic fluid, microbiological filters, and ultraviolet radiation systems to reduce the risk of bacterial contamination and fetal sepsis [10]. This is especially relevant considering that many causes of extreme prematurity are associated with intrauterine infection.

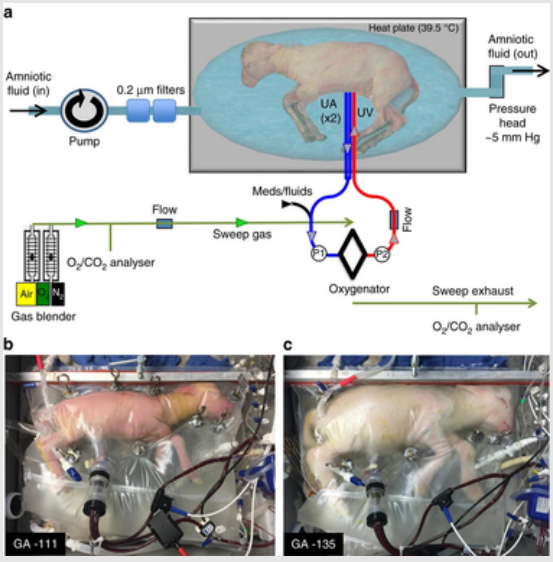


Figure 3. Main components of a modern artificial uterus system. (a) The system consists of a pump-free arteriovenous extracorporeal circuit, a low-resistance oxygenator, a closed liquid chamber with continuous exchange of artificial amniotic fluid, and an umbilical vascular interface. The diagram shows the artificial amniotic fluid inlet and outlet, filters, thermal control system, gas mixer, O2/CO2 analyzers, oxygenator, and umbilical vascular connections. (b) The lower images show a cannulated fetal lamb at 107 days of gestation on day 4 of support, and (c) the same animal on day 28, demonstrating somatic growth and progressive maturation during extrauterine support. *Adapted from Partridge et al. (2017) [11].*

One of the main physiological goals of extrauterine fetal support is to preserve lung development by preventing premature neonatal transition. At gestational ages of less than 24 weeks, the lung remains in early canalicular and saccular stages, characterized by incomplete alveolar development, immature vascularization, and insufficient surfactant production [2]. Early exposure to air ventilation can induce alveolar inflammation, barotrauma, and arrest of physiological lung development.

Several experimental studies have demonstrated favorable pulmonary outcomes using artificial uterus systems. In the EXTEND model, the lungs showed normal histological progression to more advanced saccular stages, with alveolar architecture comparable to intrauterine controls of equivalent gestational age [5,6]. Furthermore, some animals subsequently achieved successful transition to conventional ventilation, suggesting sufficient lung development for later neonatal adaptation.

Other studies have shown less pulmonary inflammation and reduced tissue injury compared to premature infants who underwent early conventional mechanical ventilation [1]. These findings support the hypothesis that a significant portion of the lung damage associated with extreme prematurity stems from early exposure to air ventilation rather than solely from structural lung immaturity.

Neurodevelopment is another of the most relevant aspects evaluated in contemporary models. Extreme prematurity is frequently associated with intraventricular hemorrhage, white matter injury, and neurocognitive impairments secondary to systemic inflammation, hyperoxia, and hemodynamic instability [4]. Therefore, one of the potential benefits of the artificial uterus is providing a hemodynamic and metabolic environment closer to that of intrauterine life.

Initial histological studies using EXTEND showed macroscopically normal brains, with no significant evidence of hemorrhage or cerebral infarctions [6]. Subsequently, Cohen *et al.* performed comparative transcriptomic analyses between brains of control preterm infants, normal intrauterine fetuses, and animals maintained in EXTEND. The authors found that the brain molecular profiles of the animals subjected to extrauterine fetal support were considerably more similar to physiological fetal controls than to conventional preterm infants [4].

Specifically, they observed reduced activation of inflammatory pathways mediated by TNF, IL-1, and TGF-β, as well as better preservation of mechanisms related to energy metabolism and neuronal mitochondrial function. These findings suggest that extrauterine fetal support could reduce some molecular mechanisms involved in encephalopathy of prematurity.

Taken together, the experimental evidence suggests that these systems can partially preserve hemodynamic stability, umbilical circulation, lung development, and some neuroprotective mechanisms.

The main physiological outcomes reported in contemporary models are summarized in Table 2. However, miniaturization, anticoagulation, and biocompatibility continue to limit their clinical translation.

Table 2. Main physiological results reported in experimental models of extrauterine fetal support.

Physiological area	Observations	Translational limitations
Cardiovascular	Preservation of fetal and umbilical circulation, with hemodynamic stability and partial autoregulation.	Sensitivity to circuit resistance, with risk of cardiac overload, thrombosis, and umbilical vasospasm.
Pulmonary	Lungs filled with fluid, progressive lung maturation, and less injury associated with mechanical ventilation.	Lack of human clinical evidence and uncertainty regarding its reproducibility in extremely premature human infants.
Neurological	Reduced exposure to hemodynamic fluctuations, systemic inflammation, and hyperoxia. Partial preservation of neuroprotective mechanisms.	Insufficient evidence on long-term neurodevelopment and differences between the ovine and human brain.

Continuation

Metabolic and inflammatory	Reduced activation of inflammatory pathways and better preservation of cellular energy metabolism.	Findings limited to preclinical models and experimental molecular analyses.
Global development	Progressive somatic growth and maintenance of physiological conditions similar to the intrauterine environment.	Challenges remain regarding miniaturization, anticoagulation, optimal duration of support, and human clinical application.

Summary of cardiovascular, pulmonary, and neurological findings observed in animal models subjected to extrauterine fetal support, as well as their main translational limitations.

TRANSLATIONAL CHALLENGES AND ETHICS

Despite the experimental advances achieved in recent years, the clinical application of the artificial uterus in humans continues to face significant technical, physiological, and bioethical limitations. Although platforms such as EXTEND have demonstrated partial preservation of fetal physiology and progressive organ development in animal models, there is still insufficient evidence to establish safety and efficacy in extremely premature human infants [2,3].

One of the main translational challenges is anticoagulation. Due to prolonged blood contact with extracorporeal surfaces, most current systems require systemic heparinization to prevent circuit thrombosis. However, extremely premature infants are highly susceptible to intraventricular hemorrhage and other hemorrhagic complications, making anticoagulation one of the main barriers to future clinical application in humans [3]. Consequently, several groups are currently working on biocompatible surfaces and less thrombogenic circuits that would reduce or even eliminate the need for prolonged systemic anticoagulation.

Miniaturizing the extracorporeal circuit presents another significant challenge. Many successful experimental models were developed using ovine fetuses, which are considerably larger than the most extremely premature human infants. Reducing the size of cannulas, oxygenators, and circuits involves complex difficulties related to vascular resistance, hemodynamic stability, and maintaining adequate flow driven solely by the fetal heart [2].

Furthermore, the obstetric transfer to the extrauterine fetal support system is one of the most physiologically critical phases of the process. The goal is to prevent the fetus from prematurely initiating the neonatal transition before establishing functional extracorporeal circulation. To this end, the most successful experimental models have used controlled cesarean sections and modified EXIT procedures, temporarily preserving placental circulation during umbilical cannulation [7]. However, standardized human obstetric protocols for this procedure are still lacking.

From a bioethical perspective, the artificial uterus raises complex questions related to fetal viability, informed consent, and the limits of medical intervention. These technologies partially modify the traditional boundaries between fetal and neonatal physiology, sparking debates about the definition of birth, reproductive autonomy, and candidate selection [8]. Most authors agree that initial clinical applications should focus on improving the functional prognosis of premature infants within the current limits of neonatal viability, rather than indefinitely expanding human viability.

DISCUSSION

The development of the artificial uterus represents a significant conceptual shift in the management of extreme prematurity, as it moves the therapeutic focus from supporting immature organs to temporarily preserving fetal physiology. Unlike conventional neonatal intensive care, which aims to sustain life after an established neonatal transition, extrauterine fetal support attempts to prevent this transition from occurring prematurely. This difference is not merely technical but also pathophysiological: the primary problem in extremely preterm infants lies not only in organ failure secondary to immaturity but also in the need to prematurely force the adaptation of a fetal organism to neonatal conditions for which it is not yet biologically prepared. From this perspective, the artificial uterus does not simply seek to replace pulmonary or cardiovascular functions but to modify the physiological timing of the transition to neonatal life.

Available experimental evidence suggests that preserving fetal physiology can reduce some of the central injury mechanisms associated with extreme prematurity. Maintaining fluid-filled lungs, preserving umbilical circulation, and avoiding early air ventilation reduce the exposure of the immature lung to positive pressures, relative hyperoxia, and mechanical inflammation. This explains why the most promising results have been observed in lung development, hemodynamic stability, and partial preservation of neurodevelopment [4,5].

However, this enthusiasm should be interpreted with caution. Most of the evidence comes from animal models, primarily sheep, whose physiology does not fully replicate the human condition. This limitation is particularly relevant in the central nervous system, as the human premature brain has specific vulnerabilities, such as germinal matrix fragility and an increased risk of intraventricular hemorrhage. Therefore, although the transcriptomic and structural findings are promising, they do not yet allow us to conclude that the artificial uterus will be neuroprotective in humans.

Another critical point is that the system's success hinges on a delicate physiological balance: the circuit must perform sufficient gas exchange without increasing resistance to the point of overloading the fetal heart. This tension explains why miniaturization, vascular resistance, and umbilical cannulation remain

key barriers. Furthermore, even if physiological stability is safely achieved, uncertainties persist regarding the optimal duration of support, candidate selection, and the actual impact on long-term neurodevelopment.

Comparisons between systems show that an ideal model has yet to emerge. EXTEND has demonstrated the most consistent results with its physiological approach using a pumpless arteriovenous circuit and a closed fluid environment, but other models, such as EVE, Michigan, and Toronto, show that some technical solutions can improve certain aspects while sacrificing others. Pumped systems can stabilize flow but deviate further from fetal physiology; pumpless systems are more physiological but depend critically on fetal cardiac function and minimal extracorporeal resistance.

The difference between conventional mechanical ventilation and the liquid support of the "Biobag" system lies not only in the use of more advanced technology, but also in a profound transformation of the physiological approach to extremely premature infants. While mechanical ventilation attempts to artificially replace respiratory function by introducing air into structurally and functionally immature lungs, exposing them to pressure, oxygen, and the risk of lung injury, the Biobag system avoids forcing a premature respiratory transition and maintains the fetus in a liquid environment similar to the intrauterine environment. In this model, gas exchange does not depend on the lungs, but on extracorporeal circulation connected to the umbilical cord, which allows for the preservation of fetal physiology and promotes the progressive maturation of organs. Therefore, the artificial uterus should not be understood merely as a technical improvement over mechanical ventilation, but as a paradigm shift: instead of adapting the immature fetus to the conditions of the extrauterine world, it seeks to temporarily preserve the biological conditions of the uterus to allow for a more natural and physiological development.

From a translational perspective, the main challenge will be defining whether this technology should aim to increase overall survival or improve survival without severe disability. This distinction is clinically relevant. If the artificial uterus merely shifts the viability threshold without improving functional outcomes, it could reproduce some of the dilemmas already present in critical neonatology. Conversely, if it succeeds in reducing pulmonary and neurological injury, its clinical value would be far greater: it would not only allow for longer life but also for living with fewer long-term consequences.

Clinical application will also necessitate a redesign of the relationship between obstetrics and neonatology. Fetal transfer to the artificial uterus will likely be one of the most complex moments, since any early exposure to air, loss of umbilical blood flow, or thermal instability could trigger the neonatal transition that is precisely what the technology seeks to prevent [7]. Therefore, future implementation will require highly specialized teams, neonatal rescue protocols, and rigorous candidate selection criteria.

Finally, the artificial uterus raises questions that extend beyond the technical aspects. Clinical extrapolation from ovine models remains uncertain due to significant differences in brain, cardiovascular, and placental development, as well as small sample sizes, limited follow-up, and methodological heterogeneity. There are also no defined criteria for candidate selection, optimal duration of support, neonatal rescue strategies, or long-term neurological safety parameters. Therefore, this technology should be understood as a promising experimental platform, but one still far from routine clinical practice. Its true impact will depend on whether it improves functional survival, not just artificially prolonging viability.

CONCLUSIONS

Extrauterine fetal support and artificial uterus technologies represent one of the most innovative areas of contemporary fetal and neonatal medicine. Their development has allowed progress from rudimentary models of extracorporeal oxygenation to physiological platforms capable of partially preserving fetal circulation, maintaining fluid-filled lungs, and promoting organ maturation outside the uterus.

Experimental evidence demonstrates that systems such as EXTEND can maintain hemodynamic stability, continuous lung maturation, and neurodevelopmental profiles relatively close to normal fetal physiology in extremely premature animal models. These findings suggest that a significant portion of the injury associated with extreme prematurity may be related not only to organ immaturity but also to premature neonatal transition and early exposure to air ventilation.

However, human clinical application remains limited by challenges related to anticoagulation, miniaturization, umbilical cannulation, infection control, neurological safety, and ethical regulation. Overall, the artificial uterus continues to be a promising preclinical technology. Its future value will depend on whether it succeeds in improving functional survival and reducing long-term consequences in extremely premature infants.

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Conflicts of interest

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Ethical considerations

This work is a narrative literature review and therefore did not involve the direct participation of human subjects, the collection of identifiable clinical data, intervention on patients, or the performance of experimental procedures on animals. For this reason, it did not require approval from a research ethics committee or informed consent. The information analyzed comes exclusively from previously published scientific articles, reviews, and experimental studies. However, because the topic of the artificial uterus involves relevant bioethical debates regarding fetal viability, informed consent, limits of medical intervention, candidate selection, and future clinical application in humans, these aspects were critically addressed within the manuscript.

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