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Artificial womb technology – A more physiologic solution to treating extreme prematurity

Felix R. De Bie [a,*], Chase C. Binion [b], Ryan M. Antiel [a]

[a] Department of Surgery, Duke University, Durham, NC, USA
[b] Department of Surgery, University of Virginia, Charlottesville, VA, USA

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ABSTRACT

Treatment of extreme premature infants (EPI) is limited by developmental immaturity primarily of the lung. A paradigm shift towards a more physiologic treatment of EPI as fetal neonates or *fetonates*, by keeping them in a womb-like environment to allow continued organ maturation, is the rationale for artificial womb technology. In this review, we discuss the artificial placenta and womb technology, it's rationale, the history of its development, the most recent preclinical models described in the literature and finally pertinent ethical considerations.

The challenge of extreme prematurity

According to the World Health Organization, 0.4 % of infants worldwide are born extremely premature, defined as before 28 weeks gestational age [1,2]. Despite this seemingly small fraction, extreme prematurity continues to stand out as a major cause of infant morbidity and mortality, even within developed nations [3,4]. Between 2013 and 2018, survival rates at hospital discharge in the United States were 10.2 % at 22 weeks gestational age (GA), 77.9 % at 25 and 93.7 % at 28 [5]. Despite the strides made in neonatal intensive care, which have enhanced the survival rates of extremely premature infants (EPI), increased survival is associated with severe morbidity among survivors, which is attributed to the structural and functional organ immaturity and iatrogenic injury [6]. The extreme premature brain, lungs, and eyes are especially susceptible to hemodynamic instability and ventilatory insufficiency, however, gastrointestinal, renal, and cardiovascular systems are often also affected, causing long term morbidity [7,8]. The spectrum of chronic morbidities is further compounded by neurodevelopmental delays, along with social and behavioral disabilities [9].

Rationale for artificial womb and placenta technology

Lung development is arrested by gas ventilation in EPI [10]. At the limit of viability (22–24 weeks GA), lungs of EPI are in the late canalicular pulmonary developmental phase, characterized by a paucity of fully-formed alveoli and a thick alveolar/capillary interface [11,12], making the lungs inefficient for gas exchange leading to respiratory failure [13]. Furthermore, the immature lungs are susceptible to inflammation and oxidative stress injury, contributing to a chronic respiratory disease, referred to as bronchopulmonary dysplasia (BPD) [13,14]. Treatment modalities to address the functional and structural immaturity of the lungs include exogenous surfactant, prenatal corticosteroids, and minimally invasive ventilation. However, these treatments only imperfectly prevent respiratory failure in EPI [15,16]. The rationale for artificial placenta (AP) and womb (AW) technology therefore is to delay pulmonary gas exchange while ensuring continued organ maturation, in particular that of the lung. This fundamental shift in therapy, i.e. to treat EPI as *fetonates* (i.e. fetal neonates) [17], is hypothesized to reduce mortality and morbidity in EPI.

Model development

The concept of using extracorporeal oxygenation to support EPI, was first voiced around the time of the development of primitive oxygenator technology in the early 1950's [18]. In 1958, Westin et al. cannulated seven previable human fetuses in a warmed perfusion-chamber and connected their umbilical vessels to a film oxygenator, which prolonged their life up to 12 h [19]. Appropriately, further experimentation was performed using animal models trialing different pumps, oxygenators, fluid containers, types of vascular access and circuit configurations, which gradually improved oxygen delivery and survival times throughout the years [8]. Due to significant advancements in neonatal care in the 1970's (i.e. prenatal maternal steroid [20], exogenous surfactant administration [21–23], and positive pressure mechanical

* Correspondence to: DUMC Box 3704 – 230, Erwin Road, Durham, NC 27710, USA.
E-mail address: felix.debie@duke.edu (F.R. De Bie).

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ventilation [24,25]) the interest in AW-research temporarily abated. However, recognition of the limitations of these therapies in the 1990's renewed interests in AW-research, focusing efforts on development of oxygenator-technology and closer inclination towards fetal and utero-placental physiology. Omissions of pumps from the circuit, with the development of low resistance oxygenators, stable umbilical vascular access and sterile fluid submersion allowed for closer mimicking of uterine and placental physiology which over time has culminated in increased survival on circuit with less morbidity [8].

Current models

Several research groups have developed different models of AP and AW technology. Although frequently used interchangeably, AW and AP models differ in the extent to which they attempt to recreate fetal and utero-placental physiology. In addition to substituting the core placental functions i.e. gas exchange and nutrition, AW models also keep the fetus insulated in a warm fluid-environment, and use strictly umbilical access. Below, we review five current models whose success and failures have been published within the past five years. Table 1 provides an overview of the specifications of the five models discussed below.

Children's Hospital of Philadelphia (USA): EXTra-uterine environment for neonatal development (EXTEND)

The EXTEND device was developed for extreme premature fetal lambs and is comprised of a pumpless arterio-venous, low resistance oxygenator circuit, connected to the umbilical vasculature, and a closed, sterile fluid environment in which lambs are fully submersed [26].

In their 2017 publication, Flake and colleagues reported up to 28 days survival on circuit of 106–117 day GA lambs, followed by successful ventilation. While on circuit, hemodynamics were stable without refractory hypotension, nor use of vasopressors or corticosteroids, and the oxygen delivery and circuit flows physiologic, without need for external flow regulators. Due to sterility and continuous exchange of synthetic amniotic fluid, bacteremia was not observed, even without prophylactic antimicrobials. Somatic growth and continued organ maturation was reported in the lambs on circuit. Lungs of lambs on EXTEND progressed from the canalicular to the saccular phase of lung development, without corticosteroids or tracheal occlusion and pulmonary function assessed by mechanical ventilation was equivalent to age-matched control lambs [8]. Structural brain and cardiac analysis revealed no injury or developmental abnormalities as compared to age-matched controls [26,27]. Neurodevelopmental maturation was demonstrated by progressive consolidation of sleep/wake cycles in fetal lambs on circuit [27], and while cardiac contractility was temporarily reduced during a one-week accommodation phase on circuit, cardiac function and contractility returned to normal for the remainder of time on circuit [27]. Furthermore, normal mitochondrial function in liver, kidney, skeletal muscle and heart reflected fetal metabolic health [28].

The strength of the EXTEND device is that it closely mimics fetal/placental physiology through the pumpless arterio-venous circuit configuration, umbilical cannulation, and use of a low-resistance oxygenator, and the fetal/maternal fluid environment through the biobag and fluid exchange circuit. However, while four-week survival on circuit, continued organ maturation and subsequent transition to neonatal life were demonstrated in fetal lambs that were equivalent from the perspective of lung development, these lambs were considerably larger (1.0–2.0 kg) than EPI (<1.0 kg) [29,30]. Initially, experiments with weight-equivalent lambs of 85–95 days GA weighing 0.48–0.85 kg resulted in high-cardiac output failure hampered by developmental immaturity [31]. In more recent experiments with extreme premature lambs of 90–95 days GA (weighing 0.7–1.3 kg) the group adopted a more liberal circuit flow titration which resulted in stable hemodynamics and oxygenation on EXTEND, adequate growth, normal cardiac and brain development, and survival up to 21 days on circuit [32]. In terms of vascular cerebral maturation, fetal lambs are discrepant to human development as the ovine germinal matrix maturation occurs earlier and therefore may have been less prone to ICH than their human fetal gestational equivalent [33]. Another limitation of the lamb model is the difference in umbilical vasculature: lambs have two umbilical arteries (UA) and two umbilical veins (UV), whereas humans have two UA's and one UV. In the experiments, one ovine UV was ligated at the time of cannulation to mimic the human umbilical cord.

Tohoku University, Sendai (JAP) and University of Western Australia, Perth (AUS): ex-vivo uterine environment (EVE)

The most recent version of the EVE is similar to the EXTEND in composition, using a pumpless arterio-venous circuit using umbilical canulation, a low-resistance oxygenator and a closed, sterile fluid environment in which lambs are fully submersed [34]. Specifications of each model are detailed in Table 1.

In their most recent publication, Usuda and Kemp and colleagues reported up to 14-day survival on circuit for lambs cannulated on GA 95 with a mean weight of 656 ± 42 g [34]. While fetal systemic circulation was maintained with physiologic parameters and without infection, decreased organ weights and humerus lengths in animals on AW compared to GA-matched controls, suggested reduced growth [34]. Although the lack of growth hormones e.g. IGF-1 through placenta and amniotic fluid, as well as and excessive cortisol levels due to hydrocortisone use for refractory hypotension may explain the stunted growth, the scant knowledge about fetal ovine nutrition may also have contributed to the described growth discrepancy [34]. In earlier studies, the group investigated systemic and organ-specific inflammation, demonstrating increased systemic and pulmonary inflammation, however in the presence of bacteremia [35,36]. Hydrocortisone was added to the EVE-protocol to suppress inflammation, stimulate lung maturation and prevent hypocortisolemic refractory hypotension [36]. In the absence of infection and with corticosteroids administration, the inflammatory reaction was subdued [37,38].

A strength of the EVE model is the successful cannulation and maintenance of fetal lambs that were size-equivalent to the 22–25 week human EPI, despite the fact that in most developmental respects the 95 day lamb is more like an 18 week human fetus. In addition to reduced somatic growth and dependence on hydrocortisone to maintain hemodynamical stability, other adverse outcomes included fetal hydrops and white matter injury observed throughout experiments [37,39].

Hospital Sant Joan de Déu, University of Barcelona (ES)

The artificial womb (AW) model as described by the Gratacos and colleagues also mimics the EXTEND in composition. It also uses a pumpless arterio-venous circuit using umbilical cannulation, a low-resistance oxygenator, and a semi-closed, sterile fluid environment in which lambs are fully submersed [40]. Specifications of the model are further described in Table 1.

In their most recent publication, the team reported a maximum survival of 7 days for lambs delivered at GA 110–115 days in their AW system with an ultrasound-estimated weight of 1681 ± 77 g [40]. Their study design included fetal lambs who were maintained on AW support for 1–3 h, 4–24 h, and 48–168 h [40]. They reported an important learning curve in success of cannulation and transition to AW support, with 25 %, 70 %, and 80 % of lambs surviving in the 1–3 h, 4–24 h, and 48–168 h groups, respectively [40]. The most common causes of death during cannulation or AP support were air emboli in the EC circuit, thrombotic complications, and equipment failure. Similar to all other reported AP/AW systems, anticoagulation was required with unfractionated heparin (Table 1). In their group with the longest survival (48–168 h), the group reported age-appropriate flows, clearing of lactate, as well as restoration of physiologic pH and heart rate.

A limitation of this AW model is the semi-closed nature of the AW

Table 1
Overview of currently described preclinical AP and AW models.

	Artificial Placenta model	**Artificial Womb model**			
	Specifications				
Group	Michigan, USA	Perth, AUS & Sendai, JAP	Philadelphia, USA	Barcelona, ES	Toronto, CAN
Model name	VV preemie ECLS	Ex-Vivo uterine Environment (EVE)	EXTra-uterine Environment for Neonatal Development (EXTEND)	-	-
Year of first publication of the current model, (references using the current model)	2013 [47,48,50,51,55–58,60,64]	2017 [35–39,65,66][§]	2017 [26–28,31,67–74]	2023 [40]	2021 [43,44]
Species, GA at cannulation (range)	Lambs, 130–135	Lambs, 112–115	Lambs, 105 – 117	Lambs, 110–115	Piglets, 91–106
Circuit configuration	VV	VA	VA	VA	VA
Pump, type	Yes, Roller pump	No, N/A	No, N/A	No, N/A	No (11/12), N/A; Yes (1/12), Roller pump
Cannulation, cannula size, abdominal cannula placement	JV/UV (10–12Fr), intraabdominal	UV/2 *UA (10/2 *8Fr), intraabdominal	UV/2 *UA (12/2 *12Fr), Extra-abdominal	UV/2 *UA (10–14Fr) Extra-abdominal	UV/UA (2.1–3.3 mm), Extra-abdominal
Fluid incubation (volume)	No submersion. Fluid-filled endotracheal tube.	Sterile complete submersion (6 L)	Sterile complete submersion (2–4 L)	Semi-closed, complete submersion (10 L)	Sterile complete submersion (NS)
Prophylactic use of antimicrobials	Piperacillin-tazobactam, metronidazole & fluconazole	Meropenem & fluconazole	No	Ceftazidime & meropenem, ultraviolet light sterilization	Piperacillin-tazobactam
Anticoagulation drug (ACT goal)	Heparin (200–250 s)	Heparin (180–220 s)	Heparin (150–180 s)	Heparin (200–250 s)	Heparin (>300 s)
Corticosteroids (Yes/No, type)	Yes, methylprednisolone	Yes, hydrocortisone	No	Yes, hydrocortisone	Yes, hydrocortisone
Other medications	PGE1, erythropoietin, epinephrine (prn), norepinephrine (prn) & dopamine (prn), Diazepam (prn) & buprenorphine (prn).	Lipo-PGE1, Erythropoietin & Milrinone (first 24 h).	PGE1, Erythropoietin, insulin, buprenorphine (prn) & propofol (prn)	PGE1, pRBC	PGE1, papaverine, epinephrine (prn)
Temperature control	Heat-exchanger (circuit) & dry heated waterbed (bottom).	AF warmer, radiant warmer (top) & heating pad (bottom).	AF warmer, air warming (top) & dry heated waterbed (bottom).	AF warmer	Heat-exchanger (circuit) and radiant warmer (top) & heating pad (bottom).
Max. reported survival (reference)	17 days [48]	7 days [37]	28 days [26]	7 days [40]	2 days [44]
Successful transition from AP/AW model to normal ventilation (reference)	Yes [50]	No*	Yes [26]	No*	No*
Long-term survival after weaning from the AP/AW model (duration).	No*	No*	Yes (6 months)	No*	No*
Reported problems and failures leading to mortality (reference)	Cannula-related [47,51,60] Cardiac arrhythmia [60] Pericardial tamponade [60] Cardiac arrest [51]	Equipment failure [36,38] Thrombo-embolism [37] Cannula-related [38]	Equipment failure [71] Cannula-related [71] Umbilical spasm [71] Circuit clotting [71]	Cannula-related [40] Air or Thrombo-embolism [40] Equipment failure [40]	Cannula-related [43,44] Air/thrombo-embolism [43,44] Failure to maintain temperature [43,44] Heart failure [44]
Perceived advantages	▪ Easy access to the fetus.	▪ Upon failure of AW, conventional neonatal care can be provided. ▪ Close mimicking of native physiology.			▪ Similar umbilical cord anatomy to humans ▪ Size-equivalence to human fetuses
Perceived disadvantages	▪ Divergence of fetal physiology (no fluid submersion, supraphysiologic PaO2, pump-driven flow, chronic intubation with tracheal occlusion, sacrifice of the right jugular vein). ▪ Lack of evidence of feasibility and efficacy in lambs equivalent to	▪ Need for a planned EXIT procedure for cannulation on AW. ▪ Relative inaccessibility of the fetus complicating care and parental bonding. ▪ Intraabdominal umbilical cannulation is not	▪ Need for a planned EXIT procedure for cannulation on AW. ▪ Relative inaccessibility of the fetus complicating care and parental bonding.	▪ Need for a planned EXIT procedure for cannulation on AW. ▪ Relative inaccessibility of the fetus complicating care and parental bonding. ▪ Use of corticosteroids	▪ Need for a planned EXIT procedure for cannulation on AW. ▪ Relative inaccessibility of the fetus complicating care and parental bonding.

(*continued on next page*)

Table 1 (*continued*)

	Artificial Placenta model	Artificial Womb model		
Specifications				
	human fetuses at the limit of viability. ■ Use of corticosteroids despite debated long-term adverse effects on the developing brain [41,42].	translatable to human fetuses because of vascular tortuosity. ■ Use of corticosteroids despite debated long-term adverse effects on the developing brain [41,42].	despite debated long-term adverse effects on the developing brain [41,42].	■ Feasibility only demonstrated in a short-term model. ■ Does not fully recapitulate in utero blood flow, heart rate, or blood gas composition. ■ Use of corticosteroids despite debated long-term adverse effects on the developing brain [41,42].

Abbreviations: VV= Veno-venous, AV = Arterio-venous, SA = surface area, PP= polypropylene, PMP= polymethyl pentene, ACT = activated clotting time, NS = not specified, N/A = not applicable, PVC = polyvinyl chloride, prn = '*pro re nata*' (when necessary), PGE1 = prostaglandin E1, pRBC = packed red blood cells (§) = the groups most recent published study describes the use of a modified circuit (single oxygenator) and an adapted cannulation technique (UV intraabdominal, 2 *UA extra-abdominal), (*) = this might be due to predefined study end-points.

environment, requiring prophylactic broad-spectrum antibiotics in the amniotic fluid, which was also continuously filtered and sterilized with ultraviolet light radiation [40]. Despite these sterilization and antimicrobial efforts, two fetal lambs on AP support died secondary to sepsis [40]. An additional limitation of this AW model is the use of hydrocortisone, which may have detrimental effects on the developing fetal brain [41,42]. Finally, the weights of fetal lambs were higher than birth weights of human EPI.

Hospital for Sick Children, University of Toronto (CAN)

Haller and colleagues investigated an AW model in fetal piglets using a pumpless arterio-venous circuit, umbilical cannulation, a low-resistance oxygenator, and a closed, sterile fluid environment in which piglets are fully submersed [43]. Further changes to the model include the incorporation of a centrifugal pump into the AP circuit [44].

Their original report describes an AW system to support fetal piglets born at 101 ± 6 days GA, with an average weight of 651 ± 240 g. A total of 68/127 (53.5 %) piglets were successfully cannulated, with subsequent successful transitioning on circuit in 12/68 (17.6 %) [43]. Those 12 piglets were maintained on AP support for an average duration of 28.5 ± 13.2 h, with a maximum survival of 51 h (3077 min) [43]. Compared to *in utero* measurements obtained prior to cannulation, UV flows were significantly lower and heart rates higher, in the piglets once on AW support [43]. To increase UV flow rates, a centrifugal pump was added to the circuit in a follow-up study in 13 piglets, born at 102 ± 4 days GA with an average weight of 616 ± 139 g [44]. Addition of a pump led to increased UV flows, and increased average survival to 46.4 ± 46.8 h [44]. The most common complications encountered were cannulation failures, accidental decannulation, UV vasospasms, thromboembolic events and, specifically in the pumped AP system; heart failure [43,44].

A major advantage of this AW model is the use of fetal pigs. With two UA's and one UV (as opposed to two UV's in sheep), the umbilical cord in pigs mimics human fetal umbilical cord anatomy more closely. In addition fetal piglets have greater size-equivalence to human EPI (<1.0 kg) [43]. The most important limitation of the Toronto model is the late gestational developmental status (near term), and the short survival on circuit. Although addition of a centrifugal pump increased survival, 4/13 (30.8 %) piglets on circuit died due to heart failure [44]. While the pump allowed for higher UV flows and reduce cardiac afterload, the generated suction draining the fetal heart disturbs the natural cardiac pump-function and contributes to afterload imbalance, ultimately causing cardiac strain [45]. Like other groups, they reported a considerable technical learning curve (cannulation, transition on circuit), and administered corticosteroids which may have detrimental effects on the developing fetal brain [41,42].

University of Michigan (USA): veno-venous premature ECLS

The initial model developed by Mychaliska and colleagues in 2009, was an AW model, a pumpless AV circuit with umbilical vessel cannulation and fetal fluid submersion [46]. However, despite adequate gas exchange, systemic hypotension and progressive cardiac and circulatory failure, limited survival of fetal lambs on circuit to four hours [46], even when a pump was added to overcome the high circuit resistance [47]. Subsequently, the Michigan group left the path of developing an AW model and pursued an AP model instead, which consists of a pump-assisted veno-venous circuit with cannulation of the UV and the internal jugular vein [47]. As a surrogate for fluid submersion, fetal lambs were intubated, and endotracheal tubes filled with fluid and capped.

Throughout the years, the reported average survival in this model reached almost two weeks, albeit in older, more mature fetal lambs (GA >118) [48]. In these lambs with a pulmonary development equivalent of 28 weeks GA in humans [49], the group demonstrated continued lung maturation during the 7–10 days on circuit and comparable lung function to GA-matched controls upon ventilation [50,51]. It should be noted that by capping the fluid-filled endotracheal tube, tracheal occlusion was applied which similarly to corticosteroids administered throughout the entire run, independently promote lung maturation [52–54], hence preventing attribution of the continued development to the "artificial placenta" alone [8]. In 48-h experiments, regional cerebral oxygenation, blood flow and autoregulation was not dysregulated [55]. In one-week experiments, no white matter injury or intracranial hemorrhage was found and cerebral maturation was normal [56]. Despite preserved mucosal architecture, epithelial injury was observed in the small bowel, presumably due to the absence of amniotic fluid ingestion, vasopressor-induced splanchnic hypoperfusion, or a combination [57].

One of the proposed strengths of the model is that it was demonstrated to support the hemodynamics of near-term lambs upon failure of a postnatal trial of mechanical ventilation [58]. However, this strategy would likely fail in more premature lambs with lung development equivalent to human EPI, as it does not delay initial lung ventilation and therefore would not permit continued lung maturation. Recently, the group reported on the use of iNO (added to sweep gas) and nitric

oxide/argatroban-coated tubing, obviating the need for systemic anticoagulation in one-week experiments, which greatly reduces the risk of intracranial hemorrhage on circuit [59]. Limitations of the model are the lack of studies in extreme premature lambs, no reports of cardiac function despite the need for a pump, vasopressors, and hydrocortisone to maintain stable hemodynamics, as well as the need for supra-physiological partial oxygen pressures to ensure adequate oxygenation and reports of inconsistent ductal patency despite infusion of prostaglandin E1 [50,55,60]. Importantly, cardiac functional data has not been reported by the group.

Perinatal life support consortium

The Perinatal Life Support (PLS) consortium, is a collaboration between the universities of Eindhoven, Aachen, and Politecnico Milan, funded by a European Horizon 2020 grant. While the group states on their website that they aim to develop an AW model, they have not published data in animal models. In two studies, they have focused on understanding and envisioning the processes of clinical delivery onto an AW system and umbilical cannulation, using dry simulation exercises and interviews including obstetricians and neonatologists [61,62]. Discussion points regarding the transfer process were the type and use of anesthesia and uterine relaxants, maternal positioning, maternal-fetal monitoring and a rescue protocol [61]. For umbilical cannulation the discussion points were cannulation technique, cannula fixation, anticoagulation, and management of vasospasm [62].

Ethics

The publication by the Philadelphia group reporting four weeks survival on EXTEND, sparked widespread public media attention [17,63]. Commentary in academic literature soon followed, discussing the ethical ramifications of AW technology. The large majority of those papers focused on the speculative futuristic AW technologies that would ultimately culminate in *complete ectogenesis* (the entire genesis of a human being outside of a human body), rather than on EXTEND [63]. Despite this mismatch between the ethical discussion about *complete ectogenesis* and the nature of the imminently available EXTEND technology, both are frequently conflated. We have argued that this conflation may impede clinical implementation and wider social acceptance of a therapeutic strategy for EPI that well may offer them the prospect of better outcomes. This conflation of ethical concerns diverts attention away from these infants and the important ethical work that needs to be done to understand what would be in their best interest and how to partner with the parents around issues of informed consent and shared decision-making [63]. In an effort to avoid conflation and help organize discussion on AWT ethics we developed a comprehensive framework, organizing the broad range of ethical concerns and considerations regarding AWT. A scoping review of the literature identified four groups of arguments: 1. potential benefits and harms, 2. decision-making authority of parents, 3. legal status and protections, and 4. fairness of access. Each of these groups were then discussed per *domain* as delineated by human prenatal development, based on stages of anatomic and physiologic development in combination with the currently available technological support [17]. In parallel, each of these *domains* can be viewed along a continuum from likely to unlikely (or frankly impossible) clinical applications. The ethical considerations differ markedly depending on when AW technology is used, and different ethical weight should be placed when discussing remote possibilities of far-fetched applications compared with the current intended and probable future applications [63]. Regarding the current intended uses of AW technology, death vs disability, barriers to research participation and need for C-section to deliver onto AW have been identified as salient ethical considerations.

Conclusion

Artificial womb technology to temporarily support EPI allowing for continued maturation in a womb-like environment, is closer to clinical translation than ever before. During the last 70 years different configurations and models have been trialed, which culminated in the 2017 study by the Philadelphia group reporting four week-survival in lambs using the EXTEND device, while demonstrating continued organ maturation. Several other groups have since tried to reproduce the model and the outcomes, however, have not been able to attain similar outcomes yet, highlighting the challenges of the endeavor. Lamb and piglet models have different advantages, and therefore can be used complimentarily to study different aspects in developing AW technology. Published ethical considerations regarding AW technology tend to speculate on futuristic complete ectogenesis, risking conflating it with the preclinical devices developed for support of EPI.

CRediT authorship contribution statement

Ryan M Antiel: Writing – review & editing, Conceptualization. **Chase C Binion:** Writing – review & editing, Data curation. **Felix Rafael De Bie:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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