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Ethics Considerations Regarding Artificial Womb Technology for the Fetonate

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ABSTRACT

Since the early 1980's, with the clinical advent of in vitro fertilization resulting in so-called "test tube babies," a wide array of ethical considerations and concerns regarding artificial womb technology (AWT) have been described. Recent breakthroughs in the development of extracorporeal neonatal life support by means of AWT have reinitiated ethical interest about this topic with a sense of urgency. Most of the recent ethical literature on the topic, however, pertains not to the more imminent scenario of a physiologically improved method of neonatal care through AWT, but instead to the remote scenario of "complete ectogenesis" that imagines human gestation occurring entirely outside of the womb. This scoping review of the ethical literature on AWT spans from more abstract concerns about complete ectogenesis to more immediate concerns about the soon-to-be-expected clinical life support of what we term the fetal neonate or fetonate. Within an organizing framework of different stages of human gestational development, from conception to the viable premature infant, we discuss both already identified and newly emerging ethical considerations and concerns regarding AWT and the care of the fetonate.

KEYWORDS

Artificial womb technology; artificial placenta; bioethics

INTRODUCTION

In 2017, using the *EXTra-uterine Environment of Neonatal Development* (EXTEND) artificial womb technology (AWT) system, our group reported survival of fetal lambs for up to four weeks, maintaining stable fetal hemodynamics, oxygenation, normal somatic growth, and continued organ maturation (Partridge et al. 2017). Although components of the AWT system had been developed incrementally over the last 60 years, our study represented a major technical advance toward ongoing support of fetal physiology, and with that, the possibility of a novel therapeutic means of providing life support to infants born so prematurely that without this mode of therapy, death or substantial disability are the most likely outcomes (Antiel and Flake 2018; De Bie et al. 2021).

The report sparked widespread public interest and media speculation about the imminent arrival of so-called human "ectogenesis" (literally, genesis outside of the body) and the ensuing consequences and ethical concerns (Kingma and Finn 2020). Commentary in the academic literature soon followed, urging the field to identify and discuss relevant ethical considerations in anticipation of clinical translation and implementation of AWT (Mercurio 2018; Sahoo and Gulla 2019). Indeed, since 2017 more than 30 scholarly publications have addressed ethical ramifications of AWT. Interestingly—and importantly—most of these papers have focused on the very extreme and currently technically impossible use of AWT for "complete ectogenesis" (that is, the entire process from conception to birth occurring outside of a human body).

In this paper, we sought to identify the broad range of ethical concerns and considerations regarding AWT. To do so, we conducted a scoping review. The methodology and results of this review are detailed in Supplement 1, while Supplement 2 lists all the identified ethical considerations with corresponding references. Our goal then was to organize these considerations

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into a comprehensive framework to organize further discussion, and not to analyze each identified issue or argument in depth. In what follows, after first providing some background information, we start by describing a mental map that we used to organize our effort, with four stages of human conception and development, from the gamete and embryo, through the fetal stages, all the way to the care provided to the still-very-much-developing premature neonate, and the corresponding technological support used at each stage. We performed a scoping review for each developmental stage, focusing on cataloging identified ethical concerns and considerations, which are heavily concentrated at the two ends of the developmental spectrum (namely regarding the ethics of artificial zygote fertilization and implantation, as well as embryonal culture, at one end, and on the other the ethics of care of prematurely born neonates). After presenting our findings for these ends of the developmental spectrum, we then extend into the realm of imminently feasible AWT, examining which of these ethical concerns or considerations can and should be extrapolated into this emerging realm of clinical practice, and seeking to identify novel concerns and considerations.

BACKGROUND AND PATHOPHYSIOLOGIC RATIONALE

Extreme prematurity, defined as birth earlier than 28 weeks estimated gestational age (EGA) affects 0.4% of infants globally according to the World Health Organization (Chawanpaiboon et al. 2019). Despite the relatively low incidence, extreme prematurity remains a leading cause of infant morbidity and mortality even in developed countries (Matthews, Macdorman, and Thoma 2015; Patel et al. 2015). In the United States in 2012, survival rates were 9% at 22 weeks EGA, increasing to 81% at 25 and 94% at 28 weeks (Stoll et al. 2015). Continued advances in neonatal intensive care (such as minimally invasive ventilation, exogenous surfactant, and prenatal corticosteroids) have improved survival of extremely premature infants. Yet those who survive suffer from increased severe, chronic morbidity due to structural and functional organ immaturity and iatrogenic injury (WHO 2012).

At 22–24 weeks EGA, pulmonary immaturity prevents adequate gas exchange at birth, resulting in respiratory failure that threatens life independent from placental support (Bancalari and Jain 2019; Coalson 2003; Costeloe et al. 2000). Gas ventilation in premature lungs also leads to an arrest in lung development, potentially leaving survivors with a life-long debilitating respiratory condition called bronchopulmonary dysplasia (Baraldi and Filippone 2007; Carraro et al. 2013; Jobe 1999). Keeping the lungs fluid-filled in extremely premature infants would hence allow continued pulmonary maturation and reduce mortality and morbidity in this population (De Bie et al. 2021; Te Pas 2017).

Current AWT aims to achieve exactly that by providing a womb-like incubation, ensuring oxygenation via an oxygenator connected to the fetal umbilical vessels in addition to providing nutrition and a warm, insulated, fluid-filled environment supporting fetal hemodynamic physiology and continued maturation. In doing so, AWT fundamentally alters the approach to the medical management of extremely premature infants, considering them as neonates kept in a fetal physiological state, that is, as fetal neonates or fetonates.

FOUR DOMAINS OF PRENATAL DEVELOPMENT AND MEDICAL SUPPORT

Throughout this manuscript we have adopted four distinct domains delineated by human prenatal development, based on stages of anatomic and physiologic development in combination with the currently available technological support (Figure 1).

Domain I: Fertilization and Implantation (0–2 Weeks Conceptional Age)

Fertilization of a human egg outside of the maternal body and subsequent successful implantation was first performed in 1978 in the United Kingdom, resulting in the birth of the famous "test tube baby" Louise Brown (Steptoe and Edwards 1978). In vitro fertilization (IVF) since then has become the cornerstone of assisted reproductive technologies, which in the United States in 2018 was involved in 1.9% of births according to data available from the Centers for Disease Control and Prevention (CDC 2018). Upon fertilization, the zygote is typically cultured for three to five days before it is implanted in the womb to become an embryo. In an experimental setting however, continued research efforts have led to optimization of culture conditions allowing human embryo culture until 14 days conceptional age (CA)(Deglincerti et al. 2016; Shahbazi et al. 2016). In most jurisdictions, legal restrictions prohibit the culture of human embryos beyond 14 days of development (Pera 2017). Although the authors of this experimental work invoke these legal reasons for not

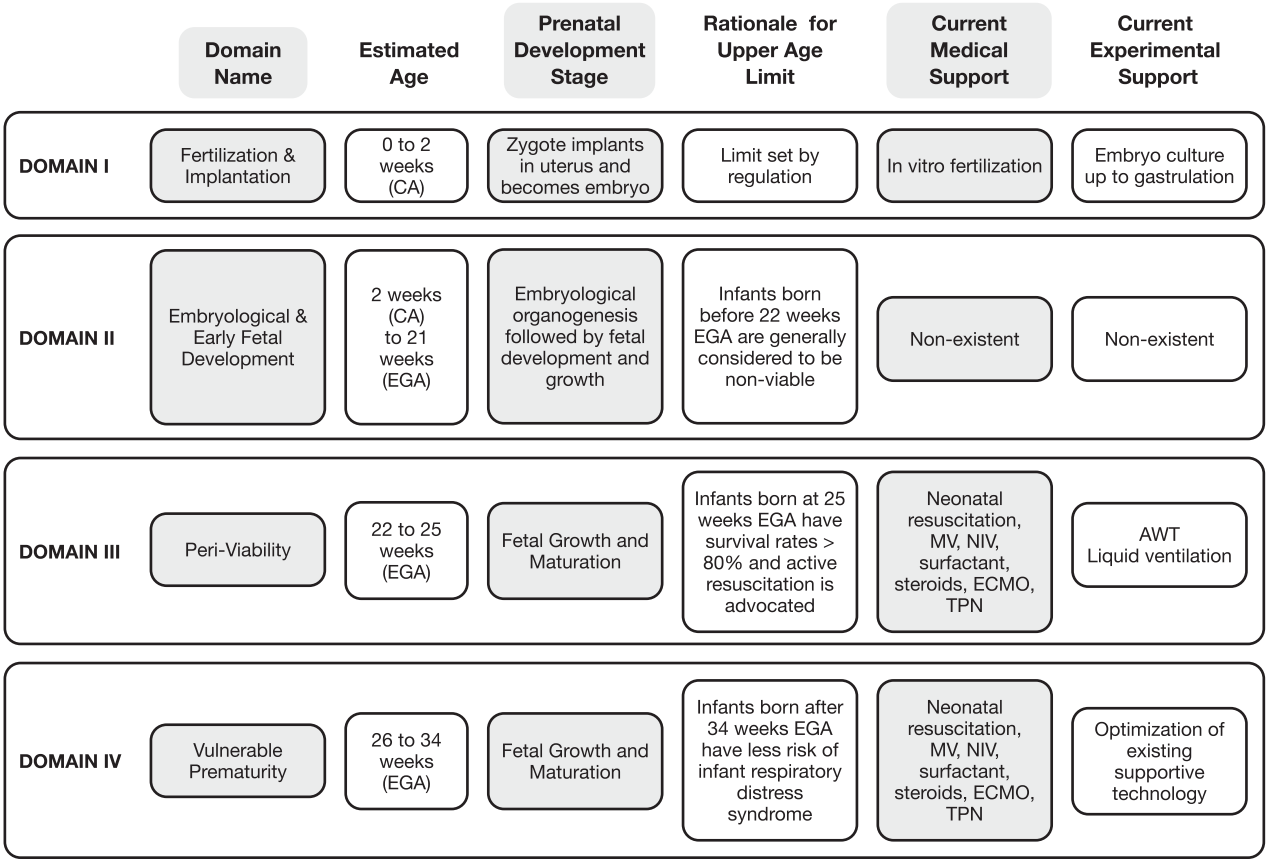

Figure 1. Four domains of prenatal development and corresponding current medical support and experimental support.
Legend: EGA, estimated gestational age; CA, conceptional age; MV, mechanical ventilation; NIV, Noninvasive ventilation; ECMO, Extracorporeal membrane oxygenation; TPN, Total Parenteral Nutrition; AWT, artificial womb technology.

going beyond the two-week hallmark, their work and findings have been used to advocate for an extension of these legal and moral limitations (Morris 2017). In 2021, the International Society for Stem Cell Research (ISSCR) updated their guidelines, recommending that studies proposing to grow human embryos beyond the two-week mark be considered on a case-by-case basis, and be subjected to several phases of review to determine at what point the experiments must be stopped (ISCCR 2021; Subbaraman 2021).

Domain II: Embryological and Early Fetal Development (2 Weeks CA-21 Weeks EGA)

After two weeks CA, embryological development is defined by organogenesis and the formation of structures indispensable for life. At 11 weeks EGA, the embryo becomes a fetus and development is primarily characterized by growth and maturation of organ systems, which will continue until birth. The start of 22 weeks EGA is generally considered the lowest threshold of viability, with little hope for survival even if aggressive neonatal resuscitation is provided at the time of birth; not until the end of EGA of 22 weeks does the prospect of survival start to rise (Di Stefano et al. 2021; Rysavy et al. 2015; Stoll et al. 2015). To our knowledge, no clinical or experimental extra-uterine life support technologies currently aim at intervention within domain II. Conceivably, however, if AWT is proven efficacious at EGA >22 weeks, adaptations of the AWT may be used in the late stages of domain II.

Domain III: Peri-Viability (22–25 Weeks EGA)

Since the survival rate of infants born prior to 22 weeks EGA is extremely low, most professional and government guidelines in highly developed countries advocate for palliative comfort care at this stage. Over the ensuing three weeks (EGA 22–25 weeks),

recommendations incrementally change due to increasing survival rates, with most guidelines recommending active care for infants born at 25 weeks EGA (Ecker et al. 2016; Guillén et al. 2015; Raju et al. 2014; Rysavy et al. 2015). Despite increasing survival rates due to aggressive resuscitation and improved clinical neonatal care, infants born in this gray zone of viability often suffer severe somatic morbidity, long-term neurodevelopmental delay, and behavioral disability (Anderson et al. 2016; Glass et al. 2015; Stoll et al. 2010; Wood et al. 2000).

Current clinically available technological support in domain III mainly focuses on cardio-respiratory resuscitation followed by minimally invasive mechanical ventilation when possible, escalating to tracheal intubation and mechanical ventilation when necessary. Experimental approaches such as liquid ventilation and artificial womb technology aim to delay the first gas exchange in premature lungs at 22–25 weeks EGA, intending to ensure continued pulmonary development and to improve overall survival and clinical outcomes (Eichenwald et al. 2020; Te Pas 2017).

Domain IV: Vulnerable Prematurity (26–34 Weeks EGA)

Infants born prematurely before 35 weeks estimated gestational age are at substantially increased risk of infant respiratory distress syndrome (IRDS), also known as hyaline membrane disease. Fifty years ago, IRDS was essentially uniformly fatal. Since then, with advances of neonatal mechanical ventilation technology beginning in the 1970s and the advent of surfactant replacement therapy in the 1980s, expectations of survival for infants born at earlier EGA rose, such that currently an infant born in the United States at an EGA of 26 weeks has an 85% chance of surviving (Stoll et al. 2015).

Accordingly, since mortality and morbidity markedly improve beyond 25 weeks EGA, active supportive care is now generally advocated and offered in highly developed settings (Guillén et al. 2015). Current clinical technology to support the domain IV viable premature infant is similar to what is available for domain III peri-viable infants, with research mainly focused on improving existing treatment modalities.

At the same time, major catastrophic medical complications—such as severe intraventricular hemorrhages or necrotizing enterocolitis, in addition to destructive lung disease—still arise with sobering frequency for infants in domain IV. As we will detail in the next section, many of the ethical considerations guiding how to respond to such situations, including de-escalation or discontinuation of intensive interventions, have been addressed.

ETHICAL CONSIDERATIONS OF THE FOUR DOMAINS

In summary, established and effective technological support exists for domains I and IV, is imperfect but clinically widespread for domain III, and is currently non-existent for domain II.

Consensus has generally been reached related to ethical considerations raised for domains I and IV, which is reflected in the existence of guidelines from relevant institutes and even legislation (Ama 2014; Aziz et al. 2020). The same is largely true regarding the current technology for domain III, although clinical ethical dilemmas are encountered far more often due to shortcomings of current clinical standard of practice (Guillén et al. 2015; Lantos 2018; Pignotti and Donzelli 2008). The ethical considerations and concerns thus far raised for domain II have not yet been synthesized or addressed in guidelines.

We will describe and discuss the ethical considerations for each domain under four general headings.

1. "Potential Benefits and Harms" includes considerations of the principles of beneficence and non-maleficence, the "best-interest standard" that guides much of pediatric ethics, and the consequentialist notion of weighing the pros and cons of medical interventions. This heading is then further subdivided, focusing on primary stakeholders, including embryos, fetuses, fetonates, prematurely born infants, parents, and society.
2. "Decision-Making Authority of Parents" considers the degree to which parents hold decision-making authority on behalf of the embryo, fetus, fetonate, or prematurely born infant, regarding the use of medical technology and interventions, and what limits, if any, constrain this authority.
3. "Legal Status and Protections" specifically refers to the legal standing and protections afforded to the embryo, fetus, fetonate, or prematurely born child.
4. "Fairness of Access" addresses concerns about inequitable distribution of benefits bestowed by the technology or intervention due to disparities of access.

ETHICAL CONSIDERATIONS OF DOMAIN IV

We start with a consideration of the ethical issues identified in Domain IV (vulnerable prematurity, 26–34 weeks EGA) because AWT is more likely to share similar ethical concerns with this domain than with domain I.

Potential Benefits and Harms—Prematurely Born Infant

Benefits attributed to active neonatal resuscitation are improved survival and better functional outcome in survivors. Nevertheless, vigorous resuscitation at the time of birth for an infant *in extremis* is sometimes called into question, as these infants may survive but live with severe comorbidities that greatly diminish their quality of life. In such scenarios, ethicists have pondered whether these infants should have been allowed to die at the time of birth or shortly thereafter rather than being kept alive via resuscitation and ongoing invasive interventions (Lantos 2007; Wilkinson 2011). In current clinical care, if an infant is gravely ill at the time of birth or has already suffered various forms of grievous *in utero* injuries, the parents, in conjunction with the medical team, can place limitations on the extent of resuscitation.

Potential Benefits and Harms—Parents

The parents of most domain IV infants who undergo resuscitation benefit when their children survive and experience improved functional outcomes. Conversely, parents experience psychological distress and financial difficulties if the surviving child is severely disabled. The most common harms (more aptly termed burdens) experienced by pregnant mothers who are progressing toward a premature birth are the interventions they undergo (such as tocolysis or receipt of prenatal steroids or antibiotics) to improve neonatal outcomes. These interventions are always provided with the mother's informed consent.

Decision-Making Authority of Parents

Both ethically and legally, parents have considerable but circumscribed authority regarding the medical care their children will receive, exercised by either providing or refusing to provide permission for specific interventions. The boundaries of this authority are clearer regarding what interventions can be refused by notions of what would constitute medical neglect and are less clear regarding requests for interventions deemed by medical judgment to be "futile" (Feudtner and Nathanson 2018; Lantos 2018).

Legal Status and Protections of Prematurely Born Infants

The legal status of prematurely born infants is clear and not in question: these infants have full rights and protection under the law as stated in the "Born-alive" act (US Congress 2002). Special protections were first promulgated in early 1984 as the federal "Baby Doe" regulations (which were struck down two years later by the Supreme Court), and in 1985 they were also written as an amendment to the federal Child Abuse Prevention and Treatment Act, focusing on "instances of withholding of medically indicated treatment from disabled infants with life-threatening conditions."(Doj 1984, 1985; Kopelman 1988).

Fairness of Access

In the context of the United States (and in many other highly developed industrialized nations), access to NICU care is far less limited than is access to other forms of healthcare, such as NICU follow-up care (Bockli et al. 2014; Edwards and Horbar 2018). Within the NICU setting, disparities in the structure, process, and outcomes of care are of persistent concern (Sigurdson et al. 2019).

ETHICAL CONSIDERATIONS OF DOMAIN I

Potential Benefits and Harms—Embryos

The key benefit from successful in utero transfer of an in-vitro embryo, is being granted the chance of existing, of life. The most cited harm of IVF is the storage, discarding and research use of un-implanted embryos. Moral and legal weight of this harm of denying further development to initiated biological life hinges on ascribing personhood and its concomitant protections to the embryo. Other embryonal harms caused by IVF are increased risk of ectopic pregnancy, birth defects, prematurity, low birth weight, and childhood cancer (Cdc 2016; Spector et al. 2019; Zhao et al. 2020).

Potential Benefits and Harms—Parents

The most prominent benefit attributed to IVF is increasing couples' reproductive autonomy and fulfilling often very strong desires to have a child by overcoming infertility. IVF however carries certain physical risks to the mother (e.g., ovarian

hyperstimulation syndrome and complications related to egg-retrieval including bleeding, infection, organ damage) and remains a high-cost, low-success procedure which can be psychologically and financially draining. In case of transfer of several zygotes, multiple gestation may occur, posing its own set of potential harms to both the mother and infants. Similar to treatments in Domain IV, the increased incidence of disability following IVF can pose psychosocial burden on parents and family.

Potential Benefits and Harms—Society

IVF is perceived by some as interfering with nature or playing God, causing societal perception and acceptance of IVF to vary widely among different cultures and communities, often related to prevailing religious beliefs. A potential harm related to IVF is that when falsely perceived as a sure-fire procedure, IVF can give the erroneous belief that delaying pregnancy has no consequences. Specific ethical questions arise when IVF is used to conceive at advanced maternal age and with specific practices associated with IVF (e.g., preimplantation diagnostics, gamete donation, surrogacy and pregnancy reduction in case of multiple gestation) (Harrison et al. 2017).

Decision-Making Authority of Parents

We focus here only on potential disagreements between parents. Currently, contracts are signed between the parents before creating an embryo via IVF, clearly stating what should happen in case of parental disagreement and with the supernumerary frozen embryos. Some scholars have suggested that in the case of disagreement between parents, a "status-quo approach" be adopted in which change needs a stronger justification than allowing things to remain as they are. In the context of stored embryos, this means that frozen embryos could not be destroyed if the two parties disagreed over their fate.

Legal Status of Embryos

Creation of human embryos in laboratories has resulted in ontological, moral, and administrative ambiguity with important differences between countries and states, based on divergent definitions of life, person- and patient-hood which entail dignity, custody and legal protection (Jasanoff and Metzler 2020).

Fairness of Access

Despite the fact that IVF is widely available in the developed world, the costs of the procedure remain high (average cost of $25,000 or more in the US), limiting access to the technology to those who can pay for it or whose insurance covers it, generating a fundamental socio-economically driven inequality (Insogna and Ginsburg 2018; Katz et al. 2011). Furthermore, in combination with the low procedure success rate, the limited resource of donated oocytes generates problems of fair distribution or resource allocation.

ETHICAL CONSIDERATIONS OF DOMAIN III

In this section, we start to examine ethical considerations regarding AWT directly, following the same approach we have established for currently used technology supports. When balancing potential benefits and harms of AWT, we distinguish between the imminently envisioned use of AWT for *medical* reasons (e.g. prematurity or pathologic pregnancy) versus the more distant use for *non-medical* reasons (such as avoiding pregnancy). The comparator in both scenarios is very different: "high risk of poor outcomes with currently available care" in the first, versus "physiologic, healthy pregnancy" in the second.

Potential Benefits and Harms—Fetonate

The primary population for whom AWT would generate benefit are extreme prematurity infants born at EGA 22–25 weeks, although the use of AWT could potentially also be envisioned to protect fetuses from pathological gestational states such as intra-uterine growth restriction, chorioamnionitis, or oligo- and anhydramnios, among others. Reducing morbidity and mortality in these patient populations is the obvious envisioned benefit of AWT. The technology could also be used to improve the feasibility and safety of targeted, repeated prenatal therapy (fetal surgery, pharmaco-, gene or stem cell therapy).

The primary harm of AWT at this stage would be the risk of death or severe disability caused by AWT or its complications. Severe negative effects secondary to AWT could include short- and long-term physiological effects, e.g., intracranial hemorrhage due to heparinization of the fetonate on AWT. In addition, potential psychological and behavioral effects secondary to the lack of physical maternal-fetal bonding should be thoroughly examined (Landau 2007). In cases of *medical* AWT, these potential harms ought to

be compared to the current NICU standard care and its inherent physical risks as well as hampered physical maternal-fetal bonding. As with Louise Brown (the first child born resulting from IVF), long-term effects are hard to investigate in experimental animal models, hence will remain unanswered until well after the first human research subjects reach an age allowing for these assessments.

Potential Benefits and Harms—Parents

At EGA 22–25 weeks, the potential benefits of AWT to the mother are markedly less thoroughly explored in the literature. Besides hope for increased survival and reduced morbidity of their fetonate, benefits for parents could occur in scenarios where the pregnancy endangers maternal health (e.g., pulmonary hypertension or cardiac failure), or when corrective procedures (medicine, gene or stem cell therapy, surgery) could be performed without risk of maternal morbidity. AWT could also benefit parents by sparing them having to witness their premature infant supported on a ventilator with intravenous lines, instead allowing them to observe their fetonate in a quiet, protected, and relatively normal developmental environment (Partridge et al. 2017).

A maternal burden of AWT is that fetal extraction via C-section (as is currently described in all successful AWT models) entails a higher perioperative risk for maternal complications (such as bleeding, complicated extraction, higher risk of uterine rupture in future pregnancies) at earlier stages of pregnancy. Of note, C-section is currently often used as a method of delivery for extreme premature infants in distress, and AWT following vaginal delivery may become possible in the future.

Because premature infants born between 22 and 25 weeks gestation already experience high mortality and long-term morbidity in the form of pulmonary and neurodevelopmental complications, the uncertainty of AWT may exacerbate the emotional and psychological burden of unpredictable fetal morbidity on the parents.

The lack of physical maternal-fetal bonding during the fetonate's course of treatment with AWT may also have a psychological, emotional, and behavioral effect on the mother. "New baby motherhood," often associated with self-fulfillment and meaning, may be diminished by this experience, emphasizing the importance of investigating and optimizing the maternal experience of AWT.

Potential Benefits and Harms—Society

AWT holds the possibility of potential economic benefit in the form of cost savings due to reduced comorbidities of extreme premature infants placed on AWT (Kendal 2015). Alternatively, AWT might escalate costs by leading to longer NICU stays for infants who would not have survived previously (Wilkinson and Di Stefano 2020). Whether AWT is cost-effective will require formal analyses. A clear benefit of pursuing AWT research is that society is acquiring improved understanding of fetal physiology and development, contributing to the existing scientific body of knowledge.

While some have suggested that AWT may alter relationships between parents, and between parents and their fetonate, we believe that these possibilities are unlikely to happen to any significant degree in Domain III (but would happen in more extreme usage of AWT in Domain II). Similar concerns were expressed initially about IVF in Domain I (Cynthia B. Cohen 1996), but as IVF has become standard of care, these possibilities seem not to have occurred (Golombok, Maccallum, and Goodman 2001; Mcmahon et al. 1997).

Decision-Making Authority of Parents

Without a doubt, if proven efficacious, AWT will fundamentally change obstetric and neonatological decision-making paradigms in neonatal resuscitation. A multidisciplinary approach involving obstetricians, neonatologists, and surgeons to guide clinical decision making will be needed. Although the decision whether to undergo C-section in order to transfer the fetus to AWT falls under maternal autonomy, questions about the extent of maternal autonomy arise in obstetrics when the interest of the mother and the fetus seem to present tradeoffs. For many authors however, the mother's decision to undergo fetal extraction via C-section should remain to be considered "supererogatory" since it entails additional risks for the mother (Antiel and Flake 2018; Overall 2015; Wilkinson and Di Stefano 2020).

Once the fetonateis being supported by AWT, decision making would become a shared parental responsibility and, for major care decisions, both parents would need to agree. If complications such as sepsis or intracranial hemorrhage were to develop while on AWT, and the possibility of ceasing life-sustaining interventions arose, the decision-making process between parents and NICU providers would be the same as for other forms of NICU care.

Legal Status of the Fetonate

We think the best way to describe the person who would receive current AWT is as a "fetal neonate" or fetonate. Neonatal pertains to the fact that the subject is removed from the womb, hence is newly (*neo*) born (*natus*). At the same time, the core objective of the AWT is to conserve fetal physiology, justifying the use of the modifying term fetal. The primary term here is *natus*: the birth of the fetonate from the uterus, even if immediately followed by AWT, endows the fetonate with full rights and protections (Colgrove 2019).

Doubtless, debates regarding terminology and status will continue. One set of authors state that the development of AWT may catalyze the bestowal of "patient" status to the fetus (Segers, Pennings, and Mertes 2020). Another author notes that the patient on the ventilator is described as an infant, while the patient supported by AWT has been described as a fetus. In the hypothetical scenario where one twin is placed on a ventilator while the other goes into a biobag, this difference in nomenclature could "carry with it assumptions about moral status, inherent rights, and obligations" (Mercurio 2018).

Fairness of Access

The existence of AWT may expose or exacerbate inequalities in access to care. With the need for continuous intensive bedside clinical monitoring and treatment, like all forms of NICU care, AWT is anticipated to be expensive. Cost may therefore become a barrier to access, and multiple authors have pointed to this cost barrier as potentially increasing social inequity (Abecassis 2016; Cavaliere 2020; Romanis 2020). Initially, AWT is also expected to be a limited resource, raising questions about who should make allocation decisions and how.

ETHICAL CONSIDERATIONS OF DOMAIN II

We now will address concerns arising from the prospect that AWT might be used in fetuses born prior to 22 weeks EGA, before the current limit of viability. At the outset, we note that the technological support of fetonates less than 22 weeks would require overcoming significant developmental and technical challenges. Given the immaturity of their autoregulatory capacity, younger fetuses rely to a greater extent on placental and maternal regulation, exponentially complicating AWT support. Not only would the system need to be remarkably miniaturized, support would be required for a longer period of time (with attendant increased complications) and would have to adapt to a rapidly growing fetonate over time. Extension of AWT to earlier gestational ages would therefore most likely increase the risk and reduce the potential benefits of AWT (Hornick et al. 2019; Usuda et al. 2019). If AWT were to be used in late domain II, the ethical considerations would likely be very similar to domain III. One practical consequence of this evolution would be the altering of the limit of viability, which is a definition primarily based on the probability of survival. Because a "limit of viability" concept is used in legislation regarding abortion in many jurisdictions, numerous scholars have debated potential legal consequences of AWT use in late domain II (Abecassis 2016; Alghrani 2009; Cohen 2017).

We believe that completely bridging domain II—which is to say, to successfully transition from diffusion-oxygenation in embryo culture to umbilical vascular oxygenation for fetuses—is nothing more than a technically and developmentally naïve, yet sensationally speculative, pipe dream. Nevertheless, the concept of "complete ectogenesis" and associated concerns dominate the bioethical literature on artificial wombs. For the sake of completeness, we address the most discussed (reasonable) ethical questions raised in the literature specific to domain II, which quite often regard complete ectogenesis (which is to say, from Domain I forward to full gestation).

Potential Benefits and Harms—Embryo, Fetus, and Fetonate

Earlier application of AWT would extend the window of opportunity for earlier and more impactful therapeutic interventions in congenital anomalies and earlier rescue from pathologic gestational states, which could improve outcomes. Furthermore, complete ectogenesis has been hailed as an alternative to abortion or certain IVF practices, as radically earlier-in-gestation AWT could be used as an alternative method to end a pregnancy or prevent an embryo from existing only in a frozen condition. These practices would, in turn, generate a whole set of different ethical and public policy questions.

Potential Benefits and Harms—Mother

Complete ectogenesis would surmount many forms of infertility, hence enabling biological parentage while avoiding the use of surrogacy. In the feminist literature much of the discussion has centered on the potential of this futuristic technology to increase gender equality physically and socially. In the

workplace, complete ectogenesis would enable biological parenthood without leaves of absence due to pregnancy-related health conditions or childbirth per se.

Yet despite being hailed by some authors as a "liberation from the biological yoke of pregnancy" (Firestone 2003), feminist literature has also outlined potential harms of complete ectogenesis. A concern is that it could lead to the devaluation or even pathologizing of pregnancy, and may diminish women's experience of deriving meaning, empowerment, and self-fulfillment from this unique aspect of female biology. In the unlikely event that complete ectogenesis would become equal to natural pregnancy in terms of outcomes, AWT could become a tool of coercion guided by the idea that women regarded as "substandard gestators" could be pressured to use AWT for the safety of the fetus, hence violating maternal autonomy. Conceivably, the choice for gestation through ectogenesis (or, alternatively, through a womb-bearing pregnancy) might eventually be stigmatized.

Potential Benefits and Harms—Society

Some authors have raised concerns related to the impact of complete ectogenesis technology on "commodification of pregnancy, babies and motherhood" (Rosen 2003), and the "disconnect between sexuality and procreation" (Abecassis 2016). Furthermore, potentially devoting government funding to the development of complete ectogenesis in a context of restricted resources will raise additional considerations.

Fairness of Access

If complete ectogenesis ever becomes possible, the conjunction of high cost and low availability will undoubtedly result in disparities in access and use and questions of which parents should have priority in the use of such technology.

Legal Status

AWT in domain II would still result in fetonates, and as suggested above, these persons would have full legal rights and protections. Complete ectogenesis, with all embryologic and fetal development occurring outside of a womb, would pose novel questions in these regards.

CONCLUSION

Following recent breakthroughs in the development of neonatal life support by means of AWT, ethical interest has spiked, generating over 30 scholarly publications over the past three years.

As currently envisioned, AWT would enable "partial ectogenesis," aiming to provide care for extremely premature infants that is much more in line with their physiology, treating them as fetal neonates. This use is nearing clinical translation. Despite remarkably difficult technical barriers, and hence remoteness of becoming reality, the concept of "complete ectogenesis" and associated concerns dominate the bioethical literature on artificial wombs. A framework of different stages of human gestational development helps to articulate ethical considerations and concerns with respect to different potential uses of AWT.

AUTHORS' CONTRIBUTIONS

All authors participated in the design of the study and interpretation of the data; FRDB and SKB performed the data analysis; FRDB, SDK and CF drafted the manuscript; all authors revised the manuscript for key intellectual content. All authors read and approved the final manuscript.

DISCLOSURE STATEMENT

A.W.F. and E.A.P. are coauthors of a patent "*Extracorporeal life support system and methods of use thereof*" (Patent no. WO2014145494 A1). A.W.F. is coauthor on multiple additional patents and pending patent applications related to AWT . He is also a paid medical consultant for Vitara Biomedical Corporation. The other authors report no conflict of interest.

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