Navigating the Ethical Landscape of the Artificial Placenta: A Systematic Review

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Navigating the Ethical Landscape of the Artificial Placenta: A Systematic Review

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Abstract

Objective: To present the ethical debate on the artificial placenta (AP) by identifying, distinguishing, and organizing the different ethical arguments described in the existing literature.

Method: We conducted a systematic review of the AP ethical literature. Articles were selected based on predefined inclusion criteria: discussing ethical arguments, on AP, written in English. QUAGOL methodology was used for analysis.

Results: Forty-five articles were included. We identified three main themes. First, foundational-ethical issues. There is substantial disagreement on whether the AP subject should be considered an infant or a new moral entity. While physiologically it stays a fetus, it sits outside the womb. Second, reproductive ethics issues. Few authors believed that the AP would increase reproductive choices. However, the majority warned

that the AP could limit reproductive choices by creating pressure to use it in healthy pregnancies or as an alternative to abortion. Third, research ethics issues. Publications mostly focused on selection of the in-human trial participants.

Conclusions: AP ethical literature focuses mostly on the potential use of AP as an alternative to abortion or healthy pregnancies rather than on the intended use as treatment after extremely premature birth. Furthermore, all but one article originated from high-income western countries, and no article discuss the AP from a global health perspective. We conclude, therefore, that the current ethical literature on AP is imbalanced: it leans more towards science fiction than actual clinical and technological reality, and important perspectives like global health are currently missing from the existing body of literature.

1 Introduction

The artificial placenta (AP)[1] is being developed to improve survival rates and quality of life of extremely premature infants (EPIs) born between 22 and 28 weeks of gestation. Because of their extreme prematurity, these infants need resuscitation at birth often followed by months of neonatal intensive care. Despite medical improvements, mortality and morbidity remains high especially among infants at the lowest gestational ages (22-24 weeks).(1, 2) Morbidity is partially iatrogenic,(1, 3, 4) for example, mechanical ventilation is necessary as the lungs are too immature for proper gas exchange, which can lead to scarring and inflammation. By mimicking the function of the amniotic sac, amniotic fluid and placenta, the AP aims to preserve a physiological fetal state, and therefore prevent severe complications of extreme prematurity.(5) Four research teams are currently in the animal testing phase of the development of an AP prototype for treating EPIs.(6-10)

Reflecting on the AP's ethical implications while it is yet to be developed and implemented is necessary if we want to integrate ethical reflection in the development of the technology. The ethical debate on the AP is complex. First, it involves many different stakeholders (e.g. parents, developers, clinicians, ethicists) each with their own perspectives, questions, and interests.(11) Second, even though the AP is meant for neonatal treatment, it raises many ethical questions beyond the domain of neonatology.(12) For example, should it be offered as an alternative to abortion? Third, the debate still contains some ambiguity between artificial placentas and artificial wombs, i.e., currently non-existent

[1] Authors use different terms to identify this type of technology depending on whether they are referring to a specific prototype (e.g. biobag or EVE), an aspect of the technology (e.g. artificial amnion and placenta technology), or its general aim (e.g. artificial womb technology). We use the term artificial placenta as it encompasses all the different specific prototypes while differentiating it from artificial wombs able of maintaining an entire pregnancy outside the human womb.

technology that should be able to fully maintain a gestation outside the human womb (full ectogenesis). This ambiguity makes it difficult to distinguish the arguments related to the two different technologies. Hence, in this article, we aim at disentangling the AP debate by identifying, distinguishing, and organizing the different ethical questions and arguments described in the literature through a systematic argument-based review. This could help experts to better understand the current debate and identify potentially overlooked issues. This, in turn, contributes to further inclusion of ethical considerations in the further development and implementation of the AP.(11)

2 Methodology

We conducted a systematic review of argument-based literature.(13, 14) A systematic search of Medline®, Embase®, Web of Science™, and Scopus® electronic databases was conducted on November 17th 2022, and updated on November 13th 2023. The Philosopher's Index was initially considered; however, the search yielded only 10 hits, all of which were already included in the other databases. Therefore, it was replaced with Scopus. Search strings consisted of two categories of words, one identifying the technology (e.g., artificial placenta, partial ectogenesis), and another focusing on ethics (e.g., ethics, morals) (Additional file 1). A librarian from the Leiden University Medical Centre assisted with the development of the search string. Results were merged and duplicates were deleted before conducting title, abstract, and full-text screening. We used the "snowball method" and citation tracking on every included article to identify additional relevant publications.(15)

Eligible articles were selected based on predefined inclusion/exclusion criteria (Table 1). Two authors (AC and ADB) independently screened titles, abstracts, and full texts using Rayyan. Disagreements about inclusion were resolved by discussion with a third author (LDP) until consensus was reached. A PRISMA flow diagram(16) summarizes the literature search process (Figure 1).

As there is no standard for assessing argument-based literature,(17) for quality appraisal we relied on the journals' peer review process to assume that the quality of included articles was sufficient. This is acceptable as the aim of our review is descriptive not normative.(17).

Data analysis and synthesis followed the Qualitative Analysis Guide of Leuven (Additional file 2).(18, 19) The analysis was conducted in an interdisciplinary research team comprising expertise in medicine (EJV, ADB), and bioethics (AC, LDP, CG).

3 Results

We identified forty-five eligible publications, whose characteristics are described in Table 2. The included literature is recent, with most publications published from 2020. Most publications originated from western English-speaking countries (UK, North America, Australia). Further, many included articles were written by the same first author. Most of the authors are scholars in philosophy, bioethics, or health law.

We identified three main themes: foundational-ethical issues; reproductive ethics issues; and research-ethics issues (Figure 2).

3.1 Foundational-ethical issues: The moral status of the subject in the AP

Disagreement exists on whether the subject in the AP is an infant or a new moral entity.(20-23)Several terms were coined to identify the subject in the AP, e.g., gestateling, fetonate or perinate.(24) Others stated that the best way to describe the subject of the AP is "a fetus (physiologically) that we treat as a neonate (morally)", explaining that ontological and moral status do not necessarily coincide.(24) Yet others stated that an agreement on terminology is necessary because these terms are morally loaded, meaning that they will affect our perception of the subject in the AP and the care provided.(23, 25, 26)

The subject in the AP is a new moral entity

Some authors claimed that the subject in the AP is a new moral entity(27-34), i.e., a human being in the process of ex utero gestation.(30) According to them, as the subject in the AP is a distinct and unique moral entity, the concepts and rules that apply to fetuses or infants should not apply to the subject in the AP.(27, 28, 30-34) For example, it could be justifiable to end the life of the subject in the AP who is suffering, whereas most jurisdictions prohibit infanticide.(33) Hence, they said, new forms of protections for the subjects in the AP are necessary.(27, 28, 30-34) Three main reasons were brought up to justify conceptualizing the subject in the AP as a new moral entity.

First, some authors claimed that subjects in the AP are not physiologically born.(27, 28, 30-32) They explained that birth implies a change of location from the womb to the external environment *and* a change of physiology, e.g. the lungs inflate. The subject in the AP is geographically but not physiologically born because it did not change physiology.(27, 30-32) Moreover, Kingma and Finn explained that a fetus has an additional organ and body parts that the infants lack: a placenta, an umbilical cord, and an amnion and chorion.(27) Although the subject in the AP is separated from the womb like an infant, it still possesses these fetal organ and body parts albeit synthetic, making it a new moral entity distinct from a fetus or an infant.(27)

Second, according to Romanis, subjects in APs have no capacity to live independently.(30-32) Romanis explained that the physiological change

grants infants independent capacity for life, whereas subjects in the AP did not physiologically change and, consequently, are still completely dependent on the AP.(30-32)

Third, according to Romanis, while the preterm infant has direct contact with the parents and the external environment, “The gestateling is shut off from the outside world and does not touch, smell, or interact with anything other than its artificial gestator. This isolation will influence the perception of and, on occasion, the feeling attached to each entity”.(30; p. 754) Implying, in this way, that subjects in the AP will be perceived and treated differently than infants.(30-32)

The subject in the AP is an infant

Others claimed that the subject in the AP is an infant(20-22, 24, 35-37) for a number of reasons.

First, they believe that the subject in the AP is born because,(20-22, 35, 36) based on the conventional definition of birth, “being born” means being completely expelled from the womb, and showing evidence of life, such as breathing or having a heartbeat.(20-22, 35) The subject in the AP is completely expelled from the womb and shows evidence of life as it has a heartbeat, thus it is born.

Second, they maintained that the subject in the AP has some capacity to live independently.(36) Referring to the EXTEND prototype, they explained that for the AP to work, the subject has to be sufficiently developed to survive the surgery required to transfer the subject to the AP; blood vessels large enough to be cannulated; and a heartbeat strong enough to maintain circulation as the majority of AP prototypes are pumpless systems powered by the subject’s heart. Further, Colgrove elicited that, even accepting Romanis’ claim that the subject in the AP has no independent capacity for life, the conventional definition of birth does not require independency to identify a live birth as it refers to evidence for life “however supported”.(20, 21) Finally, Wozniak & Fernandez reminded that no infant has independent capacity for life because they all need care to survive, and, therefore, this is not a real difference between the subject in the AP and any other infant.(36)

Third, they argued that the physiology and appearance of EPIs are more similar to a fetus than to an infant. However, parents and healthcare providers treat them as children.(24, 37) Mercurio warned against introducing a new term for subjects in the AP, as it could suggest that they are not given the same level of care and compassion as other infants in the intensive care unit, even though AP has the same goal and targets the same population as conventional intensive care. (37)

Two publications conceded that the term gestateling “provides us with a clearer way of referring to a particular kind of newborn”,(20, p.724) namely if an infant is treated with AP.(20, 37) However, according to these

authors, this does not imply that the subject in the AP is not an infant in the same way in which EPIs are specific infants born extremely prematurely, but they are infants nonetheless.(20) Therefore, they believed that subjects in the AP have the same rights and protections as any other infant and that we cannot morally justify killing the subject in the AP, although we can still withhold or withdraw AP as we do for other infants in intensive care.(20-22, 35)

3.2 Reproductive ethics issues: Impact on reproductive choices

As a general indication, Krom et al. proposed to use the capabilities approach to obtain a comprehensive and nuanced understanding of how the AP will affect the pregnant person and the infant, specifically EPIs. For example, a risk of prematurity is survival with severe disability, but long-term medical and social support is often insufficient. Hence, they explained that AP is not a stand-alone solution but needs to be incorporated in a broader system of healthcare.(38) Two specific reproductive ethics issues could be identified in the literature: how the AP will affect reproductive choices in general, and how it will affect abortion rights in particular.

AP and reproductive choices

A first question in the literature is whether AP will increase or decrease reproductive choices. Kennedy elicited that AP might increase reproductive autonomy by increasing reproductive choices. For her, AP could be an alternative to abortion for those who do not want the child or an abortion, it could prevent social pressure to keep the child as AP can be used before the pregnancy becomes visible, and it could allow women with risky pregnancy to better care for their own health without losing the child. To the opposite, seven publications warned that AP might reduce reproductive autonomy.(26, 39-44) Three publications explained that AP might increase social pressure to use it for the fetus' benefit(26, 43, 44) because the existence of technology often generates an urge to use it, as happened when ultrasound was introduced.(44) They warned that this pressure might increase once the fetus reaches viability, when some assume that directive counselling for fetal benefit should be the ethical standard.(44) Five publications warned that AP might also increase inequalities for vulnerable minorities. For example, access to AP might be limited to traditional family units, as it already happens in some countries for in vitro fertilization, or it might be too expensive for poorer people.(39-43) Therefore, they warned that AP implementation should be preceded by structural interventions aimed at avoiding further inequalities.(39-43)

A second question in the literature is whether pregnant people should be allowed to choose AP as an alternative delivery option even when it is not medically indicated. Nelson maintained AP should be allowed regardless of medical indication because doctors should not be the gatekeepers of reproductive choices. For her, allowing someone to make decisions on behalf of an autonomous person is an infringement of autonomy. She

explained that breach of autonomy is not a neutral act as it results in a loss of control, which, in turn, generates anxiety, distress, and delivery-related post-traumatic stress disorder.(29) Holmes and Hosford also concluded that AP might be acceptable for non-medical reasons, e.g., if the pregnant person chooses AP to pursue their career or education, as these will benefit not only the person but also the child and society.(45) To the opposite, two publications maintained that the risks for the pregnant person and the subject are too high to justify AP when not medically indicated.(46, 47) In analyzing AP acceptability based on Islamic legal maxims, Muhsin et al. concluded that using AP when not medically indicated – specifically to avoid the burdens of pregnancy, for single fathers or gay couples, and for abortion - is not consistent with Islamic precepts.(48) However, they explained that treatment with AP for EPIs or risky pregnancy is compliant with Islamic precepts to preserve life and reduce harms to the infant and the pregnant person.(48)

A third question in the literature is whether a pregnant person should be allowed to refuse AP if medically indicated. Romanis and Adkins and Takashima et al. concluded that a pregnant person should not be obliged to choose the AP regardless of medical indication.(49, 50) However, Takashima et al. believed that, in this case, the pregnant person could be subjected to some sort of mild punishment such as blame.(49)

AP and abortion

There are two main points discussed: if and how the AP will affect abortion rights; and whether it should be an alternative to abortion.

Will the AP affect abortion rights?

Six publications claimed that AP might lower the viability threshold, i.e. the gestational age at which a fetus is considered capable to support life if delivered and treated.(25, 26, 37, 41, 51-53) According to them, depending on how we reinterpret viability it might reduce or expand abortion rights because several abortion laws rely on viability thresholds to determine when abortion is permissible. Cohen theorized that the AP might support EPIs as young as 18 weeks, which might affect abortion in two ways. First, a fetus might be considered viable already at 18 weeks. He postulated that jurisdictions that do not allow abortion above the viability threshold, will prohibit abortion from 18 weeks onward. Second, AP might expand abortion rights in countries in which abortion is currently prohibited. He postulated that, instead of a total ban on abortion, pregnant persons will be allowed to choose AP.(51) To this regard, Kendal answered that viability is not an intrinsic characteristic of the fetus, but it depends on external factors (e.g., technological and pharmaceutical equipment available in the hospital), and indeed, it varies greatly worldwide. As AP is not the only technology challenging viability, she warned, it ought not to affect abortion laws.(53)

Kendal maintained that the AP will make the fetus more visible and that anti-abortion movements might use AP images to advocate against abortion, similarly to what they did when ultrasound images were first introduced. Hence, she said, we need to develop AP in a way that maximizes the positive impressions of AP, i.e. it improves EPIs' care and reproductive choices, while minimizing the negative aspects, i.e. limitations on abortion rights.(54)

Should AP be an alternative to abortion?

Two authors believed that AP will shift the abortion debate from "does a person have a right to terminate a pregnancy" to "does a person have a right to the death of the fetus?"(51, 55) In their words, historically the abortion debate focused on whether there is a right to terminate the pregnancy, regardless of whether the fetus could survive, because survival was impossible. However, they continued, some maintained that, should the aborted fetus survive, then the biological parent has no right to request the death of the fetus. They explained that because AP will allow to terminate a pregnancy without having to terminate the fetus, the abortion debate will shift focus on whether pregnant people should be allowed to choose for an abortion that leads to the death of the fetus when AP is an available alternative.(51, 55) This leads us to the next aspect of the debate: should AP be an alternative to abortion?

Two authors claimed that, assuming that AP is safe for the fetus and not riskier than abortion for the pregnant person, AP will provide an alternative to abortion.(55, 56) Simkulet claimed that AP is a moral compromise between prochoice and prolife theorists.(56) He explains that prochoice theorists would renounce the right to choose an abortion that leads to the fetus' death, in favor of AP followed by adoption. Simkulet explained that AP would not infringe pregnant persons' autonomy because they can still terminate the pregnancy. Prolife theorists would obtain their goal of preventing the death of the fetus. However, he acknowledged that current AP is riskier than abortion and, therefore, it should not be a compulsory alternative to abortion for the time being.(57) Similarly, Stratman claimed that AP should substitute abortion because it allows to interrupt a pregnancy without killing the fetus.(55) The author bases this statement on two assumptions. First, parents do not own a child or a fetus, so they don't have right to its destruction, and even if they do own it, it does not make its destruction moral. Second, the harms of biological parenthood (i.e., the harms resulting from having a biologically related human against their will) are not grave enough to warrant the death of the fetus. Hence, parents do not have a right to the death of the fetus.

To the opposite, others claimed that AP is *not* an alternative to abortion, and that considering it as such is ethically problematic for the following reasons.(40, 41, 52-54, 58-60) On a practical level, they said, most abortions occur in the first trimester through the ingestion of two pills, whereas AP can only be effective from 22/23 weeks and requires a complex C-section.(40, 41) Therefore, they warned that advocating for AP as an

alternative to abortion means obliging pregnant people to stay pregnant longer than they want, to undergo an invasive surgery instead of the safer and less invasive option, and to take something from the person (i.e. the fetus) without the person's consent.(40, 43, 53, 58, 60) Further, this would oblige someone to become a biological parent against their wish.(40, 58) In their opinion, all of this would constitute an infringement of bodily autonomy. Finally, two authors explained that enforcing AP as an alternative to abortion will increase the number of vulnerable infants in the adoption system.(58, 59) Conceptually, these authors reject the idea that abortion is a moral issue to be solved.(39-41, 52, 53) They explained that abortion is a basic form of reproductive care and, as such, it should be accessible regardless of AP. If we conceive abortion in this way, they said, abortion and AP can coexist, meaning that a pregnant person should be allowed to decide whether they want to carry on the pregnancy, have an abortion, or opt for AP. Finally, some warned that considering AP as an alternative to abortion will criminalize those who cannot afford it.(39, 40) Horn pointed out that in the US women can already be punished for behaviors that place the fetus at risk, and that introducing AP as an alternative to abortion will worsen it.(39, 40) As AP will likely be an expensive technology, making it compulsory will penalize poorer people, as they might be punished for not using a technology they cannot afford.

3.3 Research-ethics issues: Development and trial

Mercurio and Romanis stated that the safety and efficacy of AP should be assessed through a clinically and ethically solid clinical trial in which the interests of science (i.e. producing generalizable knowledge) and the interests of the individual participants (e.g. avoiding harm) should be balanced.(25, 32, 47) Kukora et al. explained that different AP prototypes work differently. They warned that while some ethical considerations apply to all prototypes, e.g. the importance of minimize risks for EPIs and pregnant persons, other are prototype-dependent, e.g., considering the C-section risks for delivery and future pregnancies of prototypes requiring a planned C-section.(61) Similarly, Flake et al. explained that different AP prototypes have different risk profiles, meaning that we have to assess the risks of each individual AP prototype before starting the trial.(62) Two main aspects of the development and trial are considered: The design of the AP, and the selection of research participants.

The AP design

Included publications explained that it is important to give attention to the design of the AP as its aesthetic can contribute to how it is perceived and used(26, 54) because images generate ethical intuitions.(54) For example, Kendal explained that much of the distrust toward AP can be explained by the fact that we already have a long history of sci-fi imaginary (e.g., The Matrix) that portrayed artificial wombs sustaining entire gestations in pods as a crucial negative element of their dystopias. This, in turn, might have created a negative perception of AP because, although AP cannot sustain an entire pregnancy, people tend to associate the two. Because of

that, Verweij et al. explained that it is important to involve society in the AP debate to create realistic expectations of what the AP can do. (26, 54) They also pointed out the importance of involving parents and caregivers in the design process and to consider their input on design choices. For example, if we know that parents prefer to always see their fetus, the AP could be made transparent.(26, 54)

Selection of participants

Seven publications focused on which fetuses should be selected for the first in-human trial based on potential risks (e.g., psychosocial development risks) and benefits (e.g. higher chances of survival).(25, 32, 34, 37, 63) According to them, EPIs of 22-23 weeks have a high mortality rate with current care and, therefore, the experimental AP treatment could be justifiable as it could be their last chance to survive. EPIs of 24-25 weeks already have better survival rates, meaning that AP treatment might be even more beneficial to them. However, this also means that the experimental AP treatment would be less justifiable because they already have higher chances of survival with regular care. Within this discussion, four publications took an explicit stance and maintained that it is acceptable to include in the trial infants so premature that without AP death or severe disability is the likely outcome.(37, 61, 63, 64)

Included publications focused on which parents should be involved in the clinical trial and how to counsel them.(25, 26, 44, 50, 63) They identified a set of eligibility criteria for potential participants. First, AP should only be proposed to pregnant persons for whom the caesarean is already indicated and for whom it would be better not to be pregnant. That is because AP requires an early caesarean that involves higher risks for the pregnant person than vaginal delivery or late caesarean. Second, the pregnant person (and if present the partner) received appropriate counselling. They should receive all necessary information regarding the experimental treatment, including the uncertainty of outcomes, and the fact that the pregnant person will be a parent *and* a research subject.(25, 26, 50, 61, 63) Further, counsellors must pay attention to avoid therapeutic misconception, i.e., the mistaken belief that the experimental treatment will be curative.(26, 63) To be appropriate, counselling also needs to be nondirective(26, 44) to avoid undermining pregnant people’s safety for the sake of the fetus.(44, 61) To this regard, Romanis and Adkins advocated for a non-fetal-centric counselling.(50) They pointed out how much of the literature focuses on how AP will affect the infant but not on how it will affect the pregnant person, whereas it might have important consequences for the pregnant person beyond the physical risks and consequences of the C-section. They emphasized how AP might lead to feelings of pregnancy loss and failure in pregnant persons due to preterm delivery, and that counsellors should be aware of potential effects of AP on pregnant people and include them in the counselling. They advised counsellors to use a language that conveys the important message that AP is substituting current neonatal care not the pregnant person’s role.(50) They also advised to provide psychological support for pregnant persons after the

preterm delivery.(50) Finally, parents should have enough time to decide, and properly understand all the information and possible implications of their choice.(26, 63)

4 Discussion

Based on our analysis of the forty-five eligible publications, we identified three main gaps in the existing literature.

4.1 Lack of consistent terminology

We already discussed that there is no agreement on the correct terminology to identify the subject in the AP.(24) While new terms such as “gestateling”(31) or “fetonate” are proposed(12), some articles refer to the subject of AP as “infant”(20). Similarly, we found different terms to identify the technology itself. We chose the term artificial placenta but others refer to it as artificial placenta and amnion technology(30) or artificial womb.(65) This terminological confusion is aggravated by the fact that the technology is often too ambiguously described often conflating the AP with full ectogenesis. Conflating the two misrepresents how the AP functions, its applications, and the ethical issues it raises.(9, 47, 66) Developers warn that using terms like 'artificial wombs' or suggesting that APs can function at any stage of pregnancy may create public hostility towards the AP. This could hinder the implementation of a potentially better therapeutic option for EPIs.(47, 67) This misrepresentation is probably most evident in the abortion debate. Those in favor of using AP as an alternative to abortion often conflate APs with artificial wombs(65) or, even if they acknowledge that APs can only achieve partial ectogenesis, their arguments do not appropriately consider the possibilities and limitations of existing APs.(55, 56) Current APs are unable to maintain EPIs of less than 23 - maybe 22 - weeks of gestation and in many cases a modified and riskier C-section will be necessary. Advocating for enforcing AP as an alternative to abortion in the current technological context would mean obliging pregnant persons to be pregnant longer than they wanted and to undergo a major surgery instead of opting for earlier safer and less invasive abortion methods. On that, we agree with Romanis and Horn that in discussing proposals that would affect people’s autonomy and wellbeing so heavily, we need to either clearly state that we are speculating about a non-existing technology or refer to the description of existing technologies.(41) To clarify, we are not advocating for the end of speculative thinking. We are advocating for a more consistent and responsible use of language. One that correctly identifies the technology at hand and the related ethical issues.

4.2 Lack of ethical reflection on issues related to the first in-human trial and implementation

The AP is a clinical device being developed to treat EPIs, so the first in-human trial will inevitably involve vulnerable EPIs.(32) Furthermore, the in-human trial and implementation of the AP for EPIs are expected to occur in quick succession.(10, 68) The potential quick introduction of the AP in

clinical practice, makes the ethical reflection on the trial and implementation necessary and urgent. Despite that, only twelve out of forty-five included articles discussed research ethics and clinical-ethics issues related to the first in-human trial and implementation of the AP specifically for EPIs.

Most included articles were speculative and discussed the moral status of the subject or the possibility of using the AP as an alternative to abortion or as an alternative delivery method, which will only occur in a distant future, if it will ever occur. Consequently, the ethical issues raised by the AP for EPIs and their families are currently understudied. We believe this is ethically problematic as EPIs and pregnant persons will be the ones bearing the risks of the first trial and implementation of AP. We do not exclude that the AP will be used beyond its original scope once it is proven safe and effective. Therefore, we do not undermine the importance of discussing potential future applications of the AP and their impact on the wellbeing and reproductive autonomy of pregnant people. What we found problematic is the current imbalance between the articles discussing these future scenarios and the articles discussing short-terms applications of AP. Hence, we advocate for more research on the ethical issues related to the trial and implementation of AP for EPIs.

A related issue is the lack of empirical studies, particularly of studies involving prospective AP users, such as neonatal professionals or EPIs' parents. We found only two empirical studies on the topic,(69, 70) of which only one involved prospective users, i.e. neonatologists.(69) The other involved reproductive rights advocates and focused also on other assisted reproductive technologies. We advocate for integrating more empirical studies on users' perspective in the development of the technology. This could help producing a technology that truly answers the needs of the users. This could also help us identify potentially overlooked but important ethical issues. For example, the main topic discussed was the subject's moral status and its name. This is an important discussion in the legal and academic sphere. We underlined multiple times how the ambiguity in terminology and definitions might hinder communication and affect AP acceptability. Further, different moral entities have different rights and, therefore, whether the subject in the AP is a fetus, an infant, or a new moral entity does matter. However, scientific terms are not always used in the clinical context, where healthcare providers adapt their language to how the pregnant person conceptualizes the fetus. For example, when the pregnant person considers the fetus as "their child", the gynecologist is likely to talk about the child rather than the fetus during visits and ultrasounds.(24) Similarly, we can imagine that if parents consider the subject in the AP "their child" nurses and neonatologists will call it a child rather than gestateling, fetonate, or subject of AP, even if these terms might be scientifically more correct. Beyond terminological differences, this also implies that parents might perceive different ethical issues than clinicians and academics. Hence, it is important to engage with parents and other stakeholders to obtain a comprehensive understanding of the ethical issues raised by AP and to address all the relevant issues.

4.3 Lack of a global ethics perspective

Most included studies originated from the US or the UK. We already know that attitudes toward active treatment of EPIs vary across countries and that they are influenced by individual or cultural perceptions of what makes a good outcome.(71) This, in turn, might influence healthcare professionals' perspectives on what is a good AP outcome and on when it is appropriate to use the AP. Hence, we need a more international approach if we want to have a truly nuanced picture, one that involves not only researchers but also stakeholders worldwide. This means not only to conduct more empirical studies in different countries, ideally including comparative studies, but also to actively create opportunities for international dialogue and discussion. Further, practices might differ even more across high-income and low-income countries. For example, we know that in low-income countries EPIs are generally not resuscitated for lack of resources.(72-74) This opens a question of fairness and accessibility. For example, to what extent will AP be available to low- and middle-income countries? How should we make this resource more globally accessible? Most included articles discuss fairness and accessibility within country. They warn that even in high-income countries AP might increase inequalities as it will be inaccessible for the most vulnerable persons and couples either because too expensive or because of legal limitations.(39, 42, 52) We can imagine that, if access issues will occur at a national level, they will likely occur also on a global scale with lower-income countries having less access to AP than richer countries. We agree that it is important to ensure a fair distribution of the AP within country, but we need a more nuanced and comprehensive debate on justice and equality that looks at access inequalities not only within-country but also cross-countries.

4.4 Strengths and limitations

This systematic review is based on forty-five publications on ethical aspects of the AP. Data collection and synthesis were conducted in an interdisciplinary group. To our knowledge, this is the first review that systematically presents ethical arguments related to the AP specifically rather than discussing it along with other artificial womb or reproductive technologies. This allowed us to isolate arguments specific to the AP and to give an in-depth and nuanced overview of this debate. However, due to the narrow focus of the review and the ambiguity regarding terminology and technology description that still permeates the ethical literature on artificial womb technologies, some articles and arguments were ineligible.

All but two publications originated from high-income western countries. Several articles had the same first authors. Six first authors are healthcare professionals; all other articles are written by scholars in ethics or law. This might limit the generalizability of results as ethical arguments are at least partially culturally sensitive. This could also indicate that despite the considerable number of included articles, the AP debate is still in its

infancy and that there is not much interaction between scholars, clinicians, and developers.

5 Conclusions

Our review shows that the AP ethical literature is imbalanced. Most included publications focused on the possible use of AP as an alternative to abortion or healthy pregnancy instead of for the treatment of EPIs – for which it is in fact being developed, and will be actually used. Consequently, reflection on the ethical implications of the AP for treatment of EPIs and pregnant persons is urgently needed as they will be the ones bearing the risks of the AP first in-human trial and subsequent implementation. Further, there is lack of a global ethics perspective. There is a need for a more international approach that involves also low-income countries as well as a broader reflection on the ethical implications of AP on a global scale. For example, we urgently need an ethical discussion on justice, fairness, and equal distribution of this potentially life-saving resource within and across countries.

6 Figures and supplementary materials

FIGURE 1. Process of electronic literature search for identifying and selecting articles. Flowchart is organized according to PRISMA guidelines outlined in Liberati et al.(16)

FIGURE 2. Distribution of included publications based on the identified themes and sub-themes.

SUPPLEMENTARY MATERIAL 1. Overview of Bibliographic Databases Searched, Search Strings Used, and Search Results of Articles Identified

SUPPLEMENTARY MATERIAL 2. Data analysis and synthesis

7 Tables

TABLE 1. Inclusion and exclusion criteria for selection of articles

	Included	**Excluded**
Types of publication	Published articles.	Dissertations, books, book chapters, guidelines, ethics policies and codes, because these publications cannot be systematically searched, which will affect the reproducibility.

Topic	• Publications focusing on the artificial placenta as a technology that mimics the placenta and amniotic sac, and that partially maintain the fetus outside the human womb. • Publications focusing on artificial placenta specifically for infants born at 22-25 weeks of gestation (domain 3 in De Bie et al. 2023). • Publications focusing on partial ectogenesis. • Publications containing original ethical arguments. Articles that use existing concepts and theories to develop an original normative stance, or a new theory or concept are included. Similarly, articles that develop new concepts or theories to support an existing position are included.	• Publications on artificial wombs as a technology able to maintain the whole gestation outside the human womb. • Publications focusing on full ectogenesis; e.g., Smajdor 2007.(75) • Publications that do not clarify whether they refer to artificial placentas or artificial wombs as previously defined; e.g., Räsänen 2017.(76) These two technologies are different and different ethical arguments might apply. Our aim is to review arguments related to the artificial placenta technology specifically. Including articles that do not specify what technology they are referring to will introduce vagueness and bias. • Publication focusing on IVF as partial ectogenesis. • Publications describing clinical trials or the technical functioning of the artificial placenta without ethical reflection. • Publications describing legal regulations without ethical reflection. • Reviews that present a mere overview of existing ethical arguments without elaborating a normative stance, because (1) no new original content is presented, and (2)

		reviewed articles are already included with the risk of duplicating results and over emphasizing certain positions.
Language	Publication language is English.	Non-English language publications.
Date	Screening of articles was not limited by publication date; entire date range was included in searches of Medline®, Embase™, Web of Science™, Scopus® databases.	NA

TABLE 2. Characteristics of included publications (N=45)

CHARACTERISTICS	NUMBER OF PUBLICATIONS
Article type	
Full article	26
Commentary	19
Year of publication	
2020-2023	38
2015-2019	7
First author's number of included publications	

Romanis E.C.	6
Colgrove N.	3
Horn C.	3
Kendal E.S.	2
Kingma E.	2
Mercurio M.R.	2
Simkulet W.	2
Verweij E.J.	2
Werner K.M.	2
Cohen G.I, Kennedy S., Nelson A., Overall C., Rodger D., Segers S., Stratman C.M, Wozniak P.S., De Proost L., Krom A., Cordeiro J.J., De Bie F.R., Esquerda M., Hine K., Holmes J., Kimberly L.L., Roesner N., Takashima K., Muhsin S.M., Kukora S.	1 (each)

Country of first author's affiliation	
USA	20
UK	14
The Netherlands	4
Australia	2
Canada, Belgium, Spain, Japan, Singapore	1 (each country)

First author's professional background[1,2]	
Philosophy, bioethics	14

Healthcare	6
Law	6
Not found	3

[1]To determine the first author background we looked at the professional titles indicated in the papers and at the professional biography in the indicated institution website.

[2]Authors with multiple publications were only counted once.

8 Abbreviations

AP, artificial placenta; EPI, extremely premature infant; QUAGOL, qualitative analysis guide of Leuven.

9 Additional Requirements

9.1 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

9.2 Author Contributions

Dr. Cavolo contributed to the study design, screened the bibliographic search results, reviewed all included articles, drafted the initial manuscript, and reviewed and revised the manuscript.

Drs. De Boer contributed to the study design, screened search results, reviewed all included articles, and reviewed the manuscript.

Drs. De Proost contributed to the study design, reviewed all included articles, and reviewed the manuscript.

Dr. Verweij and Dr. Gastmans critically reviewed the manuscript for important clinical intellectual content and provided mentorship.

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9.5 Data Availability Statement

The datasets generated for this study can be provided upon request to the corresponding author.

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Figures

FIGURE 1. Process of electronic literature search for identifying and selecting articles. Flowchart is organized according to PRISMA guidelines outlined in Liberati et al.(16)

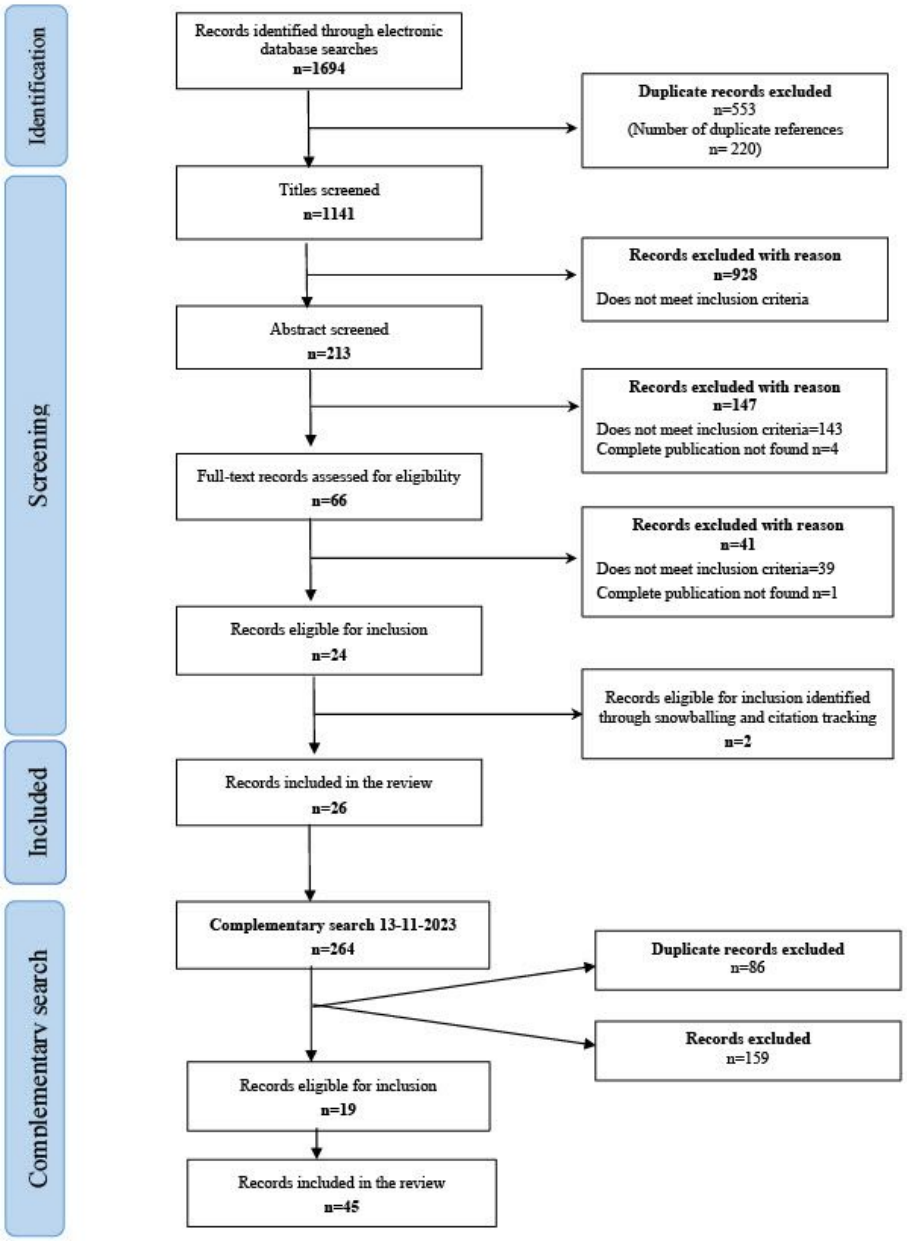

Figure 1

Process of electronic literature search for identifying and selecting articles. Flowchart is organized according to PRISMA guidelines outlined in Liberati et al

FIGURE 2. Distribution of included publications based on the identified themes and sub-themes.

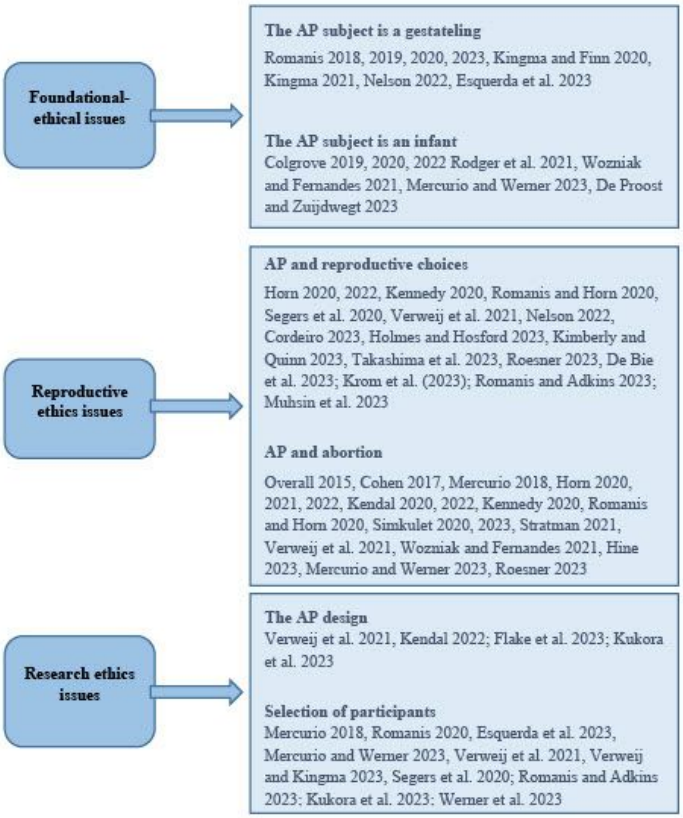

Figure 2

Distribution of included publications based on the identified themes and sub-themes.

Supplementary Files

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- Additionalfile1searchstring.docx
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