Artificial placenta: imminent ethical considerations for research trials and cinical translation

Verweij, E.J.; Kingma, E.

26. Accessed February 16, 2023. https://www.npr.org/sections/health-shots/2021/05/26/1000126212/new-guidelines-would-allow-experiments-on-more-mature-human-embryos
Romanis, E. C. 2018. Artificial womb technology and the frontiers of human reproduction: Conceptual differences and potential implications. *Journal of Medical Ethics* 44 (11):751–5. doi:10.1136/medethics-2018-104910.
Sedgewick, H. 2017. *The growing season*. London: Harvill Secker. https://www.helensedgwick.com/book/the-growing-season/

THE AMERICAN JOURNAL OF BIOETHICS
2023, VOL. 23, NO. 5, 85–87
https://doi.org/10.1080/15265161.2023.2191054

OPEN PEER COMMENTARIES

Artificial Placenta – Imminent Ethical Considerations for Research Trials and Clinical Translation

E. J. (Joanne) Verweij[a] and Elselijn Kingma[b]

[a]Leiden University Medical Center; [b]King's College London Faculty of Arts and Humanities

De Bie et al. (2023) propose an organizing framework for different stages of human gestational development from conception to the viable premature. They also identify ethical considerations and concerns regarding artificial womb technology (AWT) and care of the fetonate by a scoping review.

De Bie et al. (2023) note that most of the recent ethical literature has focused on complete ectogenesis, at the expense of tackling important more immediate ethical considerations. We agree and therefore contribute a commentary directing research effort toward the following overlooked important immediate considerations: (1) the role and status of the mother; (2) research ethics, including the therapeutic misconception; and (3) hard and soft impact on the parents. Since we believe that the widespread and misleading framing of ectogestation as "the artificial womb" is substantially to blame for the literature's misdirection, we will use the more accurate (and less sensational) terminology "artificial amnion-and-placenta technology (AAPT)."

THE ROLE AND STATUS OF THE MOTHER

Much attention in the literature has focused on the legal and ethical status of the fetonate (Colgrove 2019; Romanis 2018). However, it seems to be forgotten that the first patient in AAPT is the mother.[1] In the first-in-human trials, she is the person whose consent should be sought. She will also be a direct patient—subject of the cesarean section currently deemed necessary to enable a transfer of the fetus onto the AAPT. As de Bie et al. (2023) note, cesarean sections have risks, which are aggravated in earlier stages of pregnancy. Extreme preterm cesarean sections are technically more challenging to perform as the lower segment of the uterus is not well formed—and also leave a comparatively larger scar. This incurs risk for the mother, for the neonate, and also for any future fetuses gestated by the mother. Examples of maternal risks are hemorrhage, serious infections and rupture of the uterine scar in a subsequent pregnancy.

It seems De Bie et al. (2023) seek to justify these risks by noting that "C-section is currently often used […]for extreme premature infants in distress." We do not think the concern can be so easily dismissed. Most guidelines counsel reluctance about early cesarean sections—a notable exception being pregnancies posing risks to the mother's life. The indication for an (extremely premature) cesarean section should be proportional: the increased chances for the neonate should outweigh the risks for the mother.

It is also important to consider that a timely transfer to the AAPT might require a cesarean section is performed earlier than would otherwise be clinically indicated. But nothing is so uncertain as obstetrics;

CONTACT E. J. (Joanne) Verweij e.j.t.verweij@lumc.nl Department of Obstetrics, LUMC, Leiden, Netherlands.
[1]We note that not all pregnant persons are, or will continue to be, their (future) child's mother. "Mother" in this paper stands in for "pregnant person being considered for AAPT."

sometimes early labor that you think is guaranteed to result in imminent, fails to progress and the pregnancy continues. A cesarean and AAPT-transfer might then happen unnecessarily. And where cesarean sections (as most are) are done because of fetal stress, it is doubtful whether a distressed fetus should be transferred into the AAPT.

Optimistically de Bie et al note the future possibility of a post-vaginal-birth AAPT transfer. However, it is not described how the obvious challenges—such as the difficult timing and the need for preventing or reversing the neonatal phsysiological transition, including blood pressure/distress and respiration—might be overcome.

RESEARCH ETHICS, INCLUDING THERAPEUTIC MISCONCEPTION

De Bie et al. (2023) claim that AAPT is nearing clinical translation, but provide no information on how this clinical translation is envisioned. It is best practice and, in most countries, obligate to translate technical innovations to clinical practice in a research study. Research trials are expected to meet national and international ethical requirements (World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects; World Medical Association 2013).

As mentioned in a previous publication: "clinical research must be conducted according to the ethical principles of proportionality and subsidiarity; in the context of first-in-human studies with AAPT this means that the attributable risks to the group of pregnant women and extremely premature infants should be minimized and that the risks and burdens should be commensurate with the potential benefits of the technology" (Verweij et al. 2021).

Here are some (but not all) important research ethical considerations for the first in-human AAPT trials:

1. The research participant (i.e. the mother) needs thorough, well-balanced, high-quality information counseled by an *independent* doctor. Uncertainty is an important aspect of counseling as—this being research—much remains unknown and extrapolation from animal to human studies is uncertain. Such counseling requires time to think; absorb information; ask questions; consult with loved ones; and so on. Counseling can therefore not be done during contractions.
2. In- and exclusion need to be determined. These have ethical as well as scientific desiderata: they are meant to ensure that findings are extrapolable and follow the aim of research; but also need to minimize harm to participants. Since both mother and fetus/fetonate are primary research subjects, potential harms should be minimized for both. Given the above-discussed cesarean-section risks, one inclusion criterion should be a medical reason to perform a cesarean section to prevent an additional risk for the pregnant person. Another inclusion criterion should be that the fetus' chances in regular neonatal intensive care are very poor.

The ethical requirement of risk minimization demands careful patient selection in the first trials. Certain patients with pre-eclampsia fill all criteria mentioned above. Placental insufficiency results in a maternal and fetal disease. The maternal disease, in severe cases, can result in an eclampsia, stroke or death. This is only resolved by ending the pregnancy. Fetal growth is often restricted, suggesting poorer NICU outcomes-for-gestational-age. Importantly: patients do not present in labor, leaving time for counseling.

We also note the risk of therapeutic misconception: where research participants mistakenly believe that research interventions are made on the basis of their individual therapeutic needs, rather than for research purposes (Lidz et al. 2015; McDougall et al. 2016; Sheppard, M. K. 2016; Verweij et al. 2021). Therapeutic misconception is common in research already. In the first AAPT trials, where experimental treatment and clinical practice will be intertwined, it will be even more difficult to draw a clear line (Verweij et al. 2021). Furthermore pregnant persons in disturbing situations are always looking for hope, and mothers will, and are socially strongly encouraged to, do anything necessary for their child to survive. It will be almost impossible not to escalate hope in this situation, and therefore doubtful that mothers who choose to participate in an AAPT will do so in the (required) proper and full understanding that the aim of this research is the generation of future knowledge—not the rescuing of their child. (McDougall et al. 2016; Verweij et al. 2021).

HARD AND SOFT IMPACTS FOR THE PARENTS

Lastly, a note on the hard and soft impacts for the parents (Verweij et al. 2021). De Bie et al (2023) note that the "AWT could also benefit parents by sparing them having to witness their premature infant supported on a ventilator with intravenous lines." That is one consideration; it is important to also reflect on others. Parents may find it difficult to see their "baby"

in a fluid-filled bag—unable to hold or touch it. "Kangaroo care" as well as "skin-to-skin" has many positive effects, including on bonding (Flacking et al. 2012). Hard impacts like survival and morbidity no doubt will be core outcomes of any study, but "soft" outcomes, even though more difficult and time-consuming to study, should not be forgotten (Swierstra 2015).

FUNDING

This work was supported by H2020 European Research Council. Grant Number: 679586 Framework Programme; ZonMW Klinisch Fellowship 90719039.

ORCID

E. J. (Joanne) Verweij http://orcid.org/0000-0002-9343-9957
Elselijn Kingma http://orcid.org/0000-0001-9787-3198

REFERENCES

Colgrove, N. 2019. Subjects of ectogenesis: Are 'gestatelings' fetuses, newborns or neither? *Journal of Medical Ethics* 45 (11):723–6. doi:10.1136/medethics-2019-105495.

De Bie, F. R., S. D. Kim, S. Bose, P. Nathanson, E. Partridge, A. W. Flake, and C. Feudtner. 2023. Ethics considerations regarding artificial womb technology for the fetonate. *The American Journal of Bioethics* 23 (5):67–78. doi:10.1080/15265161.2022.2048738.

Flacking, R., L. Lehtonen, G. Thomson, A. Axelin, S. Ahlqvist, V. H. Moran, U. Ewald, and F. Dykes, Separation and Closeness Experiences in the Neonatal Environment (SCENE) Group. 2012. Separation and closeness experiences in the neonatal environment (SCENE) group. Closeness and separation in neonatal intensive care. *Acta Paediatrica* 101 (10):1032–7. doi:10.1111/j.1651-2227.2012.02787.x.

Lidz, C. W., K. Albert, P. Appelbaum, L. B. Dunn, E. Overton, and E. Pivovarova. 2015. Why is therapeutic misconception so prevalent? *Cambridge Quarterly of Healthcare Ethics* 24 (2):231–41. doi:10.1017/S0963180111400053X.

McDougall, R., D. Martin, L. Gillam, N. Hallowell, A. Brookes, and M. Guillemin. 2016. Therapeutic appropriation: A new concept in the ethics of clinical research. *Journal of Medical Ethics* 42 (12):805–8. doi:10.1136/medethics-2016-103612.

Romanis, E. C. 2018. Artificial womb technology and the frontiers of human reproduction: Conceptual differences and potential implications. *Journal of Medical Ethics* 44 (11):751–5.

Sheppard, M. K. 2016. Vulnerability, therapeutic misconception and informed consent: Is there a need for special treatment of pregnant women in fetus-regarding clinical trials? *Journal of Medical Ethics* 42 (2):127–31. doi:10.1136/medethics-2014-102595.

Swierstra, T. 2015. Identifying the normative challenges posed by technology's 'soft' impacts. *Etikk I Praksis – Nordic Journal of Applied Ethics* 9:5–20.

Verweij, E. J., D. Proost, L. van Laar, J. O. E. H. Frank, L. Obermann-Borstn, S. A. Vermeulen, M. J. van Baalen, S. van der Hout-van der Jagt, and M. B. Kingma. 2021. Ethical development of artificial amniotic sac and placenta technology: A roadmap. *Frontiers in Pediatrics*. 9: 793308.

World Medical Association. 2013. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. *Journal of American Medical Association* 310 (20):2191–4. doi:10.1001/jama.2013.281053.

THE AMERICAN JOURNAL OF BIOETHICS
2023, VOL. 23, NO. 5, 87–89
https://doi.org/10.1080/15265161.2023.2191032

OPEN PEER COMMENTARIES

No Substitute: The False Promise of Artificial Womb Technology as an Alternative to Abortion

Benjamin Patterson Brown[a] and Katie Watson[b]

[a]Warren Alpert Medical School of Brown University; [b]Northwestern University Feinberg School of Medicine

In their scoping review of the literature on artificial womb technology (AWT), De Bie et al. report that "complete ectogenesis has been hailed as an alternative to abortion," (De Bie et al. 2023, 74) because "radically

CONTACT Benjamin Patterson Brown benjamin_brown@brown.edu Division of General Obstetrics and Gynecology, Women and Infants Hospital of Rhode Island, Providence, RI 02905-2499, USA.