REPRODUCTION
POINT OF VIEW

Synthetic embryos: a new venue in ethical research

Adrian Villalba[1,2], Jon Rueda[2] and Íñigo de Miguel Beriain[3]

[1]*Institut Cochin, INSERM, CNRS, Université Paris Cité, Paris, France,* [2]*Department of Philosophy 1, University of Granada, Spain and* [3]*Ikerbasque Resarch Professor, Spain*

Correspondence should be addressed to A Villalba; Email: adri.vife@gmail.com

Abstract

In brief: Two independent groups have reported the development of 'artificial embryos'. Those are *in vitro* models made of mouse embryonic stem cells, without the need for egg or sperm, and grown *ex utero* without requiring implantation. This system might open new venues in bioethical research if human cells show the ability to replicate this system.

Abstract: The recent publications reported in 2022 reveal the possibility of obtaining mouse embryos without the need for egg or sperm. These 'artificial embryos' can recapitulate some stages of development *ex utero* – from neurulation to organogenesis – without implantation. Synthetic mouse embryos might serve as a valuable model to gain further insights into early developmental stages. Indeed, it is expected for these models to be replicated by employing human cells. This promising research raises ethical issues and expands the horizon of ethics in regard to the development of the human embryo. From this point of view, we state some of the new open venues for bioethical research.

Reproduction (2023) **165** V1–V3

The recent publication by Amadei *et al.* (2022), along with that of Tarazi *et al.* (2022), reveals the possibility of obtaining mouse embryos without eggs or sperm. Indeed, these so-called 'artificial embryos' can recapitulate some stages of development *ex utero*, without implantation, employing technology developed by Aguilera-Castrejon *et al.* (2021). This novel tool constitutes a milestone in the field of developmental and synthetic biology, allowing scientists to get new insights into both pregnancy and embryo development.

The creation of a method for mimicking mouse embryo development by surpassing utero implantation *in vitro* (Aguilera-Castrejon *et al.* 2021) is the first milestone grounding said tour de force in embryo modeling. The experimental setup consisted of a novel method based on the combination of static and rolling culture bottles, together with a novel culture medium composition, allowing *ex utero* development from pre-gastrulation to advanced organogenesis. However, this tool makes matter more complex when employed to grow embryos solely from stem cells, without the need for gametes to subsequently undergo fertilization. Independent research groups have been able to recreate mouse embryo development based on this novel culture technique, thus reaching mid-gestation stages from embryonic stem cells (ESCs) alone. In the case of Amadei *et al.* (2022), they mixed and aggregated three different mouse cell lines: naïve ESCs, trophoblast stem cells (TSCs), and extra-embryonic endoderm-like cells (XEN) genetically modified to transiently express *Gata4* (a major driver in endoderm differentiation). Both TSC and XEN cell lines are extra-ESCs that interacted with naïve ESCs to promote the formation of synthetic embryos and their subsequent neurulation. Similarly, Tarazi *et al.* (2022) mixed naïve ESCs with two additional ESC lines expressing either *Cdx2* or *Gata4* (upon doxycycline treatment) to differentiate them into trophectoderm and primitive endoderm, respectively.

These new embryo models are thought to be useful for properly understanding the implantation process, a key stage in which most spontaneous abortions occur. The already proposed model is intended to provide new insights into early development processes. As decades of bioscience research have shown, what can be done in mice can often be done in humans. From blastoids (Kagawa *et al.* 2022) to gastruloids (Moris *et al.* 2020), previous embryo models that were originally proved with mouse cells have now been adapted to work with human samples. Thus, it is expected to deploy this novel strategy with human cells at some point.

These promising investigations, nevertheless, raise ethical issues – especially if used with human cells. On the one hand, there are ethical reasons for trying to create synthetic human embryos through stem-cell technologies. In addition to providing valuable knowledge in basic science, human synthetic embryos may lead to laudable applications in regenerative medicine, organ transplantation, or assisted reproduction.

However, this mid-gestation stage also raises some concerning ethical questions. What if functional

ISSN 1470–1626 (paper) 1741–7899 (online)
https://doi.org/10.1530/REP-22-0416
Online version via https://rep.bioscientifica.com

primitive nerve structures were created in their ectogestation? Consider some parallels with the abortion debate. For many years, the gradual formation of specific neural structures in the fetus has been a key aspect of the ethical and legal debate (Derbyshire & Bockmann 2020). In most countries where abortion is legal, it is only so before a certain stage of fetal development, beyond which voluntary termination of pregnancy is usually prohibited. Similarly, should the destruction of synthetic embryos be avoided from any particular period of embryonic development? Additionally, if primordial germinal structures can develop into a complete human being, how would the reproductive freedom apply in this case? Without the need for eggs or sperm to undergo *ex utero* development, this process could be reached with single reproduction purposes and then the reproductive freedom of both the donor and the so-called artificial embryo could lead to inconsistencies.

There are other more ethically puzzling implications. These disruptive innovations decouple the notion of 'embryo' from the fertilization of an egg with sperm and its maternal gestation. The moral status of human artificial embryos may thus seem uncertain. To what extent should we consider them as 'real embryos'? This question is hard to answer because the definition of a human embryo is highly controversial. Some nations, including Spain, believe that only fertilized eggs can be regarded as such. Others, such as the Netherlands and Belgium, believe that any cell or group of cells with the potential to develop into a human should be regarded as an embryo, regardless of how the fetus was generated. At the EU level, the Court of Justice for the European Union stated in 2011 (Case C-34/10, Oliver Brüstle v Greenpeace) that the concept of 'human embryo' shall be understood in a wide sense. Accordingly, it considered that every human ovum, once fertilized, shall be recognized as a 'human embryo' if that fertilization indeed initiates the process of human development. Both a non-fertilized human ovum into which the nucleus of a mature human cell was already transplanted and a non-fertilized human ovum whose division and further development were stimulated by parthenogenesis shall also be classified as 'human embryos'. However, the same Court reversed its stance years later, adopting a somewhat narrower definition of what an embryo is: in Case C-364/13 (International Stem Cell Corporation v Comptroller General of Patents, Designs, and Trade Marks), it stated that human ova (irrespective of whether the egg was fertilized or 'activated' by techniques such as nuclear cell transfer) which were 'capable of commencing the process of development of a human being just as an embryo created by fertilization of an ovum can do so' should be considered human embryos (de Miguel Beriain 2017). Keeping this criterion in mind, should the embryos created by Amadei *et al.* (2022) be considered 'real embryos'? This is hard to assess. Indeed, it is far from clear if these embryos could technically complete the gestation period through this method.

On the other hand, how should we consider such entities during the *ex utero* developmental process? Moreover, and more speculatively, if the future baby develops in an artificial womb from scratch, to whom does the moral responsibility belong about this human once they are born? It is not so obvious that any possible answer to this question would imply the donors of the genetic material, since in many countries, like Spain, the legal mother is the one giving birth independently of the genetic origin of the future child. Actually, this inconsistency still matters in current debates about *in utero* fetal development (Derbyshire & Bockmann 2020).

In both articles, the authors agreed that it could be technically possible to switch from *in utero* to *ex utero* development for 'artificial embryos', and vice versa (Amadei *et al.* 2022, Tarazi *et al.* 2022). Inferring this possibility to human cells, should we ban their implantation in a woman's womb? These and many other ethical questions should receive greater attention as this fascinating research progresses in the future. And of note, in the light of novel applications with human cells that might give rise (or not) to human embryos or similar primitive structures, proper legislation should be discussed and proposed in advance to the recurrent application with samples from human sources.

Our conclusion is that this novel technique to develop 'artificial embryos' not only paves the way for the future of experimental embryology but also opens a completely new and unexpected venue in bioethics research. Much effort is needed and required to further explore the abovementioned questions, which might shift most of our current paradigms about reproductive ethics and become game-changing in our future understanding of human reproduction.

Declaration of interest

The authors state that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

The authors report funding from La Caixa Foundation (LCF/BQ/ DR20/11790005), Eusko Jaurlaritza (Ayudas a Grupos de Investigación IT-1066-16), and Fundació Grífols (BEC-2022-05).

Author contribution statement

AV and JR conceived the study and wrote the paper. IdMB contributed with some of the ideas included in the paper and revised the manuscript.

References

Aguilera-Castrejon A, Oldak B, Shani T, Ghanem N, Itzkovich C, Slomovich S, Tarazi S, Bayerl J, Chugaeva V, Ayyash M *et al.* 2021 Ex utero mouse embryogenesis from pre-gastrulation to late organogenesis. *Nature* **593** 119–124. (https://doi.org/10.1038/s41586-021-03416-3)

Amadei G, Handford CE, Qiu C, De Jongh J, Greenfeld H, Tran M, Martin BK, DY C, Aguilera-Castrejon A, Hanna JH *et al.* 2022 Synthetic embryos complete gastrulation to neurulation and organogenesis. *Nature* **610** 143–153. (https://doi.org/10.1038/s41586-022-05246-3)

de Miguel Beriain I 2017 "Patenting human embryonic stem cells in the European Union context: an updated analysis of a complex issue." In *Safety, Ethics and Regulations*, pp. 263–273. (https://doi.org/10.1007/978-3-319-59165-0_12)

Derbyshire SW & Bockmann JC 2020 Reconsidering fetal pain. *Journal of Medical Ethics* **46** 3–6. (https://doi.org/10.1136/medethics-2019-105701)

Kagawa H, Javali A, Khoei HH, Sommer TM, Sestini G, Novatchkova M, Scholte Op Reimer Y, Castel G, Bruneau A, Maenhoudt N *et al.* 2022 Human blastoids model blastocyst development and implantation. *Nature* **601** 600–605. (https://doi.org/10.1038/s41586-021-04267-8)

Moris N, Anlas K, van den Brink SC, Alemany A, Schröder J, Ghimire S, Balayo T, van Oudenaarden A & Martinez Arias A 2020 An in vitro model of early anteroposterior organization during human development. *Nature* **582** 410–415. (https://doi.org/10.1038/s41586-020-2383-9)

Tarazi S, Aguilera-Castrejon A, Joubran C, Ghanem N, Ashouokhi S, Roncato F, Wildschutz E, Haddad M, Oldak B, Gomez-Cesar E *et al.* 2022 Post-gastrulation synthetic embryos generated ex utero from mouse naive ESCs. *Cell* **185** 3290–3306.e25. (https://doi.org/10.1016/j.cell.2022.07.028)

Received 11 November 2022
Accepted 23 February 2023
Available online 23 February 2023
Version of Record published 14 March 2023