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human reproduction

Human Reproduction, 2024, **39(11)**, 2387–2391
https://doi.org/10.1093/humrep/deae228
Advance Access Publication Date: September 30, 2024
ESHRE Pages

Ethical considerations on the moral status of the embryo and embryo-like structures†

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†ESHRE pages content is not externally peer reviewed. The manuscript has been approved by the Executive Committee of ESHRE.

ABSTRACT

The current article provides an ethical reflection on the moral status of the human embryo, which is a crucial factor in determining permissible actions involving embryos and the extent of their protection. It advocates for the extension of the research period for embryos to 28-days post fertilization. It also states that integrated embryo-like structures (ELSs) should not currently be given the same moral status as natural embryos. However, if they pass the relevant tests, they should be subject to the same rules as natural embryos.

Keywords: 14-day rule / embryo model / embryo research / ethics / pre-implantation embryo / ART

Introduction

This article is an update of and replaces the previous ESHRE Task force Ethics and Law paper 'The moral status of the pre-implantation embryo' (Shenfield *et al.*, 2001). The present article reconsiders this position in view of two emerging questions: (i) should the 14-day rule for embryo research be maintained? and (ii) what moral status should be attributed to embryo-like structures (ELS)?

Moral status of the embryo

The moral status attributed to a human embryo determines our ethical obligations towards it, sets boundaries on our actions involving embryos, and specifies the level of protection it warrants. Widely varying degrees of moral status have been attributed to human embryos, ranging from an absolute moral status, equal to that of persons, to no moral status at all, similar to that of other human cells, with the majority of views in between these two extremes. The previous ESHRE document (Shenfield *et al.*, 2001), in line with most European legislation and regulations, adopted a gradualist view of the moral status of the embryo, i.e., the moral value increases with its biological development, meaning that the moral status is very low at the start of embryogenesis but increases as the embryo approaches the foetal stage 8 weeks later. Given that even very early embryos are already accorded some moral status, this cannot be grounded in properties that we commonly consider to be morally relevant (for example when determining the moral status of different animal species), such as the ability to feel pain, consciousness, or agency. Rather, the status at this very early stage is connected to the potential to grow into a human being with the relevant characteristics. While this 'argument from potential' is contested in the philosophical literature (Pereira Daoud *et al.*, 2024), for the purposes of this document, we will confine ourselves to the observation that the potential to become a person is considered to be very important by many participants in the current debate.

Embryo research

The attribution of a (limited) moral status to very early embryos has led to several restrictions on embryo research. Examples of such restrictions are that research should be limited to goals that have significant scientific and medical value, should be subject to rigorous expert oversight, and should be pursued only when alternative methods for obtaining the intended knowledge are

Received: August 26, 2024. **Editorial decision:** September 16, 2024.

unavailable. A distinction is also commonly made between supernumerary embryos (left over from ART) and research embryos (created specifically for research) (Devolder, 2005). Many countries permit embryo research using donated supernumerary embryos, but prohibit the creation of embryos for research purposes, as stipulated by the Oviedo Convention (Council of Europe, 1997). Other countries allow the creation of embryos for research if the research cannot be carried out using other material (Mertes, 2012).

In embryo research (including basic research into early human development, embryonic stem cell research, and applied research in the context of reproductive medicine), the 'natural' embryo, formed by the fertilization of an egg cell, remains the gold standard. In many countries, thousands of supernumerary embryos that were donated for scientific research remain unused and are eventually destroyed or stored indefinitely (Pennings, 2024). Research on these embryos is the most efficient way to gather the desired knowledge. In addition, it corresponds to the wishes of the patients who donated their embryos for research to avoid unnecessary wastage that would result from their immediate destruction. For some specific types of research, embryos are also generated by transferring a somatic cell nucleus into an enucleated egg cell (somatic cell nuclear transfer (SCNT) or 'cloning') or by transferring the nuclear spindle from one zygote into an enucleated zygote ('spindle transfer'). The most recent addition to embryo research is the use of ELSs, to be discussed further in this document.

The 14-day rule

Following the recommendation of the USA Ethics Advisory Board report in 1979 and the UK Warnock Report in 1984, many countries have adopted the rule that no embryo should be cultured *in vitro* for research purposes beyond 14 days of development (14-day rule), roughly coinciding with the emergence of the primitive streak that marks the beginning of individuation (the embryo is no longer able to twin) and the completion of implantation (14 days after fertilization). Over the past 40 years, researchers did not call for an expansion of this limit, as it was technically impossible to keep a morphologically intact embryo alive *in vitro* for a longer period of time. This may, however, be possible now due to continuous progress in embryo culture, although questions regarding the representativeness of these *in vitro* cultures for *in vivo* development remain (Deglincerti *et al.*, 2016; Shahbazi *et al.*, 2016). This development prompted the International Society for Stem Cell Research to call for scientific, regulatory, and public deliberation on the desirability of extending the permitted period of embryo culture beyond 14 days in its 2021 guidelines (International Society for Stem Cell Research, 2021).

Whether an extension beyond 14 days is morally acceptable or not depends to a large extent on the rationale behind the current time limit, more specifically whether it represents a defining moment in embryogenesis when moral status 'kicks in' or rather a carefully chosen, but debatable, point on a continuum of increasing moral status. According to the former, the current 14-day limit signals a threshold from which point on a human embryo acquires an *absolute* moral status that categorically prohibits its destruction. However, in order to defend this position, proponents of the 14-day limit would need to identify and argue for the specific feature of the 14-day embryo that provides it with such status. Additionally, this perspective requires addressing any inconsistencies this stance may have with practices such as abortion. Some refer to the primitive streak as a decisive biological threshold (approximately around 14 days of development), but it remains unclear to what extent this event is morally relevant. A more convincing understanding of the 14-day limit is to consider it as a contestable demarcation rather than as a rigid moral boundary. This explanation implies that the 14-day limit on embryo research is not about a sudden change in the embryo's moral status at that specific time, but rather a practical boundary where the balance of ethical considerations shifts. This perspective suggests that beyond this point, the relative (morally relevant) benefits resulting from that act, such as the pursuit of potential scientific and medical advancements, no longer clearly justify the harm done by destroying an entity with an evolving moral status. In this case, the 14-day limit does not reflect a categorical boundary but a well-considered (and debatable) cut-off point, based on the principle of proportionality.

Starting from that perception, it can be argued that the balance between the harm caused by the destruction of a 28-day embryo and the benefits in terms of the knowledge that can be gained through research (and which may eventually result in therapeutic options to cure diseases) can be positive (Appleby and Bredenoord, 2018). This position is largely based on the argument that even in the third and fourth week of development, there are still very few reasons to attribute a significant moral status to the embryo, while studying these 2 weeks of development is very valuable as it provides us with crucial insights in terms of the origins of organ development, developmental disorders, congenital abnormalities, and issues related to fertility such as implantation failure. Crucially, to gain these insights in the timeframe between 14 and 28 days, scientists cannot yet rely on embryonic tissue obtained after spontaneous or induced abortions, as retrieving such early embryonic tissue is near impossible. Once beyond 28 days, this becomes a valid alternative route. The principle of subsidiarity, which specifies that preference should be given to the least controversial option, therefore pleads against culturing embryos beyond 28 days, while the principle of proportionality argues for culturing embryos beyond 14 days if necessary to obtain the scientific knowledge. It has therefore been proposed to allow research on embryos *in vitro* until 28 days of development (Health Council of the Netherlands, 2023). This limit is, just as the 14-day culture limit, an artificial threshold, not committed to the idea that an embryo beyond that moment possesses an absolute moral status. Instead, it represents a point at which the balance between moral benefits (scientific and medical progress) and moral concerns (the destruction of a human embryo) shifts from positive to negative, particularly because at that point, a less controversial alternative is available (that is, research on aborted tissues).

The moral status of embryo-like structures

Different terms (e.g. stem-cell embryo models, synthetic embryos, and stem-cell-derived embryos) are used to indicate the entities in this debate. This document opted for the broad term 'embryo-like structures' (ELSs).

In recent years, ELSs have been created from embryonic or induced pluripotent stem cells (Liu *et al.*, 2021; Yu *et al.*, 2021; Oldak *et al.*, 2023). These structures vary widely in composition and complexity. A consensus is emerging that categorizes ELSs into two main types: integrated and non-integrated. Integrated ELSs contain all cell types required for the development of both the foetus and its supporting (extraembryonic) tissues. Conversely, non-integrated ELSs are less complex and lack some (or several) tissue types. At the end of this spectrum are entities that,

although created from pluripotent stem cells, only contain cell types of a specific organ, to produce so-called organoids. As these are organ models, rather than embryo models, we will not discuss them further below. However, some features of an entity (such as the ability to feel pain or to acquire consciousness) may be considered morally relevant independently of the entity's capacity to develop into a person. The presence of these features would also be morally relevant in non-integrated ELSs.

The integrated versus non-integrated distinction refers to the developmental potential of the entity: can the entity, when placed in the right conditions, develop into a human being? At present, there is no hard evidence one way or the other that fully integrated human ELSs have been generated. As human ELSs are being created in a research context and it is unethical to transfer them into a uterus, their developmental potential remains speculative. Two positions can be adopted towards this uncertainty. On the one hand, one could argue that due to the current lack of scientific evidence confirming that these entities can develop into a human being, they should be attributed a lower moral status than natural human embryos, or perhaps none at all. However, the problem with this position is that it cannot meaningfully be challenged, given the general consensus that direct testing of the developmental potential by transferring an ELS to a human or non-human uterus is unacceptable. On the other hand, one could argue that if it cannot reasonably be excluded that this entity could develop into a human being, we should accord it the same moral status as a natural human embryo. This means that the same restrictions should be imposed on research on ELSs as on research using natural human embryos. This can be considered a precautionary approach. However, the criteria for when the relevant developmental potential cannot be reasonably excluded may affect the present research with integrated ELSs. If being morphologically and molecularly indistinguishable is sufficient for this, current research on integrated ELSs should perhaps already be regarded as morally equivalent to research using natural human embryos (Health Council of the Netherlands 2023). However, in order to avoid restricting valuable research for this reason, stricter criteria may well be proposed, for instance the application of a Turing test (a metaphorical test of indistinguishability). Two such tests have been suggested: (i) does the entity go through the same steps of embryogenesis as natural embryos during a certain period and (ii) do similar structures result in live births in other species (Rivron *et al.*, 2023). In fact, these tests have also been applied to entities created through SCNT where, upon meeting specific developmental benchmarks, they were considered equivalent to natural embryos in moral status. We propose a two-pronged test where entities have to pass both prongs (same developmental steps and live births in several mammalian species) in order to pass. Only those integrated ELSs that pass this test should receive the same moral status as natural embryos. At present, none have passed this test.

Innovative methods are being explored to navigate the ethical complexities of ELS research. One such strategy involves ways to actively avoid the possibility of an ELS being equivalent to a natural embryo. These adaptations would allow research to be carried out in countries where legal restrictions do not allow research on natural human embryos. For instance, certain genetic modifications could be built into the pluripotent stem cells to prevent the derived ELSs from developing properly after a certain developmental stage (Pereira Daoud *et al.*, 2024). These genetic modifications should preferably not affect the otherwise normal development of the ELS during the intended culture period in order to maintain its usefulness for scientific research. A second approach could be to work with non-integrated ELSs that would exclude trophoblast-like cells, essential for placenta formation, inherently limiting the developmental potential of ELSs (Rossant and Fu, 2023). However, trophoblast cells play a crucial role in providing early developmental signals, hence their absence would present challenges to maintaining normal development patterns and cell lineage formation during early development. Such models would thus be less representative and scientifically robust.

Integrated ELSs are, however, not necessary for every research project. The principle of subsidiarity states that one should not use an entity with a higher moral status if the research can be done using an entity with a lower moral status (Pennings and Van Steirteghem, 2004). As a consequence, non-integrated ELSs should be used in research, whenever reliable and efficient, given their lower moral status compared to integrated ELS or natural embryos. Non-integrated ELSs inherently lack the complexity and potentiality that integrated ELSs or natural embryos possess, as they do not encompass the broader developmental blueprint for a complete organism. Therefore, integrated ELSs should only be created or utilized when non-integrated models are insufficient for the research objectives. This approach implicitly acknowledges that integrated ELSs possess a certain level of moral status due to their closer resemblance to natural embryos, although it stops short of directly equating them with natural embryos, at least until they pass the Turing test(s).

There are specific research projects for which integrated ELSs may be the best model. Replacing natural embryos with integrated ELSs would be especially helpful for three specific reasons: (i) scalability, ELSs can be produced in larger quantities than natural embryos, enhancing the robustness of scientific findings; (ii) standardization, multiple genetically identical ELSs can be created and compared, and (iii) customizability for research needs, ELSs can be engineered to model specific genetic conditions and developmental disorders, potentially leading to more precise understanding and treatments. However, ELSs cannot replace the use of natural embryos (whether created for research or supernumerary) in all research projects because ELSs are unsuitable for studying certain processes that take place during the very early cleavage divisions of the embryo, such as pronuclear fusion, extrusion of the second polar body, parental-specific epigenetic remodelling, compaction or embryonic genome activation, or for investigating the safety and efficiency of CRISPR-CAS gene-editing technology in human embryos, a potentially interesting technology to repair monogenetic diseases in the future. Moreover, research using natural embryos will be essential to benchmark integrated ELSs given our current lack of comprehensive understanding regarding how well integrated ELSs replicate specific developmental processes. Also, it may not be allowed to replace donated natural embryos with integrated ELSs if countries with a prohibition on the creation of research embryos decide that the creation of integrated ELSs falls under this prohibition.

If the research limit for natural embryos is extended to 28 days of development (when the embryo has completed neurulation, shows blood circulation and has beating heart cells), consistency would demand that the same limit should apply to integrated ELSs, in case natural embryos and integrated ELSs are deemed equivalent. However, it may be difficult to apply x-day rules to integrated ELSs since it is unclear to what extent these structures follow a similar developmental chronology to reach specific developmental milestones and cell types as natural embryos

beyond 14 days. For example, human pluripotent stem cells in 3D culture in the presence of specific factors seem able to differentiate into structures resembling the primitive streak within 14 hours (Hyun *et al.*, 2020). A possible solution would be not to count days but to refer to developmental stages, with specific morphological structures and cell types indicative of development. An integrated ELS could then be kept in culture for research until it reaches the same developmental stage as a natural embryo at 14 or 28 days post-fertilization.

Recommendations

ESHRE makes the following recommendations regarding the two debated points related to the status of the embryo:

- The 14-day limit should be extended to a 28-day limit. This recommendation is based on a careful evaluation of the scientific literature, which suggests significant benefits from studying later stages of embryonic development that cannot be accessed within the current 14-day framework. The proposed extension aims to strike a balance between respecting the human embryo and harnessing the potential scientific and medical benefits that could arise from researching more advanced stages of development.
- At present, integrated ELSs should not be given the same moral status as natural embryos. However, once it can be shown that integrated ELSs go through the same steps of embryogenesis as natural embryos *in vitro* and once integrated ELSs would result in live births in several mammalian species (i.e., pass the relevant Turing test), they should be subject to the same rules and regulations as natural embryos.
- Integrated ELS should be kept in culture for scientific research only until they reach an equivalent developmental stage to that allowed in natural embryos (14 or 28 days).
- A qualified ethics committee should assess whether the creation of integrated ELSs is necessary to achieve the scientific objectives. The committee should ensure that research employs (i) the least controversial model necessary (prioritizing non-integrated ELS models or other alternatives over integrated ELSs) and (ii) the shortest developmental period necessary to achieve the scientific objectives, based on the principle of subsidiarity. When integrated ELSs become indistinguishable from natural embryos, donated natural embryos should be prioritized for research as no new entities with a similar status to a natural embryo should be created when the research can be carried out on existing natural embryos. When the need for scalability, standardization, or customization excludes the possibility of using donated embryos, the use and creation of integrated ELSs should be permitted.

Data availability

No new data were generated or analysed in support of this article.

Acknowledgements

The authors would like to acknowledge the authors of the previous version of this ethical reflection, as well as the members of the ESHRE Ethics Committee 2022–2025 for their comments and external experts Alfonso Martinez Arias en Nicolas Rivron for their comments. We would also like to acknowledge Nathalie Vermeulen who has coordinated this revision on behalf of ESHRE's Central Office.

Authors' roles

G.P., W.D. and H.M. drafted the manuscript. M.P. and S.C.d.S.L. provided and verified the scientific information. All authors critically revised and approved the manuscript.

Funding

European Society of Human Reproduction and Embryology (ESHRE).

Conflict of interest

None declared.

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Human Reproduction, 2024, 39, 2387–2391
https://doi.org/10.1093/humrep/deae228
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