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Human stem-cell-derived embryo models: When bioethical normativity meets biological ontology

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A B S T R A C T

The use of human stem-cell-derived embryo models in biomedical research has recently sparked intense bioethical debates. In this article, we delve into the ethical complexities surrounding these models and advocate for a deeper exploration of their biological ontology to discuss their bioethical normativity. We examine the ethical considerations arising from the implementation of these models, emphasizing varying viewpoints on their ethical standing and the ethical obligations associated with their development and utilization. We contend that a nuanced comprehension of their biological ontology is crucial for navigating these ethical quandaries. Furthermore, we underscore the indispensability of interdisciplinary cooperation among bioethicists, biologists, and philosophers to unravel the complex interplay between biological ontology and the normative framework of bioethics. Moreover, this article introduces a novel combinatorial approach to resolve the ethical dilemma surrounding these models. We propose a distinction between models that closely emulate natural embryos, based on the status of synthetic embryos, and those capable of reproducing specific dimensions of embryonic development. Such differentiation allows for nuanced ethical considerations while harnessing the value of these models in scientific research, paving the way for a more comprehensive ethical framework in the context of evolving biotechnologies.

1. Introduction

The exploration of embryonic development has long stood as an ethically intricate focus within the sphere of biological research. This field not only engenders scientific inquiries but also raises profound ethical and philosophical questions concerning the identity and moral status of the human embryo (DiSilvestro, 2005; Grinnell, 2004; Evans, 2004). Recent breakthroughs in the field of embryology have significantly expanded our understanding of these complexities and have given rise to novel avenues of research within the domain of bioethics (Villalba et al., 2023; Blasimme et al., 2023; Rivron et al., 2023a). Specifically, the groundbreaking contributions by two independent groups (Amadei et al., 2022; Tarazi et al., 2022) have unveiled a striking possibility: the creation of so-called "synthetic embryos", a concept that challenges the conventional paradigm of embryogenesis by suppressing the need for gametic contributions to engage embryonic development in mice. These "synthetic murine embryos" are in vitro models showing a remarkable capacity to faithfully recapitulate critical developmental stages outside the uterine environment, effectively bypassing the necessity for implantation, enabled through novel culture techniques (Aguilera-Castrejon et al., 2021). These revelations have introduced an unprecedented concept into the realm of developmental biology – the proposition that every individual cell possesses the information to orchestrate the early stages of development. Subsequently, these approaches were applied to human cells, with many groups being able to recreate embryonic human structures from pluripotent stem cells (Oldak et al., 2023; Weatherbee et al., 2023; Pedroza et al., 2023), by inducing their differentiation into both embryonic and extraembryonic lineages and assembling them (Fig. 1). These models are thought not only to provide key knowledge in early embryogenesis by circumventing the use of natural embryos, but also to explore the mechanisms leading to implantation failure and spontaneous abortion (Fudge, 2023; Rossant et al., 2021).

These models possess essential attributes that warrant their comparison to human embryos, such as the sustained presence of various cell lineages akin to those found in early post-implantation embryos, self-organization of fundamental embryonic compartments, and evidence of developmental dynamics that parallel the progression of a structurally organized early post-implantation human embryo (Oldak et al., 2023; Weatherbee et al., 2023; Pedroza et al., 2023). Although, at present, these models can accurately replicate only certain embryonic structures, it is anticipated that they will closely approximate natural embryos with successive iterations. Hence, it becomes imperative to address the question of their ethical use. If these models are indeed analogous to natural embryos, it follows logically that they should be accorded a

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similar moral status. Consequently, their application in research should be limited to their current uses. Conversely, if these models exhibit sufficient dissimilarity, an entirely novel ethical framework distinct from that applied to natural embryos might be warranted. Utilizing human stem-cell-derived models in place of natural ones can help obviate the need for the latter. However, it hinges on the premise that these models are dissimilar enough to address the research questions that scientists seek to explore.

This paradox presents a dilemma in which embryo models are either equivalent to natural embryos or sufficiently divergent to serve as exceptionally representative surrogates. The extent of their similarity to their natural counterparts plays a pivotal role in determining their normative status. Notably, prior examinations of the normative aspects of these models, conducted under various approaches like consequentialism (Blasimme et al., 2023), have failed to address this ontological dimension. As a result, a deficiency in our comprehension of the ontology of human stem-cell-derived embryo models impedes the construction of proper ethical frameworks for the regulation of their applications.

In this article, we delve into the recent achievements and ongoing endeavours in the field of developmental biology, exploring the ontology of human stem-cell-derived embryo models. In what follows, we start by discussing previous approaches to the problem and pointing out the weaknesses and dead ends. Then we analyze this problem from an ontological perspective. By identifying a paradox regarding the ontological status of human stem-cell-derived embryo models, we propose a combinatorial approach to solve it and define an ethically acceptable normativity. This approach relies on identifying the biological parameters being modeled and delineates which among them would confer upon the model a moral status akin to that of the human embryo. Finally, we conclude by pointing out an approach to discerning the normativity of these models regarding their embryological features.

2. Previous approaches and the paradox of human stem-cell-derived models

In a recent article (Blasimme et al., 2023), Alessandro Blasimme and Jeremy Sugarman discuss the moral status of these new biological entities by adopting a lens of pragmatism and consequentialism. When considering pragmatism, specifically pragmatic consistency that evaluates the utilization of these models in terms of the success in their practical application, the authors assert that stem-cell-derived embryo models hold a moral equivalence to natural embryos. However, they aptly counter this argument by highlighting the dissimilarities between in vitro models and natural embryos, thereby questioning the appropriateness of subjecting research involving these models to the same legal framework as that established for human embryos. Hence, they reject this pragmatic perspective based on the experimental inequality between models and their subject of study. Indeed, it is legitimate to question why these models should be employed if they are different enough from their natural counterparts.

On the other side, in light of a consequentialist perspective, ethical justification emerges from the potential scientific benefits and medical advancements achievable through the utilization of these models in experimentation. Needless to say, obtaining socially relevant benefits is a crucial objective in research ethics. This viewpoint opens the door, however to justifying a considerable portion of research that is presently restricted to embryos, as the expected benefits are likely comparable, if not superior. Following this approach, the consequentialism proposed by Blassime and Sugarman could potentially compromise the established arguments regarding the slippery slope in human embryo research. If we accept their premise that the creation of embryo models is a vital endeavor aimed at gaining valuable insights into the early stages of human development to advance urgent therapeutic solutions, an alternative perspective comes to light: the ethical utilization of surplus embryos discarded from assisted reproductive technologies (ART).

Furthermore, even if we were to adopt a consequentialist viewpoint, considering that it might legitimize the use of these embryo models based on the potential benefits they offer, we can draw a parallel with historical claims made in stem cell research. Over two decades ago, a similar consequentialist argument was put forth to support the use of embryonic stem cells derived from human embryos, with promises of groundbreaking therapeutics on the horizon. However, as time has shown, many of these promises remain unfulfilled. It is not our intention to dissuade the utilization of human stem-cell-derived embryo models entirely, but rather to remember that consequentialist arguments

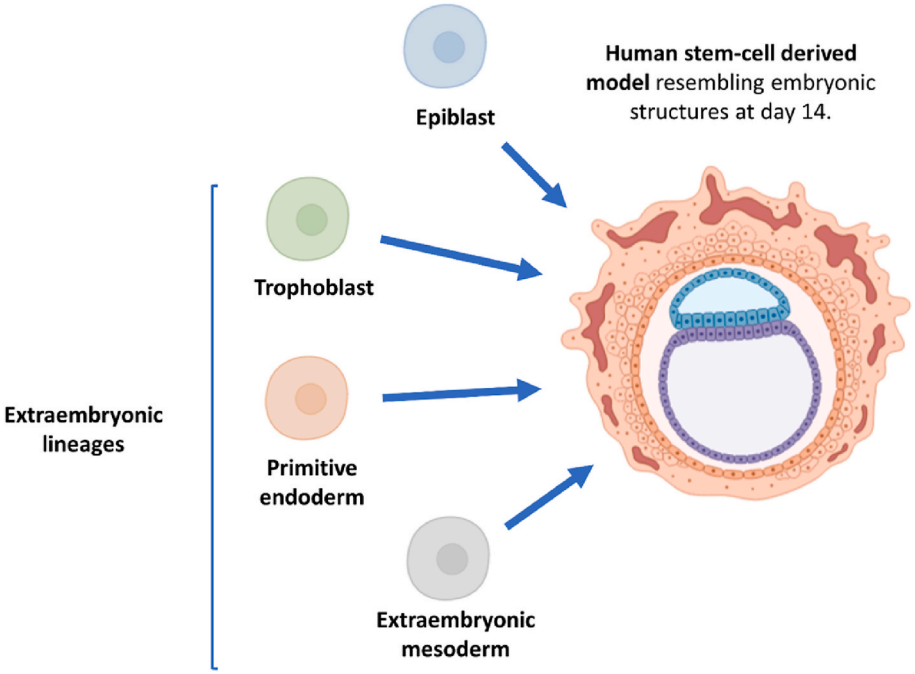

Fig. 1. Schematic representation depicting the assembly of human stem-cell-derived models capable of resembling embryonic structures at day 14 by the incorporation of stem cells differentiated into different embryonic and extraembryonic cell lineages.

depend on empirical premises that may be proven false in the future. Although studies with synthetic embryos *may* undoubtedly produce remarkable scientific benefits in the future, the intrinsic uncertainty of bioscientific progress makes us cautious about this type of consequentialist argument. Hence, Blassime and Sugarman find themselves navigating a complex terrain where two distinct ethical approaches lead to an impasse.

This potential oversight may be attributed to the authors' omission of a crucial factor inherent to these models. Unlike prospective embryos resulting from gamete fertilization, these structures emerge from pluripotent stem cells. This assertion gains support from the fact that Blassime and Sugarman disregard the categorization of these models as "synthetic embryos", as we have defended previously (Villalba et al., 2023), and also acknowledged by the International Society for Stem Cell Research (ISSCR). Indeed, the authors neglect to encompass within their analysis a fundamental consideration regarding stem-cell-derived embryo models: the ontological nature of these structures fundamentally shapes the ethical framework governing their utilization.

Following this ethical consequentialist approach, another group of scientists leading the field of embryo modeling research proposed a gradual consideration in order to maximize the societal benefits (Rivron et al., 2023b). Remarkably, while they share certain pitfalls with previous authors in their emphasis on potential benefits, they introduce two noteworthy areas of consideration. Firstly, they draw attention to the pressing need to reevaluate the legal definition of an embryo. In light of recent evidence suggesting that certain models, although incapable of developing into a newborn, meet certain criteria required for classification as embryos (Tarazi et al., 2022; Kagawa et al., 2022), they argue that this definition requires reconfiguration. Secondly, they initiate a discussion on the ontology of human embryo models. They acknowledge that current models lack the capacity to form a fetus but underscore the possibility that future iterations may bridge this gap. In a compelling twist, they propose a framework for a gradual acquisition of moral status for these models over the course of their development, mirroring the progression seen in natural embryos post-fertilization. However, this multifaceted perspective presents certain normative inconsistencies, particularly when considered in the context of abortion and the moral status of surplus embryos. Even though they appear to offer a versatile toolkit for examining ethical dilemmas, the resolution they provide is ultimately somewhat ambiguous.

The question regarding the ontological status of embryo models seems timely with the latest advances. Similarly, previous human stem-cell-derived embryo models seem far from reaching bioethical inquiries regarding either their moral status or their use. This is the case for blastoids (Kagawa et al., 2022), generated from pluripotent stem cells but completely unable to implant in non-human primates (Li et al., 2023). This limitation is a clear indication that they fall short of meeting the necessary criteria to be deemed similar to natural embryos.

The issue of whether these models should be considered similar or not to embryos formed through gamete fusion leads to a paradox. At present, it is difficult to definitively establish whether these future models would share an identical or merely similar identity with natural embryos. This ambiguity gives rise to a series of thought-provoking questions. If we were to assume that these models are indeed similar to human embryos, then it would logically follow that they should be subject to the same regulatory approaches. However, this raises the critical query: if the models are so akin to natural embryos, what purpose do they serve? In such a scenario, their necessity is brought into question, as they would seemingly replicate the functions of natural embryos. Furthermore, if both models and natural embryos are to be treated legally and morally in an identical manner, it prompts us to contemplate whether the models, in this context, become redundant.

Conversely, if we take the counter view and assert that these models are fundamentally different from natural embryos and thus should not be governed by the same bioethical and legal framework, it leads us to inquire about their utility in accurately modeling natural embryos. This, in essence, introduces another facet of the paradox of embryo modeling: either the models will become, or are anticipated to become, so akin to natural embryos that their existence becomes superfluous, or they will remain dissimilar enough to be inadequate in fulfilling the expectations placed upon them. This paradox, in turn, introduces a conundrum concerning their ontological status. It raises the question of whether or not to use these models as valuable tools in scientific research, given the uncertainty regarding their moral equivalence to human embryos. In the next section, we will delve into this complex question and propose an approach to guide decision-making regarding their use.

3. More than stem cells: the ontology of embryo models

Nowadays, we are unsure whether the latest human embryo models possess the innate potential to be classified as embryos, which hinges on their ability to successfully implant into a human uterus and develop to the stage of a newborn. While we have definitive evidence that earlier models, such as blastoids, are incapable of progressing in non-human primates (Li et al., 2023), we lack this data for the most recent human models up to this point. For these current models, certain indications suggest that they may not fully meet the innate potential required for development, as they remain imperfect replicas of natural embryos. Furthermore, seeking to establish their full development potential through implantation tests is fraught with ethical concerns. Firstly, employing stem cells from a single individual to create these models, and subsequently resulting in a newborn individual, would essentially be a process resembling cloning. Secondly, there are significant safety concerns for both the prospective mother and newborn when attempting such procedures. Hence, the ethical inquiry about the use of human embryo models cannot be addressed by accessing a clear and definitive answer about their ontological status, due to the bioethical issues related to their implantation and development. Perhaps in the future, an arguably more ethical and safe method may emerge to assess the innate potential of these models –like full ectogestation–, thus allowing for a definitive determination of their capacity. However, until such a tool becomes available, an alternative approach is necessary to reach a consensus that can provide a normative basis for their use in the interim. To this end, we have chosen to examine the question of ontological status from two distinct perspectives: the legal and the bioethical.

In summary, it is evident, we think, that current versions of human stem-cell-derived embryo models do not align with the legal definition of an embryo, and as a result, most of the associated limitations should not be applied to them. However, from a bioethical perspective, it is anticipated that future iterations of these models will move closer to natural embryos in terms of their characteristics and capabilities. In this future scenario, it may indeed be appropriate to classify these models as synthetic embryos, bearing a striking resemblance to those originating from gamete fusion (Landecker and Amander, 2023). Nevertheless, the distinction between synthetic and natural should not inherently dictate moral considerations, as this would risk falling into the trap of the naturalistic fallacy. This concept has been previously explored in the context of artificial gametes, where it is clear that we should not automatically attribute moral significance to natural properties (Smajdor et al., 2018). Therefore, current debates on the normative framework for future models become of paramount importance, as they will serve to delineate the ethical and unethical practices concerning these evolving technologies.

A possible approach to driving decision-making would be to face the ontological status of these models, which results in a paradox in our hands. Deriving decision-making from its ontology would entail determining whether they are or are not equivalent to actual embryos (and therefore be considered de facto as such). In other words, to avoid the naturalistic fallacy, the moral properties we attribute to an embryo are independent of its *mere* nature. Considering the ethical concerns surrounding the immoral practice of implanting human stem-cell-derived embryo models in human wombs, a direct assessment of their

potential is currently unfeasible. However, we can approach the dilemma of their use by reframing our evaluation. We have previously discussed the conundrum surrounding these models: either they closely resemble natural embryos, necessitating the application of the same ethical considerations, or they are substantially dissimilar, rendering them ineffective as models. An intriguing facet of scientific research involving models is that they need not faithfully replicate every characteristic of the object being modeled. Thus, we can envision a novel approach based on combinatorics. By combinatorial approach, we mean the determination of certain features or a combination of these features to determine how far the model is from a natural embryo. Thus, embryo models capable of reproducing specific but not all aspects of human embryos could be employed for research without being equated with natural embryos in terms of moral status. For instance, future models capable of mimicking the morphology or genetic regulation of early embryos but falling short in replicating aspects like cellular composition or metabolism should not be accorded an identical moral status. In contrast, models that can faithfully replicate a broad array of features found in natural embryos should be subject to similar ethical considerations. However, not all aspects of embryo development should be considered equivalently. We will contemplate the same criteria utilized to determine the onset and conclusion of life (function and development of cardiac and neural structures) to assess whether these models would or would not be morally equivalent to human embryos. In aligning with the ethical discourse surrounding the initiation and cessation of life, we aim to apply consistent and comprehensive standards to the evaluation of these models, probing the intricacies of their biological features and their alignment with the moral status attributed to human embryos. Therefore, human stem-cell-derived models that can accurately replicate both cardiac and neural structures akin to those observed in fetuses at stages beyond the abortion redline should be deemed morally equivalent to them. Consequently, the application of corresponding ethical regulations must be warranted in such cases. This criterion more precisely delineates the moral status and ethical regulations governing the utilization of specific human stem-cell-derived embryo models. It stands in contrast to vague approaches relying on gradual demarcations that are unable to establish specific distinctions.

Nonetheless, it is also crucial to duly acknowledge that bioethical analysis should also match with a legal framework. First, the legal perspectives define an embryo as a cell or group of cells with the inherent capacity to develop into a human being (Minssen et al., 2015; de Miguel-BeriainIñigo, 2015; de Miguel Beriain, 2014). Here the concept of “inherent capacity” acquires substantive importance. Indeed, while the precise definition of human life remains a subject of ongoing debate: the key point regarding the acceptability of the use of embryo-like structures for research purposes is whether they have this inherent capacity or not. And this is quite difficult to assess in the case of these new entities. On the one hand, it is clear that these models are not flawless replicas of embryonic structures but might achieve such accuracy in more refined iterations. Indeed, if they do, then a dilemma emerges: either these models must be recognized as authentic (synthetic) embryos, or the currently predominant legal definition of an embryo requires reassessment. This preliminary conclusion carries broader implications that extend to various other biological phenomena. Over years, parthenotes served as invaluable tools for researchers aiming to explore early embryonic development while circumventing ethical constraints linked to human embryo research. A human parthenote is an activated egg resembling an early-stage embryo resulting from parthenogenesis, a form of asexual reproduction without the contribution of sperm. At the EU level, with the only exception of the Case C-34/10 Oliver Brüstle v. Greenpeace exception (which was overruled by Case C-364/13) (de Miguel BeriainIñigo, 2017), parthenotes have not been designated as embryos due to their inability to implant. It’s conventionally understood that parthenotes lack the potential to develop into human beings, since the classical reproductive biology dogma postulates that an embryo originates from the fusion of egg and sperm. Consequently, parthenotes evade the classification of embryos, considering their absence of fertilization origin and the uncertain nature of their potential. However, in the US the Dickey-Wicker Amendment took an alternative option, considering parthenotes as human embryos (Rodriguez et al., 2011).

Second, previously Blassime and Sugarman acknowledged that analogous models generated from mouse stem cells can exhibit resemblances to in vivo embryos following gastrulation, suggesting the potential for human models to mirror such structures after the 14-day threshold (Blasimme et al., 2023). However, many legal frameworks regulating abortions hinge on the biological milestone of the emergence of early neural and cardiac structures. Then, should similar criteria be extended to these models? To get a satisfactory answer, more scientific data and comprehensive ethical research are required about the similarities and differences between these models and embryonic structures. Given the inherent limitations of current models, which seem unable to undergo proper development and thus do not possess the required innate potential, it is reasonable to assert that the 14-day rule should not be applied to them.

Third, embryos produced through nuclear transfer (cloning) diverge from the conventional need for both sperm and egg nuclei. Nonetheless, these embryos are endowed with a moral status akin to that of naturally conceived embryos, leading to the application of analogous ethical norms in terms of in vitro generation and manipulation. A relevant perspective that influences the ethical context of nuclear-transfer embryos is their origin from the biological material of an existing individual. To our knowledge, in countries that have legislation in this regard, human cloning has been universally prohibited. Interestingly, a parallel could theoretically be drawn to these embryo models, as they too derive from the biological material —stem cells— of an individual. Whether this aspect bears relevance in the bioethical discourse remains unexplored and deserves further attention in the future.

Finally, it is imperative to foster a consensus aimed at identifying measurable properties and parameters for a meaningful comparison between these models and natural embryos. This endeavour mandates close cooperation with the scientific community and collaboration across diverse scientific societies. While this combinatorial approach may not definitively resolve the intricate ontological questions surrounding human stem-cell-derived embryo models, particularly if we consider implantation in human wombs as immoral, it provides a constructive pathway to navigate the ethical challenges associated with their application. Overall, models that closely mirror the characteristics of natural embryos to the extent that they can be classified as synthetic embryos based on cardiac and neural development should be granted an equivalent moral status. Conversely, models capable of reproducing only select aspects of early embryonic development should be recognized as valuable sources of knowledge within those specific domains. However, they should not be accorded equivalent moral status to natural embryos, even though they serve as useful tools for modelling particular parameters of human embryos.

4. Conclusions

In summary of the above discussion, we have explored the following premise: the ontological categorization of stem cells possessing the capacity to develop into embryonic structures remains undefined. Therefore, it becomes a matter of utmost importance to establish a consensus on the ontological classification of human stem-cell-derived embryo models before constructing a comprehensive legal and bioethical framework to delineate their ethical standing. Importantly, even with the potential consensus on the models’ ontology and the ensuing ethical norms, the fact that the embryonic developmental program is enclosed within pluripotent stem cells, far beyond gamete fusion, gives rise to a host of additional moral quandaries intertwined with other biological tools. At their current stage, human stem-cell-derived embryo models cannot mature akin to natural embryos (even though they were

implanted into a uterus, which would be arguably unethical). Yet, as these models progress in the future, they may more closely mimic natural embryos. This leads us to a critical question: where should the demarcation lie along the continuum between a mere biological entity and an embryo harbouring the potential to evolve into a fetus?

Through this article, we aim to emphasize a significant concern arising from a recent breakthrough in fundamental biology, which has direct implications for the field of bioethics. We have proposed a combinatorial approach that seeks to address this dilemma by differentiating between models that closely approximate natural embryos, approaching the status of synthetic embryos, and those that can only replicate certain dimensions of embryonic development. While previous gradual approaches have failed to delineate at which exact point embryo models should be regarded as similar to natural embryos, here we provide for the first time the parameters to bestow a similar or different moral status. We propose utilizing biological criteria grounded in the degree of neurological and cardiac development as essential markers in the development of embryonic models to confer upon them the same moral status as the embryo. This distinction allows us to navigate the ethical considerations surrounding their use, granting equivalent moral status to models resembling natural embryos and recognizing the value of those specialized in specific domains of research. Achieving a consensus within the scientific community and among various scientific societies is imperative for the effective application of this approach. As we anticipate future iterations of these models that may further blur the lines between synthetic and natural embryos, this approach offers a promising framework to guide our ethical considerations and decisions, even in the face of an ontological paradox.

CRediT authorship contribution statement

Adrian Villalba: Funding acquisition, Investigation, Writing – original draft, Writing – review & editing. **Jon Rueda:** Investigation, Writing – original draft, Writing – review & editing. **Íñigo de Miguel Beriain:** Investigation.

Data availability

No data was used for the research described in the article.

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