Embryonic models with stem cells: a pending ethical-legal reflection

Modelos embrionarios con células madre: una reflexión ético-jurídica pendiente

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Abstract

In recent years, the development of *in vitro* models with human stem cells that simulate early embryonic development has experienced great progress. Difficulties in accessing human embryos, the scarcity of embryonic material and the technical, legal and ethical challenges to research and experimentation with human embryos *in vitro* continue to be a barrier to progress in the knowledge of embryogenesis after gastrulation.

The aim of the present research work is to introduce the state of the question and to analyze the ethical-legal situation that regulates these models of development. Briefly exposing the situation in Spanish territory.

The research methodology was based on the analysis of scientific publications, legal norms and ethical principles. The main conclusion drawn

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is that the limits of embryoid research have not been described and are likely to become indispensable as research advances towards models with the potential to be transferred and gestated in utero.

Keywords: embryoid, reproduction, embryo, research, law, ethics.

1. Introduction

The study of human embryonic development through systematic and anatomical studies on the first stages of embryonic development was the beginning of a discipline that has not ceased to develop and transform itself in the last centuries: embryology. We could say that we are starting from the study of developmental biology and moving towards experimental embryology (1). In this context, advances in genetics and molecular biology have contributed to unveiling some of the most significant processes of cell differentiation (2). However, the use of non-human animal models has exposed great differences that exist in the temporal patterns of cellular organization, gene expression patterns, and so on.

At this point, in order to correctly understand and decipher human embryonic development, it is necessary to study in depth the development of human embryos during implantation and gastrulation, and there is a great lack of knowledge about the mechanisms that regulate cell differentiation and morphogenesis (6). During the first stages of human embryonic development, cellular differentiation occurs, which will lead to the constitution of tissues and organs and their organization through intercellular interactions and complex signals that will determine the pattern for the constitution of the human body of the new individual (7).

However, we are faced with numerous limitations derived from local and international legislation related to research with human embryos. Thus, at present, alternative *in vitro* models have been chosen (3). *In vitro* models based on human stem cells are capable of simulating early embryonic development, which is why it is a field

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with great expectations of progress (4), which also provides an alternative to experimentation with human embryos (5).

The aim of the present research work is to introduce the state of the question and to analyze the ethical and regulatory situation that regulates these experimental models.

2. Where do we come from? The human embryo

The fusion of the ovum and the spermatozoon forms a zygote, a cell with the extraordinary capacity to develop into a new human being. This could be the definition of an embryo from a biological perspective (8,9). However, as science has advanced, the biological, legal and social perception of the human embryo has changed in parallel (9,10,11).

The explosion of human embryology dates back to the research that led to *in vitro* fertilization (IVF) and with it the possibility of extracorporeal generation and culture of human embryos (12). This novel advance would allow the fertilization of a human egg and its survival during the early stages of its development.

After the success of IVF, knowledge of development during the first seven days has been clarifying the mechanisms through which, from fertilization and after a series of segmentations, the first event that will condition subsequent development occurs: the activation of the embryonic genome in (EAG) (7,8,13,14). After this, the steps towards embryonic compaction, polarization and blastulation begin. At this point, approximately on the seventh day of development, the human embryo must be implanted in the mother's uterus in order to survive (15). Therefore, since *in* vivo experiments are not feasible, the cellular and molecular changes that take place in the human embryo at this stage are not known exactly.

The human blastocyst will give rise to three distinct cell lineages: the trophectoderm (TE), extraembryonic tissue responsible for implantation in the stroma of the uterine endometrium and the inner

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cell mass which, in turn, at a late stage of the blastocyst will differentiate into the embryonic tissue proper, the epiblast (EPI) and a second extraembryonic tissue, the hypoblast (HyPO). While the trophoblast begins its expansion and differentiation to cytotrophoblast, syncytiotrophoblast and extravillous trophoblast during the different stages of implantation (14,16,17,18). The EPI (precursor of the cells that will give rise to the embryo) undergoes its first major reorganization during polarization implantation and partially loses its pluripotency while forming the lumen that will give rise to the amniotic cavity and the formation of the amniotic epithelium that will form the membrane of the amniotic sac essential for subsequent development. Thus, the cellular mechanisms underlying the formation of the sac lumen in humans remain unknown. The HyPO proliferates and lines the yolk sac cavity, transforming into visceral endoderm.

From this moment on, the conformation of the anteroposterior axis derived from the reorganization of the two associated structures (EPI and HyPO) takes place, and this process can be divided into two phases: on the one hand, a group of HyPO cells will mark the anterior position where the EPI will constitute the cerebral primordium, while at the opposite end of the embryo they will mark the beginning of the primitive line (PS) responsible for the bilateral symmetry of the human body (2,19). Second, large-scale cell rearrangements will determine the body structure (20). However, 14 days after fertilization, the implanted human embryo is a great unknown, the exact number of cells present in the gastrula is unknown, the exact origin of the primitive germ cells (PGCs) is unknown, and the biophysical and biochemical signals necessary to establish the body axes and constitute the organs are unknown with certainty, as animal models present insurmountable differences for the precision of these events (16,18,21,22).

The difficulties to access human embryos, the scarcity of embryonic material and the existing technical, legal and ethical challenges regarding research and experimentation with human embryos *in vitro*

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continue to be a barrier to progress in the knowledge of embryogenesis after gastrulation (6,13,21,23,24).

Thus, most of the knowledge about the gastrulation process in the human species comes from the anatomical and histological study of the different embryology collections of the last century, among which we can highlight the first great collection by Carnegie of Ronan O'Rahilly and Fabiola Müller (21,25), an international reference.

In short, they provide a new understanding of early human embryonic development beyond the blastocyst stage through the understanding of the mechanisms of differentiation and organization of body structure, as well as the molecular differences that may participate in embryonic morphogenetics during and after gastrulation, which becomes indispensable due to the high specificity of these developmental events according to the species (5,16,22), in addition to understanding some fetal pathologies, congenital malformations and spontaneous abortions (2).

3. Where do we go from here? Development of stem cell-based models: embryoids

Human embryos cultured *in vitro* provide valuable information on the self-organizing and autonomous properties of early human development (26). However, given the ethical constraints and the limited number of human embryos available for functional studies, the use of human embryonic stem cells (hESCs) and human induced pluripotent stem cells (ihPSCs) have been used as alternative models (27). Stem cells cultured under conventional conditions are themselves simple models of the different tissues of the embryo.

The improvement of hESC and ihPSC cultures, capable of differentiating into any of the cell types of the human organism, has allowed multiple experimental designs (28-30). Most of the research was based on the use of hESC from blastocysts, although ihPSCs

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behave in the same way. However, this research is less advanced than in animal models (2,5,31).

For more than a decade, methods for *in vitro* hESC culture have been developed and improved with the aim of obtaining cell growth patterns that mimic stages of early embryonic development (4). That is, to form artificial cell aggregate constructs from the use of hESCs that aim to mimic the development of parts of an embryo or a whole embryo (32). There is no clear consensus for the naming of these structures, they were initially called human micropatterned hESC colonies (33), embryoid bodies (7), synthetic embryo or SHEFF (synthetic human entities with embryo-like characteristics) (34), artificial embryo (35), structured embryonic models or Stembrioids (36), *organoid* (37), *blastoid* (23), *gastruloid* (38) and *embryoid* (39).

This system has provided us with an opportunity to discover the major morphogenetic events that normally occur after implantation of the human embryo (40), including: segregation of epiblasts and hypoblasts; polarization of the epiblast; formation of the amniotic cavity and bilaminar disc; appearance of the prospective amniotic ectoderm; appearance of the yolk sac; and differentiation of the trophoblast into cytotrophoblast and syncytiotrophoblast (14).

hECS in conventional two-dimensional culture exposed to different signals can differentiate to any embryonic tissue, so they have become a valuable tool for understanding stem cell differentiation, studying pluripotency, the potential of the human epiblast in its differentiation to cellular, and the role of cell signaling mechanisms in differentiation (2,18). However, two-dimensional culture is limited in its ability to recapitulate the natural tissue niche, including the spatial (3D) organization of different cell types and localized paracrine signaling between different structures and tissues (18).

The first morphological milestone of the human embryo during implantation is embryonic polarization and formation of the amniotic lumen of the EPI. A hESC culture under growth factor-controlled conditions is able to develop a set of three-dimensional structures that self-organize into asymmetric sacs that simulate the

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gastrulation process (41). In addition to mimicking the development of the amniotic cavity, they are able to show the cellular migratory movement that will lead to the formation of the PS (42).

Different methodologies exist to generate *embryoids*, including suspension aggregation, hanging drops, microwells, and aggrewells, as well as the addition of factors that promote survival. *Embryoids* offer several 3D models with different and complex differentiation behaviors that are useful for identifying signaling factors required in the differentiation of different specific cell types. Also to examine key cell behaviors for germ layer differentiation during embryogenesis, including epithelial-mesenchymal transition and cell migration (43). Despite the strong ability of stem cells to self-organize their own microenvironment, it has been shown that cells require additional environmental conditions to channel fate decisions and morphogenesis (14,44,45).

A 3D model capable of developing all three germ layers and undergoes an axial extension, similar to that observed in the human embryo called gastruloide, has also been described (32,36,46,47). These exhibit multiple features of gastrulation in developing embryos, in particular symmetry breaking, markers of derivatives of the three germ layers, axial extension along an anteroposterior axis and a gene expression pattern corresponding to the vertebrate body plan (2,41). The use of these models allows the dissection of selected morphogenetic events as a promising tool (7,20). The field of *embryoid* research, also referred to by some as "synthetic embryology", has two objectives: first, to design three-dimensional embryo-like structures using stem cells that mimic early embryogenesis to investigate the patterns and sequences responsible for human morphogenesis, and second, to reproduce and modify these patterns under divergent conditions to study the underlying mechanisms and the degree of sensitivity to changing factors (44). Additionally, *embryoids* could be genetically manipulated, thus allowing a better understanding of gene expression (32).

It should be noted that the models studied can be of two types: non-integrated models, those *embryoids that* lack the HyPO and the

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trophoblast, and therefore cannot form yolk sac and placenta, respectively. And the integrated models that contain all the structures necessary for implantation and gastrulation (36). In this sense these *integrated embryoids*, as gastrulation models progress could acquire the potential necessary to complete embryonic development (2).

Although it has not yet been demonstrated that any of the integrated *embryoid* models developed in animals can reach the full development of a fetus, autonomous development of integrated models has been achieved up to 14 days (36,48,49). Possibly the day will come when advances make it possible to develop key features of human embryonic development with sufficient fidelity to ethically and legally question some research (4,9).

For this reason, we must be cautious with respect to the advances in this field and open the debate on the pertinence of establishing a regulatory framework for research with *embryoid* models.

4. Limits of research with human embryos: how do we regulate *embryoids*?

It is clear that human embryology will be a very prosperous field of research in the coming years. In the early days of IVF, the ethical aspects of human embryo research were quickly questioned, although at that time the primitive culture techniques and media did not make it feasible to maintain embryos in prolonged culture. These issues gave rise to what is possibly the most relevant report on *in vitro* fertilization in history to date, the 1984 *Warnock Report*, named after the philosopher Mary Warnock who chaired a government inquiry into human fertilization and embryology (50). The report recommended restricting research with human embryos to 14 days of development, justifying this limit on several grounds: PS appears around 14 days being the first visible sign of tissue organization of the embryo just before neural tube formation (neurulation); it is also the last point at which embryo twinning can occur (some scholars suggest that this is a point of individuation). A key concern of

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the expert commission was to establish a consensus among the different moral positions in relation to the beginning of life and research with human embryos; therefore, avoiding the possibility of the embryos experiencing pain or sensitivity was a pillar on which to base the limits of research (34). In addition, we can point out that when the norm was established it was technologically unfeasible to cultivate human embryos to such a degree of development, so it did not interfere, at least initially, in research (51-53). Reaching this consensus between two opposing points of view was a clear example of the commitment to advance research while respecting the moral values of one part of society.

Because of the above, the 1984 Warnock report influenced many international legislations establishing a criterion that, although not universal, has been included in numerous regulations. The limit of embryo development at 14 days post-fertilization prevents any research in post-implantation stages such as gastrulation or the formation of the PS.

We can find a great variety of international regulations related to research with human embryos, more or less restrictive. All of them are influenced by sociocultural, political or religious factors of each country (54). Based on this fact, we can briefly outline the status of the limits established by some of the most representative countries (55):

1. Countries that have banned basic research: Austria, Germany, Italy, Russia and Turkey. These countries have bans on the use of embryos for non-reproductive or medical purposes.
2. Countries with no time limit on research: Brazil, France, Israel and the United States. Brazil's laws on hESC research prohibit "genetic engineering in human germ cells, human zygotes or human embryos," but do not address a developmental limit or other restrictions on human embryo research (41-43). Israel has a 1999 law prohibiting reproductive cloning and a set of guidelines for hESC research, but does not address or limit *in vitro* research with human embryos *(*44-46). French law

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allows the use of leftover IVF embryos for research only if scientifically justified and with prior authorization from the Agency for Biomedicine, and the United States prohibits federal funding for human embryo research through the Dickey-Wicker Amendment.

3. Countries that limit human embryo research to 14 days or PS formation: Australia, Belgium, Canada, China, India, Japan, the Netherlands, Spain, South Korea, Sweden, Taiwan and the United Kingdom.
4. Countries with an alternative time limit: Switzerland has a seven-day limit under the federal law on embryonic stem cell research.

As explained above, and returning to the main thread, most of the research is focused on the partial reconstitution of *embryoids* that have no implantation potential and have a very limited autonomous life. Likewise, no complete human *embryoids* have been generated to date. However, as we know, it is only a matter of time before the protocols and the design of the experiments achieve the formation of complete human *embryos*. As a result, the ethical implications of human *embryoid* development and research are beginning to be questioned, and a clear delimitation of the regulations governing research with these structures is needed (55-57).

We will try to reflect on several of the aspects that are the cause of ethical-legal uncertainties in relation to *embryoids* as experimental models and their effect on the 14-day time limit for research.

The first question would be the moral status according to them, for which we do not have a clear answer. We have to remember that, from the time of the Warnock report to the present day, there is still profound disagreement about the moral status of the human embryo and the beginning of life (58). The debate on the moral status of the embryo and fetus is based on deeply rooted individual and social values so that the prospects of reaching a consensus between severe and deep-rooted oppositions seem rather unlikely (59). Moreover, for multiple reasons, this debate has been extended to *embryoids,*

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which may require philosophical and sociological reflection to determine whether research beyond 14 days should or should not be allowed, whether *embryos* should be given the same legal or moral consideration as human embryos, and, in this regard, whether or not doing research on embryos would violate their dignity (51). Although it is not the purpose of this work this question about the moral status could also be extended to the status of embryos of the different (non-human) animal species used in research, we have found references at least to studies in mouse, monkey, pig...that would open the doors to a profound reflection and debate on the use of animals in research and the status of these "animal" embryos and embryoids (60-63). Rivron suggests that the range of species used could reflect a compromise between those that are less entitled to protection and those that have the capacity to develop in a manner more similar to that of humans, but this is a matter for another research (9).

As research progresses, it is likely that embryoids will reach a degree of development that largely emulates human developmental characteristics and potential. This may lead to considering the existence of a certain moral status (34). That is to say, the moral status of embryoid could be conditioned to the presence of a set of characteristics and functions proper to the human embryo. However, as has become clear with human embryos, morality does not translate easily or directly into law, so perhaps we should not expect this to influence future regulations in this or other fields of research.

The second question to be addressed is whether we consider that there is an equivalence between the human embryo and the *embryoid* generated from stem cells. This equivalence has been taken up by other authors as "human organic potential", "model problem", or "potentiality" (59). Some scientists have argued that embryos and *embryoids* are not functionally equivalent, at least for the time being. Such an argument is based on a distinction between "partial constructs and those that attempt to model integrated development (59)", i.e. those *embryoid* models that do not constitute complete organisms but part of them and, therefore, would not require the same level of supervision and regulation as human embryos (23). The

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main advantage of treating embryos and *embryoids* differently (given that there is currently no convincing evidence that they are functionally equivalent or may become so in the future) is mainly utilitarian as it provides the opportunity to investigate embryonic development while avoiding the use of human embryos.

However, proponents of the contrary position argue that *embryoids* will become functionally more similar to human embryos morphologically and genetically as research progresses (42,64). The main advantage of treating them in the same way is that it avoids any possible moral doubts, and in turn changes in legislation. This position, however, does not enjoy solid, indissoluble arguments to support it and can certainly be perceived by the scientific and biomedical sector as an impediment to scientific progress.

It is crucial that scientific societies and ethics committees ensure that the *in vitro* development of human embryonic models takes place gradually and that the quality and reproducibility of the results are guaranteed before researchers are allowed to explore later stages. Delving into this issue we can refer to the recent update from the International Society for Stem Cell Research (ISSCR) with updated guidelines for human embryo research in 2021. The ISSCR was founded in 2002 and developed rapidly and in parallel with the myriad advances in the field to become a global organization dedicated to all aspects of stem cell research and its clinical translation (65). It is likely that the future possibility of similarity influenced the cautious wording of the ISSCR guidelines as a plausible reason for treating them legally distinct (66). The ISSCR has chosen to classify embryoid models as *Non-integrated:* these will be those models that mimic only specific aspects or tissues of human embryo development and often do not have associated extraembryonic membranes. These non-integrated embryoid models are reportable and of category 1B:

> Research that is reportable to the oversight process but not normally subject to further review, at the discretion of the appropriate committee and/or local policy. Examples include research

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> involving the in vitro formation of human stem cell-based embryonic models that are not intended to represent the integrated development of the whole embryo (67).

A second group are *integrated embryoid models*: these contain the relevant embryonic and extraembryonic cell types, which could achieve further complexity and development through additional culture *in vitro,* must undergo full specialist review, and are category 2:

> Forms of research with embryos and embryonic models that are permissible only after review and approval through a specialized scientific and ethical review process. Examples include: Research involving in vitro culture of human embryos where embryos are maintained in culture until primitive line formation or 14 days, whichever occurs first, or the generation of stem cell-based embryonic models that represent the integrated development of the entire embryo, including its extraembryonic membranes. These integrated stem cell-based embryonic models should be maintained in culture for the minimum time necessary to achieve the scientific goal (67).

Because *embryoids* (stem cell-based) are not considered equivalent to human embryos in most legislation, the ISSC made the decision that integrated *embryoids* should not be subject to the restrictions of the 14-day rule. However, for ethical and safety reasons, it does include a prohibition on the transfer of any human *embryoid* into the uterus of either an animal or human embryo in category 3B:

> Prohibited Research Activities. Research under this category should not be carried out due to the broad international consensus that such experiments lack convincing scientific justification and are widely considered unethical (66).

Linked to the above, we could suggest the need to redefine the limits and suggest that less complete models should be preferred whenever possible.

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It is necessary to point out that, in contrast to the traditional conception of the development time of human embryos as perfectly linear and delimited, in which all of them must go through different stages to evolve, among them, the generation of the PS, embryoids place us in a new scenario. These models do not progress linearly; instead, they mimic specific developmental points. An *embryoid* could mimic gastrulation (around D+17 in human embryos) in less than 14 days and, moreover, without having developed PS. In other cases, some structures may develop starting at a later stage than PS formation. In this context, it would not be appropriate to regulate *embryoid* research according to the 14-day limit of the Warnock Report. In this situation, one could consider regulation focused on the embryoids themselves: what cells they contain (e.g., extraembryonic tissue), their capacity to develop complex structures (such as neural connections), or what stages of development they have reached (34,55). In any case, determining new boundaries is a highly complex endeavor in itself.

The fourth aspect to consider is the benefits derived from embryoid research. As such, as we have pointed out, some authors defend that embryos should not be considered equivalent to human embryos, thus research with them is a feasible alternative to the use of human embryos under ethical and social criteria. Let us remember the great importance of taking into account the search for proportionality and the balance between the risks and benefits of scientific advances in order to have the necessary public confidence to carry out the research (68). Preclinical evaluation of this stage of development would be particularly informative for future advances in other therapies as there is currently a significant knowledge gap in the early post-implantation stages.

Arguments in favor of extending the limit are largely based on the potential scientific and clinical benefits that scientific research brings to improving people's lives and therefore advocate allowing it to continue. Some of the potential benefits could be directed toward (4,23):

– Achieving a better understanding of how stem cells differentiate to different cell lines and developing human stem cell

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differentiation culture methods to achieve greater fidelity with the processes.
- Study and understand germ cell biology.
- Improving infertility treatments, with greater understanding of embryonic development, gastrulation and implantation.
- Improvement of family planning and design of new contraceptive methods that prevent fertilization or implantation.
- Preventing abortions due to causes related to suboptimal implantation.
- Prevent abnormalities in placental development and early losses.
- Study and understand the implications of genetic and epigenetic changes.
- To achieve a better understanding of key stages of early human development.
- Development and evaluation of drugs for specific targets in embryogenesis or their teratogenic effects during pregnancy.
- Development of cell and tissue therapies for transplantation.
- Development of structures similar in function and size to human organs for pharmacological studies or even transplantation.

However, appealing to the beneficence of research and its technical feasibility to extend the limit for embryoid research may raise certain doubts. We could explain it with the similarity of gene editing in embryos, allowing a potentially beneficial and feasible technique, exclusively for these reasons could err on the side of a high degree of optimism of scientific progress, without assessing the present or future risks. Today, authors such as Harris and Lovell-Badge argue that it is a matter of certainties about the benefits and certainties of technical feasibility: embryo research has been shown to be beneficial and feasible (65,69). In this sense, we must consider these qualities in conjunction with the rest of the points discussed.

The principle of proportionality today constitutes, perhaps, the best known and most recurrent "limit of limits" (70). Despite being

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a legal principle, it is applied in different fields and disciplines such as bioethics or biomedical research. Its correct application is very useful to discern the moral legitimacy of a decision, in particular, we must consider the relevance of limiting or not such research. In research with embryoid models it is important to analyze the quantitative and qualitative aspects related to the means and ends of the research, the probability of success and the ratio between risk and benefit (71). This principle requires that the end justifies the means and the value obtained with the research outweighs the associated burden (9,72).

Another classic argument that is often introduced when dealing with new biomedical technologies is the slippery slope argument (73,74), which moves us toward the precautionary principle, whereby research should take a cautious approach to the balance between risk and harm (74,75). The slippery slope argues that allowing a certain practice (in this case, allowing *embryoid* research by extending the currently standard 14-day limit) could consequently induce unethical or illicit practices in such research, or even lead to the permissibility of research on fetuses and newborns (51), or open the door to the permissibility of techniques such as germline genome editing. The argument expresses the concern that once we become accustomed to research on pre-embryos, we will extend permission for research on embryos at a later stage of development; once we become accustomed to this as well, then we will allow research on fetuses and newborns.

To these reflections we should add a few words about the figure of Informed Consent. The use of hECS and hiPSC in the creation of embryoid models has become a very interesting alternative, which, however, may raise concerns regarding informed consent.

Informed consent is the ethical-legal tool that ensures the maximum guarantees of respect for an individual's autonomy in both research and healthcare. Informed consent safeguards the rights of individuals in the event of the intention to participate in or donate cells or embryos left over from IVF for research. In this regard, it

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should be noted that the purposes of *embryo* creation research must be clear. Indeed, we must question whether cell or embryo donors know what they are signing when they are asked for their consent (76), the main reason being that cell or embryo donors may be unaware of the processes involved in hESC culture, cell reprogramming, and storage in cryobanks for future research. Based on this fact, would it not be imperative to inform them about the possibility of forming embryos with genetic characteristics identical to the donated cells/embryos (except for epigenetic modifications or those derived from the derivation of the cell line)? (77) Do they consent to research in the development of *embryoid* models? If so, will these models be partial or complete (78)? Such questions can be complex for donors of cells and supernumerary embryos, not knowing the implications and information related to the use of hESC and hiPSC. Ultimately, for *embryoid* research and development, there must be real, complete, informed consent that is adequate to the understanding of the population.

In summary, the future of human embryoid culture beyond 14 days to study gastrulation and PS formation, early development of the germ layer, nor has a concrete regulation of early organogenesis been established, all of which will certainly encounter different barriers according to each legislation.

To conclude, some national legislative systems have already regulated this uncertainty: Japan has adopted the view, albeit unofficially, that there is still no scientific consensus on whether blastoids have the capacity for ontogenesis if implanted in utero. Therefore, their regulation treats blastoids differently from blastocysts (79).

Both the United States and the United Kingdom have adopted the same position (55). Australia, on the other hand, has taken the position that blastoids should be treated in the same way as embryos, given certain morphological similarities between blastoids and embryos, and given that some of these similarities are consistent with the regulatory definition of "embryo" (80).

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Given that research can achieve a high degree of similarity with natural human embryos, the need to expressly prohibit the use of these embryoids, or similar structures for reproductive purposes, as well as their uterine implantation for research purposes, has become evident (23), as stated in the ISSCR.

5. What do we find in the Spanish regulations on embryoid research?

In Spain there are a large number of regulations in the biomedical field whose interconnection is sometimes difficult to summarize. Most of these regulations date from the beginning of this century and reflect the commitments acquired with the Convention on Human Rights and Biomedicine (CBDHM) of 1997 (81). Specifically, we are talking about Law 14/2006 of 26 May on assisted reproduction techniques (and its implementing regulations)(82), Law 14/2007 of3 July, on Biomedical Research, Royal Decree 2132/2004, of 29 October, establishing the requirements and procedures for requesting the development of research projects with stem cells obtained from supernumerary pre-embryos, Royal Decree-Law 9/2017 of May 26, amending RD-Law 9/2014 of July 4, establishing the quality and safety standards for the donation, procurement, evaluation, processing, preservation, storage and distribution of human cells and tissues and approving the rules of coordination and operation for their use in humans (83).

Research with embryoids generated from stem cells is subject to the above rules, as well as to ethical supervision measures, good research practices and the control of the competent collegiate bodies. The aforementioned laws also establish certain restrictions on interventions related to the creation of embryos for research purposes, interventions aimed at modifying the human genome if they affect the germ line, and also those related to research with human cells, tissues, embryos and fetuses (84).

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It is important to start from the definition of embryo contemplated in the Spanish regulations:

> The embryo is the stage of embryonic development from the moment the fertilized oocyte implants in the uterus until the beginning of organogenesis, which ends 56 days after fertilization. The pre-embryo is an in vitro embryo from fertilization of the oocyte until 14 days after fertilization (85,86).

The regulations mention fertilization as part of the definition of embryo, thus excluding the figure of the embryoid (given that its formation does not imply fertilization), we could ask whether the regulations are permissive in this sense (87).

Biobanks are authorized in Spain in accordance with RD 1716/2011, of November 18, which establishes the basic requirements for the authorization and operation of biobanks for biomedical research purposes and the treatment of biological samples of human origin and regulates the operation and organization of the National Register of Biobanks for biomedical research and the National Bank of Cell Lines as well as the obtaining of samples for the development of embryoids in research.

In relation to the IC for obtaining and generating cell lines and embryoids, it has the added difficulty of understanding the particularities resulting from the genetic information of the sample and its possible uses. A plausible revision of the content of these ICs would be worthwhile.

Moreover, in Spain, methods for embryoid formation including SCNT and parthenogenesis are regulated, and therefore methods developed from hESC or hiPSC are permissible (86,88). Now, many of the laws and other national regulations were developed to address other issues such as reproductive cloning, hESC research, and research with human embryos from IVF, but may now be applying to embryoid research.

As a result, the regulatory position on the boundaries of embryoid research has not been developed and it is likely that determining

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whether there should be or is a restriction on embryoid research will require careful review of the language and associated definitions within national laws and guidelines.

6. Conclusions

Given the reflections and arguments we have described embryoids as a research model, in order to describe the current state of development and the ethical-legal uncertainties they raise, we can emphasize that they are a useful scientific tool and an ethical alternative to human embryo research. The main guideline for human embryo research is the 14-day limit proposed by the Warnock report. Although it is the most common regulation, it may not be valid for *embryo* research. Most countries do not have clear guidelines on embryo research and their limits are poorly defined.

Normative regulations could consider the justification of the research, the quality of the research, the potential benefits, and the ethical commitment of the project in order to delimit its uses.

As a main conclusion in this work, we highlight the need for the development of legal guidelines with respect to the limits of research, since they will be crucial as the models are perfected and progress is made in the development of a complete embryoid with the potential for transfer to the maternal uterus. It is plausible to establish a prohibition on the creation and development of *embryos* for transfer to the uterus, whether or not they are intended to produce a pregnancy.

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