

Research on supernumerary embryos: the challenge of reconciling opposing interests and fast-evolving technologies

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Abstract

The paper addresses the issue of the legality and ethical admissibility of invasive experiments on embryos and the correlated one of the degree of legal protection and dignity to be recognized for human embryos, particularly in light of the growing importance that scientific research on embryonic stem cells has been gaining from the clinical and biomedical standpoints in the therapeutic treatments of diseases so far considered incurable, in the interest of public health. Furthermore, the issue of experimentation on cryopreserved supernumerary human embryos is still extremely polarizing, which makes it harder to arrive at shared solutions. The author hopes for a broad-ranging debate at the international level, for the ultimate purpose of achieving shared regulatory frameworks. *Ter 2021; 172 (4):358-362. doi: 10.7417/CT.2021.2340*

Key words: human embryo, embryo dignity, scientific research, comparative law

Introduction

The issue of human embryo research is very complex and multifaceted, since there is no universally acknowledged definition of embryo (1). The ability to produce test tube embryos and perform diagnostic, therapeutic and scientific interventions on them have made the issue of human embryo status, and the respect owed to it, a matter of great relevance and interest. The notion of human embryo does not yet have a shared definition on a scientific level. According to the 1984 Report of the Committee of Inquiry into Human Fertilization and Embryology, the embryo does not acquire its status at the moment of fertilization, but rather fourteen days after implantation in the uterine mucosa (2, 3). In this period of time, science uses definitions such as “pre-embryo” or “early embryo”, totipotent, which has not yet developed the cerebral cortex and whose growth begins between the eighth and the tenth week. Before the fourteenth day and

up to the sixth month, the pre-embryo and the embryo have no personal life. The pre-embryo, in its first two weeks of formation and before the appearance of the primitive streak, could be the subject of experimentation. The prerequisite for allowing experimentation on the embryo is that within this period, as the so-called primitive streak has not yet appeared - which marks the transition from total or pluripotent cells to specialized ones - the embryo cannot be deemed fully formed yet. The primitive streak, in fact, constitutes the first element of identification of the embryo, before which it is still possible to divide the embryo without killing it. Two opposing views exist on the issue of embryonic status: the one that considers the embryo a human being from the moment of fertilization and the one that deems the embryo as a “person” not from conception, but only when the egg and sperm fusion occurs, thus engendering a new genome. The genome is one for each individual. According to the latter view, the embryo is not an individual in the first days of life, because in the early stages following conception the embryo is totipotent, hence it is capable of merging with other pre-embryos. The early “human being” starts being a person only after fertilization, i.e. when the brain structures begin to develop. At a fundamental level, the fact that the embryo is not yet a person only means that it is not entitled to full moral and legal guarantees that are owed to fully-fledged persons. So, the underlying issue is how to establish what degree of protection should be granted to the embryo. The debate on this issue is still open and the results in terms of policies and regulations, in Europe and elsewhere, are far from consistent, as we shall see.

What fate for supernumerary embryos?

The issue of experimentation on supernumerary embryos created during the application of *in vitro* fertilization techniques, but not implanted in the maternal uterus is very controversial. Science argues that cryopreserved embryos can remain in this state indefinitely. In fact, the temperature reached by liquid nitrogen (196 °C, 384.8 °F) can block

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the degradation process, which can resume only if the embryos are brought back to higher temperatures. Therefore, in order to know whether an embryo is still viable, it must be thawed and transferred into the womb. If an embryo is sufficiently viable it can start a pregnancy, but it can also be used in scientific research. If, on the other hand, an embryo is damaged, it is unusable for either purpose.

For “surplus” embryos, still potentially usable for reproductive purposes, but abandoned by their parents, the National Bioethics Committee, in a 2005 opinion proposed the so-called “Adoption by birth” (4). Such an option entails that the abandoned embryo is thawed and tries to develop towards birth. The “adoptive” parents, unable to procreate naturally, can thus avoid the complications stemming from adoption and live the experience of a child born from the womb of the woman who wishes to become a mother, and for whom the implantation will be carried out. The Committee’s proposals do not seem effective at solving the problem. Firstly, it is worth noting that “embryo adoption” could never include the very high number of embryos in a state of abandonment. Furthermore, diseased embryos, i.e. those that cannot be implanted, also fall within the category of abandoned embryos. For such embryos, however, adoption is hardly a feasible option. As for embryos unsuitable for transfer, the chief issue is about their fate, especially in relation to their use. In a 2007 opinion, the National Bioethics Committee hoped that a set of standards for ascertaining the death of the embryo could be identified, which would make it possible to donate embryonic cells for research, similarly to what happens with the donation of organs from deceased donors (5). From such a perspective, the removal of stem cells from the embryo would be viewed as a sort of solidarity contribution that the donating couple makes to scientific research in order to develop therapies for major incurable diseases, and would give a socially valuable meaning to the inevitable death which inevitably awaits non-implantable embryos.

In fact, if the embryo is a human life worthy of the same degree of dignity as a person, indefinite storage in liquid nitrogen, without any prospect for development, arguably undermines such dignity. The solidarity-based solution, on the other hand, undoubtedly entails a measure of due respect for the embryo, which, although it cannot be legally equated with a human being, must be treated in a manner consistent with the fact that a human life can develop from it (6). In addition, it is worth bearing in mind that no direct production of embryos takes place for scientific research purposes, which is prohibited by art. 18, paragraph 2, of the Oviedo Convention, as the embryos used would only be those created for assisted fertilization procedures and no longer usable for this purpose. Secondly, the voluntary, conscious embryo donation (therefore in compliance with the precepts of informed consent) rules out the risk of exploitation of the human body for profit, which is clearly prohibited by art. 3, paragraph 2, point 3, of the Charter of Fundamental Rights of the European Union.

Nonetheless, some fear that by admitting experimentation on supernumerary embryos, the ethically unacceptable effect of deliberately creating surplus embryos *in vitro* could be incentivized, for the sole purpose of allocating them to scientific research, regardless of specific reproductive pur-

poses. This would conflict with the bioethical principles laid out in the Oviedo Convention.

In order to avert this risk, some propose permanent cryopreservation of diseased embryos until natural death. This solution would avoid reducing them to mere biological material or to a set of cells without intrinsic value that can be destroyed for research purposes. Those who support this viewpoint propose the promotion of scientific studies and alternative research methods with respect to the use of embryonic stem cells according to a general precautionary principle.

Does cryopreservation serve embryo dignity?

The cryopreservation technique, still unregulated and destined to last indefinitely, does not uphold the dignity of the embryo for several reasons. First of all, the fate of the cryopreserved embryo is sealed: it is destined to stay frozen for ever; even if it were thawed, its chances of survival would be few. Science has in fact not yet ascertained whether there are risks for the unborn child and for the mother, in the event that an embryo is implanted whose cryopreservation had lasted a long time. In our opinion, condemning the embryo to endless cryopreservation is essentially inhuman, in that it does not respect its core values and dignity that are to be upheld at all times. Dignity is tied to life, whereas the cryopreserved embryo is closer to a condition of death than life. Therefore, if authorizing scientific research on embryos inevitably means sentencing them to death, leaving them in a state of endless cryopreservation still leads to their slow but inexorable extinction.

European Court rulings decisions and national legislative frameworks

In Europe, there is currently no broad consensus on the problem of supernumerary embryos not intended for implantation. For this reason, the European Court of Human Rights has granted a wide margin of appreciation to Member States (7, 8) on how to regulate research in such a sensitive realm while guaranteeing the right balance between state interests and the interests of those directly impacted by such norms. In practical terms, according to the European Court of Justice, each State enjoys “a high margin of appreciation” in evaluating every aspect of the legislative tools to be enacted. The evaluation must be subordinated to “scientific evidence” broadly acknowledged at the international level. In the well-known case *Brüstle v. Greenpeace* (9), the European Court has spelled out a rather broad notion of human embryo, which even includes “a non-fertilised human ovum into which the cell nucleus from a mature human cell has been transplanted and a non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis”. Overall, whenever a unit exists, even single-celled, from which the process of forming a human being can be started, then such a unit ought to be viewed as a human embryo within the meaning and for the purposes of Directive 98/44 / EC (10). The Court has also asserted that the prohibition also applies in the event that the invention for

which protection is requested has a scientific purpose: the Court in fact has argued that “the exclusion from patentability concerning the use of human embryos for industrial or commercial purposes set out in Article 6(2)(c) of Directive 98/44 also covers the use of human embryos for purposes of scientific research, only use for therapeutic or diagnostic purposes which is applied to the human embryo and is useful to it being patentable” (11). Also within the Council of Europe, article 18 of the Oviedo Convention on human rights and biomedicine asserts that “The creation of human embryos for research purposes is prohibited” (12).

The legislative solutions implemented by individual European states appear to be very diverse, with varying degrees of restrictions. In some states the matter is currently unregulated, while others, for example Andorra, Latvia, Croatia and Malta, have enacted legislation that prohibits any research on embryonic cells. Other states, such as Slovakia, Germany, Austria and Italy, allow this type of research if the purpose of the experiment is aimed at protecting the life of the embryo, or if the research uses cells imported from abroad as long as they were obtained on a date prior to May 1st 2007, from supernumerary embryos no longer usable for reproductive purposes (13).

The UK has a somewhat permissive legislation. The English Human fertilization and embryology act authorizes both the legal reassignment of supernumerary embryos derived from assisted procreation techniques to research - provided that consent is granted by the couple who provided the genetic starting material - and the creation of embryos *in vitro* for the purposes of experimentation. In Spain, Ley 14/2006, sobre Técnicas de Reproducción Humana Asistida has codified the notion of pre-embryo, the only one that can be used for scientific research, with the informed consent of the couple - or of the woman who has resorted alone to assisted fertilization practices - and the favorable opinion of the *Comisión Nacional de Reproducción Humana Asistida* (14) The law specifies that the embryos stored in the assisted reproduction center can also be used for scientific research purposes if the couple or woman have not renewed their will as to the fate of the embryos within four years. In France, a piece of legislation enacted in 2019 legalized research on supernumerary embryos unsuitable for pregnancy obtained in the process of *in vitro* fertilization and no longer part of a parental project.

In Italy, medically assisted procreation is regulated by law no. 40. The law has provisions for embryo protection: article 13 prohibits any experimentation on human embryos of any kind (paragraph 1), allowing it only if it pursues exclusively therapeutic and diagnostic purposes aimed at protecting the health and development of the embryo itself, and if no alternative methodologies are available. It should be noted, however, that under such legislation, “embryo protection” merely consists of the indefinite cryopreservation of embryos which will never have any chance to be born, and are therefore destined for progressive deterioration. It would have been more sensible and appropriate to draw a distinction between embryos potentially destined for implantation and embryos in a state of abandonment which, with certain requirements and limits (e.g. the couple’s consent), could be used for scientific research, as is the case in other European countries.

The Constitutional Court amended Law 40/04 and made it “compatible” with the principles and values enshrined in the Italian Constitution and international conventions (such as articles 1, 5, 18 of the already mentioned Oviedo Convention) and with European Convention on Human Rights precepts. In fact, through its ruling 151/09, the Italian Constitutional Court has lifted the ban on producing more than three embryos and removed the obligation to implant at the same time all the embryos produced. In addition, ruling n. 96/2015 has allowed preimplantation diagnosis and granted fertile couples carrying genetic transmissible diseases access to medically assisted procreation techniques (15). This means that, in the case of embryos affected by the disease, the couple can also decide not to proceed with the implantation. Produced and non-implanted embryos are destined for cryopreservation (16). Just as importantly, ruling n. 229/2015 has declared the illegitimacy of the part of the law that criminalizes the selection of embryos even if exclusively aimed at avoiding implantation in the uterus of the sick ones. Following the aforementioned judgments, the biological material at the embryogenesis stage derived from the application of ART techniques and not usable for reproductive procedures has substantially increased (17). ART centers are obliged to preserve the embryos, even if the commissioning couple has declared their intention to abandon them or donate them to research. The issue of regulating the use of cryopreserved embryos is therefore still unsolved. Alternative solutions are needed if the dignity of such embryos is to be properly safeguarded.

Technology runs faster than regulatory frameworks

On the thorny issue of research on human embryos, finding shared solutions is particularly challenging. Non-implanted and non-implantable embryos cannot be considered mere things, nor can they be reduced to genetic material devoid of any intrinsic value, because they are connected to the life they carry, but at the same time they are not fully-fledged human beings: they are only potentially so, since they have no way to develop and be born. The “secular” approach approves of research on embryonic stem cells because it considers the embryo a mere pool of cells and biological material, while the personalistic and sacred concept of human life views it as an individual, endowed with human dignity (18-20). This is a topic that encompasses moral and religious beliefs, as well as the interpretation of the concept of human dignity (21).

There is no denying that whenever thorny issues such as birth, death, the availability of one’s own body come into play, there will always be approval by some, met with bitter disapproval by others who espouse different principles and beliefs. Polarization is certain to be compounded as new biotechnologies develop which will make it possible to genetically edit humans yet to be born. Genome-editing techniques such as CRISPR-Cas9 are set to be fine-tuned and probably, in a not so distant future, applied in order to modify embryos and thus make humans impervious to disease, or enhanced at the genetic level (22-24). Human ever-expanding knowledge of DNA and RNA genes has already opened up new opportunities for the prognosis of major diseases (25-28)

and towards a more patient-centered medicine, with specific sets of molecular alterations identified for each patient, so as to enable better focused therapeutic approaches. Soon, time may be ripe for taking it even further: achieving genetic editing at the embryonic level.

Manipulating embryonic DNA is an extremely contentious proposition, because it could radically upset human evolution and over time, even society as we know it (28). Still, it is undeniable that by harnessing major scientific and technological innovations, the legal and ethical boundaries in that realm have been dramatically pushed (29). In light of the fact that science is moving in uncharted territory as far as such techniques are concerned, it is essential to shed a light on the science that could make embryo editing possible, but also on the legal, ethical, and social ramifications which it entails (30). Such applications are so far banned in virtually all developed countries, but could such restrictions be some day circumvented in the same way bans on surrogacy and other assisted reproductive technologies have been? (31-33) In addition, the prevailing attitude towards human genome editing appears to be slowly changing: the US National Academies of Science, Engineering and Medicine (34) and the UK's Nuffield Council on Bioethics (35) have issued statements highlighting the need for the establishment of new regulations and guidance over human genome editing, conceding that such practices may be deemed morally possible'. In a development just as noteworthy, Japanese lawmakers have devised draft guidelines meant to allow the use of gene-editing tools in human embryos for research purposes (36). Recently a research group in the UK has received approval to conduct human embryo gene editing, provided that said embryos are destroyed after 14 days (37).

Closing remarks

In light of all the complexities and competing interests at stake, we feel that it is incumbent upon legislators to strike a tenable balance between respect for life, of which even sick embryos are bearers, and the needs of scientific research, in order to guarantee a sensible set of regulations between two fundamental conflicting values, while taking into account deeply-held social, moral and ethical values. We believe that on the subject of cryopreserved embryos, which gives rise to complex ethical issues, it is not appropriate to leave such choices up to the sole determinations of national parliaments. Although lawmakers are certainly legitimized as elected officials, in our opinion, it would be advisable to directly involve the people, to whom sovereignty truly belongs, through popular votes. As recently happened in Ireland in regard to abortion legalization (38), it seems appropriate that voters are called on to express their will on issues such as euthanasia (39, 40), heterologous fertilization (41), surrogacy (42-45) and other controversial practices (46), homosexual parenting (47, 48) and all the other dilemmas arising from the most innovative medical practices which impact the personal sphere of each individual, their culture and deepest and most deeply rooted convictions. It will then be up to the legislator to act in compliance with the decisions of the citizens, drafting and enacting bills inspired by values such as solidarity, in order to find a reasonable balance between

opposing needs, to stave off the risk of arbitrary experimentation and to foster the appropriate and responsible use of embryos in scientific research in compliance with well-established ethical precepts (50, 51). Legislators will have to evaluate the opportunity (also on the basis of scientific evidence internationally validated and acknowledged) of potentially using for research purposes diseased embryos only or even those that are scientifically non-biopsiable". It will also be up to the legislator to determine the duration of the cryopreservation period, as well as the opportunity after such periods to consult the couple to whom the embryos belong in order to verify if they confirm their decision to abandon the embryo and assign it to experimentation and find the most suitable rules to avoid the "commercialization" of residual embryos. The common feeling is that they cannot be allowed to go to waste, but neither can they be created only as tools for medical purposes.

In any case, the problem of treating cryopreserved embryos now constitutes an urgency to be addressed at the national, European and international levels, also in light of the different ways in which individual national legal systems have dealt with such issues. It is therefore strongly desirable to start a broad-ranging discussion at the international level, involving ethics experts, scientists and jurists, in order to pave the way for a shared set of regulations, while bearing in mind that it is far from easy to find a solution liable to satisfy everyone. The contentious issue of embryo research is characterized not only by ethics, but also by the unremitting and unstoppable nature of scientific progress.

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