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The donation of embryos for research: maintaining trust

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Background

There are few areas of research that are as contentious as research on human embryos. Even within Europe, very diverse policies have been developed in regard to embryo research. Some countries – such as Germany, Ireland and Poland – strictly prohibit the destruction of embryos in research, based on the argument that embryo research violates the dignity of human life and/or conflicts with religious teachings. Other countries – such as the UK, Sweden and Belgium – not only allow, but even fund the creation of embryos explicitly for research purposes. These policies are supported by the principles of freedom of research, beneficence and proportionality, as embryo research leads to improvements in healthcare that outweigh the ethical concerns involved (Mertes 2012). Most countries have adopted a pragmatic approach, balancing the arguments mentioned above, in which the destruction of donated 'spare' embryos is allowed, but not the creation of embryos for research purposes, making the so-called discarded–created distinction (Devolder 2012). Although there is much to be said about the legitimacy of making this distinction, only research involving spare embryos – and therefore the least controversial kind of embryo research – will be discussed in this chapter. Spare embryos are embryos that have been created in the course of an IVF treatment, but will not be used for transfer in fertility treatment. This can be due to various reasons: the parental project might be abandoned or completed, certain embryos may not be eligible for transfer due to genetic defects or poor prospects of further development or transfer may no longer be possible due to legal restrictions on age at transfer or a maximum storage period of the embryos. In ideal circumstances, IVF patients are asked which disposition option they prefer for their spare embryos: donation to other infertile patients/couples, donation to research or destruction, although not all options are always offered. While there is great variance between countries, high rates of embryo donation for research purposes have been repeatedly reported (Samorinha et al. 2014).

Although many countries currently allow embryo research with these donated spare embryos, the freedom to perform research on human embryos is still under threat, as illustrated by the success of the Citizens' Initiative 'One of Us'. This initiative claimed that 'the EU should establish a ban and end the financing of activities which presuppose the destruction of human embryos, in particular in the areas of research, development aid and public health', based on the belief that '[t]he human embryo deserves respect to its dignity and integrity' (European Commission 2012). This initiative managed to gather 1,721,626 signatures from twenty-nine different European countries (mainly from Italy, Poland, Spain, Germany and Romania) and was therefore allowed a hearing at the European Parliament in April 2014. This feat has only been accomplished by two other initiatives: one campaigning against vivisection, the other for the availability of drinking water. After the hearing, the European Parliament decided not to comply with the demands of 'One of Us', but this campaign shows that embryo research remains contentious, even in countries where it is currently allowed. Therefore, it is important to maintain the trust of those who presently do support research on human embryos.

Embryo research is valuable both in clinical and in basic research. In clinical research, the most straightforward application is the optimisation of infertility treatment. When a new protocol is introduced into the clinic, for example a new cryopreservation technique, this is ideally first tested on embryos that will not be transferred and grow into a person, in order to avoid harm to future people (Dondorp and de Wert 2011). Besides this clinical research, also basic research into, for example, embryo development and human embryonic stem cell research are only possible if human embryos are made available to researchers.

Classical view on embryo research versus empirical findings

In the ethics literature on embryo research, the central issue is the moral status of the (pre-implantation) embryo. The general expectation is that those who attribute a high moral status (or even personhood) to the early embryo oppose embryo destruction and that those who attribute a low (or even no) moral status to the early embryo support embryo research (or at least do not object to it). It is therefore not surprising that many of the countries outlawing embryo research have a strong religious basis. If one believes that ensoulment takes place at conception and/or that the sanctity of human life needs to be protected, then the 'killing' of an embryo cannot be made right by referring to the benefits of the ensuing research (just as the killing of people for research purposes cannot be justified). On the other side of the spectrum, if one observes from a secular perspective that the early embryo has none of the features which might bestow on it a moral status (sentience, consciousness, rationality), then sacrificing embryos for the advancement of science and healthcare is not problematic at all.

One would expect similar considerations about the moral status of the embryo to be decisive when deliberating whether or not to donate spare embryos to embryo research. However, research into the motivations for (not) donating spare embryos to research has shown that the moral status that is attributed to spare embryos is but one factor that influences the decision whether or not to donate to research. Other, equally important factors indicative of a willingness to donate are feelings of reciprocity towards science and medicine, altruism and a willingness to help others, positive views of research in general and high levels of trust in the medical system (Samorinha et al. 2014). Also, besides the *inherent* value of the embryo that the moral status refers to, the *instrumental* and *symbolic* value that people attribute to their embryos is an important predictor of intent to donate (Provoost et al. 2009; 2012).

A first group of factors predicting the intent *not* to donate are – as expected – related to the perception of the embryo, either as a person (or more specifically a child, a brother or sister of existing children) or as a symbol of the relationship with the partner. People who attribute a high *moral* status to their embryo or a high *symbolic* status (as a symbol of the relationship between two partners) are less likely to donate embryos for research. However, even in the group of people who claim to attribute personhood to their embryos, some participants were still willing to donate them for research (Provoost et al. 2010). Besides the moral and symbolic status, also the instrumental status of the embryo was important, in the sense that many people did not want all the efforts they invested in the creation of their embryos to go to waste after their IVF treatment. A high instrumental value was therefore correlated with a higher willingness to donate embryos for research.

A second group of factors are related to a lack of trust in the researchers or a lack of information about the research projects. Specifically, people reported to be concerned about their embryos being given to other patients accidentally (Lyerly et al. 2006) or being 'grown' in the lab to a stage that they felt uncomfortable with (Provoost et al. 2010). These findings send a clear message to the research community: people are willing to donate embryos to research – sometimes even despite attributing a high moral or symbolic status to their embryos – provided they are reassured that the embryos will be used in valuable research that the donors support. In what follows, a number of elements to consider will be set out.

Information before donation: specific or general?

Openness is the first prerequisite for maintaining trust. Ideally, when someone is asked to donate embryos for research, specific information about the research project that their embryos will be used in should be provided. This is, for example, recommended by the ASRM's Ethics Committee (Ethics Committee of the American Society for Reproductive Medicine 2013) for

the US and by the HFEA's Code of Practice (Human Fertilisation and Embryology Authority 2009) for the UK. However, this standard may conflict with practical considerations. In general, a preferred disposition option for spare embryos is asked of IVF patients before starting treatment. This is done to avoid having to continue storage of embryos of which the progenitors cannot be contacted, are indecisive or have deceased at a point when, for example, the maximum storage period is reached. However, although the patients can be informed about the research projects that are ongoing at the moment when they start treatment (which enables a specific consent for the donation of fresh embryos), they cannot receive any specific information about the research projects that will be conducted five years later, while their embryos may easily be stored for that length of time. In this case, there are two options: (1) only allowing research with embryos of which the progenitors can be contacted so that they can give specific consent to use their embryos in a well-defined project; or (2) ask consent for different categories of research, for example research into embryo development, stem cell research, research into genetic diseases. The second option has the advantages that it is more practical to implement for both the clinic and the researchers than recontacting the patients and that embryos that were allocated to research by the parents at the beginning of treatment are not destroyed against their wishes because they cannot be contacted to indicate the exact project for which they want to donate. A blanket consent to *any* embryo research is inappropriate and unnecessary, given the easy implementation of the second option, although potential donors are of course free to donate for all possible categories.

Besides the general research categories (e.g. embryo development, embryo implantation, cryopreservation, genetic diseases), there are at least four applications/protocols which are especially sensitive to ethical concern and for which it is therefore desirable that donors give their explicit consent: stem cell research, research into germline gene editing, research in which the embryo is extensively cultured and transfer of embryos to other researchers.

When embryos are used for the derivation of stem cell lines, the embryos themselves are destroyed, yet cells containing their DNA can be cultured for a very long period of time. One might say that although the embryo itself is destroyed, its genetic blueprint is still 'alive', which is not the case in other types of destructive embryo research. This has several implications. For example, theoretically, if a cell nucleus from that line would be inserted into an oocyte and activated, a new embryo could be created that would be almost genetically identical to the original embryo (although the mitochondrial DNA will be that of the oocyte and epigenetic changes will be present). Although this is not a very likely application, some potential donors may find the mere possibility disturbing. Others, however, may consider it a comforting idea that the embryo they donate will (potentially) go on living in a different form. Besides the physical immortality of a stem

cell line, another issue might be that researchers worldwide would gain access to these cells and that the genetic characterisation of a stem cell line could reveal information about the donors. In principle, their names will not be linked to the stem cell line, but with the advent of direct-to-consumer genetic testing services which also link different people in their databases, it is not unthinkable that a stem cell line would be traced back to a certain family. Also here, for some people this may not be an issue at all, while others may have a clear preference to donate their embryos to other types of research instead.

Also for research into genome editing, a specific consent of the embryo donors is an absolute prerequisite. The possibility of modifying the genome of human embryos has sparked calls for a moratorium (either on clinical applications or also on research applications) in the research community and sparked fears of designer babies and a return of eugenics in the general population (Baltimore et al. 2015; Lanphier et al. 2015). Given the opposition in the general population to genetically modified organisms – partly based on rational concerns over monopolies, partly based on irrational fears and the yuck factor – it is hardly surprising that genetically modified human embryos instil fear and discomfort in many. At the same time, as previously argued, genome editing is a fantastic tool in research and should therefore not be banned a priori in embryo research (Mertes and Pennings 2015; Savulescu et al. 2015). As for human embryonic stem cell research, however, only the embryos of those donors who do not have personal objections to genome editing should be used in this kind of research, regardless of whether their opposition is based on rational or irrational arguments. Disregarding donors' personal opinion on this topic, although possibly benefiting science, would be disrespectful towards donors and might undermine trust in the research community considerably, as the message will be conveyed that researchers will do 'whatever they want' with donated embryos.

A third type of embryo research for which specific consent needs to be obtained in order to maintain trust, is research in which embryos are being extensively cultured. Until recently, concerns about extensive culturing of donated embryos was unwarranted, as nobody succeeded in culturing the embryo for an amount of time anywhere near the maximum period of fourteen days. Thus, the fourteen-day limit that was recommended by the Warnock Report in 1984 and adopted by several countries, is still a common rule thirty years later. However, with recent advances suggesting that it is now feasible to culture an embryo beyond the fourteen-day limit, there have been calls to extend the limit to twenty-one days in order to be able to study stages of embryo development beyond implantation and the primitive streak (Deglincerti et al. 2016; Shahbazi et al. 2016). Without wanting to engage in this debate here, I shortly want to note that there are two possible ways of regarding the fourteen-day limit. Some regard it as an arbitrary limit that was set as a middle ground between different opinions on the ideal limit, with some people preferring a limit that allows for longer

culturing, others preferring it to be more restrictive. Others regard it as a non-arbitrary limit, linked to the biological phenomenon of the primitive streak and the point at which the embryo is certain to be an 'individual' as twinning can no longer occur. The relevance of these biological facts from a moral point of view is dubious, but especially religious people tend to accord significance to them. It is therefore not improbable that some people would allow their embryos to be cultured for two, but not for three weeks. On a more general note, although there are sound scientific arguments for the extension of the fourteen-day limit, such an extension may also fuel opposition against embryo research. Reproaches of researchers going down a slippery slope and changing the rules as soon as they become obstacles are bound to be voiced and will undermine trust. A new middle ground might be found in allowing research up to twenty-one days in very exceptional cases, but this subject will undoubtedly be heavily debated.

A fourth procedure that is linked to the danger of undermining trust is transfer of embryos to other researchers and other facilities. At first glance, one would think that when an embryo is donated to research, it does not really matter whether the research is carried out in the research institution connected to the hospital where treatment was received or elsewhere. In fact, to avoid undue pressure on patients to donate and to avoid concerns regarding malpractice, the treating physician and the researcher using the embryos should not be one and the same person, which may be an argument to loosen the ties between the clinic and the research, rather than keeping them tight. However, as mentioned above, at least part of the motivation to donate embryos to research is trust in and reciprocity towards the institution where they received IVF treatment. The same relation of trust is most likely not present with other institutions performing embryo research and there may even be instances of mistrust towards other particular laboratories, for instance in the case of commercial spin-offs, or if the other institution is of a different religious background or subjected to different legislation and/or oversight. Just as for stem cell research, genome editing and extensive culturing, transfer of embryos is not necessarily problematic, but as it might be perceived as problematic in specific cases, it is better to err on the side of caution and obtain an explicit informed consent of the donors to make sure that their trust is not betrayed.

For all four of these 'ethically challenging' applications – stem cell research, genome editing, extensive culturing and transfer of embryos to other institutions – the difficulty in obtaining an informed consent for the donation will be to explain the possible issues without introducing fear (rather than alleviating fear).

Information after donation

Also, after the donation, measures can be taken to encourage trust in embryo research. Currently, there is little communication about the number

of embryos donated to research each year, the number of embryos used in research each year, the goals of the research projects in which they are used, the scientific output of those projects and which types of embryos are used (fresh, frozen or – where applicable – created for research). A first report of this kind has recently been published by members of the Belgian federal commission for research on *in vitro* embryos (Pennings et al. 2017).

It is also highly desirable that the results of all studies using donated human embryos become part of the public domain. Given the sensitive nature of embryo research, given that embryo donors cannot be compensated or otherwise rewarded for their donation (although there have been calls to do this, see de Lacey 2006) and that the main motivations of embryo donors are reciprocity and the desire to help other people, their embryos should not be used to further the interests of commercial companies/spin-offs without serving the common good. If not, donors may feel that researchers are taking advantage of their altruism to further their own – non-altruistic – goals of profit-making. This does not necessarily mean that all inventions based on research in which embryos were destroyed should be unpatentable – contrary to what was decided by the European Court of Justice in the famous *Brüstle* v. *Greenpeace* case in 2011 (European Commission 2011).[1] However, the research itself, the findings about reproductive biology, embryogenesis, outcomes of different cryopreservation techniques etc. should be made public. By sharing this research, the recipient of the donated embryos in turn shows reciprocity towards the donors/IVF patients. A policy of mandatory sharing of information also prevents needless repetition of research with the valuable and scarce resource that human embryos are.

Conclusion

While the debate concerning research on human embryos is often reduced to a debate on the moral status of the embryo, several studies have found that the reason why IVF patients do or do not donate their embryos for research depends on many other factors as well. One of those factors is trust in the scientific community. Therefore, it is important that the confidence that embryo donors entrust in scientists is not betrayed. In this chapter we set out some recommendations on how to maintain this trust. A first prerequisite is that the donors are informed about the (type of) research that their embryo will (possibly) be used in. Although due to practical limitations it may not always be possible to obtain consent for the specific research project that an embryo is used in, this cannot be a reason to move to a blanket consent. A middle ground can be found by requesting consent for several categories of research, so that the patients are able to exclude types of research that they object to. For four specific applications/protocols, an explicit and specific consent is advocated: stem cell research, genome editing, extensive culturing and transfer of embryos to other research facilities. This does not pretend to be an exhaustive list, but at least for these four

applications, we can imagine the possibility that even embryo donors who do not object to embryo research per se, might nevertheless object to these kinds of use of their embryos. By seeking explicit consent, we can prevent potential donors from refraining from donating to research all together from fear of one of these applications. In order to maintain the trust not only of donors, but also of the general public, transparency around the embryo research that is being performed is important. Information on how many embryos are used for which kind of projects and what the outcomes of the research are, should therefore be made public.

Note

1 Article 6(2)(c) of the EU's Directive 98/44 (Directive on the legal protection of biotechnological inventions) states that 'uses of human embryos for industrial or commercial purposes' are unpatentable as this would be 'contrary to *ordre public* or morality'. In its verdict in *Brüstle* v. *Greenpeace*, the European Court of Justice concluded that this prohibition on patenting also covers the use of human embryos in research, products whose production necessitates the prior destruction of human embryos and processes for which a base material is required which is obtained by destruction of human embryos, even if the description of the technical teaching claimed does not refer to the use of human embryos. This verdict in fact excludes the entire field of human embryonic stem cell research from patentability.

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