Stem cell-derived gametes, iterated *in vitro* reproduction, and genetic parenthood

doi:10.1136/medethics-2014-102521

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This special issue of the Journal incorporates a series of articles on ethical questions raised by stem cell-derived gametes (SCDGs), understood here as gametes or gamete-like cells created in the laboratory from human pluripotent stem cells. The series includes five original research papers covering a wide range of ethical questions: Robert Sparrow's feature article sets out to stimulate debate on the possible use of SCDG technology to create multiple generations of human embryos *in vitro* (***see page 725***, Editor's choice); César Palacios-González, John Harris and Giuseppe Testa develop and deploy an ethical framework for assessing research uses of SCDG technology and appraise a range of fertility treatments that it may enable (***see page 752***); Heidi Mertes distinguishes a number of accounts of genetic parenthood and explores their implications for possible clinical applications of SCDGs (***see page 744***); Timothy Murphy discusses the possible use of SCDG technology to enable same-sex couples to have genetically related children and challenges some assumptions that have underpinned ethical discussions of this topic to date (***see page 762***); and Anna Smajdor and Daniela Cutas explore a number of ethical and legal questions raised by the possible use of SCDGs to create a person's genetic child without her consent (***see page 748***). This Concise Argument focuses on Sparrow's feature article and accompanying responses.

ROBERT SPARROW ON '*IN VITRO* EUGENICS'

In his '*In vitro* eugenics' Robert Sparrow describes a possible future application of SCDG technology in which multiple generations of human embryos would be created in the laboratory. Egg and sperm cells would first be generated from existing or new human pluripotent stem cell lines. The resulting eggs would be fertilised using the sperm to create zygotes and ultimately embryos. Embryonic stem cells would then be harvested from these embryos and used to create new egg and sperm cells, which would in turn be used to fertilise one another to create further embryos. This process could be iterated, in principle indefinitely, but it could also be interrupted to allow one of the resulting embryos to be implanted into the uterus of a woman and perhaps carried to term.

As Sparrow acknowledges, there are a number of possible practical and ethical barriers to the development of 'iterated *in vitro* reproduction' or 'iterated IVR', as I will call the technology. However he concludes, following a substantial discussion, that there is a good prospect that these barriers will be overcome. He thus proceeds to consider some possible applications of the technology. The most controversial of these applications would involve the deployment of selective crossing techniques during the repeated fertilisation process in order to allow for the creation of a child with a desired genotype. Sparrow notes that the use of his envisioned technology in this way will raise a number of concerns about safety and the wellbeing of the future child. However, he offers a number of grounds for thinking that such safety-related concerns are unlikely to ground a decisive objection to this application. He thus calls for further discussion of the other ethical issues that it would raise.

Moreover, he briefly discusses one possible issue himself. He suggests that any children created via iterated IVR would be 'genetic orphans'—individuals with no living parents—since their most immediate ancestors would be now-deceased embryos. Thus, suppose that a couple wishing to have a child adopt the iterated IVR procedure. They provide eggs and sperm which serve as the sole inputs into the process and an embryo produced following several iterations is implanted into the woman, who carries it to term. Though Sparrow does not consider precisely this sort of case, his views on genetic parenthood imply that the couple are not the genetic parents of the resulting child, though they will presumably become her social parents. That child, on his view, has no living genetic parents.[i]

[i]See also Sparrow R. Orphaned at conception: the uncanny offspring of embryos. *Bioethics* 2012;26:173–81.

Some might see this as constituting an objection to the envisioned application of SCDG technology. It might be argued, for example, that the child is likely to be disturbed by his or her lack of genetic parents and that this makes it ethically impermissible to bring such a child into existence. Sparrow is not persuaded by this objection, but notes that the unusual genetic relationship between the social parents and their social child does have interesting implications for potential arguments *in favour* of the technology. One possible argument for allowing prospective parents to use other genetic selection technologies, such as pre-implantation genetic diagnosis, would be to enable them to have the healthiest or most flourishing possible genetic child that they can have, but this could not be an argument for the use of iterated IVR, for this will not allow the prospective parents to have a genetic child.

RESPONSES

Seven Commentaries (***see pages 732–740***) are offered in answer to Sparrow's paper before Sparrow responds (***see page 741***). Later in the issue, a Brief Report by Helen Watt (***see page 759***) also takes up issues raised by Sparrow.

Three themes are prominent in these responses. The first concerns Sparrow's provocative nomenclature. Two of the commentaries (those by Mathews and Fujita *et al.*) object to Sparrow's terminology and particularly to his inclusion of the term 'eugenics' in his label for what I above called 'iterated IVR' (as his title suggests, Sparrow refers to the technology as '*in vitro* eugenics').

The second theme is a focus on Sparrow's perceived scientific and ethical optimism. A number of commentators argue that the technical barriers to the development or deployment of iterated IVR are higher than Sparrow acknowledges. For example, da Fonseca *et al.* point to a number of technical difficulties, additional to those mentioned by Sparrow, that they believe will need to be overcome for iterated IVR to serve as a useful enhancement technology, while Mathews argues that the practical limitations on iterated IVR are likely to make it less attractive, as a means of influencing the genetic traits of future children, than genetic engineering techniques that are currently developing rapidly. Similarly, Pugh suggests that the ethical barriers may be higher than Sparrow admits. He argues that those concerned about creating embryos destined for destructive stem cell research are likely also to object to iterated IVR, even where done in the name of reproduction rather than research.

Finally, a number of commentators maintain that Sparrow underestimates the ethical significance of his observations about genetic parenthood. Siegel and Mertes both suggest that the failure of iterated IVR to preserve a genetic parenthood relation between the users of the technology and the resulting child may significantly diminish demand for the technology. Murphy argues that the status of children produced via iterated IVR as genetic orphans generates a 'formidable' ethical challenge to the technology. Meanwhile Watt, in her Brief Report, objects to the process of iterated IVR on the grounds that it would involve forcing the intervening generations of *in vitro* embryos into genetic parenthood.

SOME REFLECTIONS ON GENETIC PARENTHOOD

Interestingly, none of the commentators question Sparrow's claim that the users of iterated IVR would not be the genetic parents of the resulting child (though see Mertes' stand-alone paper, ***page 744***, for a related discussion). However, there may be scope to challenge this claim, at least in cases where the iterated IVR process takes egg, sperm or induced pluripotent stem cells from the users of the technology as genetic inputs.

What makes one individual the genetic parent of another? A initial, rough-and-ready definition might hold that *P* is the genetic parent of *C* if and only if (a) *C* inherited some (or perhaps some specified proportion) of his or her genetic material from a gamete derived from *P*, and (b) the genetic material was not transmitted from the *P* to *C* via another individual.[ii] The first condition serves to rule out cases in which *C* is not the genetic descendant of *P*. The second serves to rule out cases in which *C* is the genetic descendent of *P*, but not a direct descendant; the relation is one of genetic grandparenthood or some more indirect genetic relation, not one of genetic parenthood.

Condition (a) is too restrictive, however. There are other species that reproduce asexually, without the creation of gametes, yet we would I think still want to maintain that there can be genetic parenthood relations between the members of such species. This suggests that we need to drop the reference to gametes in condition (a).

Condition (b) also requires modification. In every normal process of human reproduction, the parents pass genetic material to the resulting child via another 'individual': not an individual human being, but an individual gamete. Yet this would not lead us to conclude that, in normal reproduction, the reproducing individuals are really the genetic grandparents of the resulting child. This suggests that we need to specify what kind of individual the intermediate descendant would need to be in order to break the genetic parenthood link. Plausibly, it would need to be a human being.

If we adopt the modifications suggested by these thoughts, then we might end up with something like the following account: *P* is the genetic parent of *C* if and only if (a*) *C* inherited some (or perhaps some specified proportion) of his or her genetic material from *P*, and (b*) the genetic material was not transmitted from *P* to *C* via another *human being*. Note, however, that on this definition, the users of iterated IVR may well qualify as the genetic parents of the resulting children, provided their genetic material was one of the inputs into the process. This is because it is not obvious that the intervening generations produced in the course of iterated IVR are generations *of human beings*. Some authors deny that zygotes and early human embryos qualify as human beings on the grounds that they lack the required intercellular integration.[iii] The embryo becomes a human being only when its component cells become integrated with and dependant on one another. Before then, the embryo is better thought of as simply a colony of human stem cells. On this view, early embryos are rather like gametes: they are not human beings themselves, they are rather intermediaries formed in the creation of one human being from others.

One attractive feature of this view can be seen by considering the case of monozygotic twins. Monozygotic twins are created by the splitting of one zygote or early embryo, which goes out of existence when the splitting occurs. The twins are in some sense the genetic descendants of the zygote or embryo that split to create them, yet we would not want to say that the initial zygote was their genetic parent whereas the individuals from whom that zygote was formed are the genetic grandparents. Rather, we would say that the couple that created the initial zygote are the genetic *parents* of the twins. The view that zygotes and early embryos are not human beings combined with the account of genetic parenthood that I offered above is able to accommodate this: it allows us to maintain that the couple are the genetic parents of the twins since the intervening individual is not a human being.

Likewise, if we accept these views, there is a case for concluding that a child produced via iterated IVR would be the genetic child of those whose genetic material served as the input into the IVR process, for the child arguably inherited a proportion of her genetic material from those individuals, and the intervening individuals via which this material was inherited were not human beings.

[ii]The concepts of 'inheritance' and transmission via' employed here would clearly need to be further explained.

[iii]See, for example, Persson I. The origination of a human being: A reply to Oderberg. *Journal of Applied Philosophy* 2009;26:371–8.