Special Section: Open Forum

Embryonic Stem Cell–Derived Gametes and Genetic Parenthood: A Problematic Relationship

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The recent success in generating live offspring from embryonic stem cell (ESC) –derived gametes in mice sparked visions of growing tailor-made sperm for men faced with infertility.[1] However, although this development will almost certainly lead to new insights into the processes underlying spermatogenesis and thus in the possible causes of male infertility, it is less certain if deriving sperm from ES cells, which are in turn derived from a sterile man, can make someone a genetic parent. As the gap between newly envisioned reproductive technologies and natural reproduction widens, the question thus needs to be asked if these possible therapies still lead to genetic parenthood.

In the first part of this article, we review special reproductive settings in which it is difficult to argue why someone is—or is not—a genetic parent of the resulting child. Procedures that are discussed are ooplasmic transfer, reproduction through fetal oocytes, reproductive cloning, and haploidization.

In the second part, we analyze what the core elements are upon which our judgments regarding genetic parenthood are based. The aim is not to indicate what kind of parenthood generates parental rights and obligations. Other authors have repeatedly and extensively argued that genetic derivation is not or should not be the key factor in the establishment of these rights and obligations. Rather, parental rights and obligations should be rooted in elements such as causation, intentionality, or foreseeability.[2] Nevertheless, genetic parenthood is desired by many and therefore it is important to have an account of what the term stands for.

Finally, we tackle the question of whether ESC-derived gametes would create genetic parenthood.

Ooplasmic Transfer and Oocyte Nuclear Transfer

Ooplasmic transfer (also called cytoplasmic transfer) involves the injection of a small amount of ooplasm from a donor egg into a recipient oocyte of which the ooplasm is unable to support normal embryonic development. It was first successfully performed in humans in 1997 but was subsequently banned in the United States.[3] The main reason for concern is that mitochondrial DNA (mtDNA) from the donor is mixed with the recipient's mtDNA and that both are present in some of the offspring.[4] It is currently uncertain whether this form of heteroplasmy has any negative effects on the resulting child.

Although the amount of mtDNA contributed by the donor is minimal in this technique, a similar procedure is being researched that would include all of the

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donor's mtDNA and none or little of the recipient's. In oocyte nuclear transfer, pronuclei from a fertilized egg are transplanted into an enucleated donor egg. This procedure would prevent the transmission of mitochondrial diseases to an affected woman's children. Although in this case the mtDNA is not mixed, one objection persists against both ooplasmic transfer and oocyte nuclear transfer, namely, that the resulting child would have two genetic mothers: one providing the nuclear DNA (and in the former case most of the mtDNA) and another providing mitochondrial DNA.[5]

The question then arises of whether it is reasonable to designate the "ooplasm donor" as a genetic parent. The influence of mtDNA on the child will be very limited, especially compared to the influence of half the nuclear DNA originating from the "other" genetic mother. On the other hand, it is somewhat premature to dismiss the importance of mtDNA as having no influence at all, because a number of hereditary diseases are passed on through mtDNA and because it may also have an impact on certain behavioral traits.[6] Robertson has suggested that if one wants to accord a maternal role to the donor, a clear distinction should be made between a "major genetic mother" and a "minor genetic mother" because the contribution of one "mother" is marginal compared to the second mother's contribution.[7] The donor of the enucleated oocytes would contribute a mere 37 genes, in contrast to an estimated 24,000 genes contributed by the originators of the nuclear DNA, or 0.15% of the total genome.[8]

Fetal Oocytes

A second possible development blurring the notion of genetic parenthood is the use of fetal oocytes for reproductive purposes. The procedures for the collection of oocytes from normal healthy women are very demanding and hold certain health risks. In addition, only a limited number of oocytes can be retrieved per cycle, resulting in an acute shortage of donor oocytes for infertility treatment and medical research. One possible alternative source of egg cells would be aborted female fetuses, whose ovaries could be transplanted into women lacking ovarian function or whose oocytes could be removed, in vitro matured, and used in infertility treatments. Due to the morally charged nature of this kind of procedure, it is unlikely to find its way to the clinic anytime soon and should thus be considered as a thought experiment rather than a clinical reality. There seem to be two ways to represent the hypothetical situation of a child born from such a "fetal" oocyte: the creation of a child that has no genetic mother or the creation of a child whose genetic mother is a fetus.[9] In the latter scenario, the donor of the fetal material is likely to be regarded as the child's grandmother (possibly at a very young age). Here the question arises of whether one can be a (genetic) grandmother without ever being a (genetic) mother.

Reproductive Cloning

The use of donor ooplasm and the possibility of using fetal oocytes in infertility treatment are not the only advancements that are forcing us to rethink genetic parenthood. The prospect of making children that are genetically identical to an existing person poses an even greater challenge to the common outline of a

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family tree. Several mammals have been cloned by transferring a somatic cell nucleus of the "original" animal to an enucleated oocyte, which is then artificially activated to start embryogenesis. This procedure is called somatic cell nuclear transfer (SCNT), but is better known as "cloning." Reproductive cloning in humans is so far purely theoretical because it is still unknown if the procedure has any chance of success. Given the levels of risk involved and the controversy surrounding this procedure, it is banned by many countries. For the sake of argument, however, we will envisage a situation in which children can be produced by cloning a prospective parent. Not 50% of the nuclear DNA would be identical, but virtually 100%. Does this mean that that person is even more a genetic parent than someone who only contributed half of his/her child's DNA or does it mean that the parents of the somatic cell donor, each contributing 50% of the nuclear DNA, are the actual genetic parents rather than grandparents (possibly together with the "mitochondrial mother" who provided the oocyte used in the SCNT procedure)? In the latter case, the person who was cloned would gain an identical twin brother or twin sister rather than a child.[10] This claim would seem legitimate when parents decide to clone one of their children, but when an adult decides to clone him- or herself, are we then willing to accept that people can become genetic parents without participating in their child's creation in any way? If not, should parents be required to give their permission when their children want to have themselves cloned?

Artificial Gametes by Haploidization

Reproductive cloning may not be appealing to many prospective parents because most couples long to have a baby that is related to both partners. The solution for people who lack usable gametes then consists of creating gametes tailored to their DNA. One route that is being explored to achieve this goal is somatic cell haploidization.[11]

Artificial haploidization relies on the ability of an oocyte to reduce a diploid nucleus by means of meiosis, resulting in pronuclei with haploid, single-chromatid (1n, 1c) chromosomes. When an artificial *female* gamete is needed, a donor oocyte is enucleated, receives the somatic cell nucleus (2n, 2c) of the prospective mother, and is then activated by the prospective father's sperm, leading to the formation and extrusion of a polar body containing half of the female nucleus' chromosomes. When a *male* gamete is needed, the male somatic cell nucleus is transferred to an intact oocyte of the female partner, which then needs to be artificially activated, leading to the extrusion of not only half of the female's but also half of the male's genetic material in a (pseudo) polar body.[12] Although these techniques sound promising, it has been repeatedly questioned if these kinds of artificial gametes can constitute chromosomally normal embryos. Much research is still needed to achieve a correct distribution of the chromosomes between the pronucleus and the (pseudo) polar body, which is a problem for the substitution of both the male and the female gamete.[13] Additional problems have been reported regarding genomic imprinting and incomplete reprogramming. Specifically it seems very unlikely that correct imprinting can occur when the male gamete needs to be substituted.[14] If, however, it would one day be possible to use this method of reproduction, possible confusion about who would be the genetic parents would be limited to the

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question of whether the woman who provided the mtDNA (in the case of an artificial female gamete) should be regarded as a mother.

Criteria for Genetic Parenthood

We turn now to the common notion of genetic parenthood and which criteria can be used to define it, keeping in mind these new reproductive possibilities and the questions that follow from them.

The Importance of Genetic Information and Physical Contribution

The main aspect of genetic parenthood clearly lies in passing on genes to the next generation. A first important distinction that needs to be made is that between passing on the information that is contained in these genes and passing on genes as physical entities.[15] Although generally it is impossible for someone's genetic information to be passed on without contributing the physical gene, identical twins are an important exception. Because they pass on the same genetic information to their children, the only factor that distinguishes the father from the uncle or the mother from the aunt is who contributed the physical genes. Thus, passing on genetic information is not a sufficient condition on which to base genetic parenthood, for it is not valid in the absence of a physical connection between parent and child.

The Importance of Reshuffling

In the case of reproductive cloning, requiring genetic derivation both on an informational and physical level does not suffice to determine who a clone's genetic parents are. Here the child is derived from the genes of its "original version," but another basic feature of human reproduction is missing: the mixing of two different genomes into a new individual. Silver and Silver have dubbed the person whose cell was used for cloning a "genetic progenitor," whereas they consider the people whose genomes were reshuffled to form the child's genome the genetic parents.[16]

If this distinction is adopted, the requirement of a *direct* physical contribution for genetic parenthood is invalid. However, the requirement of physical derivation of some kind needs to be retained. Instead of requiring direct physical derivation, it may be sufficient to require that a genetic parent be a physical cause of the child. This would explain why identical twins do not consider each other's children as their own and, at the same time allows retaining the idea that a child's genetic parents are the people whose genomes were reshuffled to constitute that child's genome. Thus, in the case of clones, both their progenitor as the parents of the progenitor are physical causes of their existence, but the progenitor needs to be ruled out as a candidate-genetic parent because his/her genes were never reshuffled.

The distinction between genetic information and physical genes is once again important with regard to reshuffling. Imagine the situation in which a clone would have children. If reshuffling the genetic *information* would be decisive, both the clone and its genetic progenitor would be genetic parents of the child. This is counterintuitive; most people will ascribe genetic parenthood only to

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the clone, whereas the progenitor of the clone will socially be regarded as an aunt/uncle or grandparent. Thus, parenthood is only ascribed to the person whose *physical* genes are reshuffled rather than to anyone whose genetic information is reshuffled.

A Definition of Genetic Parenthood

We have now reached a more precise definition of what is normally denominated as genetic parenthood: *X is considered a genetic parent of Y if (i) X passes on genetic information to Y, (ii) X is a physical cause of Y's existence, and (iii) X's physical genes were reshuffled once to constitute Y*.

According to this definition, a woman whose fetus' oocytes were used cannot be the mother of the resulting children because two reshufflings of the genome took place between her and the child. She is therefore the child's genetic grandmother. In the case of mtDNA being transferred by an oocyte donor, there is a physical causal connection, but there is only a very limited transfer of genetic information, and, because the contributed mtDNA is not reshuffled, the oocyte donor is not considered a genetic parent. When a clone is created, both the genetic progenitor and the progenitor's parents pass on their genetic information and are a physical cause of the clone's existence. The progenitor's genes were, however, not reshuffled, thus leaving only his or her parents as the genetic parents of the clone, and he or she is at the same time a sibling and genetic progenitor. Using gametes created by haploidization results in the transfer of genetic information, a physical causal relation, and reshuffling. Once technically possible, it would therefore be a valid method to achieve genetic parenthood. In the case of an artificial female gamete, the donor of the (enucleated) oocyte can again be ruled out as a possible genetic parent.

Embryonic Stem Cell-Derived Gametes

Having clarified the elements that underlie genetic parenthood, we can now return to our original question. Can genetic parenthood be established by reproduction through ESC-derived gametes? This hope has certainly been vocalized since the successful production of both sperm cells and egg cells from mouse ESCs in vitro and especially since the recent success in obtaining live births from mouse ESC-derived sperm cells.[17]

The procedure involves the transfer of the nucleus of a somatic cell from the infertile patient to an enucleated oocyte, which is then artificially activated, creating a cloned embryo. After 5 days, the inner cell mass of the embryo can be isolated in order to derive stem cells. These stem cells are then coaxed into becoming eggs or sperm, which, after an IVF procedure, could theoretically result in genetic offspring from the original donor of the somatic cell and his or her partner. Because "male" stem cells can become both eggs and sperm, this technique might even allow two men to have a baby together that is 50% genetically related to both of them. Another possibility is to produce children with just one genetic parent that would deliver both the "natural gamete" and the artificially derived gamete. This would not create a clone because the genetic material would be reshuffled.[18] If the sperm cell contains the X chromosome, the resulting child could even be a girl resulting exclusively from a

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man. Creating a child with literally a "single parent" would, however, create significant concerns related to inbreeding.

Just as for somatic cell haploidization, reservations about the numerous technical hurdles involved in using ESC-derived gametes are warranted. But in the latter case, we must also wonder if the procedure actually reaches its goal; is the donor of the somatic cell incontestably the genetic parent of the resulting baby? Because the child would have 50% of its DNA in common with the person whose somatic cell is used to create the stem cell line, the donor would have no problem passing a paternity or maternity test. However, even though the cloned embryo would only live for 5 days in this procedure and not be more than a ball of 150 cells, it may be regarded as an extra generation. So although using ESC-derived gametes could provide an infertile person with a child sharing 50% of his or her genetic makeup, in terms of family lineage, they are only related in the second (if the clone is regarded as a child of its genetic progenitor) or even third degree (if the clone is regarded as an identical twin of the progenitor). Thus, the child stands in a similar relationship to the progenitor as the children of the progenitor's identical twin (or clone), which, as we discussed earlier, is not acknowledged as a parent–child relationship.

Reproduction by means of ESC-derived gametes fulfills two of the three conditions that were formulated as requirements for genetic parenthood: Genetic information is passed on and the infertile patient is a physical cause of the child. However, not the patient's physical genes were reshuffled, but the embryo's.

This problem has not been discussed in recent literature on the possibilities of artificial gametes for infertility treatment.[19] Testa and Harris, for example, suggest that "from an ethical and legal perspective, this procedure is most appropriately framed as a therapeutic intervention to treat infertility. It replaces in vitro the physiologic function normally responsible for reprogramming the germline genome, analogously to the well-established medical technologies that replace other deficient bodily functions." By this wording it seems as if the procedure mimics in vitro what normally occurs in vivo, which is actually not the case. The procedure rather mimics the case in which someone's clone reproduces. As noted earlier, in that case we are not inclined to regard the genetic progenitor of the clone as a genetic parent, and it is not clear why this should be different when the clone does not grow into a person. In the case of ESC-derived gametes, the cloned embryo from which the gametes are derived can be considered as a genetic parent of the child, and, as a consequence, the person whose somatic cell was used to create that embryo is not a genetic parent.

Alternatively, it can be argued that ESC-derived gametes do lead to genetic parenthood because the child contains half of the parent's genome. In this case, however, consistency requires that other widespread assessments of genetic parenthood are equally adjusted. For instance, identical twins will have to be considered as one entity because they only represent one genotype, and thus whenever one twin becomes a genetic parent, so does the other. For most people, especially for an identical twin sibling who is struggling with infertility, this will, however, not be a realistic assessment.

Therefore, the prospect of curing infertility with the help of embryonic stem cells on a therapeutic level—rather than using them as a research tool—needs to be put into perspective and there needs to be openness about its shortcomings.

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Conclusion

Many people turn to reproductive medicine to fulfill their dream of becoming a genetic parent. Anticipated new reproductive methods differ profoundly from natural human reproduction, and the question arises of whether the link that is established between parents and offspring corresponds to the criteria for genetic parenthood. More specifically, the prospect of producing gametes derived from customized embryonic stem cells presents such an enormous "detour" from natural reproduction that some inquiry is warranted into the question of whether it can deliver what it promises, namely, genetic parenthood.

By reviewing and analyzing a number of existing and hypothetical reproductive possibilities, a core notion of genetic parenthood is defined. Three conditions are identified to determine when someone can be considered a genetic parent: (i) genetic information has to be passed on from parent to child, (ii) the parent needs to be a physical cause of the child, and (iii) physical genes have to be reshuffled once while going from parent to child.

Based on these three conditions, genetic parenthood cannot be obtained through ESC-derived gametes, because it would not be the infertility patient's genes that would be reshuffled but those of the cloned embryo. This does not mean that recent successes in the generation of artificial gametes have no importance for the treatment of infertility. The study of ESC-derived gametes is expected to lead to insights that will eventually lead to therapies, but should not be regarded as a possible treatment option in itself.

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