Article

In Vitro *Gametogenesis and the Creation of 'Designer Babies'*

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Abstract: Research into the development of stem cell-derived (SCD) gametes in humans, otherwise known as *in vitro* gametogenesis (IVG), is largely motivated by reproductive aims. Especially, the goal of establishing genetic parenthood by means of SCD-gametes is considered an important aim. However, like other applications in the field of assisted reproduction, this technology evokes worries about the possibility of creating so-called 'designer babies.' In this paper, we investigate various ways in which SCD-gametes could be used to create such preference-matched offspring, and what this would mean for the acceptability of IVG, if it is premised that it is morally problematic to 'design' offspring. We argue that IVG might facilitate the creation of preference-matched offspring, but conclude that this should not undermine the moral acceptability of IVG altogether—even if one concedes the premise that creating 'designer babies' is morally problematic. In the light of this, we also point at a possible inconsistency for a position that condemns the creation of 'designer offspring,' while accepting the various endeavors to have genetically related offspring.

Keywords: *in vitro* gametogenesis; gamete derivation; artificial gametes; genetic parenthood; assisted reproduction; stem cells; gene editing; designer babies

Introduction

Several research groups are aiming to create stem cell-derived (SCD) gametes, a process also referred to as *in vitro* gametogenesis (IVG). This research is primarily aimed at reproductive applications. As such, it can be seen as one of the most recent steps in the direction of facilitating people who are unable to reproduce naturally to have genetically related offspring.

While the primary goal is to help couples or individuals obtain a healthy baby of their own, many applications in the field of infertility treatment evoke fears of a push toward the creation of so-called 'designer babies'[1]—who are adapted to other preferences of the future parents than merely genetic relatedness. For instance, the company 23andMe has patented a computerized method of matching the genotypic data of the gamete donor with that of the future parent, in order to increase the chance that the future child will have the traits the parents desire.[2] It has been said that the ultimate goal is to offer this service to any couple wishing to have a baby.[3] This idea of parents-to-be 'shopping' for their future child's characteristics is ethically controversial, especially if it concerns non-disease–related traits. Also, cloning,[4] preimplantation genetic diagnosis (PGD)[5] and genome-editing tools[6] have been the subject of such fears, with regard to the creation of designer babies. *In vitro* maturation (IVM) of immature oocytes might feed similar worries, although it has, so far, not yet been a real subject of the designer babies debate. Yet, IVM could potentially make oocyte retrieval cheaper, faster and safer; which

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might significantly increase the number of available oocytes and thus facilitate selection and editing tools.[7]

Now the technology to produce SCD-gametes also feeds worries about the possibility to produce designer offspring.[8,9] Relatively early in the debate about the ethics of IVG, Mathews *et al.* pointed at this potential and controversial use of SCD-gametes.[10] More recently, researchers have warned that the SCD-gamete technology "may exacerbate concerns regarding human enhancement," raising hard questions of where to draw the line "between alterations that end harmful conditions versus eugenics."[11] It is important to critically assess the likelihood of such scenarios. At present, much of this likelihood is premised upon further scientific developments. For any of the scenarios we will discuss, scientific improvements will have to be made, both in the field of stem cell research and in the field of genomics. The technology to produce SCD-gametes in humans is far from being an established clinical practice and still raises many safety concerns. To design babies, we still have much to learn about the genotype-phenotype-relationship, DNA sequencing and DNA interpretation. Moreover, the designing of complex traits is complicated by the involvement of many different genes, and even in case of less complex traits there is the difficulty that selection, or editing, of a certain desired trait might simultaneously cause other detrimental effects (so-called antagonistic pleiotropy).[12,13] Still, it stands as an important question whether and how IVG could serve as a tool to create designer offspring and whether this would be a convincing reason to halt the development of this technique.

The structure of this paper is as follows: in the next section, we will clarify what we mean when we use the concept 'designer babies.' As this is a contested concept, we will propose a working definition for the aims of this paper. We will then explore the various scenarios in which IVG could be used to create designer babies. In the subsequent section, we will argue that IVG is neither a sufficient nor a necessary condition to design offspring. Still, IVG could facilitate the creation of designer babies, especially in combination with practices that are already more or less socially accepted. We then explore where such a possible facilitating role of IVG leaves us in terms of the moral acceptability of allowing the development of SCD-gametes. We suggest that, based on the principle of consistency, regulation rather than a ban would be an appropriate reaction to IVG, even if one condemns the creation of designer babies and fears a contributive role of IVG in this. Lastly, we conclude by pointing at a possible conflict between the wish for genetic parenthood and the creation of designer babies.

We will not argue for or against the moral acceptability of designing future offspring: such a discussion is beyond the scope of this paper and is neither new, nor exclusive to the debate about IVG. For the sake of debate, we will explore what the possible role of SCD-gametes in creating designer children means for the moral acceptability of IVG, if it is held that it is morally problematic to design offspring.

'Designing' offspring

The idea of designing offspring is controversial, and also the meaning of 'designer baby' is contested.[14] There is relative consensus about the idea that the creation of designer babies involves genetic interventions in order to influence the traits of future offspring, but this is vague, and it can be rightly asked which interventions and which traits one is talking about. For the purpose of this paper, we will define the creation of designer offspring as genetic interventions by means of editing and/or selection techniques in order to create offspring with nondisease related traits which match the future parents' preferences and which might, but need not be, eugenic.

A few words to clarify this demarcation. If taken literally, one does not *design* offspring if e.g. one *selects* embryos via PGD.[15] Greely, for instance, distinguishes 'designer babies' from 'selected babies' and reserves the former for germline interventions by means of genome editing methods like CRISPR/Cas9.[16] However, since there are also people who do not discriminate between selection methods and direct gene editing in the context of the creation of designer babies[17], we will discuss scenarios of how SCD-gametes might be used both to select and to edit in view of creating future children with desired traits.

As regards the purpose of these interventions, and thus the nature of the targeted traits, we will contrast disease related genetic interventions (e.g., traditional applications of PGD) from, on the one hand, genetic interventions aimed at enhancement (e.g., to improve general intelligence), and genetic interventions aimed at feature selection (e.g., to choose eye color) on the other hand. In contrast to the first category, we will consider the latter two categories as instances of the endeavor to create designer offspring. Much of the moral controversy surely has to do with the nonmedical, but even if one limits the discussion to this subset, it is also appropriate to distinguish nonmedical interventions aimed at enhancement, from nondisease related interventions that are not aimed at enhancement. This allows one to specify the relationship between the creation of designer babies and eugenics; we will assume that only the enhancement-variant would also be an instance of eugenics, as here, the aim is to have a child with improved characteristics. We acknowledge that there will likely be some overlap between these categories (e.g., genetic interventions to obtain athletically built offspring could be said to be in the grey area between eugenic and noneugenic creation of designer babies). This is, however, a conceptual issue that cannot be tackled within the confines of this paper. It could, moreover, be nuanced that 'eugenics' historically not only referred to creating 'better babies,' but also to "discouraging inferior members of society from having children."[18]

Given this understanding of what it means to design offspring, we will now explore the relationship between this endeavor and IVG.

Selective breeding and 'selected embryos'

'In vitro eugenics'

A first possibility to use SCD-gametes to create offspring, with traits that match the would-be parents' preferences, is Sparrow's '*in vitro* eugenics' (IVE) scenario.[19] IVE need not be used to breed "better babies"[20], but could also serve as a tool to obtain offspring with specific traits matching individual parents' preferences, either disease or nondisease related. The process holds that gametes are derived from embryonic stem cells (ESCs) and then recombined with other gametes. From these gametes, embryos are created from which ESCs are derived; to be differentiated into gametes, and so on. Sparrow prefers the scenario where it is possible to start from induced pluripotent stem cells (iPSCs) to produce gametes "by sourcing somatic cells from a large number of individuals with desired genetic traits and then deriving stem cells and then gametes from these."[21] This process would enable embryo selection in a short time span by allowing "scientists to proceed forward to multiple generations of human beings '*in vitro.*'"[22] Sparrow argues that this process of iteration could be used to shape the genome through selective breeding, by combining desired traits that arise in different embryos. This is not an instance of direct genome editing, but here one intentionally combines the SCD-gametes to obtain an embryo with the desired traits.

Apart from the scientific limits we described in the introduction, Sparrow acknowledges that there are additional barriers to IVE.[23] IVE is troubled by the inherent creation and destruction of embryos which is considered immoral by many. This is, however, not exclusive to IVE: e.g., also *in vitro* fertilization (IVF) involves embryo destruction, and if it is accepted in that context, it will require additional moral reasons to prohibit it in the context of IVE. A different objection to IVE is that it might lead to the accumulation of epigenetic changes due to keeping the many cell lines *in vitro*, which may impact the offspring's health.[24] Also, those people who would use IVE would need to sacrifice the strong genetic link with their children and it is unlikely that many people would be willing to do this for the sake of having a child with desired characteristics.[25,26] Finally, IVE would be very time consuming and less powerful than the most recent genome editing technologies.[27,28,29]

Creation and selection of embryos created from SCD-gametes

Bourne *et al.*[30] elaborated on a suggestion by Mathews *et al.*[31] that IVG could be used to produce large numbers of gametes (especially oocytes—which might also become possible via IVM) and embryos in order to screen and select genetic traits, which would allow one "to select the best child possible."[32] The application which Bourne *et al.* describe focuses on enhancement, but again this need not be the case. One could produce large numbers of embryos via IVG and then select the embryo with the desired genotype (which would, again, raise the troubled issue of embryo destruction).[33] Greely describes a similar scenario—which he calls 'Easy PGD' ('easy' because it avoids oocyte retrieval)—which combines the technology used to derive gametes "from a person's skin cells" with PGD.[34] Prospective parents will be offered genetic information on "say, a hundred embryos," which would include information on their viability and risk of certain diseases as well as information about sex, behavioral and aesthetic characteristics.[35]

Note, however, that due to the involvement of many gene variants in the expression of complex traits, and the interaction between the environment and the genome, the ability to predict phenotype from genotype will be limited, especially for complex traits like behavioral characteristics. In general, this scenario would, like IVE, be time consuming and less powerful than newer genome editing technologies. As no 'better' genes are 'added,' the choice about DNA variations in the future offspring would be restricted to those alleles of which the parents themselves are carriers.[36]

Also, much of this scenario's potential depends on the possibility to overcome the limited number of oocytes collected per person. It should, however, be noted that if IVM would yield what it is expected to yield in the future—namely a significantly increased number of available oocytes—then it may be more realistic to produce large amounts of oocytes via IVM rather than via IVG.[37] After all, IVM would require less manipulation than IVG. Moreover, if the short supply of oocytes could thus be remedied (either by IVG or IVM), this could also benefit other applications that are currently hindered by this shortage. It could, for instance, settle the deficit of donor eggs for reproductive purposes. In view of designing offspring, it could thus be made easier to create oocytes from persons with desired traits which could be made available via gamete banks. Also the technique of somatic cell nuclear transfer (SCNT) could thus be perfected, and might as well be used to create designer babies; it might be used to create children with the same genome as someone with the desired genotype.[38,39] These scenarios would, however, not lead to shared genetic parenthood, and choices about the future child's traits would, here too, be restricted to the initial genotype from which one starts, which could be overcome by direct genetic modification.

SCD-gametes and germline genome editing methods

Gene editing of preimplantation embryos seems to count as the paradigmatic way toward 'tailor made' offspring and the technological breakthrough of the CRISPR/Cas9 method makes the possibility of editing the human germline easier than ever before.[40] While some have warned about the adverse effects of off-target mutations due to inefficient gene editing, this is probably a technical issue which can be resolved by ongoing improvements in efficiency and accuracy of the technique.[41] Still, germline gene editing of embryos is troubled by mosaicism in the edited embryos (i.e. the chance that not all cells will have the intended genetic change).[42,43] Alternatively, editing gametes is hindered in males by the makeup of the sperm cells, and in females by the low technical efficiency and the low number of mature oocytes collected per patient.[44]

The issue of the low number of mature oocytes collected per patient could be overcome in the future via IVG or IVM. These oocytes could then be directly edited, provided that the level of technical efficiency would be significantly improved. Thus, for this route to become possible, production of oocytes via IVG or IVM is required, and also further research into the efficiency and safety of the CRISPR/Cas9 system during meiosis.[45] Alternatively, stem cells created from a person's somatic cell (either through induced pluripotency or ESCs via SCNT), could be edited via CRISPR/Cas9 and then differentiated into gametes.[46,47] This application is mostly referred to when the link is made between IVG and designer babies. It is said that genome editing is easier in stem cells than in gametes and embryos, although this route would possibly still hold risks associated with potential off-target mutations and antagonistic pleiotropy.[48] Even if these issues could be overcome, and even if it would be possible to generate human SCD-gametes, most traits (including medical conditions such as cancer or heart disease) would still be difficult to target because of their multifactorial nature (but this is equally true for the previous scenarios).

IVG: neither sufficient nor necessary for designing offspring

In these scenarios, SCD-gametes can be used to create designer babies. Can this possibility justify a decision to halt the development of IVG, if it is held that designing future offspring is morally problematic? If one would consider banning IVG because it could lead to the creation of designer offspring, it will be appropriate to ponder the causal status of IVG relative to this endeavor of creating designer offspring.

First, one could assert that a ban on IVG in order to avoid the creation of designer offspring would be disproportionate, since IVG is in itself not sufficient for the creation of 'tailor made' offspring. Each of the scenarios we discussed is premised upon further scientific developments; not only improvement of SCNT or the technique to generate iPSCs (at least if the genetic link to the parents is to be retained), but also improvement of genetic screening of embryos (broader: more thorough DNA sequencing and interpretation), and improvement of genome editing technologies.

Second, it could be argued that banning IVG in order to avoid the creation of designer babies would miss the mark, as IVG is not necessary to create designer offspring; there are ways to design offspring without IVG. If IVG would turn out not to be safe and/or if it would be outlawed, there would still be methods to select (e.g. PGD does not require IVG) and edit embryos with CRISPR/Cas9. PGD, for instance, is currently not (yet) used to select for traits such as height, hair or eye color, but there are centers that offer PGD for nondisease related sex selection.[49,50] Better genome sequencing and stronger ability to predict phenotype from genotype will probably expand the selection possibilities even further (even without IVG).[51] Also, if IVM could be used to obtain a high numbers of oocytes, IVG would not even be necessary in the scenarios where selection and/or editing is premised upon the availability of (many) oocytes. One could furthermore point to the fact that in many countries, choosing a gamete donor, based on the traits the future parents want their child to have, is accepted and allowed (often higher prices are paid for gametes from donors with desired traits).[52,53] This form of selection could also be considered as a way to create designer babies for which IVG is not a necessary condition either.

IVG: possible facilitator for designing offspring?

Even if IVG would neither be necessary, nor sufficient for the creation of designer babies, it could nevertheless be held that IVG could facilitate the possibility of designing offspring. Here, 'facilitate' is premised upon the assumption that gene editing technologies are not yet available, or that if they would be available, they would only be applicable on stem cells and not yet on embryos or gametes (see above). IVG would contribute by making oocyte production easier and making more gametes and embryos available from which to choose, and, in case of gene editing, it would circumvent the more difficult embryo or sperm route, in favor of editing stem cells instead, or avoiding oocyte retrieval.

One way to respond to this is that even if IVG could facilitate the creation of designer babies, this would still depend upon other steps. It would be possible in principle to halt before these next steps in combination with IVG are taken. So, it is one thing to allow derivation of gametes from stem cells for research purposes, it is another to use this technology for reproduction and it is yet another to combine this reproductive use with genetic selection, selective breeding or editing techniques for disease related traits. Applications for nondisease related traits would be yet another leap.

Yet, some nuance is appropriate here. First, it might be stated that allowing IVG could indeed facilitate a push toward accepting the creation of designer babies, if there are prior social situations/institutions in which such a development is likely to get approval. We already indicated that it is, at present, quite accepted to choose a gamete donor based on his/her physical traits, hobbies, studies, etc., so one might argue that here we are only a small step away from accepting donor conceived 'babies on demand.' The widespread acceptance of donor selection to choose the future child's traits might be feared as facilitating the acceptance of 'IVG-aided' creation of designer offspring.[54] Importantly, however, if selection in function of the child's traits is accepted in this context, additional reasons will be needed to deny this acceptability in other contexts. Second, it is true that genome editing and selective breeding in the IVE-scenario would be additional steps (as well as reproductive cloning in the case where IVG would aid SCNT from persons with desired traits), and that it is, in principle, possible to halt before these steps are taken. However, this reasoning does not really hold for the Easy PGD scenario. That is, Easy PGD differs from the other scenarios in the sense that the former is based on a practice that is already more or less accepted—traditional PGD has already been in use for several years and enjoys relative social approval for disease related traits. If it would be possible to create a large amount of embryos via IVG, this could overcome current practical limitations and increase the chances of selecting the 'best' embryo or the embryo with those traits which best match the future parents' preferences. As such, it could be argued that Easy PGD would only be a continuation of a current practice that is at present still practically limited. So the argument that IVG would be a facilitator for the creation of designer babies is probably most poignant in the Easy PGD case.

Regulation, assumed benefits and the value of genetic relatedness

Where does this leave us in view of the moral acceptability of IVG? Would such a potential facilitating role of IVG justify a decision to halt the development of SCD-gametes, provided that one condemns the creation of designer babies? Reference to the case of traditional PGD might provide insight here. It is already possible to use PGD to select embryos for nondisease related traits, and such applications are actually already being done (viz., nondisease related sex selection[55,56]), but this has not led to a decision to ban PGD. Admittedly, much depends on how PGD is regulated, which exactly proves the point—despite the possibility to use PGD for nonmedical reasons, the reaction has not been that PGD has to be banned, but rather that it needs to be regulated. Among the reasons for regulating rather than banning PGD are the value of avoiding the transmission of genetic diseases and the value of reproductive autonomy.[57]

IVG seems to be similar to this case. If one condemns the creation of designer babies, and recognizes the potential share of IVG in facilitating this, one should balance this disadvantage against the potential benefits of IVG. The assumed benefits of IVG include an increase in reproductive autonomy, and enabling genetic relatedness in parent-child relationships, which is highly valued by many. People who could satisfy their wish to have a child 'of their own' by means of IVG would be deprived of this possibility in case of a moratorium or ban on the creation of SCD-gametes. Sure enough, the value of genetic relatedness is also the reason why future parents use PGD, though it would be safer for the offspring to use donor gametes.[58] This raises the question whether the importance of being genetically related to one's children is sufficiently great to justify reproductive risk-taking.

This latter question about the importance of genetic relatedness is key to two rather general challenges for those who oppose the creation of designer offspring, but accept the various endeavors to have genetically related offspring. First, various reasons have been suggested for preferring to have genetically related offspring, and one of them is the value of parent-child resemblance. It is dubious whether this wish, to have a child who looks like you, has enough normative force to give special moral weight to the preference of having genetically related children, but the fact is that people give much attention to parent-child resemblance.[59] However, this value of resemblance is actually a wish for a child who shares some of the parents' traits. It might thus be questioned that if genetic relatedness is pursued for this reason, how does this desire to reproduce some of one's own characteristics in one's child differ from other attempts to generate offspring with specific traits. It is similar to future parents who choose a gamete donor based on his/her characteristics because of their wish that their future child would also have these traits.[60] Yet, it can be retorted that, in contrast to other 'designer methods,' these latter instances "still implicitly expresses a willingness to accept as a gift the product of a process we do not control."[61] Sandel, for instance, has argued that this sense of giftedness would be undermined by the creation of designer babies.[62] This might, according to Sandel, reduce our sense of solidarity, viz. our sensitivity to the role of chance in life, which "makes us share risks and pool resources in the form of social insurance."[63] However, this argument is premised on the idea that if we choose traits, there is no reason to expect that the costs of having these traits should be shared. Yet, it has been argued that in many cases solidarity has more to do with respect for the value of persons than with whether or not this person is responsible for being in the situation (s)he is in.[64] Moreover, in the case of designing future offspring one could hardly hold these children responsible, as they would not be the ones who chose their traits.

Second, and apart from the value of physical resemblance, it may be asked how and/or why the importance of being genetically related to one's parents differs in a morally relevant sense from other wishes that parents-to-be might have vis-à-vis their future children's characteristics. Indeed, most infertile couples do not just want a child, but want a genetically related child, which is a specific wish about the future child's characteristics that is nevertheless widely accepted in the field of infertility treatment.[65] 'Genetically related' and e.g. 'gender' or 'eye color' are all specifications for a 'child,' so why would the former be morally acceptable in contrast to preferences about other nondisease related traits? These are important questions that deserve due consideration, both in the discussion about the acceptability to create designer babies and in the debate about the moral importance of genetic relatedness in parent-child relationships.

Conclusion

It was our aim to spell out the possibilities of how SCD-gametes could potentially be used to create preference-matched offspring. We have set out the possible applications, showing that genetic interventions by means of selection or editing are neither inherent nor exclusive to the possibility of deriving gametes from stem cells. IVG might facilitate some of these interventions, but a moratorium or ban on the creation of SCD-gametes is neither necessary nor sufficient to avoid genetic interventions either by selection or editing. Moreover, this would undermine the assumed main benefit of IVG, namely to establish genetic parenthood for those people who are unable to reproduce in a natural way. This value of genetic relatedness is central to the field of infertility treatment and is highly valued by many people. However, we argued that this value also poses a challenge to the position which accepts the various endeavors to have genetically related offspring, while condemning the creation of designer offspring.

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