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ARTICLE

Germline Gene Editing: The Gender Issues

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Abstract

Human germline gene editing constitutes an extremely promising technology; at the same time, however, it raises remarkable ethical, legal, and social issues. Although many of these issues have been largely explored by the academic literature, there are gender issues embedded in the process that have not received the attention they deserve. This paper examines ways in which this new tool necessarily affects males and females differently—both in rewards and perils. The authors conclude that there is an urgent need to include these gender issues in the current debate, before giving a green light to this new technology.

Keywords: human reproduction; gender issues; germline gene editing

Introduction and State of the Art

The Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR–Cas9) technique is considered one of the most innovative germline gene editing (GGE) techniques ever developed. It was developed in 2012 by a research group led by Emmanuelle Charpentier and Jennifer Anne Doudna, who found that the adhesion of endonuclease Cas9 to CRISPR served to edit the human genome.[1]

Soon afterwards, in 2013, another United States research team[2] performed the first cut using CRISPR–Cas9 on the genome of a living mammalian cell. From those moments on, it gathered impressive attention from the research community.[3]

Currently, we appear to be at the beginning of a biotechnological contest[4] between two giants: China and the United States, both of which are seeking to take control of this promising technology. This contest has triggered research, sometimes with terrible consequences, such as in 2018, when the Chinese researcher He Jiankui claimed the birth of the first genetically edited twin girls (Lulu and Nana).[5,6]

This stunning announcement provoked shock and outcry across the entire international community because of its irresponsibility, performed by a scientist who broke both the applicable regulations and all the relevant academic principles and standards.[7,8] However, recent news warning of the risk of a new experiment taking place in Russia[9] has already come.

Therefore, the situation we face is definitively challenging. The editing of human embryos is a reality, and its implementation raises scientific,[10] ethical, and legal questions. Although the academic literature has addressed some of the issues, others call for a deeper analysis. A neglected area of investigation, deserving full attention, is the place of gender in GGE technologies. The purpose of this article is to examine the unequal situation faced by women and the necessity of taking gender considerations into debates on the acceptability of GGE technologies.

Our analysis is divided into three different parts: (1) analysis of the possible changes in human reproduction techniques that GGE might reduce women's suffering, (2) focus on possible mid and longterm social issues highlighting the loss of reproductive choices involved, and (3) policy advice on addressing these issues.

Risks and Suffering Inherent in Assisted Reproduction Techniques

The first child conceived through *in vitro* fertilization (IVF) was born in the United Kingdom in 1978.[11] In the last 40 years, the development of assisted reproductive technologies (ARTs) has been successful in helping millions of heterosexual couples who had problems conceiving offspring as well as women with no male companion (those who had decided to confront maternity in solitude or those with a female companion). However, this scenario still imposes distress and misery. Even in those cases in which assisted reproduction treatment can be financed by the Health Care System, undergoing one (or several) cycles of IVF has a clear economic and social impact for couples or single mothers who attempt it. However, the unhappy consequences are not equivalent for females and males.

An understanding of the process involved is revealing. An IVF cycle has four basic stages[12,13]: superovulation, egg retrieval, insemination/fertilization, and embryo transfer (ET). The male is needed in the third stage (insemination/ fertilization) only. Obtaining the seminal sample (both for previous analysis and to carry out the fertilization process in the morning of the egg retrieval) is generally obtained in the fertility clinic, with the only requirement being his sexual abstinence in the three days prior to obtaining the sperm sample. There is a possibility of the need to perform a testicular extraction of the sperm, but this is a technique that is used very rarely.

The process works quite differently in the case of the female. The woman must undergo previous examination at least for testing her ovarian reserve (the quantity and quality of her eggs) and to determine the depth of her uterine cavity and the technique most likely to successfully place the embryos. Once treatment is initiated, ovarian stimulation is reached by the administration of exogenous gonadotrophins (Follicle-Stimulating Hormone -FSH- and Luteinizing Hormone -LH-). These can produce side effects, among them Ovarian Hyper Stimulations Syndrome[14] that results in enlarged ovaries and a fluid shift from blood vessels to the abdominal cavity, with possible, abdominal bloating, high risk of clots within the blood vessels (thrombosis) and decreased blood supply to vital organs such as the kidneys and liver. Also, a medication for oocyte maturation to prevent premature ovulation is sometimes needed. Usually, additional drugs are also prescribed to prepare the lining of the uterus. Even with a swift acting anesthesia administered for a short period, the procedure of oocyte retrieval is painful. Anesthesia has to work fast and for a short period of time with no negative effect on the oocyte quality. Still, it is a painful process that requires pharmacological intervention.[15]

One of the most critical steps in the process of IVF is the ET.[16] It is the final step, and it can be affected by several variables such as contamination of the catheter tip with blood, mucus, or endometrial tissue, the presence of uterine contractions at the time of transfer, retained or expelled embryos, the type of catheter used, the volume and type of transfer media, and the presence of bacteria in the cervix or on the catheter tip. Sometimes ultrasound guidance is needed in this procedure. Also, after ET, bed rest has been a controversial subject, with some guides recommending extended bed rest and some virtually no bed rest, which can sometimes generate confusion and anxiety due to the different protocols. Clearly, based on the current techniques used to carry out an IVF process, the intervention is much more invasive for women rather than men.[17,18,19,20]

What Gene Editing Can Do to Women Empowerment

Moving from the scientific facts at stake, we turn to an analysis of the consequences that the implementation of this new technology might have on women. We begin with its positive aspects. First, gene editing can substantially reduce the suffering of women undergoing the IVF processes,[21] due to the possibility of reducing the number of interventions aimed at obtaining oocytes—a decided advantage. Although currently we can identify many predispositions towards certain pathologies using techniques such as preimplantational genetic diagnosis (PGD), until now we have not had any technique capable of preventing the pathology from developing later, nor any therapeutic solutions capable of successfully addressing them. As Arthur Caplan observes: "Screening embryos is useful, but it does not eliminate disease forever."[22]

This is obvious in the case of most monogenic diseases. PGD is able to tell us if a specific embryo will develop Huntington's disease or Tay-Sachs disease, or any of several others, but is unable to prevent this from happening.[23] Also, we do not currently have therapeutic resources to respond to these pathologies. Consequently, all embryos that show genes that will trigger them are simply discarded in the IVF process,[24] either by being destroyed or directed for biomedical research. This sorting considerably reduces the number of embryos available for transfer to the woman. Imagine a situation in which a woman has 10 or 11 oocytes extracted in a stimulation cycle, of which there are some that show morphological alterations or problems in their mitochondrial DNA (mtDNA) making them unsuitable for transfer. This means, in general, that at least six or seven of the embryos obtained are considered of sufficient quality to be transferred with expectations of success. Let us imagine, nonetheless, that at least three of them show the genetic combination that will make them develop, or at least be carriers of, a serious pathology. In such a case, it is likely that the final number of embryos capable of being used in the same cycle will be reduced to just two or three. Given, in turn, that the statistics of success in ARTs show that success is rarely achieved in the first attempt, it would be reasonable to anticipate that a pregnant woman would have to repeat the whole process,[25] with risk of the complications described above.

The situations we have just described would be substantially improved if we were able to handle the tools of gene editing efficiently. For example, it would be possible to tackle monogenic diseases through an intervention that would replace the pathological expression of a particular gene with its healthy version.[26] In this way, we would be recovering some embryos that would otherwise be discarded as candidates for uterine transfer, which would considerably increase the chances of IVF success with a single egg extraction cycle.[27]

Further, in other cases, such as some gender-related diseases, it is necessary to discard all embryos of the affected gender, as some dominant X-linked pathologies in male embryos and Dutch inheritances cannot be detected at the embryonic stage.[28] Nevertheless, if gene editing proves applicable to fetuses showing these traits in the future, screening based on gender will no longer make sense and the number of available embryos would, again, rise.

Finally, if, in addition, genetic alteration technologies such as Mitochondrial Replacement Techniques would ensure a greater probability of healthy development in embryos affected by mtDNA disorders,[29] or if techniques such as CRISPR–Cas9 would allow us to alter this type of DNA to increase the chances of success in the process of assisted reproduction, it would be even simpler to increase the number of embryos available.

The conclusion we could reach is that, if gene editing techniques showed their full potential, we could considerably increase the number of usable embryos in an IVF process. In the example described above, it could be possible to take advantage of perhaps 8 or 9 of those 11 embryos, instead of 2 or 3. Initial evidence suggests that human gene editing techniques can substantially improve the situation of pregnant women as they have the capacity to significantly reduce the number of needed oocyte extractions, since the possibility of enhancing the health of the embryos obtained would considerably increase the range of available embryos. This evidence, in turn, would bring with it a second advantage: It would be easier to choose the most promising embryos from among all the available ones and thus increase the success rates of the first transfer cycles. This advantage would considerably reduce not only the physical discomfort, but also the range of stress and anxiety of the pregnant woman.[30]

How Gene Editing Can Become a Tool of Oppression Against Women

As we have seen, gene editing can do much to improve the position of women in the application of ART. Therefore, at first glance, one might conclude that its discovery is good news not only *per se*, but also in terms of gender perspective. However, it is important to be aware that the introduction of gene editing tools, especially if they become widely implemented, may also imply a set of disadvantages for women.

As of today, research into gene editing involves the use of oocytes and *in vitro* embryos obtained through IVF. As described above, this procedure requires the use of biological material extracted from women bodies with its associated risks. Moreover, if experiments such as those of Dr. He Jiankui, other

similar experiments, or future clinical trials that could damage the fetuses and lead to spontaneous or therapeutic abortions, it would be the pregnant women who would suffer the harmful physical and psychological consequences.

Nevertheless, the most unbalanced effects in terms of gender may occur in the future. Let us think, in this regard, that if gene editing works efficiently and is able to provide us with the possibility of enhancing the health of our children, there would surely be many parents who would be willing to adopt this option. At the end of the day, if it is possible to modify, for example, the BRCA genes so that a daughter does not show a predisposition to cancer,[31] there will be many parents willing to do so or, even more, who think that they have a moral obligation to make use of this option.[32]

This is what authors like Julian Savulescu defend through their principle of procreative beneficence.[33] At first sight, it seems to be important enough to lead to a strong change in our social construction of obligations towards our children. We could even think that, within a few years, it would be considered immoral not to submit our descendants to genetic modifications capable of, at least, assuring them a more adequate health[34]; we will not analyze now other types of modifications, such as those aimed at enhancing positional goods, such as intelligence,[35] or kindness,[36] but, substantially, the arguments would be very similar, despite the current limitations of choosing the best-endowed embryo.[37]

This, in principle, should not include a gender bias (except for what we will say later); if it were possible to modify genetically an already born child, the responsibility would be on both parents. Nonetheless, today it is only possible to put this technology into practice by way of IVF. Furthermore, this is where gender bias is particularly strong, as IVF does not implicate the same sacrifices for men and women.[38] In these circumstances, parents may be considerably influenced by their cultural environment to adopt the IVF formula and gene editing to bring their children into this world. If most of them were to adopt this route, either voluntarily or in a more or less forced manner, that pressure would obviously increase even more in contrast to the minority who resisted using the benefits of the technique to enhance the health of their offspring—always presuming that the techniques were available to them at a *reasonable price*.[39]

The point we want to highlight here is that this form of pressure would clearly include a gender bias. In our opinion, the sacrifice, that is to say, the loss of freedom suffered by a woman who is forced to resort to IVF and gene editing, is not the same as that of a man who may not wish to do so either but ends up giving up. For him, the concession would be rather ideological, without great physical sacrifice. On the contrary, a woman might also submit to the whole series of practices that we have described above, facing the explained risks, and that, sometimes, against their own ideological position.[40] In our view, the degree of sacrifice would be considerably greater than that of her male partner.

To this obvious bias, we should add a more subtle one: In general, we tend to assume that they are mothers who care most about the health of their offspring[41] and, consequently, they have to be more predisposed than their male partners to undertake sacrifices for their children. If so, it seems obvious that women would be much more frequently the object of heavy pressures that might include, for example, the use of the *bad mother* stereotype.[42]

Conclusions

From the discussion above, we may conclude that the introduction of gene editing in human reproduction would have an undetermined and perhaps double-edged effect on the position of women seeking to conceive. On the one hand, it could substantially reduce physical suffering, due to the improvements in IVF techniques that would be introduced. On the other, however, the extension of this technology requires the use of female oocytes that can only be obtained by submitting some women to a huge cost.[43] Moreover, the success of this technology could in the more distant future introduce a separation between sex and human reproduction, triggering the use of IVF and gene editing technologies. In these circumstances, women could be forced to expose themselves to the discomforts and risks of a technology that has, as we have shown, serious drawbacks. These considerations imply the existence of a gender bias that should be included in the discussions on gene editing.

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Notes

1. Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity. *Science* 2012;**337**:816–21.
2. Cong L, Ran FA, Cox D, Lin S, Barretto R, Habib N, et. al. Multiplex genome engineering using CRISPR/Cas systems. *Science* 2013;**339**(6121):819–23.
3. Morrison M, de Saille S. CRISPR in context: Towards a socially responsible debate on embryo editing. *Palgrave Communications* 2019;**5**(110):2.
4. Choulika A. The West is losing the gene editing race. It needs to catch up. *STAT* 2018 Oct 29; available at https://www.statnews.com/2018/10/29/west-is-losing-gene-editing-race/ (last accessed 11 Feb 2023).
5. Marchione M. Chinese researcher claims first gene-edited babies. *Associated Press* 2018 Nov 26; available at https://apnews.com/4997bb7aa36c45449b488e19ac83e86d (last accessed 11 Feb 2023).
6. Regalado A. A third CRISPR baby may have already been born in China. *MIT Technology Review* 2019 July 3; available at https://www.technologyreview.com/2019/07/03/134301/a-third-crispr-baby-may-have-already-been-born-in-china/ (last accessed 11 Feb 2023).
7. Baltimore D, Charo A, Daley GQ, Doudna JA, Kato K, Kim JS, *et. al*. Statement by the Organizing Committee of the Second International Summit on Human Genome Editing. *The National Academies Sciences, Engineering, and Medicine* 2018 Nov 28; available at https://www.nationalacademies.org/news/2018/11/statement-by-the-organizing-committee-of-the-second-international-summit-on-human-genome-editing (last accessed 11 Feb 2023).
8. Council of Europe Committee on Bioethics. Ethics and Human Rights must guide any use of genome editing technologies in human beings. *Council of Europe Communications* 2018 Nov 30; available at https://search.coe.int/directorate_of_communications/Pages/result_details.aspx?ObjectId=09000016808fe117 (last accessed 11 Feb 2023).
9. Cyranoski D. Russian biologist plans more CRISPR-edited babies. *Nature* 2019;**570**:145–6.
10. Brokowski C. Do CRISPR germline ethics statements cut it? *The CRISPR Journal* 2018;**1**(2):116.
11. Malina A, Pooley JA. Psychological consequences of IVF fertilization—Review of research. *Annals of Agricultural and Environmental Medicine* 2017;**24**(4):554–8.
12. Fritz MA, Speroff L. Sperm and Egg Transport, Fertilization, and Implantation. *In*: Fritz MA, Speroff L, eds. *Clinical Gynecologic Endocrinology and Infertility*. Philadelphia, PA: Wolters Kluwer Health; 2010.
13. Nisal A, Diwekar U, Bhalerao V. Personalized medicine for *In Vitro* fertilization procedure using modeling and optimal control. *Journal of Theoretical Biology* 2020;**487**:1–27.
14. Mourad S, Brown J, Farquhar C. Interventions for the prevention of OHSS in ART cycles: An overview of Cochrane reviews. *Cochrane Database of Systematic Reviews* 2017;1:**1**–52.

15. Roest I, Buisman ETIA, van der Steeg JW, Koks CAM. Different methods of pain relief for IVF and ICSI oocyte retrieval—A Dutch survey. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2019;**X**:1–4.
16. Practice Committee of the American Society for Reproductive Medicine. Performing the embryo transfer: A guideline. *Fertility and Sterility* 2017;107(4):882–96.
17. Franco Jr JG, Baruffi RLR. Introduction to methods for collecting human gametes in assisted reproduction. *Reproductive BioMedicine Online* 2002;**5**(2):187–97.
18. See note 12, Fritz, Speroff 2010.
19. Gal M, Fertouk M, Volodarsky-Perel A, Reichman O, Holzer HEG, Eldar-Geva T. Comparison of the effect of sperm collection by condom or masturbation on the outcome of in vitro fertilization. *Gynecology and Obstetrics* 2017;**136**(3):352–3.
20. See note 13, Nisal, Diwekar, Bhalerao 2020.
21. Ishii T, de Miguel Beriain I. Safety of Germline Genome Editing for Genetically Related Future Children as Perceived by Parents. *The CRISPR Journal* 2019;**2**(6):371.
22. Caplan A. Getting serious about the challenge of regulating germline gene therapy. *PLoS Biology* 2019;**17**(4):2.
23. Koplin JJ, Gyngell C, Savulescu J. Germline gene editing and the precautionary principle. *Bioethics* 2020;**34**(1):49–50.
24. Viotti M, Victor AR, Griffin DK, Groob JS, Brake AJ, Zouves CG, et. al. Estimating Demand for Germline Genome Editing: An In Vitro Fertilization Clinic Perspective. *The CRISPR Journal* 2019;**2**(5):307.
25. de Miguel Beriain I, Penasa S. The embryo survival criterion: A moral obligation or a eugenic practice? *Romanian Journal of Legal Medicine* 2018;**26**(2):212.
26. de Miguel Beriain I. Gene editing and the slippery slope argument: Should we fix the enhancement/therapy distinction as the definitive boundary? *Science and Engineering Ethics* 2019;**25**:1258.
27. Wells D, Vermeesch JR, Simpson JL. Current Controversies in Prenatal Diagnosis 3: Gene editing should replace embryo selection following PGD. *Prenatal Diagnosis* 2019;**39**(5):345.
28. Genetic Alliance UK. What is X-linked inheritance? *Swan UK* 2017 May 22; available at https://www.undiagnosed.org.uk/support_information/what-is-x-linked-inheritance/ (last accessed 11 Feb 2023).
29. Ishii T. The ethics of creating genetically modified children using genome editing. *Current Opinion in Endocrinology, Diabetes and Obesity* 2017;**24**(6):419.
30. Regalado A. The world's first Gattaca baby test are finally here. *MIT Technology Review* 2019 Nov 8; available at https://www.technologyreview.com/2019/11/08/132018/polygenic-score-ivf-embryo-dna-tests-genomic-prediction-gattaca/ (last accessed 11 Feb 2023).
31. Guo P, Yang J, Huang J, Auguste DT, Moses MA. Therapeutic genome editing of triple-negative breast tumors using a noncationic and deformable nanolipogel. *Proceedings of the National Academy of Sciences of the United States of America (PNAS)* 2019;**116**(37):18925–303.
32. Savulescu J, Pugh J, Douglas T, Gyngell C. The moral imperative to continue gene editing research on human embryos. *Protein & Cell* 2015;6(7):476.
33. Bourne H, Douglas T, Savulescu J. Procreative beneficence and *in vitro* gametogenesis. *Monash Bioethics Review* 2012;**30**(2):29.
34. de Miguel Beriain I. Human dignity and gene editing: Using human dignity as an argument against modifying the human genome and germline is a logical fallacy. *EMBO Reports* 2018;**19**(10):2.
35. Wei D, Ha KO, Brown KV. Chinese Parents Test DNA to Check If Kids Will Become Prodigies. *Bloomberg* 2019 Nov 19; available at https://www.bloomberg.com/news/features/2019-11-19/china-baby-dna-tests-used-by-parents-to-check-for-prodigy-kids (last accessed 11 Feb 2023).
36. Persson I, Savulescu J. The duty to be morally enhanced. *Topoi* 2019;38:7–14.
37. Karavani E, Zuk O, Zeevi D, Barzilai N, Stefanis NC, Hatzimanolis A, et. al. Screening human embryos for polygenic traits has limited utility. *Cell* 2019;**179**(6):1424–35.
38. Simonstein F. Gene editing, enhancing and women's role. *Science and Engineering Ethics* 2019;**25**:1010–11.
39. Greely HT. Human Germline Gene Editing: An Assessment. *The CRISPR Journal* 2019;**2**(5):260.

40. Begović D. Prenatal testing: Does reproductive autonomy succeed in dispelling eugenic concerns? *Bioethics* 2019;**33**(8):963.
41. Simonstein F, Mashiach-Eizenberg M. The artificial womb: A pilot study considering people's view on the artificial womb and ectogenesis in Israel. *Cambridge Quarterly of Healthcare Ethics* 2009;**18**(1):90–3.
42. See note 38, Simonstein 2019.
43. Niemec E, Howard HC. Include egg donors in CRISPR gene-editing debate. *Nature* 2019;**575**:51.

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