Main Submission

In Utero Gene Therapy: A Brave New World of Designer Babies?

Spandana Amarthaluru, Michael Aw, John-Paul Oliveria

Division of Respirology, Department of Medicine, McMaster University

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Introduction

Although the notion of a "designer baby" seems to be distant science fiction, with the advent of genome-editing technologies such as CRISPR/Cas9, "designer babies" may soon become a reality. In 2015, the United Kingdom's parliament authorized the conception of the world's first genetically modified embryo (Figure 1) (1). Given that many countries including Canada, Mexico, and Australia have banned *in utero* genetic editing, this legislation is a milestone and has been met with great apprehension. Many fear this legislation will create a slippery slope promoting the normalization of "designer babies," wherein genetic modification is used not only for medical purposes, but also for the selection of desired traits to improve the "quality" of an embryo. Accordingly, this article will explore the potential applications of this technology as well as the pertinent ethical considerations.

Applications of *In Utero* Gene Therapy

Proponents of *in utero* genetic modification boast its vast potential in treating genetic disorders. Although seemingly foreign, gene therapy has already been employed postnatally in humans to treat disorders such as hemophilia B, a bleeding disorder caused by a genetic defect resulting in a lack of coagulation factor IX (FIX) (2,3). In 2011, Nathwani *et al.* employed an adenovirus-associated vector to incorporate the functional FIX gene into target human cells *in vivo*. A single infusion in adult

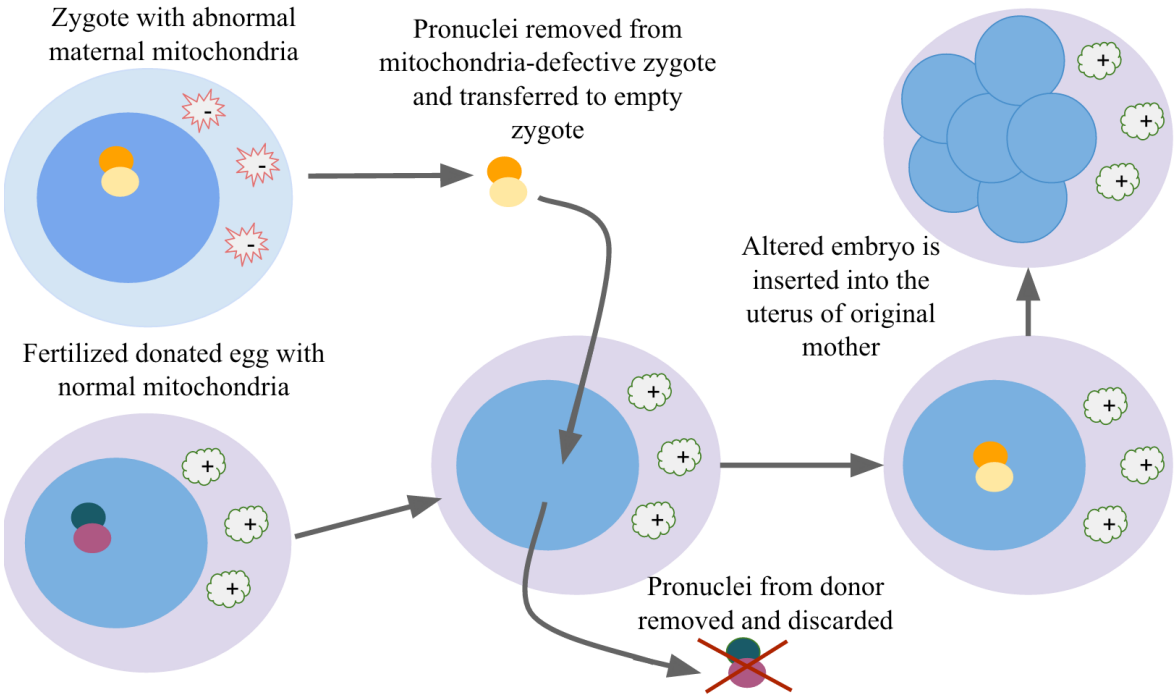

Figure 1: This genetic modification performed on the United Kingdom's first tripartite zygote allowed for the removal of defective maternal mitochondrial DNA that may have resulted in diseases, including fetal muscular dystrophy, as well as heart, kidney and liver failure. This genetic modification involves exchanging the defective maternal mitochondrial DNA with that of another female. Adapted from (10).

hemophiliacs increased long-term expression of the FIX gene, with no long-lasting toxicity (3). These results prompted discussion of using *in utero* gene therapy to treat hemophilia A, a genetic deficiency of coagulation factor VIII (FVIII) (4). Current treatments for hemophilia A involve bi-monthly intravenous infusions. Unfortunately, the annual cost of these treatments can exceed $300,000, and some patients become immunologically intolerant to the FVIII treatment, rendering it ineffective (4). The physical and financial burdens associated with this condition can therefore negatively impact the quality of life of these individuals (4).

Despite stigma surrounding prenatal genetic modification, *in utero* gene therapy may be safer and more efficacious than postnatal alterations, as cells *in utero* replicate more readily, are more responsive to genetic alterations, and early introduction of FVIII may reduce the likelihood of developing an immune response against treatment (4,5). As such, *in utero* modifications can confer cost-reducing benefits to those with genetic disorders. However, fetal development is sensitive and errors can be debilitating or fatal, as demonstrated by the phocomelia epidemic caused by the consumption of thalidomide by pregnant women for morning sickness. Nevertheless, the United Kingdom's bold leap to legalize *in utero* genetic modifications is a pivotal step towards developing a safe method for treating genetic disorders.

Ethical Considerations for *In Utero* Gene Therapy

It must be noted that current technology does not afford us the capacity to create "super-humans," per se. Furthermore, the selection of "superior" traits is often merely selection against negative traits. However, despite the apparent benefits, *in utero* gene therapy must still be accompanied with ethical consideration to address potential outcomes of selecting "superior" traits. Firstly, there are potential consequences to the fetus itself, which are nearly impossible to predict with embryonic alteration (6). Is it reasonable to subject fetuses to *in utero* modifications, even for the purpose of medical treatment, if there may be unforeseeable and inheritable outcomes? Considering the vast number of individuals affected by genetic disorders such as hemophilia A, the use of *in utero* gene therapy to treat these disorders without exploration of the long-term consequences could elicit widespread biological repercussions which will be propagable to future generations (7).

Furthermore, some claim that parents do not have the right to select traits in offspring on account of fetal autonomy (8). Although parents can significantly shape the characteristics of offspring through environmental factors (e.g. registering children for sports classes), do they have the right to modify these traits on a molecular level? Many argue that genetic selection of desired traits facilitates an unwarranted level of parental genetic autonomy (8).

Furthermore, given that *in utero* gene therapy is a relatively new practice, its associated costs may facilitate a new form of social hierarchy between those who can and cannot afford access to this technology, thereby extending socioeconomic divisions into genetic divisions that will intensify with future generations (7). By extension, the selection of "desired" traits, such as intelligence and athleticism, will provide this "designer" generation unethical advantages over those that are conceived naturally, as they may be more biologically predisposed towards "superior" traits conferring success (9).

Conclusion

Currently, genome editing technologies are nowhere near perfect. However, with time, they are sure to be utilized in novel high-risk procedures. For operations demanding high accuracy, such as human genome editing, it would be best to use TALEN. However, for cruder genetic engineering, CRISPR would be a more effective technique. Nevertheless, gene therapy is an evolving field, and extensive investigation into both techniques must be conducted in order to elucidate their efficacious utility in varying fields of science and bioengineering. ■

References

1. 3-parent babies OK'd by U.K. Parliament. *CBC News*. 2017. Available from: http://www.cbc.ca/news/world/3-parent-babies-ok-d-by-u-k-parliament-1.2942901 [Accessed 12 February 2017].
2. Almeida-Porada G, Atala A, Porada CD. *In utero* stem cell transplantation and gene therapy: rationale, history, and recent advances toward clinical application. *Mol Ther Methods Clin Dev*. 2016;3:16020.
3. Nathwani AC, Tuddenham EG, Rangarajan S, Rosales C, McIntosh J, Linch DC, Chowdary P, Riddell A, Pie AJ, Harrington C, O'Beirne J, et al. Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. *N Engl J Med*. 2011;2011(365):2357-2365.
4. Porada CD, Rodman C, Ignacio G, Atala A, Almeida-Porada G. Hemophilia A: an ideal disease to correct *in utero*. *Front Pharmacol*. 2014;5:276.
5. Colletti E, Lindstedt S, Park PJ, Almeida-Porada G, Porada CD. Early fetal gene delivery utilizes both central and peripheral mechanisms of tolerance induction. *Exp Hematol*. 2008;36(7):816-822.
6. Baird S. Designer babies: eugenics repackaged or consumer options? *The Technology Teacher*. 2007;66(7):12-16.
7. Briggs H. Haemophilia gene therapy 'solution'. *BBC News*. 2013. Available from: http://www.bbc.com/news/health-24993155 [Accessed 19 February 2017].
8. Suter S. A brave new world of designer babies? *Berkeley Technol Law J*. 2007;22(2):898-968.
9. Gardner W. Can human genetic enhancement be prohibited? *J Med Philos*. 1995;20(1):65-84.
10. Human Fertilisation and Embryology Authority. *Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2016 update.* Adapted from Figure 2, Pronuclear transfer. 2016. Available from: http://www.hfea.gov.uk/docs/Fourth_scientific_review_mitochondria_2016.PDF.

List of Abbreviations

FIX	Coagulation Factor IX
FVIII	Coagulation Factor VIII

Spandana Amarthaluru

Spandana is a 4th year Bachelor of Health Sciences (Honours) student at McMaster University. She began working with the McMaster Cardio-Respiratory Lab in September 2015 under Dr. Gail Gauvreau and John-Paul Oliveria. Her work with the lab focuses on the role of IgE and B cells in allergic asthma.

Michael Aw

Michael is a 2nd year undergraduate student in the Bachelors of Health Sciences (Honours) program at McMaster University. His association with the McMaster Cardio-Respiratory laboratory began in 2016 as a summer intern. His research interests are catered towards allergic diseases, in particular the pathology of allergic asthma.

John-Paul Oliveria

John-Paul is a 4th year Doctor of Philosophy candidate in the Department of Medical Sciences at McMaster University. He began his MSc in the McMaster Cardio-Respiratory Research Lab in 2011 and transferred to his PhD in 2013. His research focuses on the biology of B cells (IgE+ B cells and regulatory B cells) and the pathogenesis of allergic asthma. In the fall of 2017, he will be commencing a post-doctoral scholar appointment at Stanford University.