CRG Council for Responsible Genetics

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TO: Gail Dapolito
Cellular, Tissue and Gene Therapies Advisory Committee
Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike, HFM-71
Rockville, MD 20852

FDA Public Meeting
"Oocyte modification in assisted reproduction for the prevention of transmission of mitochondrial disease or treatment of infertility"
October 22-23, 2013

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INTRODUCTION

The Council for Responsible Genetics is a public policy organization that represents the public interest and fosters public debate about the social, ethical and environmental implications of genetic technologies. We appreciate the opportunity to comment on oocyte modification in assisted reproduction for the prevention of transmission of mitochondrial disease or treatment of infertility, our current opposition to any procedure that alters human gametes and the steps we believe are necessary before such work can proceed.

30 YEARS OF CRG 1983-2013

COMMENTS

Mitochondrial disease is a debilitating and life threatening genetic disorder that can cause a variety of malfunctions throughout the body, including stunted growth, an increased risk of infection, diabetes, disease of the heart, liver, and kidneys, visual and auditory deficits, and loss of coordination and muscle weakness, various neurological problems, and seizures. Most symptoms affect children before the age of 10, though mitochondrial malfunctions can play a role in age-related diseases as well, such as multiple sclerosis and Parkinson's disease.[1,2]

There is no known cure for mitochondrial disease once it develops, so if a woman is identified to be a sufferer or carrier of mitochondrial disease, she must currently refrain from having children with her own eggs.[3] She may not give her own genetic material to her offspring without passing on her disease as well. Once a woman has a child who displays mitochondrial disease, there is nearly a 100% chance that any future children will be affected by the disorder as well.

It is important to note that the techniques we will be discussing are not intended to, nor do they hold the promise of alleviating the suffering of children born with this awful disease. They are intended only for the purpose of offering women the chance to have biologically related children; as opposed to the current alternatives such women have such as using a donated egg, embryo screening or adoption. It is against this desire that the scientific, ethical, and social implications of mitochondrial DNA transfer must be weighed.

Three methods have been developed, discussed and in some cases applied to prevent the transfer of mitochondrial disease through pregnancy. They are: Pro-Nuclear Transfer (PNT), Maternal Spindle Transfer (MST) and Cytoplasmic (or Ooplasmic) Transfer. Their purpose is to modify human eggs to eliminate the prospect of transferring mitochondrial disease from a mother's egg to an offspring. In each of these procedures a baby is born with DNA from two women and one man. Only Ooplasmic Transfer has been known to have been used to produce human offspring. This application of Cytoplasmic Transfer represents the first known case of germ-line gene modification.

The first case of a human pregnancy with Cytoplasmic Transfer was reported by Cohen et al. in 1997.[4] The scientists reported a baby girl was born but that little was known about the pathophysiology of the human oocyte.[5]

Between 1997 and 2000 Ooplasmic Transplantation was used in humans at St. Barnabas Institute for Reproductive Medicine & Science on 21 women resulting in 12 clinical pregnancies. At least two babies were found to have three genomes (the nuclear component of mother and father and the mitochondrial component form mother and donor).

These experiments were performed on women, embryos and babies with no federal oversight with the exception of IRB approval and virtually no public debate.

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[1] http://www.mitoaction.org/mito-faq#whatare
[2] http://www.scientificamerican.com/article.cfm?id=dna-swap-technology-almost-ready-fertility-clinic
[3] http://blogs.nature.com/stepwise/2012/11/12/following-science-lead-to-reflect-on-the-ethics-of-mitochondrial-transfer
[4] J. Cohen, R. Scott, T. Schimmel et al. Birth of an infant after transfer of a nucleate donor oocyte cytoplasm into recipient eggs. *The Lancet* 350:186-187 (July 19, 1997).
[5] Ibid., p. 186

By 2001 Barritt et all from St. Barnabas reported 33 experimental trials of Ooplasmic Transplantation after conventional IVF attempts failed to achieve pregnancy. They cited 13 pregnancies achieved and 16 offspring delivered.[6] Of the 30 samples analyzed, 17 had mitochondrial DNA heteroplasmy with the donor mitochondria transferred to the recipient's oocytes.[7] By 2003 it was reported that 30 children worldwide were born after Ooplasm Transfer from fresh or frozen oocytes.[8] The authors stated that "these are the first reported cases of germline mtDNA genetic modification which have led to the inheritance of two mtDNA populations in the children resulting from ooplasmic transplantation."[9] Whether all these children are entirely healthy, however, remains unclear, and no follow up experiments have been completed to verify the results. The lack of testing and long-term follow-up of the children born from the procedure so far is a significant shortcoming, making evaluation of the safety and effectiveness of the technique very difficult. Before the FDA, or any government agency, undertakes an evaluation of this technique we believe it is incumbent upon the agency to use all powers at its disposal to determine the current health status of the now teenagers that underwent this procedure at St. Barnabas.

Two research groups have reported successful use of this technology in rhesus monkeys: one in 2009 and another in 2010.[10,11] The offspring were reported to be healthy. However, such studies tracked the effects of MR only to the age of three, whereas studies in mice and other animals have suggested that harmful effects may not become apparent until adulthood and that problems from swapping mitochondria show up disproportionately in males and often affect fertility. Longer-term effects on health and fertility in non-human primates born from MR must be followed at least until their sexual maturity before such conclusions should be formulated. Experiments with human oocytes have also been done, with mixed results. In one study published in *Nature* by Masahito Tachibana et al, fertilization anomalies occurred (their pronuclei numbers were off) though once fertilized, the zygotes seemed to be healthy and could produce normal stem cells. The group declared that "mtDNA can be efficiently replaced in human oocytes."[12] However, since conclusive human studies have not been completed, it is impossible to predict exactly what complications may arise in human applications. And as with all types of genetic engineering, mistakes could have staggering consequences—not just for the current individual, but for generations down the line as well.

Changes in the mitochondrial genes of gametes are considered germ-line modification. The ethical issues raised by mitochondrial germ-line modification include both our concerns around the safety of the technology itself, as well as its social policy implications.

The issues that the Council for Responsible Genetics believe must be addressed and questions that must be answered before there can be any continuation of mitochondrial germ-line modification are as follows.

1. What is the rate of heteroplasmy of children born from ooplasmic transplantation?

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[6] J.A. Barritt, S. Willadson, C. Brenner and J. Cohen. Cytoplasmic transfer in assisted reproduction. *Human Reproduction Update* 7(4):428-435 (2001).

[7] R. Levy and Y. Menezo, Cytoplasmic transfer: The risks. The 4th World Congress on Controversies in Obstetrics, Gynecology and Infertility. Berlin, German, Aopril 240-27, 2003, pp. 15-20.

[8] Neuffied Council on Bioethics, Novel Techniques for the Prevention of Mitochondrial DNA Disorder: An Ethical Review. London: Nuffield Council, 2012. http://www.nuffieldbioethics.org/sites/default/files/Novel_techniques_for_the_prevention_of_mitochondrial_DNA_disorders_compressed.pdf

[9] J.A Barritt, C.A Brenner H.E. Malter, and J./ Cohen. Mitochondria in human offspring derived from ooplasmic transplantation. *Human Reproduction* 16(3):513-516 (2001)., p. 515.

[10] http://blogs.nature.com/stepwise/2012/11/12/following-science-lead-to-reflect-on-the-ethics-of-mitochondrial-transfer

[11] http://www.nature.com/nature/journal/v461/n7262/full/nature08368.html

[12] http://www.nature.com/nature/journal/vaop/ncurrent/full/nature11647.html

2. What are the long term effects on the health of the child during growth and development from mitochondrial heteroplasmy? In their report in the journal *Science*, Reinhardt et al state that "studies of health effects of [mitochondrial replacement] on vertebrates that have reached reproductive ages are lacking."[13]

3. What animal models exist that provide insights to the effects of mitochondrial heteroplasmy? Have their results been sufficiently replicated and followed though long term study?

4. Will females born with mitochondrial heteroplasmy from ooplasmic transplantation transmit it to their progeny?

5. Have any clinical trials been planned or completed to determine the efficacy and safety of the mitochondrial disease procedures such as ooplasmic transplantation, PNT or MST? How would or have such trials been constructed? What would count as a control? How long will the follow-up be? What would the informed consent form look like?

Experts in the field have noted that there is not good science behind these experiments to date. "…therapeutic trials for mitochondrial disease have not only been generally ineffective, they have been inadequately designed, and often anecdotal or underpowered. Thus there is an urgent need in this field for rigorous, double-blinded placebo-controlled studies."[14]

6. How can we know whether third party mitochondria will increase the risk of heritable mitochondrial disease?

7. How do we know whether or not there are different responses to the two populations of mitochondria to nuclear DNA signals that can result in metabolic abnormalities in the offspring?

There is a high degree of homoplasmy throughout the body, which is critical for the healthy messaging between nuclear and mitochondrial DNA. Ooplasmic transfer resulting in heteroplasmy "may induce conflicts between nuclear DNA, recipient mtDNA, and donor mtDNA and lead to unpredictable outcomes."[15]

8. Can cytoplasmic transfer affect epigenetic modification? Two of the first 16 pregnancies involving cytoplasmic transfer had chromosomal abnormalities.[16]

9. How can society accept alterations in mitochondrial DNA in gametes but exclude modifications in nuclear DNA, when both can be the source of disease? Will any legal and policy protections be put in place to ensure that the approval of such techniques, if proven successful, won't lead to genetic engineering of gametes for enhancement purposes. What are the ethical limits?

10. What are the psycho-social implications of a child born with two mitochondrial genomes? Does mitochondrial DNA confer genetic identity? There is evidence to support that mitochondria do influence important qualities that participate in the identity of a person.

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[13] Klaus Reinhardt, Damian K. Dowling and Edward H. Morrow, Mitochondrial replacement, evolution, and the clinic. *Science* 341:1345-6: September 20, 2013.

[14] E.A. Schon, S.D, Mauro, M. Hirano and R.W. Gilkerson, Therapeutic prospects for mitochondrial disease. *Trends in Molecular Medicine* 16(6): 268-276 (2010) at p. 269

[15] R. Levy and Y. Menezo, Cytoplasmic transfer: The risks. The 4th World Congress on Controversies in Obstetrics, Gynecology and Infertility, pp. 15-20. Berlin, Germany, April 24-27, 2003.

[16] D.T Brown, M. Herbert, V. K Lamb et al. Transmission of mitochondrial DNA disorders: Possibilities for the future. *The Lancet* 368:87-89 (July 1, 2006_.

11. Mitochondrial DNA donation would have an effect on the child's parental situation. Would the child essentially have three parents? Would he or she need to have a relationship with the donor?[17] Would the donor have any parental rights?[18]

It should be noted that international organizations have voted to prevent germ-line modification. In 1998 the International Bioethics Committee of UNESCO issued a Declaration on the Human Genome and Human Rights. It was endorsed by UNESCO in 1997 and the UN General Assembly in 1998. It stated that germ-line interventions and reproductive cloning are contrary to human dignity and shall not be permitted. The Council of Europe's Convention on Human Rights and Biomedicine prohibits the modification of the human genome that is transmitted to descendents as well.

Finally, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research reported its findings in *Splicing Life* (1982) that "Especially close scrutiny is appropriate for any procedures that would create inheritable genetic changes…"[19]

Conclusion

We at the Council for Responsible Genetics at this time are opposed to any procedure that alters human gametes. Before any approval can even be considered for ooplasmic transfer we believe additional non-human research must be completed including but not limited to long term study of the effects of mitochondrial germ-line modification in a newborn. Moreover we believe significant, public and transparent legal and policy discussions must address the issue of how this procedure or other procedures that will create a three-genome baby will:

1) open up the way for other experiments on the human germ-line breaking a long standing ethical boundary between somatic cell therapy and germ line gene therapy.
2) address the issue of informed consent on a pre-natal human life
3) create a climate where genetic enhancement becomes acceptable through germ line modification.

The Council for Responsible Genetics is glad to offer any assistance it can provide as this process continues to unfold.

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[17] http://www.nuffieldbioethics.org/mitochondrial-donation/mitochondrial-donation-background-ethical-questions-arising

[18] http://www.dailymail.co.uk/health/article-1365287/Babies-THREE-parents-born-years-controversial-IVF-technique-gets-ahead.html

[19] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research*, A Report on the Social and Ethical Issues of Genetic Engineering with Human Beings."* Washington D.C.: U.S. Government Printing Office, 1982, p. 3.