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COMMENTARY

Potential Impacts of Human Mitochondrial Replacement on Global Policy Regarding Germline Gene Modification

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Abstract

Previous discussions regarding human germline gene modification led to a global consensus that no germline should undergo genetic modification. However, the UK Human Fertilisation and Embryology Authority, having conducted at the Government's request, a scientific review and a wide public consultation, provided advice to the government on the pros and cons of Parliament's lifting a ban on altering the mitochondrial DNA content of human oocytes and embryos, so as to permit the prevention of maternal transmission of mitochondrial diseases. Relevant ethical and biomedical issues are examined and requirements for the novel procedure are suggested. Additionally, potentially significant impacts of the UK legalization on global policy concerning germline gene modification are discussed in the context of recent advances in genome editing technology. It is concluded that international harmonization is needed, as well as further ethical and practical consideration, prior to the legalization of human mitochondrial replacement.

KEYWORDS: ethics, mitochondrial replacement, oocyte donation, in vitro

fertilization, germline gene modification, genome editing technology,
enhancement, eugenics, global policy, international harmonization

Introduction

A decade ago, there were many arguments for and against human germline gene modification in various contexts: medical beneficence, its safety, challenges to human dignity, and its unpredictable impact on humans (Frankel and Chapman, 2000). Subsequently, there emerged a global consensus that no germline (gamete, zygote, embryo) should undergo genetic modification. At present, most developed countries forbid such a procedure based on legislation or guidelines. However, in 2013, the UK Human Fertilisation and Embryology Authority (HFEA), having conducted at the Government's request, a scientific review and a wide public consultation, provided advice to the government on the pros and cons of Parliament's lifting a ban on altering the mitochondrial DNA content of human oocytes and embryos, with the intention to prevent mitochondrial disease transmission (HFEA, 2013a). In para 1.7 its report says: "Our advice to Government, set out in this report, is that there is general support for permitting mitochondria replacement in the UK, so long as it is safe enough to offer in a treatment setting and is done so within a regulatory frame work. Despite the strong ethical concerns that some respondents to the consultation expressed, the overall view is that ethical concerns are outweighed by the arguments in favour of permitting mitochondria replacement." Then on 27 February 2014 the UK government launched a consultation on draft regulations for the new techniques to prevent transmission of serious mitochondrial disease, which will end on the 21 May 2014. Alongside this consultation, the HFEA was asked by government to reconvene its core panel of experts to review the latest evidence on the safety and efficacy of the two mitochondrial donation techniques:

pro-nuclear transfer (PNT) and maternal spindle transfer (MST).

Mitochondrial replacement has raised ethical and social concerns worldwide. For example, views have been expressed about a slippery slope to eugenics or enhancement, the availability of alternative procedures, oocyte procurement, the identity of the resulting child, and the concept of informed consent (Baylis, 2013; Bredebnord and Braude, 2010; Darnovsky, 2013). Moreover, there are biomedical reasons to question the procedure (Koopman et al., 2012; Reinhardt et al., 2013; St John and Campbell, 2010). Furthermore, a criticism was made to dissect biological implications of tri-parental origin of offspring from mitochondrial replacement (Cohen and Alikani, 2013). Here, the author examines the key issues and attempts to clarify requirements for the novel procedure. In addition, the potential impact of the legalization of mitochondrial replacement in the UK on global policy regarding germline gene modification is also discussed.

Ethics of Mitochondrial Replacement

Mitochondrial diseases, which occur as a result of decreased ATP output from the electron transfer chain, are caused by various mutations in mitochondrial and/or nuclear DNA and are thus genetically heterogeneous. The aberrant mitochondria are transmitted via an egg (oocyte) to offspring. The estimated number of the female patients in the UK is at least 3,500 (Brown et al., 2006). However, mitochondrial replacement to prevent the maternal transmission of mtDNA defects appears to be effective only in cases of mtDNA mutations, with no nuclear DNA defects, thus serving a minority of these 3500 patients. The UK

Government expressed the view that mitochondrial replacement could save approximately 10 children each year (Department of Health, 2014). The proposed lifting by the UK of its current ban for such rare conditions was questioned because a breach of the global consensus would potentially lead to eugenics, or enhancement: parental pursuit of specific traits for non-medical reasons (Darnovsky, 2013). But one might rebut this objection in the following way: the procedure is aimed at the prevention of maternal transmission of mitochondrial diseases and neither eugenics nor enhancement is being advocated. Moreover, such a procedure for orphan diseases should be considered as health care for a minority, especially as mitochondrial replacement might be the sole effective procedure to prevent mitochondrial diseases, notwithstanding the possible use of pre-implantation genetic diagnosis to biopsy mtDNA of embryos and so identify embryos with fewer mtDNA mutations. Still, there remains a potential slope to eugenics or enhancement.

One might also assert that prospective mothers should not use such a risky germline modification, and should instead use donor oocytes, donor embryos, or consider adoption (Darnovsky, 2013). Although family building is based not only on a genetic link but also loving, caring, and nurturing, most patients would have a wish to have their own genetically-related child. Most people can sympathize with that wish.

The procedure under consideration is based on cytoplasmic replacement using nuclear transfer to exclude most mutated mitochondria. The transfer is carried out between the affected mother's oocyte and that of an unaffected cytoplasmic donor (Paull et al., 2013; Tachibana et al., 2013) or

between the parentally-derived zygote and a donor zygote or a zygote created using a donor oocyte and the father's sperm (Craven et al., 2010). Thus, the procedure needs at least oocyte donation. According to the draft UK regulations, the oocyte donor is considered as having a status similar to that of an organ or tissue donor (Department of Health, 2014). However, oocyte donation entails potential health risks such as ovarian hyperstimulation syndrome (OHSS) (Baylis, 2013). In contrast, human embryonic stem cells (hESCs) have been established from surplus IVF embryos in the UK, the US, Japan and other countries (Ishii et al, 2013). Some oocytes, which are currently cryopreserved in oocyte banks for later self-use, would go unused, and be destined to be discarded or donated for research. The surplus oocytes might ethically be used in the proposed procedure. Additionally, the donation of the oocytes with informed consent (IC) would entail no substantial payment or reimbursement to the volunteers. Yet, such oocyte procurement depends on the scale and activity of oocyte banks. In order to obtain a sufficient number of oocytes for mitochondrial replacement, ethical and practical oocyte procurement methods should be further considered.

Children born following this procedure would have nuclear DNA inherited from the parents and mtDNA mostly from a female donor. The genetic integrity of the children is almost equivalent to that of a normal birth because mtDNA encodes only 13 respiratory chain proteins (Anderson et al., 1981). However, the resultant children are significantly different from children born following ordinary IVF in terms of the additional, uncommon procedure of mitochondrial replacement. Although special emotional care might be required for the resultant children, they would most probably positively accept the oocyte modification

conducted to prevent mitochondrial diseases.

In conclusion, although the mitochondrial replacement might provide an opportunity to provide genetically-related healthy children for women suffering mitochondrial diseases, the unwanted slippery slope might occur. Moreover, an ethical and practical issue lies in oocyte procurement.

Safety of Mitochondrial Replacement

One could point out that the unavailability of informed consent by the unborn child constitutes grounds for ethical refusal (Bredebnord and Braude, 2010). Assisted reproductive technologies (ART), such as IVF and intracytoplasmic sperm injection, are currently conducted with the informed consent provided by the prospective parent(s). Informed consent for reproductive use of the mitochondrial replacement by prospective parents may be justified if the safety is equivalent to that of the ART.

However, biomedical uncertainties abound with mitochondrial replacement. First, although it has been elucidated that mutations in 228 protein-encoding nuclear DNA genes and 13 mtDNA genes are linked to mitochondrial diseases, it is less clear how specific genetic defects are linked to dysfunction at cellular, organ, and systematic levels (Koopman et al., 2012). The mitochondrial replacement should be practiced only in cases in which molecular causes are well-characterized. Second, the procedure of human mitochondrial replacement might impact negatively on highly coordinated mitochondrial-nuclear allelic interactions that have become optimized over evolutionary time (Reinhardt et al., 2013). This scientific issue suggests a

possible need to find donor oocytes compatible with a patient's oocyte nuclei. Third, the mitochondrial replacement may have unknown effects on subsequent epigenetic programming during embryo and fetal development, although it does differ from reproductive cloning where epigenetic errors have been reported (St John and Campbell, 2010). Another criticism also suggested similar concern based on the dissection of biological implications of tri-parental origin of offspring from mitochondrial replacement (Cohen and Alikani, 2013)

The HFEA, in a brief press release, insufficiently rebutted these arguments put forward by Reinhardt et al. (2013), declaring that it would be necessary to monitor the children during their lifetime and ensuring the traceability of gametes and embryos (HFEA, 2013a). Moreover, biomedical risks need to be addressed prior to legalization. The types of mitochondrial mutational diseases on which the procedure should be practiced must be identified using cell and animal-based mitochondrial disease models. The need to match a patient's nuclei with donor mitochondria would make the oocyte procurement more difficult. Again, ethical and practical oocyte procurement should be fully considered. Otherwise, the mitochondrial replacement may fail to prevent the diseases.

Impact on Global Policy

The HEFA conducted public consultations and public dialogues to form a national consensus (HFEA, 2013a). The proposed course of action was largely accepted, although it was questioned (Darnovsky, 2013). The more than 30-year history of ART, the 20 years of HFEA regulation, and the level of public

understanding all support the implementation of mitochondrial replacement to remove mtDNA defects in the UK. Yet, the ban lift potentially impacts a global health policy.

The fourteen countries, which are permissive regarding hESC research, were selected and examined regarding germline gene modification (Table 1). Most of the countries explicitly ban the conduct, but Belgium, Singapore, and Spain are ambiguous in their laws. However, germline gene modification may be rendered illegal in these three countries, since the conduct would affect the integrity of embryos and be regarded as unusual ART. The lifting of the UK ban may constitute grounds for the initiation of mitochondrial replacement in the US because the National Institutes of Health (NIH) does not ban it, but holds a moratorium on germline gene alternation under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (Table 1). Indeed, the US Food and Drug Administration (FDA) is weighing the medical benefit of mitochondrial replacement prior to the ban being lifted in the UK (FDA, 2014). In addition, the UK movement may impact Japan and China that ban germline gene modification under their guidelines, which are less enforceable than laws, and are subject to amendment. Further, the lifting of the UK ban might also impact Israel, which explicitly bans germline gene modification, but has possible exemptions (Section 5a) in the relevant law. Thus, the Israeli Minister of Health may, if human dignity will not be prejudiced, permit the medical procedure upon the recommendation of an advisory committee. Therefore, the lifting of the UK ban may facilitate lifting of the ban and initiating mitochondrial replacement in other countries.

Further Descent

Legalization in the UK might cause another slide down the slippery slope to full-blown germline gene modification because the slope to the further genetic modification will seem less steep than is the case with the current total ban.

Present-day genome editing technology, such as that now offered by Zinc Finger Nuclease (ZFN), Transcription Activator-Like Effector Nuclease (TALEN) and Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR)/Cas technologies, has demonstrated highly specific and efficient nuclear genome engineering in human cells (Gaj et al, 2013). Human T cells modified with the artificial nuclease have already been used in a clinical trial of AIDS therapy in the US (Clinicaltrials.gov, 2013). A simple injection of the CRISPR/Cas mRNAs into zygotes can modify target genes in the genome, resulting in genetically modified monkeys (Niu et al, 2014). Some researchers would advocate that genome editing is appropriate to germline gene therapy if it may repair a mutated gene without off-target mutations.

Furthermore, some people might use the state-of-the-art genetic engineering for enhancement. In the UK, a monitoring system may prevent the further descent down the slope. Uncertainties might, however, occur in a country other than the UK.

Conclusions Public opinion frequently splits about the agenda of assisted reproductive technologies. However, a well-balanced view was requested regarding the agenda of mitochondria replacement (Johnson, 2013). It is largely

recognized that mitochondrial replacement is proposed with the intent of medical beneficence. The UK parliament plans to vote on lifting the ban on mtDNA replacement, so as to initiate the procedure in 2014. However, there are a number of requirements that should be met prior to the UK legalizing mitochondrial replacement. At the very least, ethical and practical aspects of oocyte procurement, the identification of which specific mitochondrial diseases may benefit, the safety of mitochondrial replacement, and the potential impacts of the legalization on a global consensus on germline gene modification should be addressed. In particular, the HFEA has not considered what measures should be taken in order to prevent a policy situation in which other forms of human germline modification are carried out in other countries. With respect to pharmaceuticals, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities and pharmaceutical industry of Europe, Japan and the US (ICH website). Such an international harmonization should have been formed and is still needed for the legalization of human mitochondrial replacement in a global society where no germline should undergo genetic modification.

It is still not too late. Currently, the Department of Health is proceeding with a public consultation of the draft legislation (Department of Health, 2014). In the final public consultation, the UK public needs to express its opinions actively. As a member of a global society, the UK Government and the Parliament should sufficiently discuss scientific, ethical, and legal justifications for human mitochondrial replacement.

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Table 1. National Policies Regarding Germline Gene Modification			
National Policy of	Bans (or Restricts) in the US:	Relevant Law or Guidelines	References
Australia	(a) Intentionally creating or developing a human embryo by a process other than the fertilisation of a human egg by a human sperm; and (b) the human embryo contains genetic material provided by more than 2 persons	Prohibition of Human Cloning for Reproduction and the Regulation of Human Embryo Research Amendment Act (2006)	http://www.comlaw.gov.au/comlaw/legislation/act1.nsf/071AC9EAE4567778BCA2572440012F18A5?file/122006.pdf
Belgium	Implanting embryos exposed to research that affects the integrity of the embryo into human	Act on Research on Embryos in Vitro (2003)	http://health.belgium.be/portal/Healthcare/ConsultativeBodies/Commissions/Embryoinvitro/index.htm?st=serT-ext-type_IJ2L.aw#LrFXIqC3Uk
Brazil	Genetic engineering on human germ cells, human zygotes or human embryos	Biosafety Law (2005)	http://www.wipo.int/wipolex/en/ext.jsp?file_id=272171
Canada	Altering the genome of a cell of a human being or in vitro embryo such that the alteration is capable of being transmitted to descendants	Assisted Human Reproduction Act (2004)	http://laws-lois.justice.gc.ca/eng/acts/A-13.4/
China	Using human egg plasma and nucleus transfer technology for the purpose of reproduction, and manipulation of the gene in human gamete, zygote or embryo for the purpose of reproduction	Guidelines on Human Assisted Reproductive Technologies (2003)	http://www.moh.gov.cn/open/uploadfile/2005/112816435508.doc
Denmark	Implanting fertilized human eggs in a woman's uterus, if the fertilized egg are genetically changed (modified), and likely to have the damaged the egg in its further development.	Act on Assisted Fertilisation in Connection with Medical Treatment, Diagnosis and Research (1997, amended 2003)	http://www.retsinformation.dk/forms/R0710.aspx?id=84963 http://www.retsinformation.dk/forms/R0710.aspx?id=9734
Israel	Using reproductive cells that have undergone a permanent intentional genetic modification (Germ Line Gene Therapy) in order to cause the creation of a person.	Law on the Prohibition of Genetic Intervention Act (Human Cloning and Genetic Manipulation of Reproductive Cells), (1999, renewed 2004)	http://hoethics.academy.ac.il/english/DocPage3-e.html
Japan	Clinical research that intentionally conducts or may conduct genetic modification of human germ cells or embryos	Guidelines of Clinical Research Regarding Gene Therapy (2002, amended 2004, 2008)	http://www.mhlw.go.jp/general/seido/kousei/kenkyu/denshi0504ssan.html
Singapore	Developing human embryo created by other than by fertilisation of human egg by human sperm	Human Cloning and Other Prohibited Practices Act (2004)	http://www.moh.gov.sg/content/moh_web/home/legislation/legislation_and_guidelines/human_cloning_andotherprohibitedpracticesact.html
South Korea	Gene therapy on sperm, oocytes, embryos, or fetuses	Bioethics and Safety Act (2008)	http://www.moleg.go.kr/english/korLawEng/pstSeq-47518
Spain	Reproduction techniques other than artificial insemination, in vitro fertilization and intracytoplasmic sperm injection with own or donor gametes, pre-implantation embryos transfer, and gamete intrafallopian transfer.	Law 14/2006 on Assisted Human Reproduction Techniques	http://www.urecentrotenberges/en/legislation-reproduction-assida.htm
Sweden	Experiments for the purposes of research or treatment that entail genetic changes that can be inherited in humans	Genetic Integrity Act (2006)	http://www.smer.se/news/the-genetic-integrity-act-2006351/
The UK	Reproductive use of gametes or embryos other than: A permitted egg: (a) which has been produced by or extracted from the ovaries of a woman, and (b) whose nuclear or mitochondrial DNA has not been altered. Permitted sperm: (a) which have been produced by or extracted from the testes of a man, and (b) whose nuclear or mitochondrial DNA has not been altered. A permitted embryo if— (a) it has been created by the fertilisation of a permitted egg by permitted sperm, and (b) no nuclear or mitochondrial DNA of any cell of the embryo has been altered, and (c) no cell has been added to it other than by division of the embryo's own cells.	Human Fertilisation and Embryology Act (1990, amended 2008) Human Fertilisation and Embryology (Research Purposes) Regulations (2001)	http://www.legislation.gov.uk/ukpga/2008/22/contents http://www.legislation.gov.uk/ukdsi/2001/188/contents/made
The USA	Germline gene therapy (At present, clinical trial proposals for germ line alterations will not be accepted by Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH)).	NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (2013)	http://oba.od.nih.gov/dna/nih_guidelines_new.htm
* The listed countries are permissive regarding human embryonic stem cell research under the regulations.			
* The listed fourteen countries were surveyed on the policy on germline gene modification other than reproductive cloning in October 2013.			
* The survey is based on sentences of the related law or guidelines, but contains interpretation due to the translation.			
* The URL link of the references were confirmed in December 2013.			