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COMMENTARY

Potential impact 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 UK 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 mitochondrial DNA content of human oocytes and embryos, so as to permit the prevention of maternal transmission of mitochondrial diseases. In this commentary, relevant ethical and biomedical issues are examined and requirements for proceeding with this 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: enhancement, ethics, eugenics, genome-editing technology, international harmonization, IVF

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 (Table 1).

In 2013, the UK Human Fertilisation and Embryology Authority (HFEA), having conducted at the UK 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, the 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.

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On 27 February 2014, the UK Government launched a consultation on draft regulations for the new techniques to prevent transmission of serious mitochondrial diseases, which will end on 21 May 2014. Alongside this consultation, the HFEA was asked by the Government to reconvene its core panel of experts to review the latest evidence on the safety and efficacy of the two types of mitochondrial donation techniques: pro-nuclear transfer and maternal spindle transfer. 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; Bredenoord 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). Criticisms have also been made, from a biological perspective, of use of the term 'tri-parental' to describe the offspring from mitochondrial replacement (Cohen and Alikani, 2013).

This article examines the key issues and attempts to clarify requirements for the novel procedure. 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. Aberrant mitochondria are transmitted via the oocyte to the offspring. The estimated number of affected female patients in the UK is at least 3500 (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 has been questioned because a breach of the global consensus would potentially lead to eugenics, or enhancement, the 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 preimplantation genetic diagnosis to biopsy mtDNA from embryos and so identify embryos with fewer mtDNA mutations (Johnson, 2013). 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 or embryos or consider adoption (Darnovsky, 2013). Although family building is based not only on a genetic link but also on 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 a spermatozoon from the father (Craven et al., 2010). Thus, the procedure requires at the very 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 (Baylis, 2013). This situation contrasts with the generation of human embryonic stem cells, which have been established from surplus IVF embryos in the UK, the USA, Japan and other countries (Ishii et al., 2013). Some oocytes, which are currently cryopreserved in oocyte banks for later self-use, will go unused and may be destined to be discarded or donated for research. The surplus oocytes might ethically be used in the proposed procedure. Additionally, the donation of oocytes with informed consent 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 issues around 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 mitochondrial replacement might provide an opportunity to provide genetically related healthy children for women suffering mitochondrial diseases, the unwanted slippery slope might occur. Moreover, ethical and practical issues lie 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 (Bredenoord and Braude, 2010). Assisted reproduction treatments such as IVF and intracytoplasmic sperm injection are ' consent provided by the prospective parent(s). Informed consent for reproductive use of

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Table 1 National policies regarding germline gene modification.

Country	*Bans (restrictions in the USA)*	*Relevant law or guideline*	*Reference*
Australia	(i) Intentionally creating or developing a human embryo by a process other than the fertilization of a human egg by a human spermatozoon; and (ii) the human embryo contains genetic material provided by more than two 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/0/71AC9EAE45677788CA2572440012F18A/$file/1722006.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/eportal/Healthcare/Consultativebodies/Commissions/Embryoinvitro/index.htm?ssUserText = type_IE2Law#.UrFJXcqCiUk
Brazil	Genetic engineering on human germ cells, human zygotes or human embryos	Biosafety Law (2005)	http://www.wipo.int/wipolex/en/text.jsp?file_id=272171
Canada	Altering the genome of a cell of a human being or an 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/2005112816435508.doc
Denmark	Implanting fertilized human eggs in a woman's uterus if the fertilized eggs are genetically changed (modified) and the change is likely to have damaged the egg in its further development	Act on Assisted Fertilization in Connection with Medical Treatment, Diagnosis and Research (1997, amended 2003)	https://www.retsinformation.dk/forms/R0710.aspx?id=84963 https://www.retsinformation.dk/forms/R0710.aspx?id=9734
Israel	Using reproductive cells that have undergone a permanent intentional genetic modification (germline 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://bioethics.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/i-kenkyu/idenshi/0504sisin.html
Singapore	Developing a human embryo created by other than by fertilization of a human egg by a human spermatozoon	Human Cloning and Other Prohibited Practices Act (2004)	https://www.moh.gov.sg/content/moh_web/home/legislation/legislation_and_guidelines/human_cloning_andotherprohibitedpracticesact.html
South Korea	Gene therapy on spermatozoa, 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, IVF and intracytoplasmic sperm injection with own or donor gametes, preimplantation embryos transfer and gamete intra-fallopian transfer	Law 14/2006 on Assisted Human Reproduction Techniques	http://www.urecentrogutenberg.es/en/legislacion-reproduccion-asistida.htm

(*continued on next page*)

Table 1 (continued)

Country	Bans (restrictions in the USA)	Relevant law or guideline	Reference
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 (i) which has been produced by or extracted from the ovaries of a woman and (ii) whose nuclear or mitochondrial DNA has not been altered; permitted spermatozoa (i) which have been produced by or extracted from the testes of a man and (ii) whose nuclear or mitochondrial DNA has not been altered; a permitted embryo if (ii) it has been created by the fertilization of a permitted egg by permitted spermatozoa, (ii) no nuclear or mitochondrial DNA of any cell of the embryo has been altered and (iii) 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/uksi/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/rdna/nih_guidelines_new.htm

The 14 countries are permissive regarding human embryonic stem cell research under the regulations and were surveyed on their 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.URLs were last accessed in April 2014.

mitochondrial replacement by prospective parents may be justified if the safety is equivalent to that of the assisted reproduction treatment.

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). Mitochondrial replacement should be practised only in cases in which molecular causes are well characterized. Second, the procedure of human mitochondrial replacement might impact negatively on highly co-ordinated 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, 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). A similar concern regarding unexpected epigenetic changes was also raised after a dissection of the biological implications of tri-parental origin of offspring from mitochondrial replacement (Cohen and Alikani, 2013).

The HFEA, in a brief press release, inadequately rebutted these arguments put forward by Reinhardt et al. (2013), declaring that it would be necessary to monitor the children during their lifetime and ensure the traceability of gametes and embryos (HFEA, 2013b). Moreover, biomedical issues should ideally be addressed prior to legalization. The types of mitochondrial mutational diseases on which the procedure should be practised must be identified using cell- and animal-based mitochondrial disease models. Any need to match a patient's nuclei with donor mitochondria would make oocyte procurement more difficult. Again, ethical and practical oocyte procurement should be fully considered. Otherwise, mitochondrial replacement may fail to prevent 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 history of assisted reproduction of more than 30 years, the 20 years of HFEA regulation and the high level of public understanding in the UK all support the implementation of mitochondrial replacement to remove mtDNA defects in the UK. Yet, lifting the ban potentially impacts global health policy.

This study examined the 14 countries that are permissive regarding human embryonic stem cell research for their approach to 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 assisted reproduction treatment. The lifting of the UK ban may

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constitute grounds for the initiation of mitochondrial replacement in the USA, 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 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 have impacts in Japan and China, which 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 have an impact in 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 initiation of 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 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, transcription activator-like effector nuclease 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 USA (Clinicaltrails.gov, 2013). A simple injection of CRISPR/Cas mRNA 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 countries other than the UK.

Conclusions

Public opinion frequently splits over the agenda of assisted reproduction treatment. However, a well-balanced view regarding the agenda of mitochondria replacement has been requested (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. Yet, 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 USA (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 Parliament should sufficiently discuss scientific, ethical and legal justifications for human mitochondrial replacement.

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References

Anderson, S., Bankier, A.T., Barrell, B.G., de Bruijn, M.H.L., Coulson, A.R., Drouin, J., Eperon, I.C., Nierlich, D.P., Roe, B.A., Sanger, F., Schreier, P.H., Smith, A.J.H., Staden, R., Young, I.G., 1981. Sequence and organization of the human mitochondrial genome. Nature 290, 57–65.

Baylis, F., 2013. The ethics of creating children with three genetic parents. Reprod. Biomed. Online 26, 531–534.

Brown, D.T., Herbert, M., Lamb, V.K., Chinnery, P.F., Taylor, R.W., Lightowlers, R.N., Craven, L., Cree, L., Gardner, J.L., Turnbull, D.M., 2006. Transmission of mitochondrial DNA disorders: possibilities for the future. Lancet 368, 87–89.

Bredenoord, A., Braude, P., 2010. Ethics of mitochondrial gene replacement: from bench to bedside. BMJ 341, c6021.

ClinicalTrials.gov, 2013. Autologous T-Cells Genetically Modified at the CCR5 Gene by Zinc Finger Nucleases SB-728 for HIV (Zinc-Finger). <http://clinicaltrials.gov/ct2/show/NCT00842634> (Accessed in the ClinicalTrials.gov. November 14, 2013).

Cohen, J., Alikani, M., 2013. The biological basis for defining bi-parental or tri-parental origin of offspring from cytoplasmic and spindle transfer. Reprod. Biomed. Online 26, 535–537.

Craven, L., Tuppen, H.A., Greggains, G.D., Harbottle, S.J., Murphy, J.L., Cree, L.M., Murdoch, A.P., Chinnery, P.F., Taylor, R.W., Lightowlers, R.N., Herbert, M., Turnbull, D.M., 2010. Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. Nature 465, 82–85.

Darnovsky, M.A., 2013. A slippery slope to human germline modification. Nature 499, 127.

Department of Health, 2014. Mitochondrial Donation. A Consultation on Draft Regulations to Permit the Use of New Treatment

Techniques to Prevent the Transmission of a Serious Mitochondrial Disease from Mother to Child. <https://www.gov.uk/government/consultations/serious-mitochondrial-disease-new-techniques-to-prevent-transmission>.

FDA, 2014. Meeting Materials, Cellular, Tissue and Gene Therapies Advisory Committee. <http://www.FDA.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/ucm380047.htm>.

Frankel, M.S., Chapman, A.R., 2000. Human Inheritable Genetic Modifications. Assessing Scientific, Ethical, Religious, and Policy Issues. American Association for the Advancement of Science. <http://shr.aaas.org/projects/human_enhance/reports/germline. pdf>.

Gaj, T., Gersbach, C.A., Barbas 3rd, C.F., 2013. ZFN, TALEN, and CRISPR/Cas-based methods for genome engineering. Trends Biotechnol. 31, 397–405.

HFEA, 2013a. Authority Paper: Mitochondria replacement Consultation: Advice to Government. <http://www.hfea.gov.uk/7796.html>.

HFEA, 2013b. HFEA Statement Regarding the Klaus Reinhardt et al. Science Paper 'Mitochondrial Replacement, Evolution, and the Clinic'. <http://www.hfea.gov.uk/8178.html>.

ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use web site. <http://www.ich.org/>.

Ishii, T., Reijo Pera, R.A., Greely, H.G., 2013. Ethical and legal issues arising in research on inducing human germ cells from pluripotent stem cells. Cell Stem Cell 13, 145–148.

Johnson, M.H., 2013. Tri-parenthood – a simply misleading term or an ethically misguided approach? Reprod. Biomed. Online 26, 516–519.

Koopman, W.J., Willems, P.H., Smeitink, J.A., 2012. Monogenic mitochondrial disorders. N. Engl. J. Med. 366, 1132–1141.

Niu, Y., Shen, B., Cui, Y., Chen, Y., Wang, J., Wang, L., Kang, Y., Zhao, X., Si, W., Li, W., Xiang, A.P., Zhou, J., Guo, X., Bi, Y., Si, C., Hu, B., Dong, G., Wang, H., Zhou, Z., Li, T., Tan, T., Pu, X., Wang, F., Ji, S., Zhou, Q., Huang, X., Ji, W., Sha, J., 2014. Generation of gene-modified cynomolgus monkey via Cas9/RNA-mediated gene targeting in one-cell embryos. Cell 156, 836–843.

Paull, D., Emmanuele, V., Weiss, K.A., Treff, N., Stewart, L., Hua, H., Zimmer, M., Kahler, D.J., Goland, R.S., Noggle, S.A., Prosser, R., Hirano, M., Sauer, M.V., Egli, D., 2013. Nuclear genome transfer in human oocytes eliminates mitochondrial DNA variants. Nature 493, 632–637.

Reinhardt, K., Dowling, D.K., Morrow, E.H., 2013. Mitochondrial replacement, evolution, and the clinic. Science 341, 1345–1346.

St John, J.C., Campbell, K.H., 2010. The battle to prevent the transmission of mitochondrial DNA disease: is karyoplast transfer the answer? Gene Ther. 17, 147–149.

Tachibana, M., Amato, P., Sparman, M., Woodward, J., Sanchis, D.M., Ma, H., Gutierrez, N.M., Tippner-Hedges, R., Kang, E., Lee, H.S., Ramsey, C., Masterson, K., Battaglia, D., Lee, D., Wu, D., Jensen, J., Patton, P., Gokhale, S., Stouffer, R., Mitalipov, S., 2013. Towards germline gene therapy of inherited mitochondrial diseases. Nature 493, 627–631.

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