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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 mitochondrial