"Mitochondrial Replacement" Technologies and Human Germline Nuclear Modification

Alyssa Lane, MSc[1], Jeff Nisker, MD, PhD, FRCSC, FCAHS[1,2]

[1]Department of Obstetrics and Gynaecology, Schulich School of Medicine & Dentistry, The University of Western Ontario, London ON

[2]Children's Health Research Institute, London, Ontario

Abstract

In 2015 the United Kingdom became the first jurisdiction to approve "mitochondrial replacement techniques" (MRT), thereby dropping prohibitions against creating human embryos with a permanently altered genetic make-up for purposes of reproduction. MRT is a misnomer because in fact it is the nucleus of the oocyte of the woman who wants a genetically related child that is transferred to the enucleated oocyte of a woman paid to undergo IVF to provide the oocyte. MRT thus constitutes nuclear transfer, which is prohibited by criminal sanctions under sections of laws on reproductive cloning in Canada, the United States, Australia, and European countries that regulate assisted reproduction. By adopting policies permitting the use of MRT, the United Kingdom has become the first jurisdiction to counteract an international consensus prohibiting germline modification. Analyses of the legal, ethical, and societal implications of MRT in assisted human reproduction are essential.

Résumé

En 2015, le Royaume-Uni est devenu la première autorité à approuver les « techniques de remplacement mitochondrial » (TRM) et à ainsi abandonner l'interdiction de créer des embryons humains à la constitution génétique altérée en permanence à des fins de reproduction. L'expression « techniques de remplacement mitochondrial » est inappropriée. En fait, elle désigne les interventions grâce auxquelles le noyau de l'ovocyte de la femme qui souhaite donner naissance à un enfant avec lequel elle aura un lien génétique est transféré dans l'ovocyte énucléé d'une femme qui subit, contre rétribution, une FIV donnant lieu à la production de cet ovocyte. Les TRM consistent donc en un transfert nucléaire, soit une intervention passible de sanctions criminelles en vertu de certains articles des lois sur le clonage reproductif au Canada, aux États-Unis, en Australie et dans les pays européens qui réglementent la procréation assistée. En adoptant des politiques permettant le recours aux TRM, le Royaume-Uni est devenu la première autorité à s'opposer au consensus international qui entoure l'interdiction de la modification des cellules germinales. Par conséquent, il s'avère essentiel d'analyser les conséquences légales, éthiques et sociétales des TRM dans le domaine de la procréation assistée.

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INTRODUCTION

In February 2015, the United Kingdom's House of Commons[1] and House of Lords[2] voted in favour of legalizing mitochondrial replacement techniques to prevent the transfer of mitochondrial diseases. The United Kingdom is one of the first jurisdictions to withdraw prohibitions against creating embryos with a permanently altered genetic make-up.[3] Regulations were made in March 2015 and came into effect October 29, 2015. The Human Fertilisation and Embryology Authority can now grant licenses to clinics in the United Kingdom to evaluate the use of MRT in humans.[4] Once the Human Fertilisation and Embryology Authority's requirements are known, clinics in the United Kingdom can begin applying for a license to use MRT in clinical practice.[4]

MRT involves the transfer of the nucleus from the oocyte of a woman who wants a genetically related child and wants to avoid a mitochondrial disorder to the enucleated oocyte of a woman who must undergo IVF to provide the oocyte.[5,6] *MRT* is thus a misnomer for nuclear transfer,[7] which is prohibited by criminal sanctions under sections on reproductive cloning in the United States,[8] Canada,[9] Australia,[10] and European countries that regulate assisted reproduction.[11–15]

Transmission of mitochondrial DNA is maternal[16]; females born from the procedures will pass copies of the mtDNA from the "donor" to their children,[17,18] and these copies will in turn be passed on to subsequent generations through their daughter's eggs.[19–21] Currently, women at risk of transmitting a mitochondrial disorder may choose

to avoid transmission by having a clinically unrelated child through adoption or oocyte donation. Women who want to use their own nuclear DNA to have a genetically related child may choose amniocentesis[22] or chorionic villus sampling[22] after a pregnancy has been established, with consideration of pregnancy termination, or they may choose preimplantation genetic diagnosis[23–25] during an IVF treatment cycle and only transfer embryos without the mitochondrial mutation. Research regarding the long-term safety and efficacy of MRT and the certainty that MRT will result in the birth of a child without a mitochondrial disease has not yet been undertaken.[6]

Globally, the total prevalence of people affected by mitochondrial-based conditions is 1 in 5000,[26] with the majority of childhood presentations involving mutations in nuclear DNA.[27–31] As a result, MRT would likely only benefit a few individuals, and modifications of the mitochondrial genome in early embryonic cells would have germline effects that are transmitted to future generations.[19–21,32]

Science

Mitochondrial disorders can arise from mutations in mtDNA or in nuclear genes coding for mitochondria and from epigenetic factors.[28,33–41] They can result in health problems including neurodegenerative conditions, strokelike episodes, blindness, muscular dystrophy, diabetes, deafness, and death in newborns, children, and young adults.[40] Because the phenotypic expression of mitochondrial disorders is variable,[42] it is difficult to estimate the risk of occurrence and the extent to which a child could be affected.[43]

Two techniques for MRT—pronuclear transfer and maternal spindle transfer—have been developed and could prevent the transmission of mutated mtDNA to a genetically related child.[44] PNT involves the transfer of the two pronuclei from a zygote with disease-linked mitochondria into an enucleated zygote with healthy mitochondria.[45–47] MST involves the transfer of the spindle of chromosomes from an unfertilized egg with disease-linked mitochondria into an enucleated egg with healthy mitochondria.[45,47]

What is known about mtDNA mutations, nucleo-mitochondrial interactions, and the role of epigenetics on an individual's phenotype is insufficient to assess the risk-benefit ratio of MRT,[21,48–51] and cell reconstruction techniques have not been developed to the stage where there is no carryover of mitochondria from the maternal source into the donor egg or embryo.[19,48,52] In addition, there are also concerns that MRT may introduce new abnormalities in future children.[21,53] Because mitochondrial disorders in animal models do not closely resemble human disorders,[54,55] the first human studies will likely examine women desirous of MRT through IVF for a genetically related child.[56] A few generations of descendants will be required to assess any health risks, and genetic effects will likely be irreversible.[19]

Regulation

Because copies of mitochondria that would come from the oocyte "donor" would be passed on to future generations by the oocytes of women born through MRT, MRT constitutes germline modification; this is prohibited by criminal sanctions in the United States,[8] Canada,[9] Australia,[10] and many European countries that regulate assisted reproduction, such as Germany,[11] Italy,[12] Belgium,[15] and Sweden.[13] In Canada, the Assisted Human Reproduction Act (2004) bans 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.[9] In the United Kingdom, the Human Fertilisation and Embryology (HFE) Act states that eggs, sperm, or embryos that have undergone nDNA or mtDNA alteration cannot be put into a woman's body.[57] However, the 1990 HFE Act was amended in 2008 to permit regulations that would allow techniques that alter the DNA of an egg or embryo to be used in assisted conception "to specifically prevent the transmission of serious mitochondrial diseases due to mutations in mtDNA."[58] Although approval of MRT techniques would not immediately constitute approval for other kinds of heritable genetic manipulations, lifting the ban could disrupt the existing international agreement that human germline modification should not be permitted.[59]

In addition to governmental prohibitions, numerous international organizations and councils have positions placing constraints on human germline modification.[60–63] The Council of Europe's (1997) Convention on Human Rights and Biomedicine states that an intervention aimed at modifying the human genome can only be performed if it does not aim to introduce genome modification in any descendants (Article 13).[60] The Universal Declaration on the Human Genome and Human Rights from the United Nations Educational, Scientific and Cultural Organization (UNESCO) states that germline intervention is a practice that could be contrary to human dignity (Article 24) and

ABBREVIATIONS

MRT	mitochondrial replacement techniques
mtDNA	mitochondrial DNA
MST	maternal spindle transfer
PNT	pronuclear transfer