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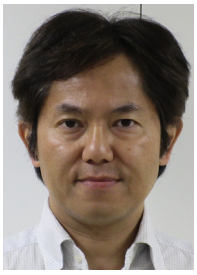
Mitochondrial manipulation in fertility clinics: Regulation and responsibility

Tetsuya Ishii [a,*], Yuri Hibino [b]

[a] *Hokkaido University, Office of Health and Safety, Sapporo, Japan;* [b] *Kanazawa University, Graduate School of Medical Science, Kanazawa, Japan*

* Corresponding author. *E-mail address:* tishii@general.hokudai.ac.jp (T. Ishii).



Tetsuya Ishii is Professor of Office of Health and Safety, Hokkaido University, Japan. He obtained his PhD in Bioscience at Hokkaido University in 2003. He subsequently joined Japan Science and Technology Agency and worked as a programme officer. In 2005, he completed the international program officer training program at the US National Institutes of Health John E. Fogarty International Center. Subsequently, he worked at the Center for iPS Cell Research and Application (CiRA), Kyoto University (Director, Shinya Yamanaka). At CiRA, he was in charge of clinical research application. Currently, he is studying bioethics, focusing on the relationship between society and biomedicine. He is a member of the European Society of Human Reproduction and Embryology, the International Society for Stem Cell Research, and the American Association for the Advancement of Science.

Abstract The clinical uses of cytoplasmic transfer and pronuclear transfer for infertility treatment have raised concerns, leading to restrictive regulatory responses in both the USA and China. In 2015, the UK legalized nuclear transfer from oocytes and zygotes to prevent the onset of serious mitochondrial disease in the children of affected mothers. A research team in the USA then performed egg nuclear transfer, with subsequent embryo transfer in Mexico, to prevent mitochondrial disease. A live birth resulted, but the cross-border activity attracted attention from regulatory authorities. In order to respond appropriately to the likelihood of the wider use of such mitochondrial manipulation techniques (MMT), the present study first surveyed countries where MMT have been clinically implemented or where such experimental procedures are advertised on the internet. Sixteen countries were selected for an analysis of the legal position regarding germline genetic modification and egg donation. It was found that regulation of the clinical use of MMT could be broken down into three categories: (i) largely prohibited (USA and China), (ii) not regulated (Northern Cyprus and Ukraine), and (iii) insufficiently regulated (the remaining 12 countries, including Mexico). The reasons for no or insufficient regulation included no intention to oversee experimental procedures, no consideration of the manipulation in eggs, unclear technical terms and ambiguous medical purposes. To protect future children, this study underscores the pressing need for regulatory frameworks with policies that cover MMT. Wider implications regarding the responsible implementation of procedures in experimental reproductive medicine are discussed.

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KEYWORDS: mitochondria, mitochondrial replacement, infertility treatment, mitochondrial disease, regulation, responsibility

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Introduction

Mitochondria are cellular organelles characterized by having their own genome (termed 'mtDNA'). Their functions are exerted through the coordinated gene expression of mtDNA and nuclear DNA (nDNA) (Ishii, 2016a). The most crucial function of mitochondria is in the respiratory chain, by which energy is produced as adenosine triphosphate while precisely regulating the generation of deleterious free radicals. Mitochondria are abundant in the human egg (oocyte), resulting in 200,000–300,000 copies of mtDNA per oocyte (Schatten et al., 2014). After fertilization, paternal mitochondria from the fertilizing spermatozoon are selectively degraded (Ishii, 2016a). Therefore, mtDNA is maternally inherited in offspring. There are approximately 30 mtDNA haplogroups in humans (van Oven and Kayser, 2009).

As some mtDNA mutations in oocytes have been considered to be associated with infertility and the onset of mitochondrial disease in offspring, several mitochondrial manipulation techniques (MMT) have been developed and used in fertility clinics. In 1997, the world's first successful MMT case was reported from the USA (Cohen et al., 1997). Donor oocyte-derived cytoplasm (ooplasm) containing mtDNA was injected into a patient's oocytes to treat an infertility case of insufficient embryonic development. Over the subsequent 4 years, this cytoplasmic transfer (CT) technique was repeated by the same group in other patients, leading to 17 live births in the USA. However, two pregnancies with Turner syndrome were identified following CT. These resulted in one miscarriage and one elective abortion. In addition, one child was diagnosed with borderline pervasive developmental disorder at 18 months of age (Barritt et al., 2001c); in a recent survey of parents, he was reported to have received special education for the pre-school year alone, and to have had episodes of depression. A family history of depression was also reported (Chen et al., 2016). Buccal smears from two of eight of the children checked after birth were found to contain donor mtDNA (Barritt et al., 2001b). Another MMT case was reported from China in 2003, this time using pronuclear transfer (PNT) – in which a karyoplast (a small bag of membrane-bound cytoplasm) harbouring nDNA and mtDNA is transferred to an enucleated zygote created using a donor oocyte – for an infertile woman who had suffered embryonic arrests (Zhang et al., 2016b). Although this attempt led to a triplet pregnancy, it ultimately resulted in no live births. A fetus was reduced to allow for better development of the other two fetuses. However, according to the case report, these fetuses died of respiratory distress and cord prolapse, respectively. CT and PNT have incurred regulatory interventions. The US Food and Drug Administration (FDA) exerted jurisdiction over CT technology by requiring that an Investigational New Drug application be filed in order to continue offering this procedure, as well as PNT, to patients (Castro, 2016; Ishii, 2015). The Chinese Ministry of Health established assisted reproductive technology guidelines and prohibited PNT in 2003 (Ishii, 2015).

An autologous type of MMT – autologous germline mitochondrial transfer (AUGMENT) – was reported in 2015 (Fakih et al., 2015). In the procedure, mitochondria are extracted from an infertile patient's 'egg precursor cells' and injected into the patient's oocyte. Canadian and United Arab Emirates (UAE) groups asserted that AUGMENT showed marked improvements in pregnancy rates; however, academic societies, such as the European Society of Human Reproduction and Embryology (ESHRE), expressed concerns over efficacy and safety due to undisclosed technical details regarding the mtDNA status, and the preparation and transfer of the mitochondria (British Fertility Society, 2017; Heindryckx et al., 2015).

On 24 February 2015, the UK became the first jurisdiction to permit the clinical use of two types of MMT to reduce mtDNA mutations that can cause serious mitochondrial diseases in offspring (UK Department of Health, 2015): PNT, and spindle nuclear transfer (SNT), in which a karyoplast carrying the second meiotic spindle from a patient's oocyte is transferred to an enucleated donor oocyte (Kang et al., 2016; Yamada et al., 2016). In the same year, a group led by a US physician performed SNT in the USA, and shipped the resultant embryo for transfer to an affiliate clinic in Mexico to prevent the onset of a mitochondrial disease (Leigh syndrome) in offspring (Zhang et al., 2017a). Although the clinical implementation resulted in the live birth of a boy, the parents requested that no further genetic testing be undertaken, unless there was a clinical benefit for the child. This could be because the risk information was explained insufficiently during the process of obtaining informed consent (Alikani et al., 2017).

Thus, MMT can alter the mtDNA content of human oocytes or zygotes through CT, karyoplast transfer (which includes carryover mtDNA) or autologous mitochondrial transfer (which might undergo mutagenesis during preparation) to treat intractable infertility or prevent mitochondrial disease in offspring. Although MMT have the potential to address unmet reproductive needs, all of these techniques remain experimental with regard to human reproduction. Moreover, the cross-border use of SNT between the USA and Mexico suggests that the clinical use of MMT is likely to spread in an unregulated manner (Ishii, 2017b; Palacios-González and de Jesús Medina-Arellano, 2017). Some studies have analysed the legalization process of PNT and SNT in the UK and the regulatory discussions in the USA (Castro, 2016; Cohen and Adashi, 2016; Cohen et al., 2015; Ishii, 2014; Schandera and Mackey, 2016). However, the current state of MMT-relevant activity and regulation remains largely elusive in many countries. In order to respond appropriately to the likelihood of the wider use of experimental MMT, the present study first identified a selection of countries in which some MMT have already been clinically implemented or advertised. We then investigated how the clinical use of MMT is regulated in 16 selected countries. Clinical use is largely prohibited in the USA and China; however, it is not regulated in Northern Cyprus or Ukraine, and is insufficiently regulated in the remaining 12 countries. The wider implications of these findings are also discussed from regulatory and socio-ethical standpoints.

Survey methods

To analyse the regulation of MMT worldwide, we attempted to identify countries in which MMT have been clinically implemented or are advertised using three approaches: (i) literature search, (ii) clinical trial database search, and (iii) internet search to locate relevant advertisements.

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