

Global Regulatory and Clinical Overview of Mitochondrial Replacement Techniques in 2023



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ABSTRACT

Mitochondrial replacement techniques offer a solution for women at risk of passing on mitochondrial disorders or experiencing infertility. Globally, the regulation of MRT is inconsistent and mostly banned, with the exception of the United Kingdom and Australia in preventing transmission of mitochondrial disorders. The regulatory landscape is constantly changing, and this review aims to explore the status of MRT in select countries as of 2023, including the UK, Australia, the United States, Singapore, Mexico, Ukraine, Greece and Albania.

KEYWORDS: Mitochondrial Replacement Therapy, Pronuclear Transfer Technique, Spindle Transfer Technique, Assisted Reproductive Technique, In Vitro Fertilization.

MANUSCRIPT

Introduction

Mitochondrial replacement techniques (MRTs) offer a solution for women at risk of passing on mitochondrial disorders to their children. Additionally, MRTs may serve as an effective technique in overcoming infertility in certain cases, particularly for older women, or women whose embryos developmentally arrest.

MRT can be performed in a number of ways, including pronuclear transfer (PNT) and maternal spindle transfer (MST). In all cases, MRT results in the transfer of the patient's nuclear DNA to an enucleated donor egg containing healthy donor mitochondria, which itself contains mitochondrial DNA. This process, creating a "three-parent" embryo, has raised regulatory concerns as it constitutes human genome modification,

leading to the prohibition of MRT in many countries worldwide.

Global regulatory standing on MRT

The United Kingdom

In 2015, The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 came into effect, to allow MST and PNT to licensed clinics only when "there is a particular risk that any embryo created by the fertilisation of eggs...may have mitochondrial abnormalities caused by mitochondrial DNA." The Newcastle Fertility Centre was the first to obtain the license, with the first cases approved in 2018 and first births reported in 2023 with the trial still ongoing^(1, 2).

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Australia

In 2022, Australia passed the Mitochondrial Donation Law Reform Bill, also known as Maeve's Law, named after a child with Leigh syndrome. A clinic that wishes to practice MRT must hold a mitochondrial donation license from the National Health and Medical Research Council Licensing Committee, which "must be satisfied that there is a particular risk of the woman's offspring inheriting mitochondria from the woman that would predispose the offspring to mitochondrial disease"^(3, 4).

Before MRT can be offered throughout the country, a clinical trial must first take place. In 2023, the government awarded a \$15 million grant to Monash University for the five-year mitoHOPE pilot program, which will be based in Melbourne in collaboration with Monash IVF⁽⁵⁾.

The United States

A 2015 US law to ban gene editing of human embryos was originally included in an annual budget bill to fund government programs. Section 749 of the Consolidated Appropriation Act of 2016 prevents the FDA from using its funding or evaluating any "research in which a human embryo is intentionally created or modified to include heritable genetic modification," which has been interpreted by the FDA to include MRT. In 2019, the ban was dropped but was ultimately reinserted after a subcommittee vote, and MRT remains effectively banned in the US to this day^(6, 7, 8).

The world's first MRT baby was born in 2016 in an effort led by New York-based Dr. John Zhang, whose team at New Hope Fertility Center created the embryos in the US and then sent them to Mexico to be transferred to circumvent US law. The baby's mother had the inheritable mitochondrial disease Leigh syndrome⁽⁹⁾.

Singapore

The Bioethics Advisory Committee (BAC) of Singapore released a consultation paper in 2018 on the use of MRT and sought the opinion of the public. In 2021, the BAC released an interim report on their position on whether or not MRT should be permitted in Singapore. Due to the international and scientific status of MRT at the time, "the BAC is of the view that it is premature at the present time to consider the acceptability of clinical application of [MRT], and in vivo research performed in human subjects in Singapore for the purpose of developing [MRT]." The BAC recommends waiting for evidence of safety and efficacy from reputable international initiatives, such as the UK's Newcastle Fertility Centre, before considering MRT for severe mitochondrial disorders⁽¹⁰⁾.

Mexico

Mexico has no specific federal laws or regulations regarding assisted reproduction, but MRT clinical research is permitted for unresolved infertility issues under certain regulations. Some Mexican states prohibit PNT due to local laws protecting life at the moment of fertilization⁽¹¹⁾.

Ukraine

Ukraine has no specific regulations for MRT. In 2017, the first baby was born using PNT to overcome infertility, and not for a mitochondrial disorder, at the Nadiya Clinic for Reproductive Medicine. Ukrainian clinics were a very popular location for medical tourism to bypass laws on the use of MRT in other countries, however this location is currently on hold due to armed conflict with Russia⁽¹²⁾.

Greece

In 2019, the first baby was born by MST to overcome infertility at the Institute of Life in Greece, in collaboration with Spanish, UK and US researchers. This birth was part of a pilot study established in 2018, that recruited 25 women with infertility due to poor egg quality to undergo MST. The results of the study were published in early 2023, which reported on the births of 6 healthy babies using the technique. One child had undergone "reversal," in which some cells showed as much as 50% maternal mitochondria. While the patient didn't have a mitochondrial disorder, this raises concerns for those who undergo the process as a treatment for mitochondrial disease^(13, 14).

Albania

The regulation of MRT in Albania is insufficient, with ambiguity regarding the definition of genome modification within the Oviedo Convention. Law 8876/2002 on Reproductive Health guides the use of assisted reproduction but falls short in adequately addressing the reproductive use of MRT in the country⁽¹⁵⁾.

Conclusion

As of early 2023, the only two countries that have implemented measures to authorize MRT in order to prevent the transmission of mitochondrial disorders are the UK and Australia. Numerous countries prohibit MRT, either explicitly or indirectly through their stance on germline editing. Consequently, women who are seeking infertility treatment have limited choices for accessing MRT, and they often have to consider countries where it is unregulated, such as Ukraine, Greece and Albania. In these countries, MRT is considered experimental and the use of this technique requires patient consent.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.