Mitochondrial Replacement Therapy: The Road to the Clinic in Canada

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Mitochondrial replacement therapy (MRT) aims to prevent the transmission of heritable disorders caused by mutations in the mitochondrial genome. Mitochondria are cellular organelles that contain their own maternally inherited genome consisting of 37 genes, 13 of which code for essential proteins in the energy-producing machinery of the cell. Pathogenic mutations in this genome have been estimated to have a minimum prevalence of >1 in 5000 in adults.[1] These mutations are associated with a broad spectrum of clinical phenotypes that range from fatal metabolic disorders in early infancy to late-onset neurodegenerative conditions. MRT thus is often the only possible intervention to enable the birth of a healthy, genetically related child for women who carry such mutations. MRT involves transferring the nucleus from an oocyte that contains pathogenic mitochondrial DNA to an enucleated donor oocyte that contains only normal mitochondrial genomes. The reconstituted oocyte then is fertilized *in vitro*, and the embryo is implanted. Alternative reproductive options may also include prenatal diagnosis, preimplantation genetic diagnosis, and egg donation, but most jurisdictions impose specific restrictions on their use,[2] to say nothing of the issues related to equitable access.

Key words: Mitochondrial replacement, assisted reproduction, criminal law

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The desire—and social pressure—to conceive biological children have been subjects of rich theoretical and health policy inquiry. The media's portrayal of some assisted reproductive technologies has played no small part in contemporary social constructions of assisted reproduction as being antithetical to "natural" processes of conception and parenting. Terms such as "three-parent baby" and "genetically modified children," for instance, have been used by numerous media outlets to describe early MRT research and development, fueling sensationalism and downplaying the still-experimental benefits of MRT.

Regulators are not immune to such public controversies; indeed, such controversies often define the resulting policy response(s), as was evident in the regulatory restrictions enacted shortly after MRT was introduced in the clinic. Many of these restrictions did not, however, detract from MRT use. Rather, they inadvertently encouraged the growth of medical tourism markets. Reports suggest that couples keen to access MRT circumvent existing legal restrictions in their home countries by travelling to countries where MRT is neither specifically prohibited nor regulated.[2,3] The first case of MRT tourism involved a baby born to Jordanian parents in Mexico. Dr. John Zhang and his team, based in the United States,

conducted the procedure in Mexico to circumvent U.S. regulations. Under Mexican law, MRT is restricted to research use and only to "solve sterility problems that cannot be solved otherwise" (p. 61).[2] Some authors argue that Zhang was in violation of this law,[2] considering the mother did not have "unsolvable" infertility problems, per se. Rather, any biological child born to her would have had a mitochondrial disorder (Leigh syndrome) that would lead to premature death.

Women with mitochondrial mutations are therefore situated at a controversial ethical, regulatory, and social nexus. Because women with mitochondrial mutations are often technically fertile, they are not afforded access to clinical infertility services, nor are they included in the strong patient advocacy communities established to support such services. Moreover, the regulatory bodies that govern access to the assisted reproductive technology that they require (MRT) fall within an ambiguous regulatory space. In addition to ethical concerns, Canadian regulators cite a paucity of safety and efficacy evidence as justification for restricting MRT use. Despite support in the United Kingdom for early phase clinical trials based on studies in animals (mice and non-human primates) and human oocytes,[3] a criminal ban on all human germline alterations is considered to apply to MRT and may foreclose the possibility for similar MRT trials in Canada. Yet, criminal law has rarely proven to be a proportionate policy instrument to govern science, particularly in rapidly evolving fields such as genetics. Definitions in criminal law tend to be too rigid to respond to scientific developments and, in the strictest sense, might not even be applicable to MRT, considering there is no consensus on whether it should be classified as a germline modification.

We argue that conflating two potential applications may inappropriately undergird the government's criminal ban on MRT applications and hinder policy development for their responsible use. The first application aims to use MRT to prevent the transmission of severe mitochondrial diseases and the second to improve fertility outcomes. These applications are ethically distinct, in our view. We propose that the former substantiates a regulatory, rather than a criminal, approach to MRT governance in Canada and that we should begin with a national consultation among interested stakeholders. Expanding the *Assisted Human Reproduction Act* (AHRA) to add definitional clarity on MRT—as with human germline gene editing[4]—is one such approach. We suggest that such a consultation will better address the regulatory challenges than will the existing criminal ban. Furthermore, it aligns with international law. Canadians have, for example, the right to benefit from scientific advances and their applications under Article 27 of the *Universal Declaration of Human Rights* and article 15(b) of the *International Covenant on Economic, Social and Cultural Rights*.

A periodic review of the AHRA was legally mandated in 2004, but no effort has been made for such a revision. Placing MRT within the necessary "modernized" debate would include discussion of the thresholds of acceptability for experimental innovations and therapies (e.g., serious, grave, or severe conditions).[5] Key decisions in a national consultation would seek to establish the proposed process for revising the AHRA. Initiating a public conversation that disseminates scientific information in a comprehensive manner would go far in alleviating the misplaced apprehension that so often limits opportunities for constructive dialogue around developing technology policy, such as that for MRT.[6] We therefore call upon Health Canada's convening authority and resources to pursue such "democratic engagement" for both scientific literacy and in the best interests of potential MRT users.

Points to Consider for MRT

1. MRT is a novel, promising intervention for heritable metabolic conditions. Canada should not curtail scientific exploration that might lead to its safe and effective clinical application. However, the first applications in Canada should be considered experimental and should meet the following criteria:
   - Diagnostic procedures preceding MRT should only be conducted in high-quality accredited clinical laboratories (i.e., should adhere to a recognized standard of practice).
   - Approval from a research ethics committee should be required for all prospective MRT use.
   - Clinical genetic/metabolic assessment should accompany diagnostic testing.
   - Appropriate follow-up of children born as a result of MRT should be mandated.
2. Implementation of MRT should be sensitive to considerations of equity of access.
3. The Canadian Standards Association should be engaged to develop standards for MRT.
4. Criminal bans are not a suitable instrument to regulate MRT. Justifications for upholding the current approach should be revisited, and new objectives and mechanisms of future policy should be broached.
5. Any legislation that purports to regulate science should be subject to periodic review, as suggested in the 2004

AHRA revision, to ensure ethics governance is robust and responsive to advances in science.

6. The revision of the AHRA should include input from all relevant stakeholders.

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