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Position Statement

Mitochondrial Replacement Therapy (MRT)

November 2019

Introduction

MitoCanada is Canada's only registered national charity focused on mitochondrial disease. MitoCanada's mission is to transform the outlook, quality of life and sense of community for people impacted by mitochondrial disease through education, awareness, patient/family support, and transformational patient-focused research. We envision a future where Canadians impacted by mitochondrial disease feel inspired, empowered, and supported until a cure is found.

MitoCanada formed a working group consisting of members of MitoCanada's staff and board, combined with leading Canadian scientists, bioethicists, and legal scholars to prepare this position statement.

Objectives of this Statement

Given that supporting research in the field of Mitochondrial Disease is one of MitoCanada's key objectives, it is also our intent to make the public aware about the clinical, safety, effectiveness, and ethical implications of new advancements in the field. There are risks and benefits with any clinical procedure, including the emerging and novel thechnology of Mitochondrial Replacement Therapy (MRT).

As a new technology, MRT presents/involves the possibility of a potentially safe technology for females who have a mitochondrial DNA (mtDNA) mutation that could result in a devastating disease that is maternally passed on to her offspring. MRT thus is often the only possible intervention to enable the birth of a healthy, genetically related child for women who carry such mutations. Special interest groups, governments, and other advocacy groups have made claims about the clinical effectiveness, and ethical considerations associated with these emerging techniques. 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.

MitoCanada has listed the following objectives for creating our position statement on this emerging technology:

- To make the pubic aware of mitochondrial disease and evidence-based options for treatment
- To inform the public about novel MRT techniques
- To educate the public about potential government legislation associated with MRT
- To address claims (sensationalist or otherwise) from special interest groups about the safety, effectiveness, and ethical concerns surrounding MRT
- To state our position regarding advancing research to better understand the potential benefits, safety, efficiacy, and limits of MRT

Background

Mitochondria are microscopic organelles in our cells known as the 'powerhouses or batteries' that convert the food we eat and oxygen we breathe into energy by the generation of adenosine triphosphate (ATP) molecules. ATP molecules undergo a complicated biochemical process that results in the release of cellular energy. The mitochondria and the generation of ATP creates more than 90% of the energy we need to sustain life, support growth, and make it possible for us to live.

In a person with mitochondrial disease, the mitochondria are dysfunctional and are not able to provide a sufficient generation of ATP. Given this, several mitochondrial diseases are caused by mutations in mitochondrial genes. Most scientists agree that mitochondrial DNA (mtDNA) is the only DNA that we inherit exclusively from our mothers. Females who carry mitochondria with mutations in mtDNA will transmit these mutations to their children. Almost all the cells of our body have mitochondria (with the exception of red blood cells), so mitochondrial diseases can affect multiple organ systems. In particular, the energy intensive organs

including the brain, heart, kidneys, muscles, eyes, and liver organs are most affected. There is no cure and only minimal therapies for mitochondrial disease. However, many people have a normal life span and their disease is well managed in some cases.

Research is underway throughout the world that will help us learn more about mitochondrial disease and also find new treatments and therapies. In the 1990s, experimental *in vitro* fertilization techniques were attempted to help individuals unable to conceive in a natural manner. These procedures laid the groundwork for the recent success in MRT. For example, nuclear transfer in spindle oocytes or in zygotes, also called MRT, has been shown to be an emerging technology for minimizing mutated mtDNA transmission from oocytes to pre-implantation embryos. In 2016, a 36 year old woman with mtDNA mutations known to cause Leigh syndrome had MRT (conducted in Mexico). Transfer of the embryo resulted in an uneventful pregnancy (i.e. no complications) with the delivery of a healthy boy at 37 weeks of gestation.

Given this recent result, the question arises, are these procedures safe in the long-term? After a review of the literature, the best answer we can provide is that we do not yet know, but so far so good. In other words, it is too soon to know, but there have not yet been any serious adverse events reported in families where these sorts of procedures have been attempted.

In addition, it is important to note, these procedures are not legal everywhere. The recent success occurred in Mexico where reproductive laws may be more lax. The legality also depends exactly on which procedure is being used. In 2015, the United Kingdom (UK) approved techniques for use in the context of MRT. However, MRT is currently illegal in Canada under the *Assisted Human Reproduction Act* (AHRA) of 2004 and research on these techniques is illegal even if the resulting embryo will never be implanted in a uterus. Overall, health agencies in Canada have yet to formally review the details around these new procedures.

Another question that has arisen, especially amongst particular special interest groups, is whether or not these procedures are ethical. These concerns are multi-faceted and include: the social implications of having three genetic projenitors (that some refer to as 'parents'), the necessity of such procedures, and heritable genetic changes that affect the human gene pool (similar concerns have been raised in relation to germline editing that affects nuclear DNA and thus raises concerns about enhancement and so called 'designer babies').

Canadian Policy Landscape and Expert Working Group Position

Canada distinguishes between somatic and germline gene editing. MRT falls under the auspice of germline gene editing, which is strictly forbidden by a criminal ban. Canada's 2004 *Assisted Human Reproduction Act* (AHRA) prohibits research involving in vitro or in vivo germline alterations, with serious sanctions ranging from a fine of up to $500,000 to imprisonment of up to 10 years.

A group of leading Canadian experts that includes scientists, clinicians, legal scholars, bioethicists, patient advocates and others, who convened over the last 3 years under the auspices of the Canadian Stem Cell Network and McGill University's Center of Genomics and Policy, held a series of workshops to explore the challenges of revising the AHRA. This led to the publication of a Consensus Statement[1], based on several academic publications[2-4], recommending that "basic and pre-clinical research on human germ cells and embryos in the earliest stages of development should be allowed" and that "mitochondrial replacement therapy to prevent the transmission of serious mitochondrial diseases ... be permitted when demonstrated to be safe and effective"[1]. The expert group also called attention to the distinction between using MRT to prevent the transmission of severe mitochondrial diseases and to improve fertility outcomes, arguing that these applications are ethically distinct and proposing that the prevention of disease justifies an immediate move away from a criminal ban toward a regulatory approach. Finally, the group called for a national consultation with interested stakeholders[2].

Summary

- New techniques have emerged that allow MRT (mtDNA from donor females transferred to mothers with mtDNA mutations) to avoid inherited mitochondrial mtDNA disorders (fatal and otherwise)
- Human oocytes reconstituted by Maternal Spindle Transfer (MST), are capable of producing a healthy live birth
- In 2015, the UK parliament voted to empower its *Human Fertilization and Embryo Authority* (HFEA) to approve the use of MRT[5] in some circumstances. The UK is the only country in the world that has approved MRT.
- In Canada, MRT falls under the AHRA and is strictly forbidden by a criminal ban preventing research.
- A working group of leading Canadian experts have stated criminal bans are not a suitable instrument to regulate MRT, which currently prohibits research.

MitoCanada's Position

MitoCanada supports further research to better undertsand the safety and efficiacy of mitochondrial replacement therapy to prevent the transmission of mitochondrial diseases.

References

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