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Mitochondrial Replacement Techniques: Remaining Ethical Challenges

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Abstract

Recent developments in the field of mitochondrial replacement technique (MRT) research and clinical practice have raised ethical concerns worldwide. We argue that the future use of MRTs requires a concerted effort among the global research and clinical community to implement and enforce responsible innovation and governance.

Keywords: mitochondrial replacement techniques; pronuclear transfer; maternal spindle transfer; mitochondrial DNA; germline modification; assisted reproductive technology; ethics; governance.

Introduction

Mitochondrial replacement techniques (MRTs) have been developed to help women who are carriers of harmful mitochondrial DNA (mtDNA) mutations to have healthy, genetically related offspring. MRTs involve the transfer of the nuclear DNA of a woman's oocyte carrying an mtDNA mutation into a donor oocyte carrying healthy mitochondria. The transfer can be performed either before in vitro fertilization (by transferring the spindle complex of diseased oocytes, i.e. maternal spindle transfer) or after (by transferring the pronuclei of the affected woman's zygote, i.e. pronuclear transfer). Since mitochondria are maternally inherited, such transfers would in theory prevent maternal transmission of mtDNA disease while preserving the genetic link between affected mothers and their offspring (Bredenoord and Hyun, 2015). The use of MRTs is particularly controversial because it is a form of germline modification.

In recent years, several scientific, ethical, and political bodies have tried to grasp the various implications of MRTs. It now appears that the technique is gaining momentum politically and scientifically. In January 2017, the UK became the first country to license the clinical use of an MRT when the Newcastle Fertility Centre was granted a license by the Human Fertilisation and Embryology Authority to use pronuclear transfer. However, this was only after the first baby born through MRT had been revealed to the world in 2016. This "world first" was accomplished by clinicians taking a regulatory detour by carrying out the MRT (which in this case was maternal spindle transfer) in their New York City clinic and then shipping the embryo to their Mexican clinic for transfer to the patient, in order to avoid a complex range of US

regulatory issues (Palacios-Gonzaález and Medina-Arellano, 2017; Zhang et al., 2017). In addition, in Ukraine a baby has been created via MRT and born (as reported in New Scientist earlier this year), albeit not for disease prevention but to rejuvenate the fertility of aging oocytes. It is also likely that MRTs will be accompanied in the clinic by some broader advances in biomedicine, including the emergence of CRISPR/Cas9-mediated genome editing and stemcell derived gametes.

In this Forum, we evaluate the ethical implications of recent developments in the field of MRT research and clinical practice. We argue that despite some clinical success surrounding the creation of babies with MRTs, this may come at the cost of encouraging the irresponsible use of new assisted reproductive and genetic technologies. We support the use of MRTs, but do so with the view that they should be used cautiously. In light of the remaining ethical challenges that still exist surrounding MRTs, we maintain that the future use of MRTs requires a concerted effort among the global research and clinical community to put in place responsible innovation and governance of these techniques.

Governance: Updates on Key Reports, Policy, and Regulations

In 2015 the UK was the first country to implement a set of laws—The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015—specifically devised to regulate MRTs (both maternal spindle transfer and pronuclear transfer) for applications in human research and clinical practice. However, the path to the UK's governance of MRTs was a culmination of several years of public consultations and publications that were regularly marked by debate and controversy (Appleby, 2015).

While the UK's laws are not a panacea, they do set out some basic parameters that must be followed in order for the use of an MRT to be licensed and which improve the likelihood that the techniques will be used safely and effectively. For instance, a license can only be granted for use in cases where it has been determined that there is a particular and significant risk that a prospective child will inherit a serious mitochondrial disease. Also, clinics seeking a license must provide a plan to follow up with any future children in order to monitor their wellbeing.

Discussion surrounding the regulation and policy aspects of MRTs has also taken place in the US. In 2016 a US FDA commissioned report from the US National Academy of Science's Institute of Medicine was published, entitled Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations. This report lays out a range of recommendations about how US researchers and clinicians should proceed with the clinical use of MRTs. There are areas where its recommendations conflict with the regulations and views of UK policymakers. For instance, unlike the UK, the US report recommends the use of sex selection to select for male embryos and for MRTs to be introduced into clinical practice via clinical research. While the US report outlines a somewhat more cautious approach to the introduction of MRTs, both the UK and US share similar perspectives with respect to the safe governance of MRTs, including the need to gather data on the outcomes of MRT pregnancies and births, the need to only use MRTs if serious mitochondrial diseases are unavoidable, and the need to minimize risks to future children.

Despite some political and social attitude differences toward the use of novel assisted and genetic technologies (Bredenoord and Hyun, 2015), it is significant that both the UK and the US have ethically endorsed the clinical use of MRTs for mtDNA disease and that each country does so while also acknowledging that MRTs are a form of germline modification. However,

as confirmed by the UK Department of Health (Appleby, 2015) and a recent National Academies of Science, Engineering and Medicine report (2017), a key distinction that must be noted is that germline modification refers to the replacement of an intact germline genome, rather than the modification of genes within a germline genome. While the endorsement of germline modification is a significant milestone with respect to changing attitudes in science regulation and policy, modifying the genes within the human germline genome is likely to continuously raise fierce scientific and ethical debates. If a time comes wherein modifying the genes within the human germline under which it is permissible will need to be determined through a process that is rigorous and transparent.

Remaining Ethical Challenges Mexico and Ukraine: Premature Clinical Applications?

Several other ethical challenges remain surrounding the clinical use of MRTs. An initial question is when MRTs should be moved to the clinic. The UK and US have demonstrated that expert debate with public involvement is valuable and that governance of MRTs can be achieved. This makes the first clinical applications in Mexico and Ukraine morally questionable. The teams of clinicians in both Mexico and the Ukraine each proceeded to create MRT-conceived babies in the absence of specific governance surrounding the use of MRTs. Fortunately, both procedures resulted in healthy babies, at least so far. After all, the mutation load in the newborn baby created in Mexico was further analyzed and showed defective mitochondria ranging from undetectable in placenta, umbilical blood, and umbilical cord to 2.36% in urine precipitate, 3.52% in buccal epithelium, 5.59% in hair follicles, 6.77% in amnion, and 9.23% in the circumcised foreskin (Zhang et al., 2017). This indicates that the risk for developing mtDNA disease is drastically reduced, but cannot be completely excluded. But even if completely eliminating this risk could be possible, then seeking areas of low governance does not appear to be the way forward for novel reproductive and genetic technologies. This stricter outlook is suggested by a recent FDA warning letter to Dr. Zhang, who led the procedure in Mexico.

The application of new medical technologies always requires finding a balance between cavalier practice and opportunity costs, between laissez-faire and overregulation. Initial applications of novel reproductive and genetic technology should at least be aimed at generating novel knowledge. The European Society for Human Reproduction and Embryology (ESHRE) and other professional organizations have condemned hasty "try it and see" approaches. In particular, reproductive medicine has a history of introducing innovations into clinical practice without proper preclinical research into their effectiveness and safety, such as embryo and oocyte cryopreservation, intracytoplasmic sperm injection (ICSI), and ooplasm transfer (Dondorp and de Wert, 2011). What we are currently witnessing in the case of MRTs is part of this ongoing historical narrative of clinicians offering a new reproductive treatment outside of formal research routes. One could argue that (fortunately) after decades of innovation, no patterns of serious safety problems have emerged from the use of IVF and other reproductive treatments; however, a strong case can be made for a more ambitious approach to innovation than this field of medicine has shown to date (Dondorp and de Wert, 2011), particularly as we enter the era of germline modifications.

The Mexican and Ukrainian events may have complex implications for these countries and elsewhere (Palacios-González and Medina-Arellano, 2017). For example, politicians in Mexico have already announced that they will initiate laws to restrict MRT. In addition, any substandard clinical application could jeopardize approval in other countries. For example, the Mexican case may unethically promote or entice other researchers to take similar risks without

due process and governance, thus, sending the wrong message that these techniques can be used elsewhere to avoid regulatory processes. This could undermine public trust, undermine policy making, and fuel a "race to the bottom" for new biomedical technologies. Therefore, the development and implementation of collective global governance is part of the global research community's responsibility to ensure that radically new biotechnologies such as MRTs (and future techniques, such as stem cell-derived gametes) are delivered safely and effectively to those who access them.

We also need to reflect on the ethics of alternative clinical applications of MRTs that are beginning to (re)emerge. For example, the recent MRT (pronuclear transfer) use in Ukraine was not to avoid a significant risk of serious disease in offspring, but instead to rejuvenate the fertility of aging oocytes, similar to the way that cytoplasmic transfer was used to treat infertility from 1997 to 2001 in the US before the FDA banned its use in 2001 (Appleby, 2015). We question the ethical permissibility of using these experimental techniques outside a research setting in cases where a prospective person is not at any risk of inheriting a serious disease. The acceptability of offering an experimental fertility procedure without sufficient scientific basis, oversight, and scientific follow-up is comparable with stem cell clinics that offer unproven stem cell "treatments," thereby exploiting the hope of often seriously ill patients. The fact that these alternative commercial uses of MRTs have been carried out in nations lacking proper regulation and rigorous oversight into MRTs further strengthens our core argument that there is a global responsibility within the research community to discourage premature use of experimental techniques, such as MRTs, and to strive for robust governance in areas where it is currently lacking.

MRTs and Donor Anonymity

The status (i.e., anonymous or non-anonymous) of mitochondrial donors was among the most discussed and controversial aspects of the UK's recent public consultation that led up to the regulation of mitochondrial donation and MRTs. Unsurprisingly, there has been continued academic debate surrounding the anonymity of mitochondrial donors in the UK since the regulation of these techniques (Haimes and Taylor, 2017; Turkmendag, 2017) and it is likely that this debate will continue to grow as additional countries consider the governance and use of MRTs.

According to UK MRT regulations, mitochondrial donors will remain anonymous, unlike gamete, oocyte, and embryo donors, which are identifiable to offspring after the latter reach the age of 18. It could be argued that the UK government's reasoning for allowing mitochondrial donor anonymity is inconsistent. One possible argument against the government policy is that mitochondrial donors should not be treated differently from gamete and embryo donors because the mere fact that mitochondria have a different quantity of genes in their genome (the quantity claim), and the fact that qualities of the genes are not responsible for the phenotypic expression of our "personal characteristics" (the quality claim), does not necessarily mean that the identity of the person who donated them would be of less interest to the person created with them. While the mitochondrial genome may be fungible, it nevertheless constitutes a fundamental part of an individual's healthy functioning body and contributes to the nature of their appearance and their course of life (Bredenoord et al., 2011). Therefore, a fresh debate informed by social science evidence (including evidence from other relevant areas of assisted reproduction) needs to be conducted about whether or not having anonymous mitochondrial donors is in the interests of mitochondrial-donor conceived persons.

MRTs and the Value of Genetic Relatedness

One additional remaining ethical issue is whether or not MRTs further reinforce the social value of genetic relatedness. The main reason prospective parents want to use MRTs is to have a genetically related child; otherwise, they could use donated oocytes or embryos, which are known to be a safe form of assisted reproduction. This area of the MRT debate raises an important question: why is genetic relatedness of value? With the emergence of gene editing technologies and stem cell-derived gametes, it may become possible to create offspring who have inherited genes of many different quantities and qualities (Bredenoord and Hyun, 2017). Techniques such as MRTs have disrupted our paradigm of what kinds of genetic relatedness should matter and society must now revisit why we place importance on whether or not we share certain quantities and qualities of genes with others. Our conclusions to these questions may influence future policies surrounding issues such as the status of donors of genetic materials in reproduction and how many individuals we may permit to genetically contribute in one instance to the creation of a person.

Conclusion

Given the considerable number of remaining ethical questions surrounding the use of MRTs, the global community of researchers has a responsibility to encourage, foster, and implement the necessary governance of these techniques to ensure that they are used effectively, safely, and responsibly. The use of MRTs can and should be viewed as an opportunity for learning and a model for how morally sound governance can be achieved for other innovative reproductive and genetic technologies in the future, including germline genome editing and stem cell-derived gametes.

As genome editing techniques improve and might move into the realm of human reproduction, it is also necessary to consider the ethical implications these techniques might have if coupled with MRTs or if they are eventually used to replace MRTs altogether. If these technologies become more effective and eventually become a feasible option for treating inheritable genetic conditions in embryos in vitro, global attitudes to the use of these techniques may adjust in the same way that they have for MRTs.

In view of the variety of legislative and regulatory jurisdictions throughout the world and even within nations, legal harmonization for MRTs is unlikely and possibly also undesirable. After all, how biotechnology regulations are framed is inevitably shaped by (political) culture and context. However, what is both necessary and possible is the development of ethical principles to guide our research. Historically, some powerful examples exist of where the international community has successfully developed international guidelines for ethical conduct in research, such as the WMA Declaration of Helsinki and the CIOMS International Ethical Guidelines for Health-related Research Involving Humans. These guidelines clearly are moral guidelines, meaning that they entail shared moral principles that countries can voluntarily use to help frame their local regulations. Their concomitant adoption by funding agencies, research institutes, and editorial policies, as has been done over the years by the Declaration of Helsinki, will contribute to the achievement of some form of improved global bioethics governance. It is a mistaken and even dangerous view to perceive science and biotechnology as autonomous forces that cannot be governed (Jasanoff, 2016).

Responsible innovation only amounts to empty rhetoric if it is not actively supported and promoted by professionals and professional societies (Dondorp and de Wert, 2011). Perhaps

what the scientific community therefore needs is something along the lines of a modern "Reproductive Asilomar," where the scientific, ethical, and societal challenges of novel reproductive and genetic technologies are explored and discussed in a deliberative, inclusive international forum. In this way, science, technology, ethics, and society could be more coproductive, rather than existing as segregated fields.

Web Resources

US FDA Center for Biologics Evaluation and Research, https://www.fda.gov/downloads/ BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/ Enforcement/UntitledLetters/UCM570225.pdf?source=govdelivery&utm_medium=email&ut m_source=govdelivery

The National Academies Press, https://www.nap.edu/login.php?record_id=21871& page=https%3A%2F%2Fwww.nap.edu%2F download%2F21871

The National Academies Press, https://www.nap.edu/login.php?record_id=24623& page=https%3A%2F%2Fwww.nap.edu%2Fdownload%2F24623

New Scientist, https://www.newscientist.com/article/2118334-first-baby-born-using-3-parent-technique-to-treat-infertility/

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