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The benefits, risks, and alternatives of Mitochondrial Replacement Therapy

Bringing proportionality into public policy debate

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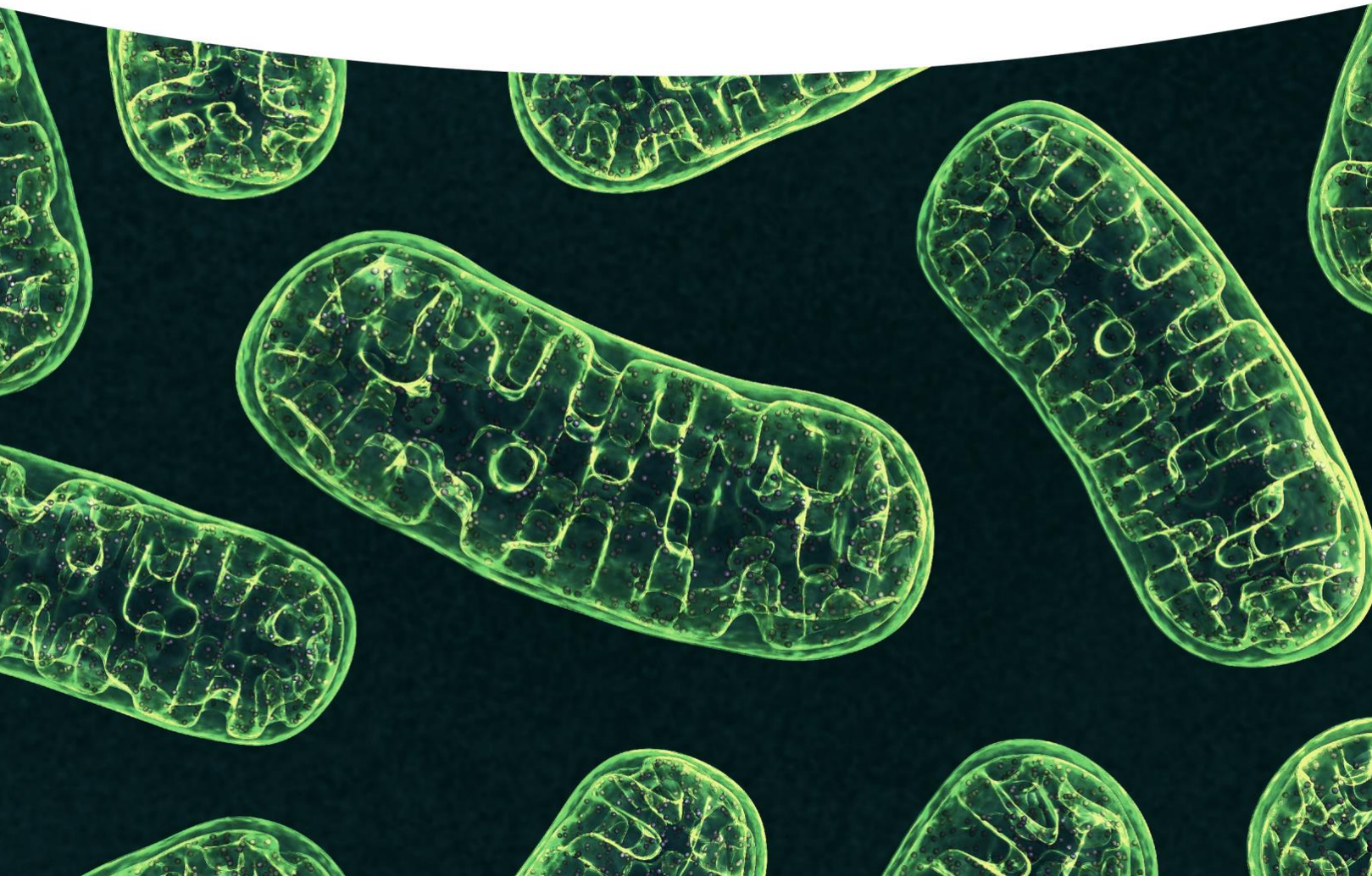

The benefits, risks, and alternatives of Mitochondrial Replacement Therapy – bringing proportionality into public policy debate. [1]

Gregory K Pike, 2022

Abstract

Mitochondrial Replacement Therapy (MRT) utilises nuclear transfer technology to replace defective mitochondria with healthy ones and thereby minimise the risk of a mitochondrial disease passing from a mother to her child. It promises much but comes with ethical controversy, significant risk of harm, and many unknowns. Forming a position on MRT requires accurate information about the current state of knowledge, and an appreciation of the ethical issues at stake. Ethical deliberations will vary depending on the framework used. There are in principle objections to MRT on the grounds of direct harm to human embryos and germline genetic modification. But even without these objections MRT can be weighed in terms of the balance between risks and benefits, alternatives and uncertainties. This paper explores the evidence and lays out the relevant issues to assist such a deliberation.

Keywords

mitochondrial disease, mitochondrial donation, mitochondrial replacement therapy, three parent baby, risks, germline genetic modification.

Introduction

MRT refers to a range of techniques in Assisted Reproductive Technology (ART) whereby defective mitochondria can be replaced with healthy donated ones immediately before or after conception to reduce the risk of mitochondrial disease passing from a mother to her offspring. The technology is limited to those conditions in which there is a deleterious genetic mutation in mitochondrial DNA (mtDNA), which represents about 20% of all mitochondrial diseases. The majority of genetic defects leading to mitochondrial diseases occur in nuclear genes that influence mitochondrial function. The percentage of defective mitochondria in any given cell type is termed *heteroplasmy*, and when reaching 100%, the cell is termed homoplastic for the defect. About 60% heteroplasmy seems to be the threshold for the expression of symptoms, and high levels of heteroplasmy can occur in offspring of an asymptomatic mother who has lower heteroplasmy. While MRT is not strictly a therapy because it does not treat an existing individual with mitochondrial disease, it nevertheless incorporates the preventive intention to minimise the risk of disease transmission.

The purpose of this paper will be to outline briefly the key issues in MRT, both practical and ethical, and then consider on balance how benefit, risks and alternatives might coalesce to inform public policy. While *in principle* objections to MRT can be raised, such as direct/intentional and indirect destruction of human embryos, even without such objections it is necessary to ask whether undertaking MRT is a reasonable proposition all things considered. A cost benefit analysis might therefore be a 'lowest common denominator' means for decision makers to think about MRT.

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[1] This is the final accepted version of Pike GK. The benefits, risks and alternatives of mitochondrial replacement therapy–bringing proportionality into public policy debate. *Clinical Ethics* 2022 Apr 4:14777509221091097.

Benefits

Mitochondrial diseases of all types are rare but potentially seriously debilitating conditions that affect 1 in 5 to 10 thousand people.[1] Because mitochondria are only transmitted from the egg to the embryo and rarely from sperm,[2] mitochondrial diseases are inherited in a matrilineal manner. There are no cures for mitochondrial diseases, only symptomatic relief, and if a woman wishes to have a child without risk of passing on a mitochondrial disease, the options are limited to adoption, embryo donation or using a donor egg that is known to be free of a defect in one of the 37 mitochondrial genes. Preimplantation genetic diagnosis (PGD) to deselect embryos with an mtDNA defect might work, but has limitations because of the unique characteristics of mitochondrial genetics. Having a child who is biologically related to both mother and father and at significantly lowered risk of a mitochondrial disease is where MRT could theoretically be used. Indeed, given that there are alternative means to have a child, the main justification for MRT rests on the desire for a genetically related child.

There are several possible MRT techniques, and while there are ethically significant differences between them, each essentially involves replacing mutant mitochondria with healthy ones from a donor. The resulting altered embryo would then be allowed to develop before transfer to the intended mother's uterus using routine methods in ART.

There are no reliable and testable accounts of MRT leading to the birth of children. In 2017, Zhang reported the birth of a healthy child by MRT, but there has been no verification or follow up.[3] There have been other reports of births using the technology for age-related infertility rather than to avoid transmission of a mitochondrial disease, but again these have not been verified.[4] Following the passage of legislation in 2015, the UK became the first country in the world to regulate and license MRT procedures. However, despite issuing over 20 licenses, there have been no reports of births, numbers of altered embryos produced or transferred, or other pregnancy outcomes.

Proof of principle has been undertaken in other species as well as using non-transferred human embryos, and there is some evidence that MRT could potentially lead to the birth of disease free offspring. This research will be discussed below when examining risks.

An important consideration for policy makers is how many women might benefit from MRT. The avoidance of disease is compelling, but besides the breadth of issues embedded in MRT, permitting a new technology inevitably demands financial and other resources that reflect the public health benefit to be attained. Indeed the resources already expended in reviewing and exploring MRT in the UK alone have been substantial, and must sit alongside the many other needs within the health sector.

In the UK in 2013, the *Human Fertilisation and Embryology Authority* (HFEA) claimed that about 10 women per year might be assisted by MRT.[5] However, not long before the parliamentary vote, a paper was published by researchers at Newcastle University who were at the forefront of research on MRT, and who were promoting its clinical application. That paper concluded that in fact 152 women per year could be assisted.[6] However, the calculation included all women *at risk* of transmitting mitochondrial disease arising from defective mitochondria, regardless of severity, and on the assumption that all those women would adopt MRT despite the potential complications - physical, psychological, ethical, and personal. The small number of licenses issued over the past 5 years in the UK may be indicative of the number of women who could benefit, although concern over efficacy and safety may also have constrained numbers. In a recent study of stakeholder attitudes in Canada, experts thought MRT would be for "very, very rare scenarios" and might apply to 12-15 women each year in that country.[7] These numbers would translate to approximately 7 women per year in the UK.

The important point to note when considering potential benefit is that as yet there is very limited research that can reliably show that the risk of mitochondrial disease transmission can be significantly lowered or avoided by using MRT. At best, preliminary research with animals and human embryos implies that success might be possible.

Risks

Method Failure

If a mitochondrial disease still transmits to offspring, then MRT will not have succeeded. But rather than outright failure, it is more likely that some degree of risk will remain. The critical question is - how much risk, on the grounds of method failure alone, would be deemed acceptable to warrant undertaking MRT?

The primary concern about potential method failure is that during the procedure some mutant mitochondria from the intended mother might be transferred to the altered embryo. Whether the technique used is Maternal Spindle Transfer (MST) or Pronuclear Transfer (PNT), the technology involves nuclear transfer that risks carriage of some mutant mitochondria along with the nucleus. Hence, rather than producing an altered egg or embryo completely free of mutant mitochondria, some degree of carry over means a low level of heteroplasmy remains. That small amount would likely not be a problem if in the vicinity of a few percent of the total mitochondria count, and there is evidence that this low level can be achieved.[8] However, there is also evidence that after MRT mutant mitochondria preferentially multiply so that heteroplasmy increases with time thereby increasing the risk of mitochondrial disease reemergence.[9]

This problem was revealed most recently by Ma et al. in their analysis of MRT in rhesus macaques. While 3 of 4 animals maintained initial heteroplasmy after MRT, the level in one animal increased from negligible to 17%. Moreover, heteroplasmy varied from one tissue type to another, leading the authors to caution "our results imply that levels of the mutant, maternal mtDNA may increase randomly in selected organs and tissues of children born post-MRT".[10] This study also revealed a different and quite unexpected finding – mitochondria from the *male* carried over in one monkey and was detected at variable levels in different tissues from negligible to 33%, evidence of a dramatic preferential multiplication of *paternal* mitochondrial DNA.

The mechanisms for increasing mtDNA heteroplasmy over time are not entirely clear but may involve 'genetic drift' either because of interaction with nuclear genes,[11] or because of 'genetic bottlenecks', whereby a reduction in the number of mitochondria during cell replication can unpredictably lead to the emergence of a daughter cell with higher heteroplasmy than the parent cell. This may be particularly acute during oocyte development and go some way to explaining why symptomatic mitochondrial disease (high heteroplasmy) can result from an asymptomatic mother (low heteroplasmy).

Whatever the case, offspring of MRT would need to be followed up extensively over time to monitor this risk, keeping in mind that consent of parents and subsequently of adult children of MRT cannot be guaranteed.

Whether MRT works is of course dependent on the successful carriage of the pregnancy, and yet it is rarely acknowledged or even recognised that with mitochondrial diseases "a high incidence of mid- and late pregnancy loss is a common occurrence …"[12]

Potential Adverse Side Effects

The possibility that nuclear genes may be involved in mitochondrial genetic drift is a subset of a broader concern about incompatibility between the nuclear genome and an introduced foreign mitochondrial genome.[13] Opinion appears widely divergent about the extent of this risk, with some arguing that adverse effects in human studies will be inevitable,[14] and others that risk is almost non-existent.[15] But potential incompatibility between nuclear and mtDNA has mostly been understood as a problem with nuclear DNA 'recognising' mtDNA, whereas the problem may also go the other way - as Muir et al. note, "mitochondria themselves may be important regulators of nuclear genes".[16] Regardless, uncertainty about this issue is itself a risk. After all, risk is about uncertainty.

One leading edge of research on mitochondria is their involvement in a far wider range of disorders than the mitochondrial diseases that are the target of MRT. For example, mitochondria have been implicated in depression and anxiety, even though as yet the genetic, epigenetic or other cytoplasmic factors that might be involved are unknown.[17,18] Mitochondria have also been implicated in aging and cancer.[19] The point is, donated mitochondria that are free of the rare defects in mtDNA that we know about might be defective in other ways, perhaps with respect to mental health, aging and cancer. Transferring donated mitochondria, along with the entire rest of the cell minus the nucleus, means transferring a huge unknown. Moreover, because the changes are heritable and irreversible, any risk to future generations has a salience that is different to the risk when harm is limited to an individual being treated or to just one generation. Such risk is of a different order and intuitively seems to demand a higher standard of certainty.

There are two other elements of uncertainty about physical risks that have been raised by MRT, both related to aspects of the procedure itself. The first is that MRT is nuclear transfer technology like that used in cloning procedures, and these procedures are known to involve risks, possibly from the form of micromanipulation used. In MST in particular, the fragile maternal spindle is being transferred, so the risk of physical damage may be greater than with PNT. Second, the reagents used to enable nuclear transfer could damage the subsequent altered embryo, a risk that has not been the subject of sufficient investigation to provide any clarity.[20,21] These risks may explain why the development of early human MRT embryos has been found to be poorer than that of control embryos.[22,9]

Human Embryos

As noted at the outset, in-principle objections can be raised to MRT regardless of safety or other risks. One of those objections involves a belief in the inherent status and dignity of human embryos that would require their protection from intentional harm. Whether one's position is that this moral status is absolute or that human embryos have *some* moral value requiring *some* degree of protection, MRT does involve the intentional destruction of human life at its earliest developmental stage as a means to an end. In a sense this destruction is one more cost in the cost-benefit analysis, and more or less so depending on one's position.

Several decades ago, in the wake of claims about stem cells and potential therapies, many nations grappled with whether to permit the use of human embryos in research, some drawing the line at only permitting the use of those who were unwanted and therefore left over from IVF treatment. The intentional creation of human embryos for research or other purposes involving their destruction was not permitted, and strict regulation would apply to the use of excess embryos.

For MRT to occur, at least in the case of PNT, the intentional creation and destruction of human embryos would be an essential element of the procedure itself, each and every time it is done. And even for MST, the intentional creation and destruction of altered embryos would be an essential part of research leading up to refining the technology for clinical application. Of course, in some legislatures, this is already happening.

These pressures highlight one of the more difficult aspects of policy with which decision makers are confronted. A line in the sand, once firmly drawn, is challenged. Where a precedent might lead next is rarely obvious. Permitting the intentional destruction of excess human embryos soon encompassed the intentional destruction of cloned and hybrid embryos, in the UK at least. Perhaps it is not surprising that the intentional destruction of embryos in MRT was first permitted in the UK. The business of slippery slopes is both complex and contentious, but a backward glance at the trajectory of changes in policy surrounding human embryos is evidentiary. And recent calls for extending the current 14-day limit on embryo experimentation are part of the downward pressure.[23]

Heritable Changes to the Germline

There is broad international consensus that heritable genetic modification to humans should be prohibited.[24] It is one thing to utilise gene therapy to change the genetic makeup of one patient in an attempt to correct a health disorder, but quite another to make changes at the embryonic stage that will then be inherited by the next generation and to future offspring. The basis of the consensus is grounded in human dignity rather than safety alone, which constitutes stronger grounds for agreement to be maintained. The Council of Europe's Oviedo Convention for example, prohibits germline genetic modification on the grounds of human rights and human dignity, not safety and efficacy.

> … the Convention … is firmly rooted in the principles of human rights and dignity … Neither human rights, human dignity, nor ethics can be peremptorily reduced to safety and efficacy. A genetic intervention can be safe and efficacious, yet objectionable on other grounds.[25]

The US and UK have parted company on the question of whether MRT constitutes heritable genetic modification. In the US, the report by the National Academy of Sciences concluded "MRT results in genetic modification of germ cells",[21] making it clear that MRT falls within the terrain of agreements like the Oviedo Convention. In the UK however, " … the Government … has consistently rejected claims that the techniques constitute genetic modification and remains firmly of that view."[26] The UK's position is to accept that MRT constitutes *germline* modification, but to distinguish that from *genetic* modification, which it deems not to occur in MRT, hence edging around the Convention. But the consensus in documents like the Oviedo Convention is about genetic modification in the context of heritability. It is the *heritability* that is the main concern, otherwise why permit genetic modification in somatic gene therapy, but not in the germline? In any case, even though MRT does not involving editing or changing a specific gene, it will nevertheless modify how the genes of the newly created embryo function, and in potentially unpredictable ways with effects well beyond one generation. This represents modification to genomic behaviour that no naturally conceived embryo experiences, with or without ART.

There is also a hint of genetic reductionism when discussion about heritability is constrained to genes, or to genetic modification alone. Genes operate in concert with one another as well as with the cellular, organismic, and external environment. MRT, contrary to what the term implies, involves replacement of *all* the cellular 'machinery' as well, that is, everything but the nucleus. It is reductionist and assumes too much to suggest that the cytoplasm is not individualised in any way, a biochemical soup that works the same regardless of where it came from or to whom it belongs. Just as it is reductionist and assumes too much to suggest that mitochondria are just like batteries than can simply be swapped. This perspective also has traction when it comes to the question of mixed parentage discussed below.

Whether MRT is strictly genetic modification or not might be debatable, but because there is broad agreement that it involves a heritable change, for this reason it interfaces with all discussions about heritable changes that involve selective modifications, genetic or otherwise. The debate about MRT is therefore also about whether alteration of future generations via biological manipulation of human embryos should be carried out, and if so, in what ways. It is a debate that has been ongoing for many decades, but MRT has upped the ante. Evans argues that a variety of value changes from the 80s onwards have contributed to acceptance of germline changes, what he calls damage to the somatic/germline barrier. This barrier had held well, but with those value changes, and now the acceptance of MRT, the risk of sliding down the slope towards less palatable outcomes is greater.[27] MRT provides additional and more immediate damage to the barrier, because procedures that actually do breach the divide have been permitted. This is why there is concern that MRT is a forerunner to the clinical application of current experiments with direct modification of genes in human embryos.

MRT achieves something else too. As Bayliss argues, it provides researchers with an opportunity to refine micromanipulation and other techniques common to MRT, cloning and gene editing.[28] MRT is greasing the slope. And despite the 'social baggage' of eugenics that still has currency,[29] using heritable change technologies to produce 'better' offspring might be a tantalising possibility for some.

Mixed Parentage

What makes a parent is complex, and especially so in the ART era. In surrogacy for example it is possible for a child to have three different mothers, genetic/biological, gestational, and social. There may even be circumstances where a fourth, legal mother, is involved. How these different aspects of parenthood work together and what they mean for a child in terms of identity or psychological formation are still under investigation, but with MRT the complexity steps up a notch because genetic/biological motherhood itself is split.

The media commonly refer to an MRT child as a 'three parent baby'[30], a designation that has been criticised as a misrepresentation that is "unfair and senseless".[20] The primary objection has been that the mitochondrial donor contributes just 37 genes, whereas the intended parent contributes at least 20000 nuclear genes.

> … it is 0.1 percent of the total amount of genetic material in terms of what makes us us … the mitochondrial DNA really is only involved in making energy; it's not about other physical, cognitive or behavioural characteristics.[31]

> … the children produced would be 2.002 – parent babies.[32]

These statements are, however, reductionist and problematic on three counts.

First, they trivialise the significance of mtDNA. It is ironic that mitochondrial genes are so important that they are the very reason MRT would be undertaken, but apparently so unimportant that their donor is effectively made irrelevant. Moreover, as noted, there is much yet to learn about mtDNA. For example, there is evidence for a relationship between mitochondrial function and intelligence.[33,34]

Second, they render meaningless the role of the other biological constituents of the egg, about which we know rather little but will undoubtedly learn more. The donor egg cytoplasm, now with a different nucleus, goes on to contribute to the developing embryo, including the placenta, so,

> In essence, the donor egg helps to make possible in a very literal sense the coming into and ongoing existence of the embryo, through its implantation and development in utero.[35]

Third, gene number alone does not necessarily signify importance or meaning. For example, humans share 99% of their DNA with chimpanzees, while on so many measures humans and chimps differ by far more than a mere 1%.[36] Moreover, how a child from MRT will perceive the significance of genetic/biological relatedness is unknown, yet there are already reasons to be cautious about possible adverse consequences for identity, as has been seen with children born of donor sperm.[37]

A similar complexity in regard to parenthood can be found in surrogacy. A surrogate who is implanted with an embryo is not a genetic parent, but is intimately involved for 9 months with the development of the child within her body, and without her the child would not develop and be born. Clearly *in utero* development creates a bond and may influence or even determine important characteristics of the person who is then born. If a surrogate-born offspring can see a surrogate, with whom he or she has no genetic connection, as an important person, even as a (gestational) mother, might not the offspring of MRT - who *does* have a genetic connection with the egg donor – similarly see her as a mother? A question that then arises is, does the offspring have the right to identifying information about the surrogate, and if the answer is yes, then why not also to information about the MRT donor? In any case, adopted children have no biological connection at all with their adoptive parents, but still see them as parents – even though their yearning for knowledge about, and sometimes a relationship with, their genetic parents is well known. So the term 'three-parent baby' is probably appropriate

given the other contexts where there are three, four, and even five parent babies (eg donor egg mother, donor sperm father, surrogate mother, social father, social mother).

Genetic relatedness in MRT is clearly important, but as Mills notes, we are genetically related to our siblings, so it is not *solely* genetic relatedness that counts in parenthood.

> … what seems to be more important is not the sharing of genetic information per se, but the fact that the sharing or mixing of genetic material (in coitus or other reproductive processes) brings into being or gives rise to the genesis of the child. In other words, that process or act causes the child to exist. This account of parentage brings into focus the significance of the fact that the child would not have existed but for the genetic contributions of its progenitors.[35]

And in MRT there are three progenitors. Mills' point is really about the significance of origins and the manner by which a child comes to be. The people involved are as much or maybe even more important than the actual detail of the inherited genetic and other biological elements. In other words there is derivative meaning beyond the strictly physical alone. Biological connectedness counts, not just *genetic* connectedness, and even genetic connectedness is relevant in a specific context – the process of bringing a child into existence – though nurture also has a key role in parenthood.

Besides the claim that mtDNA contributes so few genes as to be insignificant with regard to parenthood, another claim is often made, namely, that MRT is really just like organ donation. With organ donation, the argument goes, DNA from a third party has no bearing on parentage and is not considered to affect identity, so why should MRT be considered different? But there are at least two problems with the analogy. First, organ donation adds third party DNA to an existing individual, and in whom the addition is not passed to the next generation, unlike with MRT. In MRT, donation of mitochondria and their DNA is the very means by which the new individual comes into existence and begins the process of identity development, identity that connects with future generations. Second, organ donation is a therapeutic means of restoring lost or damaged function to an individual, but with MRT there is no lost function to restore, no individual treated therapeutically. Even in PNT where two individual single-celled embryos are involved, nuclear transfer that combines essential elements of each embryo to construct a new one stretches the notion of therapy beyond breaking point.

The organ donor analogy is important because it trivialises the role of the egg donor. So much so, that in the UK the law permits only non-identifying information about the donor to be made available to a child of MRT after the age of 16. There is also an irony about how egg donors are viewed and treated in that MRT is justified on the grounds of the desire for a genetically related child, and yet the genetic relatedness of the donor is downplayed to exclusion. In this sense, donors are essential for family formation, but as Mills puts it, "exterior to and insignificant for it".[35]

For MRT to proceed at all, the supply of eggs must be expanded well beyond what egg donation for IVF typically requires. Egg donors as a group will therefore be placed at greater overall risk compared to their role in IVF, making MRT riskier than the viable alternative. Moreover, while donated eggs in IVF are often derived from close family members, this may not be preferable in MRT because of the risk of sharing a defect in mtDNA. It is disturbing how this central issue – MRT is totally reliant upon donated eggs - quickly fades from attention in public debates and inquiries into MRT.[38]

Human eggs might be a scarce resource, but to different degrees depending on the legal context. Where payment for eggs is permitted, for example in the US, the unregulated environment exposes vulnerable women to risks that women of higher socioeconomic standing will be unwilling to take.[39] In this sense commodifying eggs is discriminatory. In the UK, only compensation is permitted, but the anonymity provided to donors for MRT might go some way to increasing supply because more women may donate if assured there will be no chance a child of MRT might seek them out in the future. Indeed, given egg supply is a problem, assuring anonymity may have been one (unarticulated) strategy to increase it. Unfortunately, that means a child of MRT is denied what is a key piece of information about their origins. This approach therefore preferences the desires of the intended parents over the rights of a child.

Other Matters

There are at least two other issues related to MRT that inform, or should inform, public policy.

One is the status of current treatments and research on treatments for individuals who have a mitochondrial disease, and the other is alternative purposes for which MRT might be used.

Treating Mitochondrial Diseases

Most papers about MRT include a blunt statement to the effect that there are no cures for mitochondrial diseases, only symptomatic relief. For many readers this then conditions acceptance of MRT as a treatment that is therefore necessary (no other options), in a sense which outweighs other concerns. In public debates about MRT and in media reports, discussion about any other forms of treatment, symptomatic or otherwise, is virtually absent. But pessimism about treating mitochondrial diseases is not justified. In fact, the landscape for treatment is rapidly evolving,[40] and there are currently over 50 clinical trials under way concerning mitochondrial disease treatment of one form or another.[41,42]

Symptomatic or supportive therapy, whilst limited, is nevertheless of significant value.[43]

> … it should be remembered that supportive therapies might be lifesaving or life preserving.[40]

There are also a range of adjunctive therapies, including "hearing aids, cochlear implants, brow suspension for ptosis, gastrostomy feeds, pancreatic enzyme supplementation, pacemaker insertion, medical treatment of cardiomyopathy, electrolyte supplementation to replace renal tubular losses, blood transfusion for sideroblastic anaemia, antiepileptic drugs and (in selected situations, after careful multidisciplinary assessment) renal, cardiac or hepatic transplantation".[44] And while none of these represents a cure as such, the impact on the lives of recipients is nevertheless positive.

After supportive or adjunctive therapies, there are some pharmacological treatments under development. Added to these are some advances in gene therapy, concerning which several clinical trials are currently underway.[44] Of particular relevance to disorders of mtDNA are strategies to shift the level of heteroplasmy and therefore reduce symptom expression.[40] This can only apply to heteroplasmy, not homoplasmy.

Overall, despite the fact that there are no outright cures, as is also true for a far wider range of conditions than mitochondrial diseases, there appears to be a hopeful sense among researchers and clinicians. Writing in 2021, Piceathly et al. commented,

> The last 5 years have seen dramatic changes in the field of mitochondrial medicine, with increased diagnostic power achieved through next generation sequencing approaches. It is hoped that the next 5 years will finally bring licensed disease-modifying medicines for people affected by mitochondrial disease.[40]

Russell et al., writing in 2020, are similarly optimistic,

> We believe that major breakthroughs in the development of treatments for mitochondrial disease will occur during the next decade.[41]

If the timeframe for some really significant breakthroughs is this close, it must be situated alongside the only global clinical trial currently underway (in the UK) of 75 children to be born of MRT,[41,45] and about which nothing has been publicly reported. It is also relevant in terms of resources. Therapeutic treatments have the potential to help a large percentage of people with a mitochondrial disease, whereas MRT might lower the risk of disease transmission for a very limited subset.

MRT for Other Purposes

Besides women with a mitochondrial disease, there are two other groups for whom MRT might be a desirable technology.

The first is older women who have poor quality eggs and who want a genetically related child. Older women are a rapidly growing group seeking fertility treatment, and the current option to use donated eggs from younger women is difficult given the limited supply of egg donors, and the fact that the child would not be genetically related to the woman receiving treatment. MRT might theoretically improve egg quality by introducing the mitochondria of younger women at the same time as retaining the nuclear DNA of the woman receiving treatment. However, despite reports from the Ukraine and Greece claiming to have used MRT to achieve the birth of children to women with persistent IVF failure,[46,47] not only has verification been lacking, but whether replaced mitochondria actually improved the outcome or was incidental to it is unknown. Moreover, whether a clinical trial is justified is controversial.[48] Nevertheless, as is often the case with new technology, its use in one very restricted context on the grounds of avoiding serious disease can provide the basis for its expansion into other areas that were initially considered inappropriate. If this were to occur with MRT and treating age-related infertility, a controversial technology could be used for a 'condition' which, however distressing for those wanting children, is arguably not a medical issue. And the market would be much, much greater.

Something similar occurs for the second group, namely lesbian couples who want a child genetically related to both women. In this context the argument that 37 genes is too small a number to constitute meaningful genetic relatedness is turned on its head. It is precisely this degree of genetic relatedness that has been said to justify using MRT for lesbian couples, one of whom provides the nuclear DNA and the other the mtDNA.[49] Cavaliere and Palacios-Gonzalez argue that the use of MRT technologies for mitochondrial diseases is non-therapeutic because no one with a disease is being treated; therefore "their therapeutic potential cannot be invoked for restricting their use only to those cases where a mitochondrial DNA disease could be 'cured'."[49] This reason, combined with "an appeal to reproductive freedom",[49] form the basis of their argument. If MRT were permitted for this reason, just as for age-related infertility, the potential market could be much greater than that for avoiding mitochondrial disease transmission.

Summary and Conclusion

MRT is a technological intervention intended to reduce the risk of transmitting an mtDNA defect from mother to child, and hence avoid a mitochondrial disease. How one thinks about MRT might be dominated by *in principle* objections to destroying human embryos or modifying the germline. Alternatively, there may be no such objections but instead a need felt to balance how benefits, risks, and existing alternatives line up. That is to say, proportionate consideration and weighting of all factors to come to a position.

If that were to be the approach, how do those benefits, risks, and existing alternatives shape up?

On the benefit side, MRT might allow a couple to have a genetically related child who is free of mitochondrial disease. There are no guarantees, research is still in the early stages, and there are reasons why the technology might not work, including the risk that it might initially appear to have succeeded, but later fail. But it could work and help perhaps 10 women per year in the UK.

On the risk side, there are many unknowns. Despite some animal and human experiments that appear to show few adverse side effects, there are others with clear warning signs. There are also theoretical risks that are reasonably grounded. Virtually nothing is sure about possible adverse effects that might only show up in future generations.

On the ethical side, MRT involves the intentional creation and destruction of human embryos, either inherent in PNT, or in all research and training leading up to clinical application in both MST and PNT.

Modifying the germline crosses a barrier that has been so strongly held as to result in international agreements prohibiting such modification. Permitting MRT might also weaken resistance to other forms of germline modification. An MRT child would have three biological progenitors, a first in human procreation and with uncertain effects on psychological formation and feelings of identity and kinship, and ancestry. MRT requires many human eggs, which are not only in short supply, but the use of which raises ethical problems specific to egg donation.

As for alternatives, a couple might adopt a child or use a donated embryo or donor egg. Neither of these options is straightforward and neither do they satisfy a desire for a fully genetically related child. A different form of alternative needs also to be taken into account, namely current and imminent treatment options for all those with a mitochondrial disease.

Finally, the whole debate about MRT is about disease avoidance, but MRT could also be used for non-medical reasons by lesbian couples and older women seeking IVF treatment. Hence, controversial technology driven by the avoidance of disease for the very few might expand considerably to encompass a far greater market motivated by a quite different rationale.

The weighting applied to each of the above and how core values coalesce in a proportionate way in decisions concerning MRT will vary greatly. When UK parliamentarians voted in 2015 to allow MRT, all were given a free conscience vote. Similarly, Australian parliamentarians will be given the same freedom for their upcoming vote. This is in recognition of the ethical sensitivities in MRT, and how any one individual will approach the evidence. This paper has sought to lay out the evidence as well as point to the key ethical issues.

MRT may turn out to be a rarely used technology with limited application and few discernable ramifications; but it might just as easily be something quite different. It may alter the reproductive landscape significantly, harm children and their own offspring, and usher in a new era in genetic modification of future humans.

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