Mitochondrial replacement techniques for treating infertility

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ABSTRACT

Mitochondrial replacement techniques (MRTs) usually aim to prevent the genetic transmission of maternally inherited mitochondrial diseases. Until now, only the UK and Australia have implemented specific legal regulations of MRTs. In both countries, clinical trials on these techniques are only permissible for cases with a high risk of severe mitochondrial disease in the offspring. However, these techniques can also be applied to treat infertility, especially for older women with impaired oocyte quality. In some countries without legal regulation of these techniques, MRTs are already offered for this purpose. Yet, this application of MRTs has received insufficient attention in the bioethical literature so far. In this paper, I examine whether there are ethical reasons to prohibit trials on MRTs in the context of infertility when they are permitted for preventing mitochondrial disease. Allowing MRTs in one context but not the other might be justified either because their application in the context of mitochondrial disease (1) is supported by a more convincing evidence base, (2) has a higher potential benefit or (3) has a lower risk. I compare both applications of MRTs with respect to these three factors. I conclude that there is no convincing reason to prohibit clinical trials on MRTs for infertility when they are permitted in the context of mitochondrial disease.

INTRODUCTION

In mitochondrial replacement techniques (MRTs), nuclear DNA is transferred from an oocyte or zygote to an enucleated donor oocyte or zygote before or after in vitro fertilisation (IVF). This usually aims to avoid the transmission of mitochondrial DNA (mtDNA) mutations from the mother to the offspring.1 Specific legal regulation of MRTs has so far been implemented in the UK in 20152-4 and Australia in 2022.6,7 In both countries, the use of MRTs within the context of clinical trials is restricted to cases with a high risk of transmission of mtDNA defects that are likely to cause severe mitochondrial disease in the offspring.

However, MRTs can also be applied to treat infertility, especially for older women with impaired oocyte quality.1 Here, the transfer of nuclear DNA from an oocyte or zygote with poor quality to a younger and healthier donor oocyte or zygote may allow women for whom IVF has been unsuccessful to have genetically related children. In some countries without specific legal regulation of these techniques, such as Ukraine, MRTs are already offered for this purpose8, and there are several reports of children born after the use of MRTs to treat infertility.8 If MRTs prove to be effective as an infertility treatment, their use in this context could become much more widespread than in the context of preventing mitochondrial disease since a much higher number of women are affected by infertility than by mtDNA mutations. Ethical analysis of this application of MRTs is thus urgently needed. Yet, with the exception of a recent short contribution by Pennings,9 this application of MRTs has received insufficient attention in the medical ethics literature so far.

This paper aims to examine whether there are ethical reasons to restrict the use of MRTs within clinical trials to the context of hereditary mitochondrial disease, as is the case in the UK and Australia. If there are no such reasons, the legal regulations in the UK and Australia seem inconsistent from an ethical point of view.

Clinical trials on a novel medical procedure are generally ethically permissible only if the risks and harms of that procedure are proportionate in relation to its potential benefits. Ethical research must also be based on a sound hypothesis supported by scientific evidence.10 Allowing MRTs in one context but not the other might thus be justified either because their application in the context of mitochondrial disease (1) is supported by a more convincing evidence base, (2) has a higher potential benefit or (3) has a lower risk than in the context of infertility.

In this paper, I will examine whether there is a relevant difference between the application of MRTs for infertility and mitochondrial disease with respect to these three factors. I will thus determine whether there are ethical reasons to allow clinical trials for one application of MRTs but not the other.

In the section Are MRTs for infertility supported by less scientific evidence than MRTs for mitochondrial disease?, I examine whether there is a difference between both applications of MRTs with respect to evidence. I conclude that both applications of MRTs are supported by a convincing evidence base that justifies examining their efficacy in clinical trials. In the section Do MRTs for mitochondrial disease lead to a higher benefit than MRTs for infertility?, I discuss the benefit of both uses of MRTs with respect to the child, the parents and society. I explain that due to their identity-affecting nature, MRTs cannot be said to provide a benefit to a specific child. I argue that...
the benefit of MRTs for mitochondrial disease is not higher than that of MRTs for infertility, neither with respect to parents nor society. In the section Do MRTs for infertility pose a higher risk than MRTs for mitochondrial disease?, I discuss risk and demonstrate that MRTs for mitochondrial disease in fact involve higher risks than MRTs for infertility, as the latter does not pose the risk of carryover of defective mtDNA.

I conclude that there is no convincing reason based on evidence, benefit or risk to prohibit MRTs for infertility when MRTs for mitochondrial disease are permissible. From an ethical perspective, legislation that allows clinical trials on MRTs in one context but not in the other therefore appears inconsistent.

ARE MRTS FOR INFERTILITY SUPPORTED BY LESS SCIENTIFIC EVIDENCE THAN MRTS FOR MITOCHONDRIAL DISEASE?

MRTs for mitochondrial disease

Mitochondria are cellular organelles essential for generating energy. They contain their own circular genome, the mtDNA, which makes up approximately 0.1% of the human genome.11 Mutations in the mitochondrial genome can lead to potentially severe mitochondrial diseases that may involve loss of vision, deafness, seizures, muscle weakness and other neurological symptoms and can lead to early death.12 Currently, there are no cures for mitochondrial diseases, and treatment focuses on symptom management.1

Mitochondria and mtDNA mutations are inherited through the maternal line and are passed on through the oocyte’s cytoplasm. As mutated and intact mtDNA can coexist in one individual,3 women may be largely asymptomatic carriers yet pass on mutated mtDNA that may manifest with severe symptoms of mitochondrial disease in their offspring.13

The two MRTs that are legal in the UK and Australia are maternal spindle transfer (MST) and pronuclear transfer (PNT). In MST, the chromosomes (specifically, the metaphase II spindle complex) are transferred from the intended mother’s oocyte (which contains mitochondria with mutated mtDNA) to an enucleated donor oocyte, which subsequently undergoes IVF. In PNT, the intended mother’s oocyte is first fertilised with sperm (usually from her partner). The pronuclei from the resulting zygote are then transferred to an enucleated zygote stemming from a donor oocyte that was fertilised with sperm from the same man. In all MRTs, the resulting offspring inherits nuclear DNA from both intended parents and mtDNA from the egg donor.11

MRTs for infertility

MRTs may also be used as an infertility treatment. The success rates of IVF are still limited, and pregnancy rates per embryo transfer remain at approximately 30%.14 MRTs might allow people who have not been able to achieve pregnancy via conventional IVF to have a genetically related child, especially women with reduced oocyte quality. Oocyte quality refers to the competence of an oocyte to be fertilised and develop into a healthy embryo and fetus. Poor oocyte quality is the primary cause of age-related infertility but may also affect younger women.15

One argument for prohibiting MRTs for infertility while allowing MRTs for mitochondrial disease is that there is a lack of scientific evidence for the former application of MRTs. For example, Chinnery stresses that ‘there is no objective evidence that mitochondrial transfer is effective [for treating infertility], so it should not be used in routine clinical practice’.16 Similarly, the European Society of Human Reproduction and Embryology (ESHRE) states that ‘until this technology has been proven to be effective and safe, ESHRE strongly discourages the use of mitochondrial donation to alleviate an infertility condition’.17

It seems evident that the routine clinical use of a novel medical procedure is impermissible until clinical trials have established that the procedure is effective. However, this does not imply that conducting such clinical trials is itself impermissible. This depends on whether there is sufficient preclinical evidence to establish uncertainty over whether the intervention in question is more effective than standard clinical practice. It is generally assumed that ethical research requires equipoise, that is, uncertainty regarding whether an intervention is more effective at achieving its intended goal than established practice.10 18 For women with poor oocyte quality for whom conventional IVF is unsuccessful, there are currently no effective alternative interventions available that allow them to have genetically related children.5 19 We can assume equipoise with respect to MRTs for infertility since it is currently unclear whether MRTs for infertility are more effective for such women than established clinical practice—that is, additional trials of conventional IVF or no treatment at all. Accordingly, if the risk–benefit ratio of these interventions is acceptable, it seems plausible to permit clinical trials on MRTs for infertility to determine whether they are in fact effective.

Similar reasoning applies to MRTs for mitochondrial disease. While it is hypothesised that MRTs will reduce mtDNA mutation load in humans, their long-term effects in preventing the transmission of defective mtDNA are not known, especially considering the risk of carryover (see section Do MRTs for infertility pose a higher risk than MRTs for mitochondrial disease?). Clinical trials are intended to examine whether MRTs for mitochondrial disease are safe and effective at preventing mitochondrial disease.4 20 Thus, the point that there is limited knowledge on how efficient these procedures are at achieving their aim applies to both applications of MRTs.

The role of mitochondria in infertility

However, some have claimed that, in contrast to MRTs for mitochondrial disease, the preclinical evidence base linking MRTs or mitochondrial function to infertility is insufficient.11 The Human Fertilisation and Embryology Authority (HFEA) states that no causal link between infertility and impaired mitochondrial function has been made.21 Chinnery claims that ‘the evidence linking age-related mitochondrial dysfunction with infertility is largely circumstantial’.16 He argues that it would be reasonable to undertake clinical trials on MRTs for infertility only if 'mechanism-based benefits of mitochondrial transfer for the treatment of infertility can be established'.16

However, various studies and reviews demonstrate that there is indeed evidence supporting the role of mitochondria in fertility as well as the potential mechanism-based benefits of MRTs for infertility.22–24 Mitochondria are essential for providing the high supply of energy that early embryo development requires. Mitochondrial dysfunction can affect the oocyte’s ability to be fertilised and lead to abnormal embryonic development.25–27 Mitochondria also play an important role in calcium homeostasis,28 management of oxidative stress and regulation of apoptosis, which renders them highly important for oocyte maturation, successful fertilisation, early embryo development and implantation.29–31

Impaired mitochondrial function has been implicated in the decreased quality of oocytes with age.32 For example, the levels of mtDNA in oocytes decrease with increased age,33 34 and point mutations in mtDNA are more common in aged oocytes.32 33 Increased maternal age is associated with reduced adenine
triphosphate (ATP) production and altered mitochondrial calcium homeostasis in oocytes. The positioning and segregation of chromosomes within the oocyte are particularly energy demanding. Lower cellular energy levels due to impaired mitochondrial function can cause disrupted chromosome alignment. This can lead to an increased incidence of chromosomal aberrations, which are a common reason for early loss of pregnancy in age-related infertility. Next to mitochondria, other cytoplasmic components, such as specific RNAs or proteins, can also influence oocyte quality, and deficiencies in these factors can impair embryonic development. As MRTs involve the transfer of the nucleus to an enucleated donor oocyte or zygote, these other cytoplasmic factors may also play a role in the effect of MRTs on infertility.

Infertility treatments based on mitochondrial function

The existing evidence linking mitochondrial function to fertility has led to the development of different techniques that transfer healthy mitochondria to the oocyte with the aim of improving fertility. A technique called 'cytoplasmic transfer' was first employed in the 1990s. It involves the injection of patient oocytes with a small volume of cytoplasm from healthy donor oocytes together with sperm. This transfer of mitochondria and other cytoplasmic components is intended to improve oocyte quality and pregnancy outcomes. Research on cytoplasmic transfer in the USA had promising clinical results and led to the birth of several children. However, before definitive results could be generated, the US Food and Drug Administration suspended the use of this technology due to concerns based on the transfer of third-party genetic material involved with the procedure—that is, the mtDNA transferred from donor to recipient. A limited follow-up study on children born after cytoplasmic transfer in one US centre does not show evidence of any detrimental health effects of the procedure.

Moreover, a Czech study that employed this technique between 2002 and 2018 demonstrates that cytoplasmic transfer improved fertilisation rates and embryo quality in women with low oocyte quality and shows that all 28 children born after cytoplasmic transfer are healthy.

Cytoplasmic transfer resembles MRTs for infertility and is supported by the same scientific hypothesis—that is, that mitochondria and, potentially, other cytoplasmic components play a significant role in (especially age-related) infertility associated with decreased oocyte quality. Animal studies have demonstrated that MRTs for infertility are technically feasible and improve fertilisation rates and embryo development.

Moreover, MRTs for infertility have already been successfully used in humans. A first pilot trial of MRTs for infertility in humans was recently conducted in Greece. The six children born as a result showed normal development in follow-ups until up to 24 months of age. This demonstrates that some patients with a history of failed IVF attempts were able to conceive and carry healthy pregnancies to term after the use of MRT. Notably, comparable results from a pilot trial in humans are not yet available with respect to MRTs for mitochondrial disease.

In conclusion, there seems to be sufficient preclinical evidence supporting the role of mitochondria and other cytoplasmic components in fertility. More clinical evidence on the efficacy of MRTs for infertility cannot be generated if clinical trials that could generate such evidence are prohibited. Overall, MRTs for mitochondrial disease are not supported by significantly more scientific evidence than MRTs for infertility.

DO MRTS FOR MITOCHONDRIAL DISEASE LEAD TO A HIGHER BENEFIT THAN MRTS FOR INFERTILITY?

In this section, I will examine whether MRTs for mitochondrial disease are more beneficial for either future children, parents or society than MRTs for infertility.

Benefits for children

MRTs for mitochondrial disease have often been referred to as ‘therapeutic’ in the context of policy debates and in the media, with media reports quoting scientists and bioethicists who describe MRTs as ‘trying to treat what are often lethal diseases’, a ‘therapy’ or a ‘life-saving treatment’. The HFEA refers to MRTs as ‘mitochondrial donation treatment’ (emphasis added), a term that has often been criticised. MRTs for infertility, on the other hand, have not been framed as techniques that treat disease.

The presumed curative benefit of MRTs seems to pertain to the future child. However, several authors have argued that MRTs should not be regarded as a cure for a future child because they affect the numerical identity of the child that comes into existence.

Numerical identity refers to the relationship between each thing and itself and no other thing—for example, I am numerically identical to the person who is writing this sentence and to no one else. According to what is known as the Origin View or gametic essentialism, numerical identity depends on the gametes that the individual originates from. The Origin View leads to the much-discussed non-identity problem introduced by Parfit. The non-identity problem, combined with a counterfactual view of harm, implies that the use of a reproductive technology cannot harm or benefit a person if use of the technology leads to a different person being born than in the counterfactual scenario in which the technology had not been used.

Following Palacios-González, we can distinguish between the clinical decision to use an MRT and the process of the MRT. Rulli claims that if MRTs are not available, prospective parents’ most likely alternative course of action is to reproduce ‘naturally’, that is, without the use of assisted reproductive technologies. The clinical decision to use an MRT instead of reproducing ‘naturally’ requires the time-consuming procedures involved with IVF, such as hormonal stimulation and egg retrieval. Therefore, if an MRT is used, different gametes will fuse than if prospective parents had instead reproduced ‘naturally’. The resulting child thus originates from different gametes than a child that would result from ‘natural’ reproduction. Consequently, the clinical decision to use an MRT does not benefit a specific child.

The process of using MRT also cannot be curative for a future child, as it is carried out before fertilisation. To reiterate, MRT involves the transfer of nuclear DNA from the intended mother’s oocyte to an enucleated donor oocyte, while PNT involves the transfer of the pronuclei from a zygote stemming from the intended mother’s fertilised oocyte to an enucleated zygote stemming from a donor oocyte fertilised with the same sperm. As the manipulation of the oocyte takes time, the sperm that fertilises the oocyte after MRT is carried out will be different from the sperm that would have fertilised the oocyte if MST had not been used. However, the process of using PNT can be curative for a specific zygote if we assume that the zygote retains numerical identity despite the replacement of all of its components except as noted by Lewens, some argue that originating from the same pair of gametes is not necessary for numerical identity. Genetic essentialism is, however, widely accepted and seems to be in line with most people’s intuitions. I will here assume that gametic essentialism is correct.
for the nuclear DNA—that is, if we assume that numerical identity depends on the nuclear genome.60 64

In contrast, Liao65 has argued that the process of both MST and PNT affects numerical identity by drawing on the Organism View, according to which oocytes are essentially cells and zygotes are essentially organisms.67 Oocytes or zygotes exist as long as they have the capacity to regulate and coordinate various life processes for which cellular or organismic continuity is necessary. According to Liao, the nucleus and the cytoplasm are jointly necessary to uphold cellular or organismic continuity. By removing nuclear DNA from the oocyte or zygote, MST and PNT both disrupt cellular or organismic continuity. By transferring nuclear DNA into the enucleated donor oocyte or zygote, a new entity with cellular or organismic continuity is created. Thus, according to this view, even the process of PNT is identity-affecting.

To summarise, if we believe that numerical identity depends on nuclear DNA, the process of MST is identity-affecting, while the process of PNT may be regarded as curing a particular zygote. However, the clinical decision to employ any MRT is identity-affecting and thus cannot be regarded as a cure for a particular child. If we believe that numerical identity requires the continuity of the organism, not only the clinical decision to employ an MRT but even the process of performing any MRT is identity-affecting.

No matter whether one believes that organismic continuity is necessary for numerical identity, the clinical decision to use an MRT for mitochondrial disease cannot be regarded as curative for the future child. What matters for determining whether MRTs for mitochondrial disease are more beneficial than MRTs for infertility is whether the actual choice to employ an MRT for mitochondrial disease in the context of a clinical trial is more beneficial than the choice to employ an MRT for infertility. Participating in a clinical trial on MST or PNT for the purpose of avoiding the transmission of mitochondrial disease cannot benefit any specific child, as the decision to participate in such a trial will influence the timing of reproduction and, thus, the numerical identity of the child. This also holds for MRTs for infertility. Both the decision to participate in a trial on MRTs for mitochondrial disease and on MRTs for infertility are identity-affecting, and neither can be said to be therapeutic for the future child.

Thus, rather than curing any individual child, the decision to employ an MRT for mitochondrial disease will bring a new healthy child into existence. Consequently, MRTs for mitochondrial disease do not provide a higher benefit for future children than MRTs for infertility. However, the fact that they do not directly benefit specific children does not necessarily mean that MRTs cannot be beneficial in other ways. They may provide benefits to the prospective parents, as well as impersonal benefits to society. I will address these aspects in the two following sections.

Benefits for parents
It could be argued that the benefit provided to parents by preventing mitochondrial disease in their offspring is higher than the benefit provided to infertile people by allowing them to have a genetically related child. This benefit is comparative: it is assumed that in a scenario in which parents prevent mitochondrial disease in their offspring, they are better off than in a scenario in which they cannot do so. This benefit is assumed to be higher than the benefit having a child provides for infertile people compared with not having a child at all.

Table 1 Comparison of using MRTs with attempting ’natural’ reproduction

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<tr>
<th>MRTs for mitochondrial disease</th>
<th>MRTs for infertility</th>
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<tr>
<td>MRT available</td>
<td>Healthy genetically related child</td>
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<tr>
<td>MRT not available</td>
<td>Genetically related child with mitochondrial disease</td>
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<td>MRTs, mitochondrial replacement techniques</td>
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To further examine the comparative benefit each of these applications of MRTs provides for parents, I compare the different counterfactual scenarios in table 1. There, I contrast the intended ideal outcomes of MRTs with the most likely outcomes if parents decide to procreate ‘naturally’ for both applications of MRTs.

In the case of MRTs for mitochondrial disease, an MRT ideally allows parents to have a healthy genetically related child, while in the most likely counterfactual scenario in which MRTs are not available and the parents attempt to reproduce ‘naturally’, they have a high risk of having a child with mitochondrial disease. For the parents, the highest potential comparative benefit of using MRTs (assuming that MRTs are effective at achieving their aim) is thus to have a healthy child over a child with mitochondrial disease.

In the case of MRTs for infertility, an MRT ideally allows the parents to have a healthy genetically related child, while in the most likely counterfactual scenario in which MRTs are not available and the parents attempt to reproduce ‘naturally’, they do not have a child at all. For the prospective parents, the highest potential comparative benefit of using MRTs is thus to have a healthy child over no child at all.

Is the comparative benefit for the parents provided by having a healthy child over a child with a mitochondrial disease higher than that of having a healthy child over no child at all? While this is difficult to quantify, there are reasons to believe that this is not the case. When taking the extent of the suffering caused by involuntary childlessness into account, it seems that there is a highly significant benefit provided by having a healthy genetically related child when it is otherwise not possible to fulfil the desire to have one.

As Brown et al.68 explain, involuntary childlessness leads to suffering as well as the thwarting of valued life projects. Becoming a parent to a genetically related child might be central to one’s conception of the good life and one’s identity. Research shows that involuntary childlessness can lead to severe and long-lasting distress and suffering.69 70 It may cause social stigma and alienation71 and is associated with various negative psychological effects, such as anxiety and depressive symptoms,72 feelings of sadness, frustration, hopelessness, guilt, inadequacy, lack of choice and control, stress,74 75 self-blame, and worthlessness.76

It could be argued that infertility-related suffering could be alleviated by adopting a child instead. However, infertility-related suffering is not necessarily associated with the lack of parenting any child; rather, it is associated with the impossibility of having a genetically related child.70

Consequently, a remedy for this significant suffering seems highly beneficial. Research shows that successful infertility treatment has a positive impact on well-being71 and that the resolution of involuntary childlessness leads to increased life satisfaction and self-esteem.78 Failed treatment, on the other hand, is associated with lower quality of life,79 psychological pain,77 stress and depression,80 even years after unsuccessful IVF treatment.79 80
Accordingly, if MRTs for infertility can improve the outcomes of infertility treatment, it seems that they would have a significant positive impact on parents’ well-being and prevent long-lasting suffering.

MRTs for mitochondrial disease, on the other hand, can prevent the suffering associated with having a child with mitochondrial disease by ideally allowing parents to have a healthy child instead. Parents may experience significant suffering by witnessing their child be affected by symptoms of mitochondrial disease and potentially even premature death. Research shows that parents of children with disabilities have a higher level of mental health problems and report a lower quality of life. However, it seems questionable to regard the suffering caused by having a child with mitochondrial disease as worse than the suffering caused by involuntary childlessness. This would evaluate having a child with mitochondrial disease as worse than having no child at all despite the desire to have one, although it does not seem possible to clearly determine which of these situations is worse than the other.

Overall, the assumption that preventing mitochondrial disease leads to a higher benefit for the parents than allowing infertile people to have a child might underestimate the suffering caused by involuntary childlessness while possibly overestimating the suffering caused by having a child with mitochondrial disease. It does not seem possible to give a clear answer to which of these scenarios involves greater suffering and, thus, which application of MRTs leads to a higher comparative benefit for the parents.

I have so far assumed that the most likely counterfactual scenario if MRTs were not available would be an attempt at ‘natural’ reproduction. This counterfactual is also assumed by Rulli, who claims that ‘if the mother chooses not to use MST, she will procreate outside the laboratory’. It is questionable, however, whether an attempt at ‘natural’ reproduction is the most likely counterfactual in both of these cases.

To determine the most likely counterfactual scenario, we can draw on empirical research investigating prospective parental reproductive preferences. Qualitative research with carriers of mitochondrial disease shows that the vast majority of women who carry mtDNA mutations feel strongly that they do not want to take the risk of transmitting mitochondrial disease. Often, such women have experienced the progression of mitochondrial disease in family members, in themselves, or in their children who are already affected by mitochondrial disease. They, thus, have a strong desire to avoid transmitting mitochondrial disease. Consequently, if MRTs are not available, prospective parents seem much more likely to pursue alternative courses of action rather than ‘natural’ reproduction (table 2).

To have a healthy child, carriers of mitochondrial disease may opt for oocyte donation, which eliminates the risk of transmitting mtDNA mutations or adoption. Both of these options are alternatives to MRTs for infertility as well. Instead of modifying low-quality oocytes by using MRTs, prospective parents can use a donor oocyte to conceive or choose adoption. The added benefit of MRTs in both scenarios is identical and consists of the genetic relatedness of both parents to the child. Another option open to both groups is to have no child at all. In any case, the comparative benefit of MRTs over this more likely counterfactual scenario (in which the prospective parents do not attempt to reproduce ‘naturally’) is identical in the case of MRTs for mitochondrial disease and in the case of MRTs for infertility.

This implies that, in the majority of cases, MRTs for mitochondrial disease do not actually prevent women who carry mtDNA defects from having offspring with mitochondrial disease. This is because in the most likely counterfactual scenario, the respective women would not choose to reproduce ‘naturally’.

In conclusion, regardless of which counterfactual scenario is assumed, MRTs for mitochondrial disease cannot be regarded as more beneficial for parents than MRTs for infertility.

**Benefits for society**

It could be argued that MRTs for mitochondrial disease are more beneficial for society than MRTs for infertility. This aspect was mentioned in the Australian government’s summary of public comments preceding the legal regulation of MRTs in Australia. It stated that support for MRTs in Australia is based, among other reasons, on the prevention of disease and disability, as well as a reduction of the burden of disease in the community, including a reduction of healthcare costs for society.

While identity-affecting interventions cannot directly benefit specific individuals, the reduction of disease may convey an *impersonal* benefit that we should take into consideration in assessing the benefit of MRTs. Many technologies are identity-affecting and cannot benefit specific individuals—but, they still have a positive impact on society overall. Reducing the incidence of mitochondrial disease through MRTs could also be regarded as beneficial from a public health standpoint—for example, by reducing mortality and burden of disease or by reducing healthcare costs.

Whether MRTs in fact reduce the incidence of mitochondrial disease depends on whether carriers of mtDNA mutations who use MRTs when they are available would choose to reproduce ‘naturally’ if MRTs were not available. As the empirical research cited above demonstrates, it does not seem likely that the majority of people carrying mtDNA mutations would take the risk of transmitting mitochondrial disease by reproducing ‘naturally’ if MRTs were not available. This significantly reduces the societal benefit of MRTs for mitochondrial disease.

Moreover, as shown above, MRTs for infertility could potentially alleviate the suffering of people who have not been able to have a child via conventional IVF. This could have a significant positive effect on society by improving overall quality of life and reducing negative mental health consequences, as well as associated healthcare costs. About one in six people of reproductive age worldwide are affected by infertility in their lifetime. Although the existing evidence is insufficient to establish how many cases of infertility could be successfully treated with MRTs, the rising incidence of age-related infertility demonstrates that a large number of people could potentially benefit from this intervention if MRTs for infertility prove to be effective. Thus, the cumulative benefit for society provided by allowing people with failed attempts at IVF to have a healthy genetically related child could be highly significant.

Ascribing a high benefit to the reduction of people with mitochondrial disease in society can also be criticised because this may express implicit value judgements about the lives of people with mitochondrial disease.
In contrast, the number of cases of mitochondrial disease that could be prevented by MRTs for mitochondrial disease is overall quite low, as mtDNA diseases only occur in approximately 1:5000 births. Only a small number of women will be able to access MRTs for mitochondrial disease, that is, those who are aware of their carrier status and have a particularly high mutation load so that they are unable to use preimplantation genetic diagnosis to select an embryo with a low level of mutated mtDNA. As the number of people affected by infertility is far higher than the number of people affected by mitochondrial disease, MRTs for infertility may benefit many more people and thus lead to a higher societal benefit.

In conclusion, MRTs for mitochondrial disease do not provide a higher benefit for future children, parents or society than MRTs for infertility. A difference in benefit thus cannot be regarded as a moral reason to treat both applications of MRTs differently.

**DO MRTS FOR INFERTILITY POSE A HIGHER RISK THAN MRTS FOR MITOCHONDRIAL DISEASE?**

Another reason to treat both applications of MRTs differently might be a difference in risk. In this section, I will compare both applications with respect to commonly discussed potential risks posed by MRTs. I will first describe the risks of each application of MRTs and then assess the potential comparative harms of using an MRT in the worst-case outcome in contrast to a situation in which MRTs are not used with respect to each application.

**Potential harms of MRTs**

MRTs first pose a risk to the health of the mother and oocyte donor due to the potential harms involved with hormonal stimulation and oocyte retrieval, which also arise with standard IVF. This risk is identical with respect to the application of MRTs for mitochondrial disease and for infertility, as the procedure is technically the same in both cases.

The further risks of MRTs pertain to the future child. Some have discussed potential psychological risks for children who may later struggle with the idea of having three genetic parents due to the transmission of mtDNA from the oocyte donor in addition to the child's two other genetic parents who contribute nuclear DNA.

Moreover, it is theoretically possible that the micromanipulation of the oocyte involved with the procedure itself may have detrimental effects on the future child, although there is no evidence of this thus far.

It has also been argued that mixing the nuclear and mitochondrial genomes from two oocytes might lead to deleterious interactions between one oocyte's nuclear DNA and the other oocyte's mtDNA, which is referred to as mitonuclear mismatch. Female children would also pass mtDNA on to their offspring, so mismatch-based harm could affect future generations as well. However, the validity of this concern has been questioned, considering that 'natural' reproduction also places mtDNA in a seminovel nuclear environment since the mitochondria inherited from the mother will previously not have been in contact with the father's nuclear DNA. The existing experimental and clinical evidence suggests that combining nuclear and mitochondrial genetic material from different oocytes is not harmful.

All of these risks do not differ between the application of MRTs for mitochondrial disease and for infertility.

The most significant concern that has been raised with respect to MRTs for mitochondrial disease is the carryover of defective mtDNA. In MST and PNT, small amounts of cytoplasm containing defective mtDNA are inevitably carried over from the intended mother's oocyte to the enucleated donor oocyte. While very low levels of carryover have been consistently reported after MST and PNT, any amount of carryover poses a risk as there is evidence demonstrating that defective mtDNA may be amplified in subsequent embryonic and fetal development. This phenomenon, which is referred to as 'reversal', could lead to the development of mitochondrial disease in the offspring even though an MRT was used. While long-term follow-up data on children conceived through MRTs are needed to establish the significance of carryover and reversal, results from a pilot study on MRTs for infertility in humans show that while in five out of six children, 99% of mtDNA originated from the donor oocyte, one child had between 30% and 60% of paternal (non-donor) mtDNA. This confirms that reversal can occur in humans in vivo.

Pennings' has argued that MRTs for mitochondrial disease pose a higher risk than MRTs for infertility since carryover is not relevant for the latter application. He, therefore, even states that MRTs should first be allowed in the context of infertility treatment to gain further knowledge on these procedures, and then in the riskier context of preventing mitochondrial disease. This would allow researchers to gain expertise and improve the technique in a less risky context.

However, it seems unclear whether the risk of carryover of defective mtDNA should be a reason to prohibit MRTs for mitochondrial disease, as people with mtDNA defects are (and should be) free to reproduce 'naturally' as well. In cases with a high mutation load, using an MRT lowers the risk of transmitting mtDNA defects compared with 'natural' reproduction. This might be a reason to permit MRTs for mitochondrial disease, despite the risk of carryover. In any case, risk does not provide a reason to prohibit clinical trials on MRTs for infertility when clinical trials on MRTs for mitochondrial disease are available.

To summarise, based on the current state of research, there is no difference between the risks of MRTs for mitochondrial disease and MRTs for infertility with respect to oocyte retrieval, psychological harm, the micromanipulation involved with the procedure or mitonuclear mismatch. The only respect in which the risk of both applications differs is carryover, which has been described as the most significant risk of MRTs for mitochondrial disease. Carryover of defective mtDNA is relevant in the context of mitochondrial disease but not in the context of infertility.

**Comparative potential harms of MRTs**

I have now laid out the potential harms of both MRTs for mitochondrial disease and MRTs for infertility. However, to assess which application poses a greater risk, these should not simply be compared with each other. Just as the benefits of each application of MRTs were assessed in comparison to a baseline outcome, that is, what would most likely happen if MRTs were not available, the respective risks should also be determined in comparison to this baseline situation. We can then compare the overall *comparative* potential harms of each application, as the respective potential harms of an intervention differ depending on the baseline situation. For example, a novel experimental cancer treatment with severe side effects leads to a much higher potential harm when there is a possibly curative alternative treatment available than in a situation in which there is no potential cure.

I give an overview of the worst outcomes in which all potential side effects of the respective application of MRTs occur.
in comparison to the baseline situation in which prospective parents attempt to reproduce ‘naturally’ in Table 3.

With respect to MRTs for mitochondrial disease, in the worst-case scenario, the parents will have a child with mitochondrial disease and the potential side effects of the MRT described above (such as mitonuclear mismatch and psychological harms) instead of a child with mitochondrial disease and no such side effects. This is because, in the worst case, carryover and subsequent reversal would lead to an increase of maternal mtDNA in the child that could ultimately cause mitochondrial disease even though an MRT was used. In this case, the MRT would not only have failed to prevent mitochondrial disease in the parents’ offspring, but it would also have caused additional side effects.

With respect to MRTs for infertility, in the worst-case scenario, the parents will have a genetically related child with the mentioned potential side effects instead of no child.

The potential harm in both cases cannot be assessed from the perspective of the child due to the identity-affecting nature of MRTs described above. However, from the perspective of the parents, it seems worse to have a child with mitochondrial disease and additional side effects of the MRT than a child with mitochondrial disease. In the case of MRTs for infertility, on the other hand, the parents’ desire for a genetically related child will have been fulfilled, and that provides a strong benefit for them in comparison to the scenario in which they do not have access to MRTs and do not have a child at all. Overall, considering the suffering associated with involuntary childlessness, it might be better for the parents to have a child with some side effects of MRTs than no child at all. Accordingly, the worst-case outcome in the case of MRTs for mitochondrial disease causes greater comparative harm for the parents than the worst-case outcome with respect to MRTs for infertility.

However, as described above, it is likely that parents who would use an MRT would not attempt to reproduce ‘naturally’ if MRTs were not available. Instead, they could make use of oocyte donation, adoption or have no child at all (Table 4).

Here, the baseline situation is identical in both cases. In both worst-case outcomes, the MRT still has the benefit of allowing parents to have a genetically related child. In both cases, they have a child with the potential side effects of MRTs. The only difference is that in the worst-case outcome with respect to MRTs for mitochondrial disease, the child will also have mitochondrial disease, while this will not be the case with respect to MRTs for infertility. Accordingly, the potential harm caused by the worst-case scenario is more significant in the case of MRTs for mitochondrial disease than with respect to MRTs for infertility.

In summary, regardless of whether parents would choose to attempt to procreate ‘naturally’ or pursue other options, the worst-case scenario leads to more significant harm for the parents in the case of MRTs for mitochondrial disease than in the case of MRTs for infertility. There is thus no ethical reason based on risk that would justify prohibiting clinical trials on MRTs for infertility when clinical trials on MRTs for mitochondrial disease are allowed.

### CONCLUSION

In this paper, I have examined whether there are ethical reasons to prohibit clinical trials on MRTs for infertility when clinical trials on MRTs for mitochondrial disease are permissible. In the two countries that have established specific legal regulations for MRTs—the UK and Australia—clinical trials on MRTs are only permissible for mitochondrial disease and not for infertility. I have examined whether there are ethical reasons for the differential treatment of these two applications of MRTs with respect to evidence, benefit or risk.

I have argued that MRTs for infertility and MRTs for mitochondrial disease are supported by a similarly sound scientific evidence base. Regarding benefit, I have first shown that MRTs cannot be regarded as benefiting a future child. I have then argued that the benefit of allowing people who are suffering from involuntary childlessness to have a genetically related child is not necessarily lower than the benefit of preventing mitochondrial disease on either an individual or a societal level. Moreover, it is questionable whether MRTs actually lead to a significant reduction in the number of cases of mitochondrial disease, as parents who would use MRTs are unlikely to transmit mitochondrial disease by procreating ‘naturally’ if MRTs are unavailable. Concerning risk, I have demonstrated that most of the risks of MRTs apply to both applications equally. However, the most important risk associated with MRTs for mitochondrial disease—carryover of defective mtDNA—does not apply to MRTs for infertility. Thus, the risk of MRTs for infertility seems overall lower than that of MRTs for mitochondrial disease.

I conclude that there seems to be no convincing ethical reason to prohibit clinical trials on MRTs for infertility when they are permitted in the context of mitochondrial disease. If we believe that legislation should be in alignment with ethical considerations, the legal regulations for MRTs in the UK and Australia should be revised.

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