Response to Senate inquiry into the 'Science of mitochondrial donation and related matters'

Biomedical Ethics Research Group – Murdoch Children's Research Institute

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We wish to be considered as potential witnesses for the subsequent public hearing regarding this inquiry.

Introduction

The Biomedical Ethics Research Group of the Murdoch Children's Research Institute analyses the ethical and social implications of biotechnologies.

We believe there is a pressing need to change Australia's regulatory framework governing mitochondrial replacement therapy (MRT). We thank the Senate Community Affairs References Committee for providing us with the opportunity to submit our views on this topic. We focus on the terms of reference which highlight the ethical and social implications of MRT.

We believe there is a strong moral case for amending Australia's legislation to allow MRT. Current laws place a conceptual barrier to MRT, banning it no matter how safe and effective it becomes. This is unethical, as it denies individuals the opportunity to access an effective treatment without a valid justification. We believe that, for ethical reasons, MRT should not be limited to male children, as has been suggested by other expert bodies.

(b) the safety and efficacy of these techniques, as well as ethical considerations

It is well documented that MRT provides a novel way for women with mutations in their mitochondrial DNA to avoid transmitting mitochondrial disease, along with its potentially devastating and life-threatening consequences, to their children.[1] There are thus clear *prima facie* grounds for permitting MRT, in the absence of countervailing factors.

The clearest potential countervailing factor is that MRT is potentially unsafe. MRT is a new technology. It could have unexpected and harmful consequences, which should be fully investigated before MRT is used clinically. Concerns have been raised about the potentially harmful effects that could arise as a result of a genetic misalignment between mitochondrial and nuclear DNA. As we are not scientists or clinicians, we will not comment on whether the current evidence indicates that MRT poses a significant safety risk. Rather, we wish to make the point that, even if there are safety risks associated with MRT, this does not justify the current legal prohibition of the technology in Australia.

There are many medical procedures that have unknown safety profiles before they enter clinical trials, but are not illegal.[2] Furthermore, many surgical techniques once commonly performed (such as arthroscopic surgery for knee osteoarthritis),[3] have now been shown to have safety risks which do not justify their potential benefits. Such practices are not subject to legal prohibitions – they are simply not performed.

The basic point is that, while safety concerns justify a cautious approach to the use of MRT, including conducting rigorous safety trials, extensive monitoring, and long-term follow up, they do not justify a legal prohibition on it.

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[1] Greenfield, A., Braude, P., Flinter, F., Lovell-Badge, R., Ogilvie, C., & Perry, A. C. F. (2017). Assisted reproductive technologies to prevent human mitochondrial disease transmission. *Nature Biotechnology*, *35*(11), 1059–1068. https://doi.org/10.1038/nbt.3997

[2] As an example see - Wijnen, M., Olsson, D. S., Heuvel-Eibrink, M. M. van den, Wallenius, V., Janssen, J. a. M. J. L., Delhanty, P. J. D., … Neggers, S. J. C. M. M. (2017). Efficacy and safety of bariatric surgery for craniopharyngioma-related hypothalamic obesity: a matched case–control study with 2 years of follow-up. *International Journal of Obesity*, *41*(2), 210–216.

[3] Mounsey, A., & Ewigman, B. (2009). Arthroscopic surgery for knee osteoarthritis? Just say no. *The Journal of Family Practice*, *58*(3), 143–145.

Furthermore, even if extensive studies do demonstrate some safety risks associated with MRT, these may well be outweighed by its potential benefits. In-vitro fertilisation (IVF) is a good analogy: IVF has well known safety risks which affect both mother and child,[4] yet these are considered to be justified by the potential benefits of IVF – namely, allowing women and couples to have children who are genetically related to them.

Concerns have also been raised about the risk MRT poses to future generations.[5] Mitochondrial DNA is passed down the maternal line. This means that if MRT harms an individual, such harms could be passed to that individual's descendants.[6] Some authors[7] and committees, including the National Academies of Sciences, Engineering and Medicine in the United States,[8] have recommended that MRT should (at least initially) be used only to create male children (who do not pass on mitochondrial DNA) to eliminate this risk to future generations until more is known about its safety. However, this 'only male' policy has several limitations that need to be considered. Firstly, it is unclear exactly who will benefit from such a policy. If, for example, MRT does pose a serious safety risk and causes severe mitochondrial disease and death in childhood, this would be tragic. However, limiting MRT to males would not benefit anyone in this scenario. Children of either sex would die before they have a chance to have children.

If MRT instead resulted in mild mitochondrial disease, which allows survival until adulthood but has harmful effects later in life, limiting MRT to males may provide a benefit, as it prevents recipients of MRT from passing on mitochondrial mutations to their children. Arguably, if MRT allows a person to reach adulthood and have children, then it would be considered a successful intervention – especially if (as would often be the case) MRT is the only method available which would allow women to have genetically related children who will not die early in infancy. If MRT allows an individual to survive several decades and have children, this is a considerable improvement. A 'male only' policy in such circumstances would mean this significant benefit is only provided to male children, raising issues of sex equality.

The process of sex selection may also have further negative impacts. For example, if pre-implantation genetic diagnosis is used, it would reduce the number of embryos available for transfer (in which case some women might need to undergo extra egg collection procedures, which are not risk-free).[9] A 'male only' policy may also have negative psychological impacts on women and couples for whom MRT is the only option to have genetically related children, as it may force them to them

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[4] Health (UK), N. C. C. for W. and C. (2013). *Long-term safety of assisted reproduction treatments in women with infertility and their children*. Royal College of Obstetricians & Gynaecologists. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK327768/

[5] Appleby, J. B. (2015). The ethical challenges of the clinical introduction of mitochondrial replacement techniques. *Medicine, Health Care and Philosophy*, *18*(4), 501-514; Bredenoord, A. L., Dondorp, W., Pennings, G., & De Wert, G. (2010). Avoiding transgenerational risks of mitochondrial DNA disorders: a morally acceptable reason for sex selection?. *Human Reproduction*, *25*(6), 1354-1360; National Academies of Sciences, Engineering, and Medicine. (2016). *Mitochondrial replacement techniques: Ethical, social, and policy considerations*. Washington, DC: The National Academies Press. Chapter 4, pp.113-148. Retrieved April 27, 2018, from http://www.nap.edu/21871; Nuffield Council on Bioethics. (2012). *Novel techniques for the prevention of mitochondrial DNA disorders: An ethical review*. Retrieved March 8, 2018, from http://nuffieldbioethics.org/project/mitochondrial-dna-disorders.

[6] Appleby (2015); National Academies of Sciences, Engineering, and Medicine (2016).

[7] Appleby (2015); Bredenoord et al. (2010).

[8] National Academies of Sciences, Engineering, and Medicine (2016).

[9] Newson, A., Wilkinson, S., & Wrigley, Al. (2016). Ethical and legal issues in mitochondrial transfer. *EMBO Molecular Medicine, 8*(6): 589-591.

to engage in sex selection in favour of male children.[10] This may cause distress for those who have ethical objections to sex selection, or who want female children. A 'male only' policy could also risk deterring individuals with these objections from undertaking MRT.

The rationale for a 'male only' policy requires that MRT be sufficiently safe to expose a single generation of male children to its risks, yet too dangerous to expose future generations of children to the same risks. We believe these conditions are unlikely to obtain. If MRT carries plausible and serious risks to future generations, then it is arguably also unethical to impose these risks on a single generation of male children. Conversely, if MRT is sufficiently safe to be used in reproduction, then – given the considerations outlined above – there are strong reasons against restricting its use to male embryos. For these reasons, should MRT be allowed, we recommend against implementing a 'male only' policy. Rather, the focus should be on understanding and minimising the safety risks to the best of our abilities before MRT is used in a clinical setting.

We comment on additional ethical considerations regarding MRT below.

(c) the status of these techniques elsewhere in the world and their relevance to Australian families;

The central benefit of MRT over alternative options for avoiding transmission of mitochondrial disease (such as adoption or egg or embryo donation) is that it allows the intended parent(s) to be genetically related to the resulting child. While being genetically related to one's child is by no means required for parenthood,[11] it is regarded by many individuals as highly valuable.[12] MRT will thus benefit Australian families by giving parents the option to have genetically related offspring.

The UK has become the first regulatory system to approve MRT as a way of avoiding mitochondrial disease. We believe Australia should become the second. Both the UK and Australia have world-leading systems for the oversight and regulation of novel biotechnologies. To ensure technologies are developed in an ethically and socially responsible manner, countries such as Australia should take the lead. If MRT is developed in countries which lack proper oversight, MRT may become available prematurely, when there are still significant safety risks. Furthermore, if the technology becomes available in other countries with poor regulatory oversight, there is a risk that Australian women and couples will engage in medical tourism. This would likely involve putting themselves at greater risk than if MRT were available in Australia.

Genetic connectedness

The moral significance (if any) of mitochondrial DNA is a matter of ongoing debate in the bioethics literature. Some authors have argued that the role of mitochondria is still not fully understood.[13] They are typically said to be responsible for energy metabolism, but there have been studies

[10] National Academies of Sciences, Engineering, and Medicine (2016); Nuffield Council on Bioethics (2012).
[11] As evidenced by adoption and the use of donor gametes or embryos, for example.
[12] Hendriks, S., Peeraer, K., Bos, H., Repping, S., & Dancet, E. A. F. (2017). The importance of genetic parenthood for infertile men and women. *Human Reproduction*, *32*(10), 2076-2087.
[13] Nuffield Council on Bioethics (2012); Turkmendag (2018).

associating mitochondria with various traits including athletic ability[14], cognitive functioning,[15] and Alzheimer's disease.[16] Even if mitochondrial DNA does not code for personal characteristics (aside from physical health), some authors have claimed that physical health (or lack thereof) is in itself a valuable personal characteristic and a major contributor to personal identity.[17]

If mitochondria only contribute to energy metabolism (and thus a person's could receive mitochondria from any number of healthy donors without effecting their identity), it could be argued that the description "Three Parent IVF" is misleading (unless there are three social parents).

(f) the value and impact of introducing mitochondrial donation in Australia;

As described above, women with mitochondrial disease and are likely to find MRT valuable as it gives them the opportunity to have genetically-related children who are free from mitochondrial disease.

An additional value of introducing MRT in Australia relates to its potential cost savings. The UK Department of Health found that allowing MRT to be used in treatment would yield a total annual net benefit of approximately A$56 million per year and A$561 million over 10 years.[18] This is due to a reduction in the costs associated with providing healthcare to children with mitochondrial disease.

Considerations of cost do not merely constitute a practical issue, but also an important ethical consideration. Consequently, there are also ethical benefits to allowing MRT, in addition to the economic benefits. In public health systems, there are limited resources available; treating one individual with an expensive treatment may reduce the resources available to others. If allowing MRT saves resources by preventing mitochondrial disease, this will benefit others by increasing the capacity of our health system. Furthermore, this would disproportionately benefit those in lower socio-economic groups who rely more on public health systems. This provides additional reasons of justice to change the law to make MRT publicly available.

In sum, we believe a consideration of the ethical aspects of mitochondrial replacement therapy, show a need to revise Australia's regulation of the technology. Mitochondrial donation holds the tremendous potential to benefit carriers of mitochondrial disease and society as a whole.

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[14] Niemi, A.-K., & Majamaa, K. (2005). Mitochondrial DNA and ACTN3 genotypes in Finnish elite endurance and sprint athletes. *European Journal of Human Genetics: EJHG*, *13*(8), 965–969.

[15] Picard, M., & McEwen, B. S. (2014). Mitochondria impact brain function and cognition. *Proceedings of the National Academy of Sciences*, *111*(1), 7-8.

[16] Mancuso, M., Calsolaro, V., Orsucci, D., Carlesi, C., Choub, A., Piazza, S., & Siciliano, G. (2009). Mitochondria, cognitive impairment, and Alzheimer's disease. *International Journal of Alzheimer's Disease.* Published online 6 July, 2009. doi: 10.4061/2009/951548.

[17] Baylis, F. (2013). The ethics of creating children with three genetic parents. *Reproductive Biomedicine Online*, *26*(6), 531-534; Palacios-González, C. (2017). Does egg donation for mitochondrial replacement techniques generate parental responsibilities? *Journal of Medical Ethics*. Epub ahead of print 25 October, 2017. doi: 10.1136/medethics-2017-104400.

[18] See UK Department of Health. (2015). *The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015*, Impact Assessment. Retrieved March 15, 2018, from http://www.legislation.gov.uk/ukia/2015/9/pdfs/ukia_20150009_en.pdf; cited in Castro, R. J. (2016). Mitochondrial replacement therapy: The UK and US regulatory landscapes. *Journal of Law and the Biosciences, 3*(3), 726-735.