ethicentre

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Community Affairs Legislation Committee
Australian Federal Parliament
Canberra, ACT, Australia

Re: Inquiry into the Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021

Dear Committee,
Thank you for the opportunity to make a submission to the above Inquiry. Ethicentre is an Australian Bioethics think tank which seeks to inform community ethical debate.

The *Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021* proposes the legalisation and introduction of mitochondrial donation techniques, which are novel Assisted Reproductive Therapy (ART) techniques which aim to allow women carrying mutated mitochondrial DNA (mtDNA) to avoid passing it on to their offspring. To date, these techniques have not led to a verified live birth anywhere in the world. The bill proposes that the techniques be approved for use in research settings, then a clinical trial setting, before being introduced into clinical practice in In Vitro Fertilisation (IVF) clinics in Australia, with no further parliamentary review. Prior to the introduction and debating of this bill in parliament, the Federal Government committed $4.4 million over four years in the 2021-22 Federal Budget (pp. [223-4]) to fund the implementation of mitochondrial donation in Australia's research and clinical settings.

Mitochondrial disease
Mitochondria are found in all human cells. They are the power-house of the cell, providing most of the energy required for it to function. When the mitochondria are not working properly, cells begin to die until eventually, in its extreme form, whole organ systems fail and the patient's life itself is compromised.

Mitochondrial function is under dual genetic control – from both the mitochondrial and nuclear DNA. Mitochondrial dysfunction can arise because of defects in either mtDNA or nuclear mitochondrial genes.[1] The majority of the genes encoding the mitochondria are in the nuclear genome, which is not impacted by the current legislation.[2] Mitochondrial gene defects are more common in adults, whereas nuclear gene defects are more common in affected children.[3]

While there is still a lot unknown about the function of mtDNA, it is known to influence many aspects of cell function, and problems such as cancer growth[4], and ageing.[5]

Mitochondrial disease is an umbrella term including a wide range of illnesses.[6] The severity of mitochondrial disease depends on how much of the DNA contains the mutation. It is possible to have DNA mutations that affect the mitochondria and not realise it, i.e. to be asymptomatic. 60 – 90% of the mitochondria in a cell must be mutated for mitochondrial disease to manifest. However, in its most severe form, diseases can be debilitating and children can die early in life. It is completely understandable that parents would want to spare their children this suffering.

Approximately 60 Australian children are born each year with severe mitochondrial disease. At most half of these children are likely to have mitochondrial disease due to mtDNA mutation[1] – the focus of this bill.

As there are no 'typical' symptoms, diagnosing mitochondrial disease, especially in children, has historically been challenging. Despite extensive research, no specific and effective cure of mitochondrial disease exists. Current treatment tries to control the symptoms.

The bill contains provisions that only women with high level of mutations would be eligible to use mitochondrial donation, which is being introduced to allow women affected with heritable mitochondrial disease to have genetically related children without passing on the mutated genes to the offspring.

Current options for building a family

We would like to note that there are already legal and ethical options for building a family for couples where the mother is known to carry mutated mtDNA. These are:

- Adoption
- IVF using a donor egg with the father's sperm. This would be effective in avoiding a wider range of mitochondrial disease in offspring than the methods proposed in the bill, in that it would avoid the inheritance of mutated nuclear DNA, which is thought to account for approximately 50% of mitochondrial disease in the community, and is a more common cause of disease in children than mtDNA mutation.[3]
- IVF using the intended birth mother's eggs with genetic screening of the embryos prior to implantation using Pre-Implantation Genetic Diagnosis (PGD). PGD can be used to identify levels of faulty mtDNA in the embryo prior to implantation, to reduce risk of passing on mtDNA to offspring.[7] This allows mother to have biological child, but is not suitable for severe forms of disease, as probably all embryos will be affected.

While sympathizing with families where mutated mtDNA exists, we would also like to note that there is no right to a biological child. It is difficult to see on what basis such a right would exist.

Procedures involved

The basic procedure in mitochondrial donation involves combining the nuclear DNA of the birth mother and the father with the healthy mtDNA of the donor mother, in order to create an embryo with the birth parents' nuclear DNA and the donated mtDNA. This embryo would be transferred to the birth mother's uterus for her to gestate.

There are several proposed procedures which are performed at different stages of human development. This is significant, as there are ethical differences between the proposed techniques. The most developed techniques are pronuclear transfer (PNT) and maternal spindle transfer (MST).

Pronuclear transfer In this procedure, two embryos are created, both using the father's sperm, but one with the birth mother's egg and the other with the donor mother's egg. The nucleus, containing the nuclear DNA, is removed from the birth

mother's embryo and replaces the nucleus in the donor embryo, This results in an embryo with the birth mother's DNA and healthy mtDNA from the donor. It also results in the death of the embryo formed using the birth mother's egg, which was only created to provide nuclear DNA and nothing else. The technology has similarities to that used in human cloning (i.e. nuclear transfer).

Maternal spindle transfer is a similar procedure, but instead of removing the DNA from embryos, and thereby destroying the embryos, the DNA is exchanged between the EGGS of the birth mother and the donor, before the embryo is created. Therefore there are no ethical problems of embryo creation for 'spare parts', as the egg alone does not hold moral significance.

Less developed techniques also allowed under the bill research are germinal vesicle transfer (GVT) and first polar body transfer (both similar to MST) and second polar body transfer (which is technically similar to PNT, with the same ethical concerns). We note that the NHMRC diagram of these techniques which has appeared in many of the government's publications on this matter is incorrect, in that second polar body transfer is likened to MST, GVT and first polar body transfer, rather than PNT).

We note also that the language in the Explanatory Memorandum for this bill fails to make the inherent embryo destruction explicit by the way the techniques are explained. The use of phrases such as 'zygotes that then develop into embryos' is inaccurate and misleading, as in fact the zygote is the name of the first cell of the embryo. We appreciate that the language in the bill itself is more accurate.

Potential problems

- Carry over Animal research has shown that small amounts of mutant mtDNA are known to carry over to the new egg/embryo when the nucleus is removed from the birth mother's egg or embryo, which could lead to re-emergence of the mitochondrial disease. The timing is not clear and the mutations may not appear for one or two generations.[6] As mtDNA is transmitted only through the female line, it has been proposed that this problem would be avoided by allowing only male embryos to be implanted. However, one cannot choose to just 'create male embryos'. Embryos created through mitochondrial donation would be screened through PGD to identify the sex, and female embryos would be discarded prior to implantation. This effectively leads to destruction of half the human embryos created through mitochondrial donation. The bill currently recommends that this option be suggested to prospective parents in pre-treatment counselling, and that the decision left to them. Note that a USA review suggested that, at the experimental stage, only male embryos be implanted.[8] However this means that all female embryos created would have to be discarded.
- Low success rates Currently IVF success rates are at best less than 20%, and, even once developed, the success rate of mitochondrial donation is probably going to be less due to technical issues.[9]
- Side-effects unknown Short and long term effects of these techniques on the offspring are not known.
- Limited benefits for mitochondrial disease in the community Mitochondrial donation will not impact:

- Asymptomatic female carriers (because they don't realise they are at risk and will not attempt to access this technology).
- Nuclear DNA mutations (implicated in approximately 50% mitochondrial disease, more prevalent in children, but not impacted by this legislation)
- New mutations in the child born and their subsequent illness.

International situation

FDA investigators in the USA expressed concern regarding "research in which a human embryo is intentionally created or modified to include a heritable genetic modification" and that "more animal trials probably need to be conducted before moving to human trials."[8] Further, if mitochondrial donation were to be allowed, the following conditions were recommended, none of which are included in the current bill:

- Nonviable human embryos to be used to develop MRTs.
- When it was not possible to use nonviable human embryos, as few embryos as possible and the least developed viable human embryos were to be used to develop mitochondrial donation techniques.
- Intrauterine transfer during initial clinical trials was limited to male embryos.
- Research would be allowed on female embryos only if clear evidence of safety from male cohorts using identical mitochondrial donation procedures emerged, regardless of how long it took to collect this evidence.
- animal testing showed evidence of intergenerational safety and efficacy; and
- significant public and scientific deliberation concerning the ethical issues raised by heritable genetic modification occurred.[8]

In the UK, mitochondrial donation has been permitted under the supervision of the Human Fertilisation and Embryology Authority since 2017.[8] Despite the work undertaken since then there have been no confirmed live births, and no data is available to assess progress.

Mitochondrial donation is not allowed in any other country. Rumors of a live birth in Mexico has not been substantiated.

Ethical concerns

1. This legislation allows IVF practices that are currently banned in Australia due to ethical concerns. That is why the *Prohibition of Human Cloning for Reproduction Act 2002* and the *Research Involving Human Embryos Act 2002* need to be amended to allow it to proceed. The proposed techniques differ from current practice in several ways:

- <u>Human germline manipulation</u>

Mitochondrial donation involves altering the human germline, that is, altering genetic material that is inherited by the next generation, for which there is currently wide agreement on the need for an international moratorium due to the limits of our genetic knowledge.[10,11,12] Organ transplantation is not a valid parallel to mitochondrial donation, as in mitochondrial donation the biological material transferred will be passed on to the next generation, while organ donation impacts the individual only.

- Human embryos created for 'spare parts'.

Two of the proposed techniques for mitochondrial donation, Pronuclear Transfer and Second Polar Body Transfer, involve creation of human embryos in order to use components of that embryo, which will result in the death of the embryo. This process is not a component of any current ART technique and commodifies the embryo. While we are aware of a range of views in the community regarding the moral status of human embryos, there is no doubt that they are generally seen as special in some way and deserving of respect.

- Cloning technology

The bill authorises a form of human reproductive cloning in the technique of *Pronuclear Transfer* (PT), creating a partial copy human embryo. This process is undoubtedly cell nuclear transfer (hence the NT of PNT) and in this way resembles the Somatic Cell Nuclear Transfer (SCNT) technique used to create Dolly the sheep. It is also nuclear transfer for the sake of bringing about live birth, currently prohibited in Australia. Cloning was widely condemned as being contrary to human dignity when it was outlawed in 2002.

- Combination of DNA from three adults in one embryo

Mitochondrial donation is new in that it combines the genetic material of three adults in one embryo. This is of ethical concern because of the ambiguity of the lineage of the offspring which it introduces. We applaud the inclusion of the establishment of a donor registry within the bill to protect the rights of the offspring to knowledge of his or her biological origins, which is known to be important to donor offspring generally. It also allows the use of mtDNA for forensic purposes, should the need arise, where human remains are identified by comparing tissue to that of the (mtDNA donor) mother.

Oocyte requirements

Research on this technology will require large numbers of human oocytes.[7] The current ban on commercialization of gamete donation should be maintained in order to avoid coercion of vulnerable females. This would include not allowing license holders or the organisations which hold them to provide direct or indirect inducements for oocyte donation.

Research ethics

The bill proposes an initial clinical trial (Stage 1) in order to allow affected families to access the techniques as quickly as possible (but before they have been shown to be safe and effective). While consistent with NHMRC guidelines that participation in medical research be voluntary, the bill raises some questions regarding research ethics:

- should affected family members be allowed to participate in a medical trial for therapy which is not known to be safe, when alternative reproductive options already exist and are legal?
- how will the safety and efficacy of the proposed techniques be established if no data is collected from the initial research, should participants elect not to be followed-up? Should not data for a minimum number of participants be stipulated before a judgement is made?

- In view of the known risk of mutant mtDNA reappearing in mitochondrial donation offspring, how long should research proceed before the procedure can be deemed safe? No length of follow-up of participants is stipulated as necessary in the bill.

Specific targets need to be set to ensure that Stage 2 does not proceed without sufficient data being collected to ensure the safety to the Australian public when the proposed techniques become clinically available. Furthermore, in view of the significance of this transition, parliamentary and possibly public scrutiny should be involved.

Summary

This is a bill to allow a highly experimental clinical trial to take place. This legislation proposes the introduction of mitochondrial donation in order to satisfy the preference of a small number of women affected with heritable mitochondrial disease to have genetically related children. It will not impact on children who are sick, or develop treatments for persons born with mitochondrial disease. It will only reduce the chance of children with faulty mitochondria being born in the future, if this technology can be developed to the point where it works. There are no guarantees that this will be the case, and it may carry risks for the offspring who are the result of mtDNA transfer, and possibly future generations. Due to the nature of this technology, it is impossible for the offspring to consent to such changes.

Allowing mitochondrial transfer to proceed in Australia defies the international call for a moratorium on human germline manipulation, as well as introducing new ART techniques which are ethically troubling. Furthermore, it is already possible for women who carry mutations of mtDNA to build a family by methods that are currently available.

Our strong preference is that this bill be abandoned or its debate postponed until such time as germline manipulation is a safer option, with international agreement that it is ethically permissible. The money allocated for implementation of this bill should instead be used to fund research aimed at treating mitochondrial disease.[13,14] Failing that, in anticipation of international condemnation, we recommend consideration of the following amendments to the bill:

Suggested amendments

1. Specifically exclude Pronuclear Transfer and Second Polar Body Transfer from the list of approved Mitochondrial Transfer techniques, also any technique that involves removing the nucleus or nuclear material from a human embryo/zygote and implanting it into a second embryo/zygote from which the nucleus is removed.

Rationale: These two techniques are problematic on two fronts. Firstly, this technique is similar to that used in human cloning. Secondly, these techniques necessitate the creation of a human embryo merely for its parts, harvest of which destroys the embryo. As other techniques are available and show promise, for example, Maternal Spindle Transfer, this project can proceed without including Pronuclear Transfer and Second Polar Body Transfer.

2. Allow implantation of male embryos only following the mitochondrial donation process in Stage 1 of the program.

Rationale: This legislation defies international scientific calls for a ban on germline genetic research. One way to minimise the impact on the human germline is to allow only male embryos to be implanted, as mitochondrial DNA (mtDNA) is inherited through the female line.

3. No human research to be allowed until animal research showed that intergenerational safety and efficacy are proven.

Rationale: In view of international concerns about germline genetic modification, clear evidence that these techniques will not have a negative impact on the human germline is required prior to use in human embryos. Animal testing should confirm its safety over at least two generations.

4. This legislation should be subject to the Gene Technology Act.

Rationale: In view of the controversial nature of this research's impact on the germline, it should be overseen by the Gene Technology Act and subject to its guidelines and expert review.

5. Requirements for pre-treatment counselling for participants in mitochondrial donation research should stipulate that the counsellor is independent and not involved in the research program.

Rationale: Currently the bill allows for 'an appropriately qualified genetic counsellor, or by any professional who is sufficiently qualified and appropriately trained in the specific issues to provide the counselling (such as a clinician with expertise in mitochondrial disease)'. To avoid coercion, the person advising the potential participant should have no role in the research project itself. Furthermore, consent to genomic research is covered by the NHMRC's *National Statement on Ethical Conduct in Human Research (2007 updated 2018)* and it should be stipulated that these guidelines should be followed.

6. Parliamentary review of the legislation is required before Mitochondrial Donation is introduced into clinical practice.

Rationale: This amendment is recommended in view of the significance of this technology in changing norms in Australian healthcare, namely

- It combines the genetic material of three adults in one embryo.
- It involves altering the human germline, that is, altering genetic material that is inherited by the next generation,
- It involves creation of human embryo specifically to use components of that embryo, which will result in the death of the embryo.
- One of the proposed techniques (Pronuclear transfer) is technically similar to human cloning, which is currently banned in Australia.

7. Mitochondrial Donation cannot proceed to Stage Two until longitudinal data is available on a minimum number of participants to demonstrate the safety and efficacy of mitochondrial donation techniques.

Rationale: Maintaining privacy of families and children is appropriately a priority in this legislation. However, while this is important, legislation should ensure that sufficient data is available to judge whether the clinical trial of mitochondrial donation shows it is feasible, safe and effective, before proceeding to Stage 2. Consideration should be given to whether intergenerational follow-up is possible. If families are not obliged to be involved in follow-up, a minimum number of voluntary participants should be mandated before the procedure becomes clinically available.

We thank you for your attention to our concerns. We would be happy to provide more information or elaborate further in person if you so require.

Yours sincerely

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References

1. Alston, C. L., Rocha, M. C., Lax, N. Z., Turnbull, D. M., & Taylor, R. W. (2017). The genetics and pathology of mitochondrial disease. The Journal of pathology, 241(2), 236-250.
2. Calvo SE, Clauser KR, Mootha VK. MitoCarta2.0: an updated inventory of mammalian mitochondrial proteins. Nucleic Acids Res 2016; 44: D1251–D1257.
3. DiMauro S, Schon EA. Mitochondrial respiratory-chain diseases. N Engl J Med 2003; 348: 2656 – 2668.
4. Tan, A. S., Baty, J. W., Dong, L. F., Bezawork-Geleta, A., Endaya, B., Goodwin, J., ... & Berridge, M. V. (2015). Mitochondrial genome acquisition restores respiratory function and tumorigenic potential of cancer cells without mitochondrial DNA. Cell metabolism, 21(1), 81-94.
5. Gaziev, A. I., Abdullaev, S., & Podlutsky, A. (2014). Mitochondrial function and mitochondrial DNA maintenance with advancing age. Biogerontology, 15(5), 417-438.
6. Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. Cell. 2012 Mar 16;148(6):1145-59.

7. Richardson, J., Irving, L., Hyslop, L. A., Choudhary, M., Murdoch, A., Turnbull, D. M., & Herbert, M. (2015). Concise reviews: assisted reproductive technologies to prevent transmission of mitochondrial DNA disease. Stem cells, 33(3), 639-645.
8. Cohen, I. G., Adashi, E. Y., Gerke, S., Palacios-González, C., & Ravitsky, V. (2020). The regulation of mitochondrial replacement techniques around the world. Annual review of genomics and human genetics, 21, 565-58
9. National Perinatal Epidemiology and Statistics Unit, Assisted reproductive technology in Australia and New Zealand 2018. UNSW Sydney.
10. Lander, E. S., Baylis, F., Zhang, F., Charpentier, E., Berg, P., Bourgain, C., ... & Winnacker, E. L. (2019). Adopt a moratorium on heritable genome editing.
11. UNESCO panel of experts calls for ban on “editing” of human DNA to avoid unethical tampering with hereditary traits. https://en.unesco.org/news/unesco-panel-experts-calls-ban-editing-human-dna-avoid-unethical-tampering-hereditary-traits
12. ISSCR Guidelines for Stem Cell Research and Clinical Translation, May 2021. https://www.isscr.org/docs/defaultsource/all-isscr-guidelines/2021-guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation-2021.pdf?sfvrsn=979d58b1_4
13. Rory J. Tinker, et al. Current and Emerging Clinical Treatment in Mitochondrial Disease, *Molecular Diagnosis & Therapy* (2021) 25: 181-206
14. Robert D.S. et al. Moving towards clinical trials for mitochondrial diseases, *J Inherit Metab Dis* (2021) 44: 22-41