POSITION STATEMENT

Mitochondrial donation:
maternal spindle transfer and pronuclear transfer

The Australian Mitochondrial Disease Foundation (AMDF) supports research to further develop safe and effective mitochondrial replacement in vitro fertilisation (IVF) techniques to assist women with maternally inheritable mitochondrial disease to have children and subsequent descendants free of this debilitating and sometimes fatal condition.

Based on the outcomes of research and public consultation to date, the AMDF also supports making mitochondrial replacement IVF techniques (mitochondrial donation) available for in-clinic use by affected women, under certain conditions.

Mitochondrial disease

Mitochondrial disease is a debilitating genetic disorder that robs the body’s cells of energy, causing multiple organ dysfunction or failure and potentially death.

One in 5,000 babies is born with a severely disabling form of mitochondrial disease, which can cause death in infancy, childhood or adulthood; a likely higher proportion of fetuses is affected. In many cases these diseases are caused by genetic mutations in nuclear genes, carried on the 46 chromosomes we inherit equally from our mother and father. Mitochondrial disease can also arise as a spontaneous genetic mistake at conception.

However, about half the time, mitochondrial diseases are caused by mutations in a separate mitochondrial DNA (mtDNA) chromosome that we inherit only from our mother. About 1 in 200 people (or approximately 120,000 Australians) carries an mtDNA mutation that can cause disease and it is likely that mtDNA disease is much more common in the community than previously thought.

The New England Journal of Medicine – Mitochondrial Donation: How Many Women Could Benefit – estimates that “the average number of births per year among women at risk for transmitting mtDNA disease is 152 in the United Kingdom and 778 in the United States”. A simple extrapolation from UK would be approximately 56 births per year in Australia given the respective population sizes and assuming roughly equal age distribution and fertility.

Currently, for women at risk of passing on maternally inheritable mtDNA disease, there are only two reproductive options available to have a healthy child: donor egg donation or, in some cases where the exact gene mutation is known, prenatal diagnosis or IVF using preimplantation genetic diagnosis (PGD).
However, these options are not available to many women at risk because most of their eggs may be carrying substantial amounts of an mtDNA mutation. Also, PGD can only reduce and does not eliminate the risk of mitochondrial disease in the resulting child, or of her passing the disease to her children.

Mitochondrial donation

The two new mitochondrial donation techniques being developed are maternal spindle transfer and pronuclear transfer (See figure above). They involve transferring nuclear genetic material from the affected mother’s egg into a donor egg that has had its nuclear DNA removed and retains only its healthy mitochondrial DNA; the resulting child therefore does not inherit the mitochondrial disease.

Maternal spindle transfer uses unfertilised eggs (oocytes), while pronuclear transfer uses eggs already fertilised by the father (one-cell embryos or zygotes). Unlike other IVF methods, both techniques could allow any woman carrying maternally inheritable mitochondrial disease to have healthy children who are genetically related to both parents.

Research evidence appears to indicate the techniques are sufficiently developed and safe for in-clinic use. Mitochondrial donation has been shown to be safe and effective in producing monkeys whose mtDNA has been almost completely replaced by donor mtDNA. Experiments have also been done in very early human embryos, which suggest the techniques allow normal embryo development. Some commentaries have raised concerns about potential safety issues based on experiments in mice and insects. However, a recent article provided reasons why these concerns are unlikely to be relevant to humans¹.
There are risks and benefits with any medical technique, including ‘traditional’ IVF, and no treatment can claim to be 100 per cent safe and effective. Risks with mitochondrial donation procedures are expected to be low and probably comparable to the risk for any couple of having a child with a severe genetic condition; the latter is about three per cent in the general population. The potential benefits appear to outweigh the risks for unborn children who would otherwise be at risk of severe mitochondrial disease.

Accordingly, the AMDF supports making mitochondrial donation techniques available under strictly controlled conditions to families at risk for having children with the most severe forms of mtDNA disease; the donor would preferably have the same ancestral mtDNA background. Affected families should be supported to make informed choices based on clearly understanding the relevant issues. As with any new IVF technique, it will be important to monitor outcomes of these procedures closely.

**Changes to government legislation in the UK**

After an extensive process involving many years of consultation and three separate expert reviews, regulations to allow mitochondrial donation have been approved by the UK Parliament:

- On Tuesday 3 February 2015 MPs in the House of Commons voted by 382 to 128 to allow mitochondrial donation.
- On Tuesday 24 February 2015 peers in the House of Lords voted by 280 to 48 to allow mitochondrial donation to be licenced for use.

The UK Human Fertilisation and Embryology Authority (HFEA) granted a licence for these techniques to be used therapeutically on a case by case basis on 29 October 2015.

**Australian Legislation governing mitochondrial donation**

Research and clinical applications of mitochondrial donation are overseen by laws made by federal and state governments. State laws are, for the most part, consistent with federal law.

In all states, legislation prohibits the use of mitochondrial donation techniques in the clinic, and research is significantly restricted.

In all states except Western Australia, research on a limited range of mitochondrial donation is permissible up to day 14 of embryo development, subject to a license being granted. In 2010, Hon. Mark Butler MP, then Federal Minister for Mental Health and Ageing, appointed an independent committee to review the two relevant acts: *Prohibition of Human Cloning for Reproduction Act 2002* and the *Research Involving Human Embryos Act 2002*. The committee’s report, released on 7 July 2011, recommended the existing legislation remain unchanged: [https://legislationreview.nhmrc.gov.au/files/legislation_review_reports.pdf](https://legislationreview.nhmrc.gov.au/files/legislation_review_reports.pdf).

The AMDF welcomed the announcement in June 2013 that the United Kingdom plans to allow mitochondrial donation techniques to be made available to at-risk women to help
prevent them passing serious mitochondrial disease in their children. Dame Sally Davies, the chief medical officer for England, said: "It's only right that we look to introduce this life-saving treatment as soon as we can."

In February 2014, the UK government issued draft regulations for further public consultation: https://www.gov.uk/government/consultations/serious-mitochondrial-disease-new-techniques-to-prevent-transmission. This followed advice from the UK’s Human Fertilisation & Embryology Authority (HFEA), which conducted an extensive consultation and public dialogue between June and December 2012. The public consultation exercise indicated that, overall, there was general support for mitochondrial donation to take place, subject to strict safeguards and careful regulation.

**Sensationalist claims**

Some groups have made sensationalist claims about the techniques being inappropriate because the children could be said to have three parents. However, this is "misleading, inappropriate and unhelpful" according to the Nuffield Council on Bioethics in London, which in 2012 reviewed the procedures from an ethical standpoint.

It is important to note that when the new mitochondrial DNA molecule is introduced, it is only replacing 37 mtDNA genes (contributing about 0.1 per cent of a person’s genetic make-up), compared with approximately 20,000 genes in the nucleus, which are not replaced. The mtDNA contribution is important for converting food into energy but appears to make no significant contribution to appearance, behaviour or other features, which are determined by the nuclear genes and environment.

Mitochondrial donation can be compared to changing the sparkplugs in an engine or a transplant into a patient with organ failure.

Other sensationalist claims relate to the creation of so-called designer babies, because mitochondrial donation would change the DNA or germline of all subsequent generations within a family. However, techniques to eradicate debilitating and potentially fatal inherited diseases cannot be considered in the same league as techniques to select for non-life threatening physical characteristic such as sex or eye colour.

The AMDF recognises there is debate about research and treatment with human embryos, and believes informed, constructive comment and consultation is necessary in exploring the issues, educating the public and allaying concerns.

We note that public consultation by the UK HFEA found general support for approval of mitochondrial donation. A 2013 survey of a large cohort of affected women in the USA found there was overwhelming support for these techniques to be made available.
The future for Australians affected by mitochondrial disease

It is important to note that mitochondrial donation techniques have the potential to assist only women who have already been diagnosed as carrying a maternally inheritable genetic mutation in their mitochondrial DNA. To put this into context, mitochondrial disease is so often undiagnosed or misdiagnosed that many women unknowingly pass the disease on to their children and only make the tragic discovery after they have had their families and they or their children become sick and a diagnosis is finally made (often after months or years and many invasive tests).

Therefore, it remains an urgent priority to improve diagnostic methods and identify gene mutations responsible for the many forms of mitochondrial disease, and to educate medical practitioners to facilitate early diagnosis and referral to appropriate healthcare.

Advances in mitochondrial disease treatment and prevention are vital not only to assist affected women to have children free of maternally inheritable mitochondrial disease, but also to assist Australians affected by other forms of the disease. More than 100 clinical syndromes and disorders have been recognised as coming under the category of mitochondrial disease, involving multitudes of gene mutations, both known and unknown.

Researchers are also discovering links between mitochondrial dysfunction and a wide range of major diseases – particularly cancer and chronic degenerative disorders such as Parkinson, Alzheimer and Huntington disease, motor neurone disease, heart disease and diabetes. Mitochondrial research therefore offers hope not only to people with primary mitochondrial diseases, but also to the millions suffering from other major diseases commonly associated with ageing.

The AMDF calls on the Australian government to reconsider its position against the human embryo research necessary to develop mitochondrial donation techniques, and to make more funds available to improve diagnosis, develop treatments and search for a cure for mitochondrial disease.

Reference

This position statement is endorsed by the AMDF’s Scientific and Medical Advisory Panel (members’ biographies are available at www.amdf.org.au/smap). It has been prepared for general information only and should not be relied on for decisions regarding medical care.

Australian Mitochondrial Disease Foundation:
1300 977 180: Helpline and general enquiries | www.amdf.org.au
Media enquiries: Moore PR, 02 9560 2826, 0402 382 363, carolmoore@moorepr.com.au