POSITION STATEMENT

Mitochondrial replacement IVF techniques:
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 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 more than 117,000 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.

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 replacement techniques

The two new mitochondrial replacement techniques being developed are **maternal spindle transfer** and **pronuclear transfer** (Figures 1 and 2). 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.

*Figure 1: Maternal spindle transfer*

*Figure 2: Pronuclear transfer*

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Research evidence appears to indicate the techniques are sufficiently developed and safe for in-clinic use. Mitochondrial replacement 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 humans.

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 replacement 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 replacement 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.

**Government legislation**

Government legislation in Australia and overseas prohibits the use of mitochondrial replacement techniques in the clinic, and research is significantly restricted.


The AMDF welcomed the announcement in June 2013 that the United Kingdom plans to allow mitochondrial replacement 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](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 replacement 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 replacement 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 replacement 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 replacement. 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 replacement 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 replacement 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.htm). It has been prepared for general information only and should not be relied on for decisions regarding medical care.

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