AUSTRALIAN MITOCHONDRIAL DISEASE FOUNDATION

Updated February 2018

POSITION STATEMENT

Mitochondrial donation: providing reproductive choice to women carrying maternally inheritable mitochondrial disease

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This document provides factual background information and outlines the official position of the Australian Mitochondrial Disease Foundation (AMDF) in support of mitochondrial donation (also known as mitochondrial replacement, transplant or transfer).

SUMMARY OF THE AUSTRALIAN MITOCHONDRIAL DISEASE FOUNDATION'S POSITION ON MITOCHONDRIAL DONATION

- Mitochondrial disease is a debilitating genetic disorder that starves the body's cells of energy, causing multiple organ dysfunction or failure and potentially death.
- One in 200 people may develop mitochondrial disease during their lifetime. In about half of cases, the disease is caused by mutations in mitochondrial genes (mtDNA), which contribute about 0.1 per cent of a child's genetic make-up and are inherited only from the mother.
- AMDF is committed to expanding the reproductive options available to Australian women/couples affected by mitochondrial disease, as has been done in the United Kingdom.
- Based on research evidence to date, AMDF is confident that mitochondrial donation techniques are sufficiently developed to be effective and safe for in-clinic use.
- AMDF believes the potential benefits of mitochondrial donation far outweigh any potential risks for unborn children who may otherwise suffer severe mitochondrial disease.
- AMDF supports making mitochondrial donation techniques available under strictly controlled conditions to Australian women at risk for having children with severe forms of mtDNA disease that could lead to a child's early death or substantial impairment.
- AMDF believes the choice to utilise mitochondrial donation should ultimately be made by the affected woman/couple. They should be supported to make informed reproductive choices based on clearly understanding the relevant issues.
- AMDF recognises it will be important to monitor outcomes of mitochondrial donation procedures closely, as it would be with any new IVF technique.
- AMDF calls upon the Australian Government to acknowledge the significant developments and advances in mitochondrial donation techniques, and to revise its legislation to allow affected women the choice to access mitochondrial donation IVF in Australian clinics.

Mitochondrial disease

Mitochondrial disease is a debilitating genetic disorder that starves the body's cells of energy, causing multiple organ dysfunction or failure and potentially death. It primarily affects the muscles and major organs such as the brain, heart, liver, inner ears and eyes, but can cause any symptom in any organ at any age.

Depending on which parts of their bodies are affected and to what degree, sufferers may: lose their sight or hearing; suffer muscle weakness and pain; be unable to walk, eat, swallow or talk normally; have strokes or seizures; develop liver disease or diabetes; suffer heart, respiratory or digestive problems; or experience developmental delays or intellectual disability.

There are few effective treatments and no cure for mitochondrial disease.

What causes mitochondrial disease?

In many cases mitochondrial diseases are caused by genetic mutations in one of the 20,000 nuclear genes carried on the 46 chromosomes inherited equally from a person's mother and father. To date, we know of more than 200 such disorders.

Mitochondrial disease can also arise as a spontaneous genetic mistake at conception.

In about half of cases, mitochondrial diseases are caused by mutations in one of the 37 mitochondrial genes (mtDNA), which contribute about 0.1 per cent of a person's genetic make-up and are carried on a separate mitochondrial chromosome that is inherited only from the mother. These are known as maternally inheritable forms of mitochondrial disease.

Who is affected by mitochondrial disease?

Research shows one in 200 people, or more than 120,000 Australians, may carry genetic mutations that put them at risk for developing mitochondrial disease or other related symptoms such as diabetes, deafness or seizures during their lifetimes.

However, mitochondrial disease is difficult to diagnose and awareness in the medical community is low, particularly for adult-onset and mild to moderately disabling forms of the disease.

Accordingly, more than 90 per cent of people at risk of the disease are potentially undiagnosed. Some may be symptomatic but undiagnosed or misdiagnosed, some are not yet symptomatic, and others are unknowingly at risk of passing the disease on to their future children.

People suffering severe or life-threatening forms of mitochondrial disease are most likely to receive a diagnosis. One in 5,000 children (or at least one Australian child born each week) will develop a severely disabling form of mitochondrial disease during their lifetime and half will die in childhood.

What reproductive options are available to affected women/couples?

Currently, prenatal diagnosis or in vitro fertilisation (IVF) using preimplantation genetic diagnosis (PGD) are the only reproductive options available to prospective Australian parents who are at risk of passing on mitochondrial disease and want to have a healthy, genetically-related child.

However, these techniques are not an option where the exact gene mutation is unknown or where most of the woman's eggs may carry substantial amounts of an mtDNA mutation, such as in maternally inheritable mtDNA disease. Also, PGD can only reduce and does not eliminate the risk of mitochondrial disease in the resulting child.

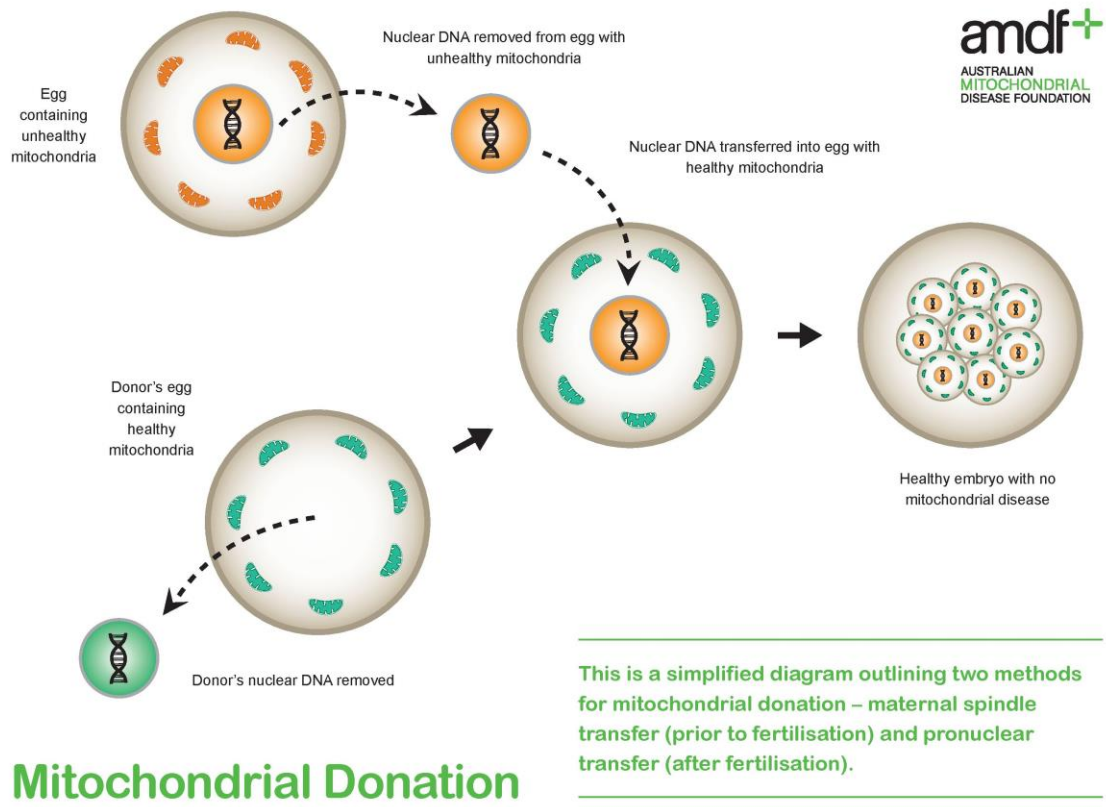
Mitochondrial donation

Maternally inheritable forms of mitochondrial disease have been the focus of ground-breaking research to develop new IVF techniques that enable an affected woman's faulty mitochondrial DNA to be replaced with healthy donor DNA to produce a genetically-related child free of the disease.

Mitochondrial donation (also called mitochondrial replacement, transplant or transfer) involves 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 two main mitochondrial donation techniques are: maternal spindle transfer, which uses unfertilised eggs (oocytes); and pronuclear transfer, which uses fertilised eggs (one-cell embryos or zygotes). See the simplified diagram below.

It has been estimated 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. Assuming roughly equal age distribution and fertility, this conservatively equates to approximately 56 Australian babies who could be born each year free from maternally inheritable mitochondrial disease.



Safety and efficacy

No treatment can claim to be 100 per cent safe and effective and there are risks and benefits with any medical technique, including "traditional" IVF. Risks with mitochondrial donation procedures are expected to be low and 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.

Mitochondrial donation has been shown to be safe and effective in producing monkeys whose mtDNA has been almost completely replaced by donor mtDNA. Experiments in very early human embryos suggest the techniques allow normal embryo development. AMDF supports selecting a mitochondrial donor with the same ancestral mtDNA background, to increase the likelihood of a successful pregnancy and a healthy child.

Making mitochondrial donation available to affected women/couples

AMDF supports mitochondrial donation being available under strictly controlled, tightly regulated conditions to women at risk for having children with severe forms of mtDNA disease that could lead to a child's early death or substantial impairment. At this time, the only country to provide regulated mitochondrial donation is the United Kingdom.

Australia

In Australia, current legislation does not allow the use of mitochondrial donation techniques in the clinic, and research is significantly restricted. Research and clinical applications of mitochondrial donation are overseen by federal and state governments; state laws are, for the most part, consistent with federal law. 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 licence being granted.

The two relevant acts were last reviewed in 2010-11, when the Federal Minister for Mental Health and Ageing appointed an independent committee to review the 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 legislation remain unchanged.

United Kingdom

The United Kingdom recently established the world's first regulated system to provide mitochondrial donation.

Following an extensive scientific and ethical review process involving ten years of public consultation and three expert reports, in October 2015 the UK Parliament approved regulations to allow mitochondrial donation to prevent maternally inheritable mitochondrial disease. In December 2016, the regulations were endorsed by the Human Fertilisation and Embryology Authority (HFEA).

UK clinics apply to the HFEA for a special licence to provide mitochondrial donation. Patients also apply individually to the HFEA to undergo mitochondrial donation treatment in a licensed clinic. In March 2017, the HFEA granted the first clinical mitochondrial donation licence to the Newcastle Fertility Centre at the International Centre for Life in Newcastle-upon-Tyne, United Kingdom, whose reproductive and genetics experts were instrumental in developing the procedure. On 6 February 2018, two UK women carrying mtDNA mutations were granted permission to undergo mitochondrial donation, giving them the opportunity to have children free of mitochondrial disease.

AMDF welcomes mitochondrial donation being available to affected women/couples in the UK who wish to have a healthy, genetically-related child.

United States

The US Institute of Medicine of the National Academies of Sciences, Engineering and Medicine in February 2016 recommended that initial clinical investigations of mitochondrial replacement techniques should be considered by the US Food and Drug Administration (FDA) under certain conditions; this followed a study by an expert committee. However, current US government policy precludes the FDA taking the recommended actions on mitochondrial donation.

While AMDF welcomes the Institute of Medicine recommendations, it does not support the proposal to initially only allow male embryos to be created through mitochondrial replacement to prevent any unforeseen consequences being passed to future generations. This would decrease the procedure's efficiency because it would involve additional manipulation of embryos and means only half the embryos could be used, requiring some women to have additional ovarian hyperstimulation.

Other international developments

In September 2016, the first live birth using human oocytes reconstituted by maternal spindle transfer to prevent mitochondrial DNA disease was announced to the media by US scientists, who carried out the procedure in **Mexico**. The findings were presented at the American Society for Reproductive Medicine Annual Scientific Congress on 19 October 2016.

While this appears to be a promising development demonstrating a successful outcome for mitochondrial donation to prevent mitochondrial disease, AMDF has concerns about the lack of regulation, independent monitoring or peer-reviewed published information, and looks forward to the publication of further details.

In January 2017, **Ukrainian** scientists announced the birth of a baby with donor mitochondrial DNA to a woman with unexplained infertility, but without mitochondrial disease, who had been unable to conceive with conventional IVF. Details have not been published to date.

AMDF does not currently support mitochondrial donation to treat infertility. As far as it is aware, the use of the procedure for purposes other than preventing inheritable disease has not been subject to rigorous scientific and ethical review or research, as has been the case for preventing mitochondrial disease.

Public consultation and opinion

AMDF notes that extensive public consultation by the UK HFEA and the Nuffield Council on Bioethics found there was general public support for mitochondrial donation, subject to strict safeguards and careful regulation. A 2013 survey of a large cohort of affected US women found overwhelming support for these techniques to be made available.

AMDF recognises there is debate about research and treatment with human embryos, and believes informed, constructive comment and consultation is necessary to explore the issues, educate the public and allay concerns.

AMDF discourages simplistic, misleading and scientifically inaccurate descriptors of mitochondrial donation and rejects the term “three-parent baby”. In fact, the resulting child has two biological parents who provide 99.9 per cent of its genetic make-up (nuclear genes that contribute to appearance, intelligence, behaviour and other personal characteristics) and a mitochondrial donor who provides 0.1 per cent of the child’s DNA (mitochondrial genes mainly responsible for converting food and oxygen into cellular energy).

Valuing people living with mitochondrial disease

AMDF values people affected by mitochondrial disease. While AMDF’s ultimate vision is to cure mitochondrial disease, its mission is to support sufferers and their families, fund research into mitochondrial disease, and educate the general public and the medical profession. In advocating for techniques to prevent children being born with the disease, AMDF supports the rights of prospective parents to choose to have healthy biological children who will not suffer the debilitating, disabling and potentially fatal consequences of severe forms of mitochondrial disease.

This position statement is endorsed by AMDF’s Scientific and Medical Advisory Panel. It is for general information and should not be relied on for medical decisions.

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