MITOCHONDRIAL DISEASE: THE NEED FOR MITOCHONDRIAL DONATION – August 2019

Mitochondrial disease is a debilitating genetic disorder that robs the body's cells of energy, causing multiple organ dysfunction or failure and sometimes death. When mitochondria are faulty, the body does not get the correct level of energy it needs to function.

1 in 5,000 Australian babies are born with a severely disabling form of mitochondrial disease that can cause death in infancy, childhood or adulthood. That is, more than one every week.

The Mito Foundation, leading international and domestic experts, patients, carers and doctors are working together to allow parents to reduce the risk of their children developing mitochondrial disease and prevent it being passed on through future generations.

Access to mitochondrial donation (an IVF based technique) would mean that around 56 children born annually in Australia with mitochondrial disease could potentially avoid inheriting this deadly disease.

MITOCHONDRIA

Mitochondria are small structures in our cells which generate the energy that powers every part of our body. Mitochondria are often called the 'powerhouses' that provide us with all the energy our body needs to walk, talk, laugh, hear, digest food, function and breathe.

All cells in the human body have mitochondria, except for red blood cells. Mitochondria have their own DNA, which controls their function and, critically, energy production. This is separate from our *nuclear* DNA, which informs who we are, our appearance and our personality.

MITOCHONDRIAL DISEASE

Mitochondrial disease is a debilitating genetic disorder. Depending on the person and the form of their mitochondrial disease, they may suffer a whole range of symptoms from loss of motor control, strokes, seizures, visual or hearing problems, cardiac and/or liver disease, developmental delay and intellectual disability.

In some cases, mitochondrial disease is caused by genetic mutations in the nuclear DNA we inherit equally from our parents. Mitochondrial disease can also arise as a spontaneous genetic mistake at conception.

However, in about half of all known cases, mitochondrial diseases are caused by mutations in the separate mitochondrial DNA (mtDNA) that we inherit only from our mother. About 1 in 200 people (or around 120,000 Australians) carry a mutation in their mitochondrial DNA that could potentially cause disease and it is likely that mtDNA disease is much more common in the community than previously thought.

PEOPLE WITH MITOCHONDRIAL DISEASE

There is no one age group affected by mitochondrial disease. Babies can be born with it while other people develop it later in life, in early childhood, in their teenage years or as adults.

IMPACT OF MITOCHONDRIAL DISEASE

The impact of mitochondrial disease can be devastating and virtually all forms of it have significant impact on patients.

Babies and young children die of Leigh disease, whilst other types of mitochondrial diseases can impact sufferers in different ways.

Many people with mitochondrial disease have repeated and/or prolonged visits to hospital. Symptoms can include temporary blindness, mitochondrial strokes, balance difficulties and digestive or eating difficulties, all requiring significant treatment and care.

Repeated seizures and loss of motor control can mean that people of all ages have to stop working and may need full time care, therefore impacting family and friends, and relying heavily on healthcare and social services systems.

PREVENTING MITOCHONDRIAL DISEASE FROM BEING PASSED ON

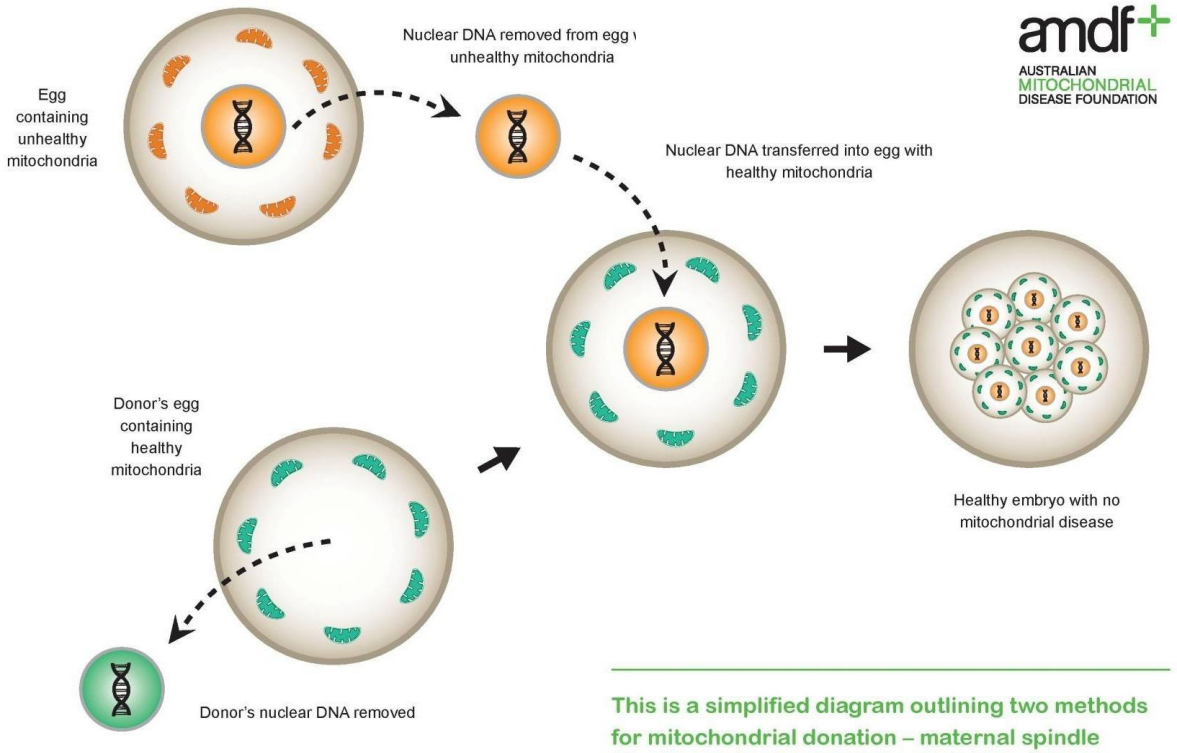
It is possible to significantly reduce the risk of mitochondrial disease being passed on. Mitochondrial disease caused by mistakes (mutations) in one of the nuclear genes involved in mitochondrial function can be prevented through prenatal testing or an IVF based procedure called preimplantation genetic diagnosis.

These approaches are generally not as reliable when the mutation is in mitochondrial DNA inherited from the mother. Mitochondrial donation is an alternate approach.

Mitochondrial donation involves removing the nuclear DNA (the unique genetic information that makes us who we are and determines what we look like) from a patient's egg containing faulty mitochondria and inserting it into a healthy donor egg, which has had its nuclear DNA removed. This prevents mitochondrial DNA defects from being inherited by a genetically related offspring. There are two techniques:

Maternal spindle transfer (pre fertilisation): The nuclear DNA, which amounts to 99.9% of the total cell DNA, is removed from the donor egg, leaving the part of the cell containing the healthy mitochondria. The nuclear DNA from the mother's egg is then inserted into this cell. The healthy egg is fertilised and is then implanted into the mother's uterus in the same way IVF is carried out already.

Pronuclear transfer (post fertilisation): As above, but the nuclear DNA is removed from the mother's egg after the mother's egg is fertilised with the father's sperm, and then transferred to the donor egg containing healthy mitochondria, which has had its nuclear DNA removed. The healthy fertilised egg is then implanted into the mother's uterus in the same way as in maternal spindle transfer.



Mitochondrial Donation

This is a simplified diagram outlining two methods for mitochondrial donation – maternal spindle transfer (prior to fertilisation) and pronuclear transfer (after fertilisation).

INTERNATIONAL EXPERIENCE WITH MITOCHONDRIAL DONATION

The use of mitochondrial donation was approved by the UK Parliament in 2015 after several years of consultation and the UK Human Fertilisation and Embryology Authority has issued the first licenses to enable parents to use mitochondrial donation. Due to patient confidentiality, no announcement about a baby's birth has yet been made but one or more children may have been born using this technique.

AUSTRALIA'S LEGAL POSITION

The key federal laws governing research and clinical practice in relation to embryology are the *Prohibition for Human Cloning for Reproduction Act 2002* and the *Research Involving Human Embryos Act 2002*.

These laws currently prohibit implantation of a human embryo that contains more than two people's genetic material. This is regardless of whether that material is simply transferred, as in mitochondrial donation, or where genetic modification is proposed.

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WHAT NEEDS TO CHANGE

Changing the law is critical to allow affected individuals the opportunity to have genetically related children without the risk of them inheriting mitochondrial DNA defects which will drastically limit their life.

The Mito Foundation, together with patients, carers and leading international experts, is calling on the Australian Government to change the necessary laws to enable mitochondrial donation by affected parents to ensure that we protect future generations from mitochondrial disease.

HOW MANY PEOPLE WOULD BENEFIT?

The New England Journal of Medicine, in an article entitled *Mitochondrial Donation – How Many Women Could Benefit,* estimates that "the average number of births per year among women at risk for transmitting mtDNA [mitochondrial DNA] disease is 152 in the United Kingdom and 778 in the United States."

A simple extrapolation from the UK means that there are around 56 children each year in Australia who could potentially benefit from this technique, given the respective population sizes and assuming roughly equal age distribution and fertility.

Whilst this may seem a relatively low number, it represents a significant burden to our health system and a major burden and fear on behalf of families at risk. Conversely, eliminating this risk does not represent a significant cost or burden to the financial sustainability of the health system and would provide parents and families a choice in regards to the health risks facing their child.

NEXT STEPS

In 2018, the Senate Community Affairs Committee undertook an inquiry into the *Science of mitochondrial disease and related matters.* Reporting in June, they made a series of recommendations including that a public consultation be undertaken about the introduction of mitochondrial donation and that 'the Australian Government prepare a consultation paper, including options for legislative change that would be required'. The Committee further recommended that the NHMRC provide advice regarding any new findings about mitochondrial donation since the introduction of mitochondrial donation in the UK.

The Government responded to this Report in February and an expert committee has been brought together, led by the NHMRC, to work on scientific and other matters raised by the Inquiry. This reflects and extends some of the work already done by the NHMRC in reviewing the legislative and scientific frameworks around embryo research and recent advances and developments from around the world that might be adopted by Australia, such as the UK's legalisation of mitochondrial donation.

Public consultation will commence in September 2019. An online consultation process is anticipated and a series of public forums will be held across the country. The foundation's experience in engaging with stakeholders and other activities, like a Citizens' Jury, has shown significant levels of support for legalising mitochondrial donation in Australia.

The Mito Foundation calls on the Australian Government to continue the work towards legalising mitochondrial donation and make this happen in a quick and timely manner so that women who carry these genetic mutations have the choice to eliminate the risk of their children inheriting this devastating and life-threatening disease.