Chapter 1

Introduction

1.1 Mitochondrial donation is a reproductive technology procedure to reduce the chances of a woman passing on mitochondrial disease—a potentially life-threatening condition—to her children.

1.2 Mitochondrial donation was legalised for use on humans in the United Kingdom (UK) in 2015. The UK is the only jurisdiction in the world that has legalised mitochondrial donation for clinical application, and to date, no children have been born using this process in the UK. Since then, there have been discussions in the Australian scientific and medical communities about the possibility of this technique being made legal for clinical practice in Australia.

1.3 This report looks at the science of mitochondrial donation, the safety and efficacy on the technique as well as the ethical considerations of such technology, and evaluates whether the Australian Government should consider making mitochondrial donation available within Australia, and if so, under what kind of regulatory regime.

1.4 The report uses information provided in the course of this inquiry, and also relies on the significant body of evidence gathered during the 12 year process to evaluate and ultimately legalise mitochondrial donation in the UK.

What is mitochondrial disease?

1.5 Mitochondria are found in the fluid surrounding the nucleus of cells. They are responsible for making energy within the cell, without which the cells would not survive. In order to work, the mitochondria have their own mitochondrial DNA (mtDNA).[1] Mitochondrial disease can be caused by mutations in the mtDNA or in the nuclear DNA.

1.6 In some cases, mitochondrial disease is caused by genetic mutations in the nuclear DNA – most of our DNA (over 99 per cent) is found in the nucleus of the cell and we inherit this from our mother and our father. Mitochondrial disease can also arise as a spontaneous genetic mutation at conception.

1.7 Mitochondrial disease varies in presentation. It can be mild with little or no symptoms or can be severe enough to be life threatening. It tends to affect parts of the body that require a lot of energy, like the brain, muscles, kidney and heart. While some symptoms can be managed, there are no effective treatments available for serious mitochondrial disease and there is no cure.[2]

1.8 Common symptoms of mitochondrial disease include developmental delays, seizures, weakness and fatigue, muscle pain, vision loss, and heart problems, leading

---

1 Deoxyribonucleic acid (DNA) is a chain of nucleotides carrying the genetic instructions for the growth, development, functioning and reproduction of living organisms.

2 House of Commons Library (UK), *Mitochondrial Donation*, Standard Note: SN/SC/6833, 29 January 2015, p. 5.

to morbidity and in some cases premature death.[3] Chapter two discusses mitochondrial disease and related illnesses in greater detail.

Causes of mitochondrial disease

1.9 In about half of all known cases, mitochondrial disease is caused by mutations in the mtDNA, which are inherited matrilineally, from mother to children through multiple generations.[4] This is because the mother's oocytes (eggs) contain significant amounts of mtDNA, while the mtDNA contained in a father's sperm is lost at fertilisation. The level of mutated mtDNA a child will inherit, or the severity of any subsequent mitochondrial disease, is unpredictable.[5]

Having children

1.10 For women with a known mtDNA mutation who want to have a child with a genetic link, there are currently two key options to reduce the chance of passing on mitochondrial disease.

1.11 The first is to use prenatal diagnosis, conducted on a pregnant woman at around 11–14 weeks gestation, usually by performing a genetic test on a placental tissue biopsy. If an mtDNA mutation is found, parents then face a choice of either continuing or terminating the pregnancy.

1.12 The other option is to use pre-implantation genetic diagnosis (PGD), where embryos are created using in vitro fertilisation (IVF) and then tested before implantation to look for embryos with the lowest proportion of mutated mtDNA.

1.13 There are limitations to this method because it cannot be used by all women with mtDNA mutations and it can only reduce, not eliminate, the risk of having a baby affected by mitochondrial disease. In some cases, there are no embryos with an acceptably low mtDNA mutation load and the IVF cycle must be abandoned.

1.14 Additionally, even if unaffected themselves, girls born after the use of PGD may themselves still be at risk of having affected children, as some abnormal mitochondria may be present in their oocytes.[6]

1.15 The full range of reproductive choices available to people with a mitochondrial mutation are discussed in greater detail in chapter two.

---

3 Committee on the Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases, US Institute of Medicine, *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations*, February 2016, p. 1.

4 This subset of mitochondrial disease is often referred to as mtDNA disease.

5 Australian Mitochondrial Disease Foundation (AMDF), *Mitochondrial Disease: the need for mitochondrial donation*, p. 1.

6 House of Commons Library (UK), *Mitochondrial Donation*, Standard Note: SN/SC/6833, 29 January 2015, pp. 6–7.

Mitochondrial donation

1.16 Mitochondrial donation (or mitochondrial replacement techniques) is designed to prevent the transmission of mtDNA diseases from mother to child by creating an embryo with nuclear DNA from the intended mother and mtDNA from a donor with nonpathogenic mtDNA through modification of either an oocyte or zygote (fertilised egg).[7]

1.17 mtDNA does not contribute to a person's genetic identity because mtDNA only provides energy to the cells. Nuclear DNA is responsible for a person's physical, cognitive and behavioural characteristics. A recipient of donated mtDNA will not resemble the donor.[8]

1.18 Mitochondrial donation only assists women with mtDNA mutations—the cause of approximately half of mitochondrial disease—and assists in reducing the risk of mothers with this form of mitochondrial disease passing it on to their children.

1.19 The various methods of mitochondrial donation and the benefits, risks and ethical considerations of the differing techniques are discussed in greater detail in chapters three and four.

Regulation of mitochondrial donation and related research

1.20 Under current Australian legislation, some forms of mitochondrial research are prohibited entirely because it requires fertilising an egg with the genetic material of more than two people, while others can be researched under license but must be destroyed within 14 days.[9]

1.21 There are two key pieces of legislation which prohibit the research and clinical implementation of mitochondrial donation in Australia. Additionally, there are a range of other regulatory instruments and bodies which are relevant to mitochondrial donation.

1.22 The National Health and Medical Research Council (NHMRC) is Australia's peak body for supporting health and medical research, including providing advice on ethical behaviour in health care and in the conduct of health and medical research. The NHMRC is responsible for administering the two pieces of legislation relevant to mitochondrial donation – *Research Involving Human Embryos Act 2002* (Embryo Research Act) and the *Prohibition of Human Cloning for Reproduction Act 2002* (Cloning Act).[10]

---

7 Committee on the Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases, US Institute of Medicine, *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations*, February 2016, p. 1.

8 Ainsley Newson, Stephen Wilkinson and Anthony Wrigley, 'Ethical and legal issues in mitochondrial transfer', *EMBO Molecular Medicine*, June 2016, p. 2.

9 National Health and Medical Research Council (NHMRC), *Submission 4*, p. 7.

10 NHMRC, *Submission 4*, p. 1.

1.23 Two relevant committees of the NHRMC include the Australian Health Ethics Committee (Health Ethics Committee) and the Embryo Research Licensing Committee.

Embryo Research Licensing Committee

1.24 The Embryo Research Licensing Committee of the NHMRC is responsible for administering the Cloning Act and the Embryo Research Act. Both Acts regulate activities that relate to mitochondrial donation and would have to be amended if mitochondrial donation was to be permitted in Australia.[11]

1.25 A detailed discussion of what is currently allowed under legislation and the amendments required to permit the implementation of mitochondrial donation in clinical practice is included in chapter five.

Health Ethics Committee

1.26 The Health Ethics Committee of the NHMRC provides advice on ethical issues relating to health, and develops human research guidelines. Guidelines relevant to mitochondrial donation include the *Ethical Guidelines on the use of assisted reproductive technology in clinical practice and research* (ART Guidelines)[12] and the *National Statement on Ethical Conduct in Human Research* (Human Research Guidelines).[13]

1.27 While the Health Ethics Committee is responsible for guidelines on how Assisted Reproductive Technologies (ART) such as IVF should be implemented, it is not responsible for the regulation and monitoring of ART use in clinical practice. The Embryo Act requires all ART clinics to be accredited by the Reproductive Technology Accreditation Committee (RTAC) of the Fertility Society of Australia (Fertility Society).[14]

Regulation of ART clinics

1.28 The Fertility Society is the peak body for those professionals involved in reproductive medicine in Australia, including gynaecologists, scientists, nurses and counsellors.[15] The reproductive medicine sector is self-regulating under the Fertility Society accreditation scheme managed by the RTAC, which regulates and licenses the 88 clinics across Australia which perform ART techniques for individuals.[16]

---

11 NHMRC, *Submission 4*, p. 1.

12 NHMRC, *Ethical Guidelines on the use of assisted reproductive technology in clinical practice and research* (ART Guidelines), 2007, https://www.nhmrc.gov.au/guidelines-publications/e79 (accessed 22 May 2018).

13 NHMRC, *National Statement on Ethical Conduct in Human Research*, 2007, https://www.nhmrc.gov.au/guidelines-publications/e72 (accessed 22 May 2018).

14 NHMRC, *Submission 4*, p. 1.

15 Fertility Society of Australia (Fertility Society), *Submission 27*, p. 1.

16 Dr Petra Wale, Board Member, Fertility Society, *Committee Hansard*, 17 May 2018, p. 41.

1.29 As part of the RTAC assessment process, ART clinics are assessed for compliance with the RTAC Code of Practice, which in turn requires compliance with the NHMRC ART Guidelines.[17]

1.30 The Fertility Society includes the scientists' sub-group Scientists in Reproductive Technology (SIRT), with over 500 members in Australia, New Zealand and internationally. The goals of SIRT are to:

> [P]romote professional excellence through education, training, research and dissemination of scientific information; to increase the profile and professional status of scientists in assisted reproduction; and, finally, to act as a resource for formulating a consensus on scientific issues and guidelines for best scientific practice, predominately for the Fertility Society of Australia but also for other professional bodies.[18]

1.31 Dr Nadine Richings, Vice Chair of SIRT, told the committee that embryologists working in ART clinics are not currently required to be certified in Australia, although SIRT is currently developing a certification scheme for embryologists to be accredited by a third party.[19]

1.32 Suggestions from the Fertility Society and SIRT on an appropriate certification and regulation framework for mitochondrial donation in Australia is discussed in further detail in chapter five.

Overseas status of mitochondrial donation

United Kingdom

1.33 The UK undertook a 12 year process to allow for the research of mitochondrial donation from 2005, leading to the legalisation of this technique for clinical implementation in 2015, and a licence to administer this as a treatment being granted to a fertility clinic in 2017.

1.34 There were a significant number of scientific and ethical reviews, as well as community consultations to ensure that the technology could be safely and ethically undertaken and that there was public support for the measure.

1.35 The timeline below gives a brief outline of the process:

Date	**Consideration**
1990	The Human Fertilisation and Embryology Authority (HFEA) is created to review information relating to embryos and advise the Secretary of State.
2005	HFEA grants research licence for pronuclear transfer.

17 NHMRC, *Submission 4*, p. 1.

18 Dr Nadine Richings, Vice Chair, Scientists in Reproductive Technology (SIRT), *Committee Hansard*, 17 May 2018, p. 42.

19 Dr Richings, *Committee Hansard*, 17 May 2018, p. 42.

April 2011	HFEA releases first scientific review and recommends further research.
June 2011	HFEA's Ethics and Law Committee considers ethical issues.
January 2012 – March 2013	HFEA undertakes public dialogue work on the ethics and public attitudes towards mitochondrial replacement. Public were generally supportive of these techniques, although concerns around safety, the donor role and the regulation of the techniques were highlighted.
June 2012	Nuffield Council on Bioethics publishes its ethical review.
September 2012 – December 2012	Open consultation questionnaire, meetings and patient focus group takes place.
January 2013	HFEA releases second scientific review.
June 2013	The Government announces it will move forward with public consultation on draft regulations for the use of mitochondrial donation to prevent mothers passing on serious mitochondrial diseases to their children.
June 2014	HFEA releases third scientific review on safety and efficacy.
December 2014	Legislation to legalise mitochondrial legislation put before UK Parliament.
February 2015	The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 passes.
October 2015	The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 come into force. Requires both the clinic and the patient to be licenced by the HFEA.
December 2016	Final regulations governing mitochondrial donation are endorsed by the HFEA.
March 2017	HFEA grants licence to provide mitochondrial donation to the Newcastle Fertility Centre.
February 2018	HFEA grants licence to undergo mitochondrial donation to two UK women carrying mtDNA mutations.

As of 30 April 2018	HFEA's Statutory Approvals Committee has considered 6 applications to carry out mitochondrial transfer.[20]

Source: HFEA, *Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2014 update*, additional information received 30 May 2018, pp. 6–8; AMDF, *Submission 26*, pp. 6–7 and AMDF, *Mitochondrial donation*, https://www,amdf.org.au/mitochondrial-donation/ (accessed 15 June 2018).

United States of America

1.36 The consultation process for mitochondrial transfer in the United States of America (USA) to date has been less structured than in the UK, mostly due to the lack of a specialised agency for human reproduction and fertility.[21]

1.37 In 2014 the USA Food and Drug Administration requested the Institute of Medicine of the National Academies of Sciences, Engineering and Medicine to review the broader implications of mitochondrial transfer. The review was quite cautious, recommending that future clinical trials are restricted to women with serious risks of transmitting mitochondrial disease to their children, and for which the mitochondrial mutation is pathogenic and highly likely to be manifested in a severe clinical way; and that mitochondrial transfer only be made to male embryos to prevent any transfer of the donated mitochondria to future generations.[22]

1.38 However, federal restrictions on funding and research 'in which a human embryo is intentionally created or modified to include a heritable genetic modification' mean that clinics in the USA cannot currently conduct research in this area.[23]

Singapore

1.39 Singapore is currently carrying out public consultation on whether or not mitochondrial donation should be permitted to prevent heritable mitochondrial disorders.[24]

---

20 Minutes for three decisions have been published: two applications were approved and for the other application, more information was requested regarding alternative options available to the patient. See *Reports archive* available at https://www.hfea.gov.uk/choose-a-clinic/clinic-search/results/17/.

21 R J Castro, 'Mitochondrial replacement therapy: the UK and US regulatory landscapes', *Journal of Law and the Biosciences*, vol. 3, no.3, 1 December 2016, pp. 726–735.

22 National Academies of Sciences, Engineering and Medicine (USA), *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations*, 3 February 2016, available at http://www.nationalacademies.org/hmd/Reports/2016/Mitochondrial-Replacement-Techniques.aspx.

23 *Consolidated Appropriations Act 2018*, Pub L No 115-141, §734.

24 Straits Times, 'Bioethics committee seeks views of emerging genetic modification technology to prevent disorders', 19 April 2018, https://www.straitstimes.com/singapore/health/bioethics-committee-seeks-views-on-emerging-genetic-modification-technology-to (accessed 8 May 2018).

Report structure

1.40 Following this introductory chapter, this report consists of four subsequent chapters:

- Chapter two outlines the impact of mitochondrial disease on individuals and their families, the rates of mitochondrial disease and mtDNA mutations and the cost to the health sector;
- Chapter three discusses the science of mitochondrial donation;
- Chapter four discusses the ethics and possible health risks; and
- Chapter five reviews the regime recently introduced in the UK to regulate the clinical implementation of mitochondrial donation, and compares that to the existing regulatory regime in Australia. Chapter five also provides the recommendations and conclusions of the Senate Community Affairs References Committee (committee).

Conduct of the inquiry

1.41 On 21 March 2018 the Senate referred the science of mitochondrial donation to the committee for inquiry and report by 19 June 2018 with the following terms of reference:

(a) the science of mitochondrial donation and its ability to prevent transmission of mitochondrial disease;

(b) the safety and efficacy of these techniques, as well as ethical considerations;

(c) the status of these techniques elsewhere in the world and their relevance to Australian families;

(d) the current impact of mitochondrial disease on Australian families and the healthcare sector;

(e) consideration of changes to legal and ethical frameworks that would be required if mitochondrial donation was to be introduced in Australia;

(f) the value and impact of introducing mitochondrial donation in Australia; and

(g) other related matters.[25]

1.42 On 19 June 2018 the Senate granted an extension of time for reporting to 27 June 2018.

Submissions

1.43 The inquiry was advertised on the committee's website and the committee wrote to stakeholders inviting them to make submissions.

25 *Journals of the Senate*, No. 90, 21 March 2018, p. 2864.

1.44 The committee also issued media releases to promote public awareness about ways individuals could engage with the inquiry. Media releases were published on the committee's website and were tweeted using the @AuSenate handle.

1.45 The committee invited submissions to be lodged by 11 May 2018. Submissions continued to be accepted after this date.

1.46 The committee published 53 submissions from government agencies, organisations and individuals. A further 7 submissions were accepted as confidential submissions. A list of submissions provided to the inquiry is available on the committee's website[26] and in Appendix 1.

Public hearings

1.47 The committee held a public hearing on 17 May 2018 in Sydney, NSW. A list of witnesses who provided evidence at the public hearing is available at Appendix 2.

Notes on references

1.48 In this report, some references to *Committee Hansard* are to proof transcripts. Page numbers may vary between proof and official transcripts.

26 See: www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/MitochondrialDonation.