Mitochondrial Donaton: The Australian Story
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Keywords: mitochondrial donation, genome editing, mitochondrial disease

Pre Proof version.
Published in: (2020) *Journal of Bioethical Inquiry,* https://doi.org/10.1007/s11673-020-09988-5

Introduction:

The landscape of healthcare is constantly changing, with new and innovative treatment techniques regularly emerging. We are also improving the ability to investigate (and prevent) specific inherited conditions through pre-implantation diagnosis and other medical interventions. One such category of medical intervention is mitochondrial donation, which is currently permitted (under strict conditions) in the United Kingdom but is prohibited in Australia. Recently, under the directions of the Hon Greg Hunt, MP (Minister for Health) the National Health and Medical Research Council (NHMRC) opened a dialogue to consider the regulatory, scientific and ethical issues of mitochondrial donation.

What is Mitochondrial Donation

Before addressing the ethical and regulatory issues around mitochondrial donation it is important to provide a brief overview of what the process involves. The following, very simple, explanation is dran from the NHMRC's Issues Paper, released as a part of the consultation process. Mitochondrial donation is a new assisted reproductive technology to help people avoid transmitting mitochondrial DNA disease to their biological children. 'Mitochondria are DNA-containing structures found in human cells. Although small, mitochondria are vital for normal cell biology and health and they provide energy for cells, and support many other important functions' (Issues Paper, p7). At its simplest, 'mitochondrial donation allows for an embryo to be produced using the nuclear DNA from a man and a woman, and the mitochondrial DNA from an egg donated by another woman. There are a number of techniques for mitochondrial donation. The aim is to replace mutant mitochondrial DNA, and avoid transmission of mitochondrial DNA disease.mitochondrial

donation involves' (Issues Paper, p14). It is the combining of DNA from three individuals that gives rise to the complex legal and ethical issues surrounding mitochondrial donation.

The Global Story

Globally there is a lack of consistency with regards to the regulation of mitochondrial monation. Indeed, there is even a lack of consistency around the nomenclature of the process. It is variously referred to as mitochondrial donation, mitochondrial transfer, mitochondrial replacement therapy. We have chosen to adopt the language of the NHMRC Review and therefore refer to it as mitochondrial donation. At the moment, the UK is the only country to have passed specific, targeted laws relating to mitochondrial donation.

In 2014, the Food and Drug Administration (FDA) in the USA requested the Institute of Medicine of the National Academies of Sciences, Engineering and Health to explore the broader implications of mitochondrial donation (although they referred to it as mitochondrial transfer). The Report (Mitochondrial Replacement Techniques, Ethical, Social and Policy Considerations(USA Report)) was released in early 2016 and referred to its 'foundational question' as being 'whether it is ethically permissile for clinical investigations of MRT to proceed' (USA Report, overview).

The conclusion of the USA Report was that mitochondrial donation was ethically permissible so long as there was compliance with governing 'conditions and principles' (USA Report, overview). A significant limitation was that it should only proceed with male embryos. The rationale for this limitation was that, because the mitochondria from a male are not passed on to subsequent generations, and therefore the heritability of the mitochondrial transfer would be limited to female offspring. However, shortly after this report was released any further investigation was prohibited via 'congressional funding restrictions on heritable genetic modification' (Pompei, 2019, 385). There relevant law is the US Act s749 *Consolidated Appropriations Act 2016* and it has been ratified every year since 2016, the FDA cannot approve or fund any further research which acts an effective prohibition on MRT in the United States.

The position in the UK is quite different and has come about after a lengthy consultation and review process. Taking place over a 12 year period, this included a number of public consultations and the commission of three scientific reviews. In 2015, the *Human Fertilisation and Embryology (Mitochondrial Donation) Regulations* were passed and the UK became the first country to specifically address mitochondrial donation in law. It is a careful and comprehensive regulatory instrument that defines specific terms, amends the *Human Fertilisation and Embryology Act 1990* and establishes a regime where clinics and participants must be licensed. So far, one clinic in Newcastle has been licensed and a number of treatment licenses have been granted. It is unknown if, or how many, children have been born.

The position in other countries is varied. Last year the Singaporean Bioethics Advisory Committee released a consultation paper which signalled a public consultation and broader enquiry. However it appears that this has not progressed and there is no indication that, despite headlines such as 'Singapore could become the second country to legalize mitochondrial replacement therapy', a change of law is imminent. In 2018 Ishil and Hibino

undertook a study of 16 countries and summarised the regulatory landscape in the following terms: 'Not regulated:Northern Cyprus and Ukraine; insufficiently regulated: Albania, India, Israel, Italy, Mexico and Taiwan; pronuclear transfer prohibited but other MMT regulated insufficiently: Canada, Czech Republic, Japan and Spain; allogeneic MMT not allowed but autologous MMT regulated insufficiently: Turkey and the United Arab Emirates; and MMT largely prohibited: China and the USA' (Ishil and Hibino, 2018, 106).

The short version of the global story is therefore that it is complicated.

The Australian Story

Before considering the Australian position it is necessary to introduce the National Health and Medical Research Council (NHMRC). It is an independent statutory agency operating under the *National Health and Medical Research Council Act 1992* (Cth). The NHMRC is, under the guidance of the CEO, tasked with inquiring into, issuing guidelinesand advising the community on matters relating to:

(i) the improvement of health; and
(ii) the prevention, diagnosis and treatment of disease; and
(iii) the provision of health care; and
(iv) public health research and medical research; and
(v) ethical issues relating to health; and

In addition there is responsibility to provide advice to the Commonwealth, the States and the Territories on these matters and to directly advise the Minister for Health (*NHMRC Act*, s7). It was in this capacity that on 23 September 2019 the NHMRC opened a public consultation on the possible introduction of mitochondrial donation into Australian clinical practice.

In 2018, the Australian Senate Community Affairs References Committee undertook an inquiry into the science of mitochondrial donation and related matters. The Report from the inquiry made a number of recommendations. In response, the Australian government asked the CEO of the NHMRC to facilitate public consultation and seek expert advice on relevant legal, regulatory, scientific and ethical issues. To facilitate meaningful public consultation, the NHMRC has released an Issues Paper addressing legal, ethical and social considerations around mitochondrial donation, and it was from this paper that the explanation of mitochondrial donation provided above was drawn. To further assist in the process, a Mitochondrial Donation Expert Working Committee (MDEWC) was established by the NHMRC CEO to provide her with expertise and perspectives on relevant issues, including assisting with the writing of the issues paper and conduct of the community consultation.

The regulation of artificial reproductive technology (ART) in Australia is complex because of its status as a federation of six states, two territories and the separate federal Commonwealth. When it comes to ART, what we have is a pot pourri of different legal and non-legal regimes. The state of Victoria was the first place globally to enact specific ART legislation, in the form of the *Infertility (Medical Procedures) Act 1984*. This Act imposed a strict system of regulation based on criminal penalties. Victorian law has undergone significant transformation over time, to respond to new technological advances, to provide

more comprehensive guidance and to reflect changing community attitudes. The early Victorian lead was followed by South Australia and Western Australia, and, much later, New South Wales. The Northern Territory requires clinics to comply with South Australian legislation. Each of the regulatory regimes is different although all recognise the paramount concern for the welfare of the child born as a consequence of the provision of ART.

This is not to say that the conduct of ART elsewhere in Australia is unregulated. The NHMRC has provided a set of helpful ethical guidelines on the use of ART in clinical practice and research. Accreditation of ART clinics by the Fertility Society of Australia and the Reproductive Technology Accreditation Council is dependent on compliance with the Council's Code of Conduct, which in turn requires compliance with these NHMRC guidelines. The guidelines have been updated to reflect technological advances and changes in community attitudes on a number of occasions, most recently in 2017. The introduction of techniques such as mitochondrial donation adds another layer of complexity to this regulatory regime as it introduces the possibility of intervention for more than mere reproductive purposes. The focus is on disease prevention (and perhaps eradication) and will result in the destruction of some embryos and the alteration of others.

From the time when IVF became a practical reality, the cloning of human beings, hitherto the realm of science fiction, started to become more tangible. The birth of Dolly the sheep in 1996 heightened concerns about this new reality, and prompted an outpouring of ethical debate and calls for legislative action. The ART-specific laws in Victoria, South Australia and Western Australia each already included provisions prohibiting human cloning. However, the definition of cloning in each statute was different and the regulatory regime associated with this technology across the nation was messy and ambiguous. In parallel with developments in cloning technology, embryonic stem cell technology was advancing at as rapid a pace. This technology, though not uncontroversial because of concerns it raised about the destruction of human embryos, was recognised as offering significant therapeutic benefits.

The governments of Australia responded rapidly to the call for legislative responses to the ethical and social concerns associated with human cloning and embryonic stem cell research. By 2002, the *Research involving Human Embryos Act* and the *Prohibition of Human Cloning Act* had been passed by federal parliament. The states and territories agreed to enact mirror legislation to ensure national uniformity. Both of these Acts placed specific and clear limitations on what could, and could not, be done with human embryos. Legislating to prohibit human cloning was uncontroversial, and the Act was passed with minimal debate. However, legislating to allow some uses of human embryos for research was more contentious. In an unusual move, members of parliament were given a 'free vote' to allow them to vote with their conscience rather than along party lines. *The Research involving Human Embryos Act*, though eventually passed, was subjected to one of the longest debates in the history of the Australian parliament. By 2005, members of parliament had sufficient comfort with the ways in which the technology was developing to allow the creation of embryos using cloning technology for research, but only under very limited, strictly regulated circumstances. The *Prohibition of Human Cloning Act* thus became the *Prohibition of Human Cloning for Reproduction Ac*t.

The *Research involving Human Embryos Act* allows certain embryos to be used for research and training, subject to strict licence conditions issued by the ERLC. The *Prohibition of Human Cloning for Reproduction Act*, in contrast, sets out that certain activities are prohibited. It is a criminal offence to undertake prohibited activities, with a penalty of up to 15 years imprisonment. Under these laws, some laboratory-based research into mitochondrial donation may be permissible in Australia under licence. However, mitochondrial donation for clinical purposes is currently prohibited. If mitochondrial donation is to proceed into clinical practice in Australia, the law will need to be amended. Public consultation is a vital step in assessing whether it is appropriate to do so.

The Australian story is therefore only just beginning and there is yet to be any formal presentation of recommendations or conclusion from the consultation process. The opening of the discussion however represent a modest first step and reflects a careful approach to possible reform.

Authors' note: We write in our capacities as law academics and as chairs of two NHMRC committees, the Mitochondrial Donation Expert Working Committee (MDEWC) and the Embryo Research Licensing Committee (ERLC). This discussion seeks to neither endorse nor challenge a change in the law and we seek instead to provide insight into this recent development.

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