

Mitochondrial donation: an introductory briefing note

Human Fertilisation and Embryology Authority, October 2014

1 Introduction

This briefing note summarises work that the HFEA has prepared for the Government over the past three years on public attitudes to mitochondrial donation and on the safety and efficacy of the techniques involved. It also sets out how the HFEA would regulate such treatments. A key aim of this note is to inform Parliamentary debate on regulations which would make mitochondrial donation lawful in the UK.

The science of mitochondrial donation is complex and this note has been written for a non-specialist audience. It has been prepared by the HFEA and has been endorsed by its expert scientific panel on mitochondrial donation.

What is mitochondrial disease?

Mitochondria are present in almost all human cells, and vary in number from a few tens to many thousands. They generate the majority of a cell's energy supply which power every part of our body. For any cell to work properly, the mitochondria need to be healthy. Unhealthy mitochondria can cause severe medical disorders known as mitochondrial disease, some of which are caused by genetic faults (mutations) in the mitochondria.

DNA in the nucleus of cells carries almost all our genes. It shapes our physical characteristics, including our appearance, and contributes to our personality (along with our upbringing and environment). We inherit these genes from both our parents. The nuclear DNA also carries many genes required for mitochondrial function.

Mitochondria have their own separate DNA, which carries just a few genes. All of these genes are involved in energy production but determine no other characteristics. And so, any faults in these genes lead only to problems in energy production.

There are many different medical disorders that can be described as mitochondrial disease. Many that arise from faults in mitochondrial genes have not been given names because the symptoms vary from patient to patient, depending on the nature of the fault and the proportion of abnormal versus normal mitochondria in each tissue. As such, they cannot be grouped together as a specific condition. The diseases range from mild to severe or life threatening, and can have devastating effects on the families that carry them. Around 1 in 6500 children is thought to be born with a serious mitochondrial disorder due to faults in mitochondrial DNA.

Unlike nuclear genes, mitochondrial DNA is inherited only from our mothers. Mothers can carry abnormal mitochondria and be at risk of passing on serious disease to their children, even if they themselves show only mild or no symptoms. It is for such women who by chance have a high proportion of faulty mitochondrial DNA in their eggs for which the methods of mitochondrial replacement or "donation" have been developed.

See a fuller explanation of mitochondrial disease at <http://mitochondria.hfea.gov.uk/mitochondria/what-is-mitochondrial-disease/>

What treatments and options are currently available?

Currently there is no known cure for mitochondrial disease and treatment options are limited. The options available to those who know they are at risk of having a child with a mitochondrial disease (usually those who already have an affected child or family member) are:

- Adoption
- IVF with donor eggs

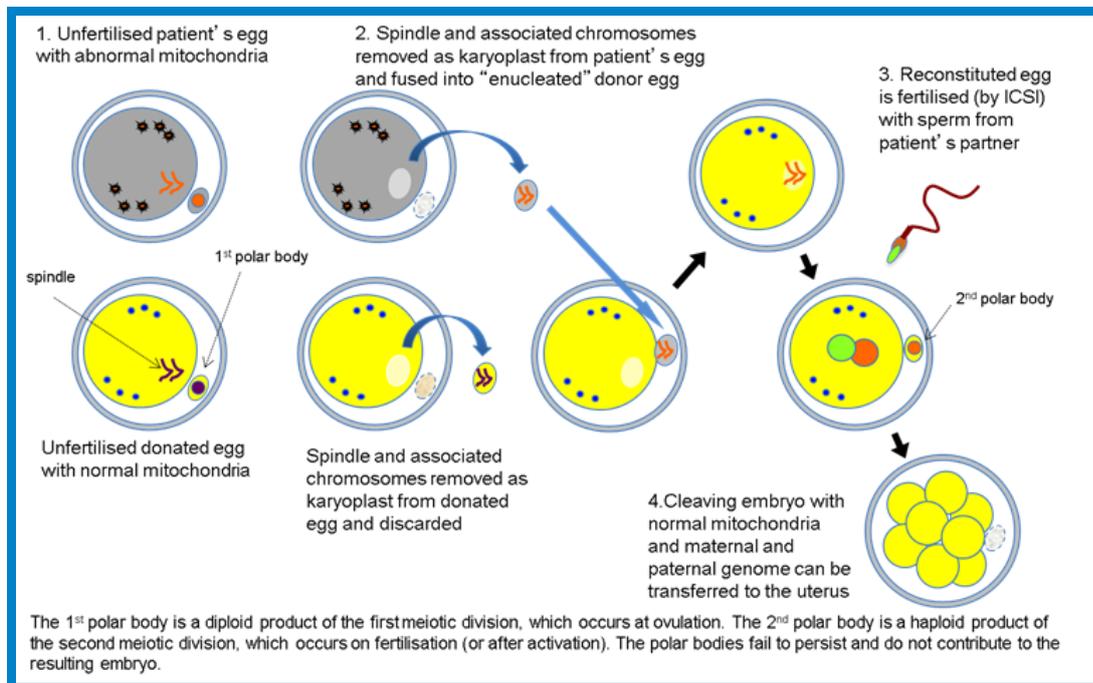
- Testing embryos during IVF: this may not result in a disease-free baby, but lowers the chance of passing on the disease. However it is not an option for some forms of mitochondrial disease
- Testing of the fetus during pregnancy (with the option of termination): the sample tested may not accurately predict the risk of disease.

For those at risk people who would like to have a genetically-related child without abnormal mitochondria, the only possible option would be mitochondrial donation.

What is mitochondrial donation?

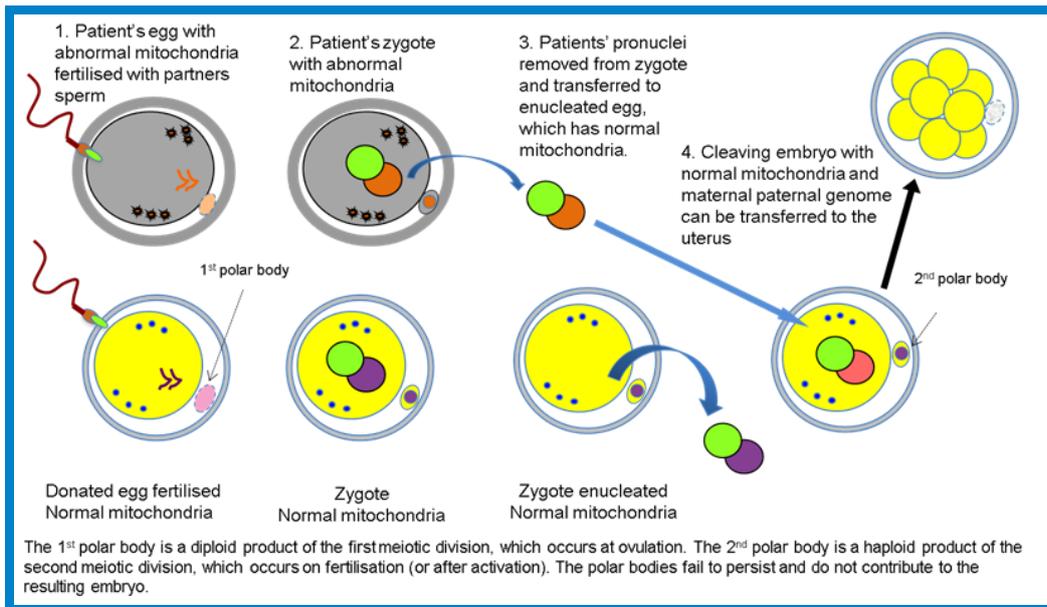
Researchers are developing medical techniques that could allow mothers to avoid passing on genetically inherited mitochondrial diseases to their children. The most developed techniques, maternal spindle transfer (MST) and pro-nuclear transfer (PNT), are based on an IVF cycle but have additional steps. Other techniques are being developed.

In both MST and PNT, nuclear DNA (the vast majority of genes in a cell, which make us who we are) is moved from a patient's egg or embryo containing unhealthy mitochondria to a donor's egg or embryo containing healthy mitochondria, from which the donor's nuclear DNA has been removed.



Maternal spindle transfer

Bredenoord, A and P. Braude (2010) "Ethics of mitochondrial gene replacement: from bench to bedside" BMJ 341. Image reproduced and amended with permission by author



Pronuclear transfer

Bredenoord, A and P. Braude (2010) "Ethics of mitochondrial gene replacement: from bench to bedside" BMJ 341. Image reproduced and amended with permission by author

See a fuller explanation, as well as a simple animation, of MST and PNT at <http://mitochondria.hfea.gov.uk/mitochondria/what-is-mitochondrial-disease/new-techniques-to-prevent-mitochondrial-disease/>

2 Public attitudes towards mitochondrial donation

At the request of Government, in 2012 the HFEA carried out a public dialogue exercise called 'Medical Frontiers: debating mitochondrial replacement'. We used a variety of methods - opinion polls, focus groups, online surveys and public meetings - to understand public attitudes to what is an ethically and scientifically complex subject. The whole dialogue process was overseen by an independent group to ensure that the material used and the questions asked were unbiased.

This extensive review found that there is general support for permitting mitochondrial donation in the UK, so long as it is safe enough to offer in a treatment setting and is done so within a regulatory framework. Despite the strong ethical concerns that some respondents to the consultation expressed, the overall ethical concerns were outweighed by the arguments in favour of permitting mitochondrial donation:

- A public representative survey, which involved face-to-face interviews of almost 1000 people, found that over half of the public are 'very' or 'fairly' positive about mitochondrial donation¹.
- Deliberative workshops found that randomly selected members of the public remain broadly in favour of the two new techniques during the process of finding out about them and the possible ethical and social issues. The principal reason given for this was because the techniques give parents the opportunity to have healthy children who are genetically their own.
- An open consultation questionnaire (involving just over 1,800 respondents) saw slightly more people opposing than supporting the techniques. However, the sample was self-selecting and like most consultations of this type can be subject to campaigns from supporters and opponents.

Those people who were opposed to mitochondrial donation often argued that its use would amount to inappropriate interference with the natural or spiritual aspect of reproduction, or that any artificial or in vitro manipulation of embryos is unethical.

Those in favour tended to focus on the benefits it could offer to parents and children, particularly the potential to allow parents the opportunity to have a healthy child. Such views were echoed strongly at one of the open consultation meetings and the patient focus group.

Patients stressed the importance of individual parents and families having the choice about whether or not to use these techniques, whilst also being aware that use of these techniques would be a medical first and there may be a degree of risk involved.

¹ Participants were asked for their initial reactions to different aspects of potential treatments for mitochondrial disease including: 'Scientists are developing techniques which could remove the chance of these mitochondrial diseases by altering the genetic make-up of an egg or embryo during IVF. What is your initial reaction to this?' Over half (56%) were 'very' or 'fairly' positive about this and 10% were 'very' or 'fairly' negative. One third (33%) of respondents were undecided ('neither positive nor negative' or 'unsure').

3 Scientific and safety issues

Besides commissioning the HFEA to assess public attitudes towards mitochondrial donation, the Government also asked the HFEA to provide advice on the safety and efficacy of PNT and MST. In order to thoroughly explore the scientific aspects of the treatments, the HFEA formed an expert scientific panel, made up of researchers and clinicians with broad expertise. The expert panel's three reports published over three years provide a solid evidence base for making policy in this area. The panel concluded that:

- There is no evidence to show that mitochondrial donation is unsafe
- Research is progressing well and the recommended further experiments are expected to confirm this view.

What research has been carried out?

The expert panel reviewed all of the significant evidence on mitochondrial donation. There have been many experiments conducted using MST and PNT in animals. PNT has been carried out since the mid-1980s in mice. MST has been carried out in a wide range of animals. More recently mice, monkeys (which have now reached adulthood and are healthy) and human embryos have been created with the specific aim of developing MST and PNT for avoiding mitochondrial disease.

The expert panel concluded that these studies have shown that the techniques are effective and that there are no worrying impacts on the resulting animals or embryos.

What are the concerns about mitochondrial donation?

The scientific evidence raises some potential concerns about mitochondrial donation. Just as we all have different blood groups, we also have different types of mitochondria, called haplotypes. Some scientists have suggested that if the patient and the mitochondria donor have different mitochondrial haplotypes, there is a theoretical risk that the donor's mitochondria won't be able to 'talk' properly to the patient's nuclear DNA, which could cause problems in the embryo and resulting child.

The expert panel carefully considered this issue and concluded that data submitted to the panel was not relevant enough to raise safety concerns². Even so, the expert panel recommended as a precautionary step that consideration be given to mitochondria haplotype matching in the process of selecting donors – even though the risks of not doing so will be very low.

Another potential concern is that a small amount of unhealthy mitochondrial DNA may be transferred into the donor's egg along with the mother's nuclear DNA. Studies carried out on MST and PNT show that some so-called mitochondrial 'carry-over' occurs. However, the expert panel noted that carry-over is lower than 2% of the mitochondria in the resulting embryo, an amount which is very unlikely to be problematic for the children born.

² The expert panel felt that the data submitted related to inbred mice and *Drosophila* in a way that did not materially contribute to an understanding of a predominantly outbred human race, and also noted that data obtained in large-scale human genome projects looking for disease associations have not found any consequences due to the exchange of mitochondrial DNA (mtDNA) haplotypes by reproduction.

What further research is needed?

Research can never answer every question before a new treatment is offered, nor can it be expected to guarantee safety or efficacy when applied for the first time in the clinic. This is particularly the case in new reproductive techniques, as research can only ever be done in animals or in human embryos which are not transferred to a woman.

However, the research carried out in this area – in macaque monkeys in the United States and in human embryo research in the UK and USA – has had reassuring results. The expert panel has concluded that it has seen no evidence to date to suggest that these new mitochondrial donation techniques are unsafe.

Although the expert panel has recommended that further experiments should take place before treatment is offered, the panel expect such research to support the conclusions it has reached so far. In its reports, the expert panel has described certain experiments as being 'critical' or 'essential'. In public discussion, there has been some misunderstanding of these terms. They are used interchangeably and are not intended to convey any technical or medical meaning. Instead they simply indicate which experiments are, in the panel's view, necessary to the consideration of the safety and efficacy of the technique.

The main area of research needed is to observe cells derived from embryos created by MST and PNT, to see how mitochondria behave. The expert panel understand that the relevant research teams are making good progress on these experiments.

The expert panel was not asked by the Government to advise on whether mitochondrial donation should be made lawful, nor on when a change in the law should be made. The further experiments that the panel has recommended could take place before or after the techniques are made lawful.

4 Regulating mitochondrial donation

When should mitochondrial donation be made available?

If Parliament approves Regulations to make mitochondrial donation lawful in treatment, that decision will not, in itself, directly lead to such treatments being offered in humans. Instead, mitochondrial donation would become part of the regulatory scheme set out in the Human Fertilisation and Embryology Act and administered by the HFEA.

How would the HFEA regulate it?

The HFEA would need to assess two things: that any clinic that wished to offer mitochondrial donation is competent to offer it and that each case of treatment is appropriate, using criteria set out in the Regulations. The decision would rest with an HFEA committee and would be based on the evidence submitted and the latest scientific advice. The committee would, in effect, carry out a further assessment at the time of the application of the safety and efficacy of the proposed technique. This would, therefore, provide an opportunity for an assessment of the results of the further experiments suggested by the expert panel.

There are likely to be few very applications to carry out mitochondrial donation. At present, only one research team in the UK is likely to be in a position to offer it to patients in the near future.

Further reading

'Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception' April 2011 http://www.hfea.gov.uk/docs/2011-04-18_Mitochondria_review_-_final_report.PDF

'Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: update' March 2013 http://www.hfea.gov.uk/docs/Mito-Annex_VIII-science_review_update.pdf

'Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: update, 2014' June 2014 http://www.hfea.gov.uk/docs/Third_Mitochondrial_replacement_scientific_review.pdf

Mitochondria replacement public dialogue: Findings and reports <http://www.hfea.gov.uk/6896.html>

Mitochondria replacement public dialogue website: <http://mitochondria.hfea.gov.uk/mitochondria/>