Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015

Briefing: The Science of Mitochondrial Donation

Prepared by the **Progress Educational Trust** and the **British Fertility Society**
29 January 2015

The **Progress Educational Trust** (**PET**) and the **British Fertility Society** (**BFS**) urge you to vote in favour of the **Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015**.

- **Who has prepared this briefing?**

The **Progress Educational Trust** (**PET**) is a registered charity whose Patron is **Baroness Mary Warnock**. **PET** was founded in 1992, as an independent voice informing debate on assisted conception and genetics.

PET has no financial stake in research or clinical practice. The ultimate beneficiaries of all the charity's work are families and individuals threatened by infertility and genetic disease, including people wanting an opportunity to give birth to healthy children.

PET first reported on mitochondrial donation as a hypothetical possibility in its flagship publication **BioNews** in 1999.[1] As research has progressed in recent years, with mitochondrial donation moving from theory to reality, PET has continued to monitor closely the relevant scientific and ethical issues.

The **British Fertility Society** (**BFS**) is a national multidisciplinary organisation representing professionals practising in the field of reproductive medicine. BFS is committed to promoting good clinical practice and working with patients to provide safe and effective fertility treatment.

Below are answers from PET and BFS to some questions that you may have about the science of mitochondrial donation, and that may arise in Parliamentary debate. Detailed references are provided in the '**Endnotes**' at the end of this briefing.

PET and BFS have also issued an accompanying briefing on '**The Ethics of Mitochondrial Donation**'.

- **What is mitochondrial disease?**

Mitochondrial disease is disease caused by faulty mitochondria – tiny, energy-generating structures in our cells which we inherit from our mother, and which are essential for each of our cells to work. When mitochondria are faulty, the effects can be devastating. Organs that need high energy levels to function – such as the brain, heart, kidneys, muscles and liver – are particularly badly affected.

Mitochondrial disease is inevitably progressive, and can be very debilitating. It can cause miscarriage, stillbirth, infant death or serious symptoms in later life – seizures, strokes, blindness, deafness, heart failure and liver failure are all common. Most of those affected will not survive to adulthood.

Mitochondria contain a small portion of their own DNA, which is separate from the nuclear DNA in the nucleus of our cells. Some types of mitochondrial disease are caused by mutations in mitochondrial DNA. Women who carry such mutations have had no reliable means of conceiving a healthy child, free of devastating mitochondrial disease – until now.[2]

- **What is mitochondrial donation?**

Mitochondrial donation is a type of IVF that involves conceiving a child using biological material from three people – the child's *parents*, plus a mitochondrial *donor*.

The Regulations permit the use of two specific mitochondrial donation techniques – **maternal spindle transfer** and **pronucelar transfer.** These techniques involve moving nuclear DNA from a mother's egg or embryo (which has faulty mitochondria) to a donor egg or embryo (which has healthy mitochondria, but whose nuclear DNA has been previously removed).

The main difference between the two techniques is that in maternal spindle transfer DNA is moved *before* the mother's egg has been fertilised (when the DNA is attached to a structure called the spindle), whereas in pronucelar transfer DNA is moved *after* the mother's egg has been fertilised and has become a single-cell embryo (when the DNA is contained in two structures called pronuclei – one from the mother, and the other from the father's sperm).[3]

- **Will children conceived via mitochondrial donation still inherit some faulty mitochondria?**

When nuclear DNA is moved from a mother's egg or embryo to a donor egg or embryo during mitochondrial donation, it is likely that a small quantity of the surrounding mitochondria (the mother's faulty mitochondria) will also be carried over.

Evidence suggests that this carryover will *not* lead to mitochondrial disease in children conceived via mitochondrial donation, or in any subsequent generations. This is because the quantity of faulty mitochondria carried over is small, estimated to account for no more than 5% of the mitochondria in the embryo that will ultimately be created. The remaining 95% or more of the embryo's mitochondria will be healthy mitochondria from the donor.

Mitochondrial disease appears in a person only if the proportion of faulty mitochondria in their cells reaches a certain threshold, which is typically around 60%. The small proportion of faulty mitochondria that might be carried over will fall far beneath this threshold.[4]

A theory has been proposed that faulty mitochondria carried over could become amplified, so that the proportion of faulty mitochondria in certain tissues of the body increases significantly. There is evidence that this can happen by chance in some tissues, but this is extremely unlikely to reach levels that would lead to disease when beginning with less than 5% faulty mitochondria. Indeed, data suggests that following mitochondrial donation, any faulty mitochondria carried over are so few in number as to become undetectable.[5]

Doctors and researchers are aware of the hypothetical risks, and will continue to monitor the situation after mitochondrial donation has been offered.

- **Could mitochondrial donation disrupt the relationship between a cell's mitochondria and its nucleus?**

There is no reliable evidence that mitochondrial donation will disrupt the relationship between a cell's mitochondria and its nucleus.

Mitochondrial DNA and nuclear DNA are jointly involved in certain processes within a cell, but these different types of DNA do not interact directly. Any interactions between the different DNA molecules are mediated via gene products (RNA molecules or protein molecules which are created from the information contained in DNA).

It is known that nuclear gene products can and do leave the nucleus and have an effect on mitochondrial DNA. However, the reverse is not true – there is no evidence of mitochondrial gene products leaving the mitochondria and having an effect on nuclear DNA.[6]

The relationship between the nucleus and the mitochondria is therefore one-sided. This makes it highly unlikely that donated mitochondria could relate to the nucleus in a dysfunctional way.

What of the converse – could the nucleus relate to donated mitochondria in a dysfunctional way? Again, this is highly unlikely.

It is worth remembering that every human being inherits half of their nuclear DNA from their father. In most if not all societies, matching paternal DNA with with mitochondrial DNA in a predetermined way is not a consideration. And yet there is no evidence to suggest that the resulting random juxtapositions of nuclear and mitochondrial DNA have any adverse effect.

- **Could mitochondrial donation cause problems due to the way mitochondrial DNA and nuclear DNA have evolved together?**

  Mitochondrial DNA and nuclear DNA are distinct, and evolve differently. There are various theories regarding the way that mitochondrial DNA and nuclear DNA may have co-evolved (that is, reciprocally affected one another's evolution).

  Some have argued that mitochondrial donation could disrupt relationships that have developed between mitochondrial and nuclear DNA via co-evolution, and that this could have adverse consequences. There is little evidence for this view.[7]

  There have been experiments on animals where co-evolved relationships between mitochondrial and nuclear DNA were deliberately disrupted. However, this has only been shown to have a mildly adverse effect in two situations, and neither of these situations is applicable to mitochondrial donation in humans.

  One situation where adverse effects have been shown involves nuclear material being transferred between different species. This is not applicable to mitochondrial donation in humans, which will involve only human DNA.

  The other situation where adverse effects have been shown involves nuclear material being transferred between different populations of the same species, but only *after* those populations have been inbred for many generations *and* have been kept separate from one another. In other words, this is a scenario where extreme genetic sameness is created, only to be suddenly disrupted with extreme genetic difference. Again, this scenario is not applicable to humans.

  Nonetheless, the most recent expert scientific review of mitochondrial donation convened by the Human Fertilisation and Embryology Authority (HFEA) has recommended a precautionary step. When mitochondrial donors are selected, it is suggested that consideration be given to matching the type of mitochondria carried by the donor with the type of mitochondria carried by the mother (although there will still be the crucial difference that the mother's mitochondria will be faulty, whereas the donor's will be healthy).[8]

Doctors and researchers will continue to keep a watching brief on any emerging evidence in this area, but hypotheses about evolution do not justify a prohibition on mitochondrial donation. Mitochondrial donation is a means of avoiding the transmission of diseases whose symptoms are, unfortunately, far from hypothetical.

- **Could mitochondrial donation cause problems with epigenetics?**

  Epigenetics refers to enduring changes in the way genes are expressed that do not involve any changes to the gene sequence.

  Some have argued that mitochondrial donation could cause problems with epigenetics. There is no evidence to support this argument. Children with faulty mitochondria do not have diseases connected with epigenetics, and there is no reason to think that such problems will start occurring with mitochondria that are healthy and happen to be inherited from a donor.[9]

  Fears about epigenetics sometimes arise when mitochondrial donation is confused with cloning. When animals are cloned, nuclear material is typically transferred from a cell at one stage of the reproductive/developmental process to a cell at a very different stage of the reproductive/developmental process. This leads to epigenetic reprogramming of the cell, which may give rise to problems later in the animal's life.

  But mitochondrial donation is a very different process from cloning – it involves nuclear material being transferred between cells at the same stage of the reproductive/developmental process. There is therefore no epigenetic reprogramming, and none of the risk that accompanies such reprogramming.[10]

- **Do further mitochondrial donation experiments need to be carried out in animals?**

  The scientific reviews of mitochondrial donation convened by the HFEA in 2011, 2013 and 2014 recommended that various experiments be performed on animals, to help ensure that mitochondrial donation is safe and efficient (to the extent that this can be known prior to the use of mitochondrial donation in humans).

  The 2011 scientific review listed *pronuclear transfer in non-human primates* as a 'critical' recommended experiment.[11] The 2013 scientific review revised this position, stating that pronuclear transfer in non-human primates was 'no longer considered a critical experiment'. Some have cited this change of view, between 2011 and 2013, as evidence that criteria necessary to ensure the safety and efficacy of mitochondrial donation are not being met.

  This is inaccurate. The review panel changed its position based on scientific evidence that emerged between 2011 and 2013, and explained its reasoning clearly and transparently in its 2013 review.[12]

  Animal models in scientific research are by their nature imperfect – there are many differences between the early embryology of humans and that of other species. After pronuclear transfer was performed successfully in human embryos, attempts to perform the same technique in macaque monkeys failed.

  The scientific review panel concluded from this and other evidence that macaques were not sufficiently similar to humans to form the basis of the experiment that was originally recommended. This does not mean that the scientific review panel lowered its standards. Indeed, the panel recommended an *additional* 'critical' experiment in the 2013 review, that was not recommended in the 2011 review.[13]

All of the panel's recommendations to date have been based on expert assessment of the latest evidence from a dynamic field of research. After three expert scientific reviews, all of which have concluded that there is no reason to think mitochondrial donation is unsafe, now is the right time for Parliament to pass these Regulations and permit the use mitochondrial donation in treatment.

- **Has mitochondrial donation in humans already taken place in another country?**

  No, mitochondrial donation has never been carried out in humans.

  The only procedures ever carried out in humans which bear some superficial similarity to mitochondrial donation are a handful of experimental fertility treatments, performed more than a decade ago. These treatments were very different from mitochondrial donation – which is perhaps not surprising, since their aim was to treat infertility and not to avoid mitochondrial disease.

  In the late 1990s, 17 children were conceived in the USA using an experimental fertility treatment which meant that these children were likely to inherit some mitochondria from a donor. The treatment involved cytoplasmic transfer, where some cytoplasm (the material in a cell that contains the mitochondria) was taken from a donor egg and added to a fertility patient's egg. The patient's egg was then fertilised.[14]

  Unlike mitochondrial donation, there was no desire or attempt to *replace* the mother's mitochondria with the mitochondria of a donor. Instead, a donor's mitochondria was *mixed* with the mother's mitochondria. Follow-up studies of the health of the 17 children conceived in this way have only recently begun, but results from these studies will be of limited relevance to mitochondrial donation.[15]

  Another experimental fertility treatment involving donor cytoplasm, which will have included mitochondria, was carried out by an American clinician on a single patient in China in 2003. The patient became pregnant with triplets, one of whom was aborted and two of whom were born prematurely and died. The clinician in question attributed this outcome entirely to multiple pregnancy and to obstetric complications, rather than to the method of conception.[16]

- **Has mitochondrial donation been ruled unsafe in the USA?**

  No, mitochondrial donation has not been ruled unsafe in the USA.

  In 2014, a committee of the US Food and Drug Administration organised a hearing to consider potential clinical trials of mitochondrial donation in humans, and also to consider experimental fertility treatments that might result in children inheriting mitochondria from a donor. (The latter is not being considered in the UK, and is not permitted by the Regulations.)

  The committee was asked to assess benefits and risks, and to make recommendations regarding the design of clinical trials. A variety of evidence and opinion was heard, some of which emphasised benefit and some of which emphasised risk.[17] The committee then asked the US Institute of Medicine to produce a consensus report on relevant ethical and social policy issues. The committee has as yet made no recommendations, and work on the report is still ongoing.[18]

  At its hearing, the committee considered this area for a day-and-a-half. This is cursory, when compared with the four years of rolling scientific assessment of the safety and efficacy of mitochondrial donation that has taken place in the UK – assessment that has taken full account of the US committee's deliberations.[19]

  Moreover, the US authorities are already in a position to consider whether or not to permit a clinical trial. This is equivalent to the position in which the HFEA will find itself, *if* these Regulations are

passed. Far from having ruled mitochondrial donation unsafe, the US authorities are in fact arguably ahead of Parliament in this respect.[20]

It is therefore all the more important that these regulations be passed, in order to give families affected by devastating mitochondrial diseases the chance to benefit from mitochondrial donation.

- **Further information**

For further information on scientific questions, see our accompanying briefing on '**The Ethics of Mitochondrial Donation**'.

For concise overviews of some of the issues surrounding mitochondrial donation, see:

- The Lily Foundation's factsheet at http://bit.ly/lilymito
- The Wellcome Trust's factsheet at http://bit.ly/wellcomemito

- **Endnotes**

1. See 'Dolly not a perfect clone', *BioNews*, 1999 – http://www.bionews.org.uk/page_10488.asp

2. See 'Mitochondrial DNA disease – molecular insights and potential routes to a cure', Russell O, Turnbull D (2014), *Experimental Cell Research*, 325(1), p 38-43 – http://dx.doi.org/10.1016/j.yexcr.2014.03.012

3. The two methods are explained with diagrams on p14-17 of the *Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception* – http://www.hfea.gov.uk/docs/Third_Mitochondrial_replacement_scientific_review.pdf

4. See p24-27 of the *Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception* – http://www.hfea.gov.uk/docs/Third_Mitochondrial_replacement_scientific_review.pdf

5. The amplification theory was originally explored by Eric Shoubridge and colleagues in the following papers:

   - 'Random genetic drift in the female germline explains the rapid segregation of mammalian mitochondrial DNA', Jenuth JP, Peterson AC, Fu K, Shoubridge EA (1996), *Nature Genetics* 14(2), p146-151 – http://dx.doi.org/10.1038/ng1096-146
   - 'Tissue-specific selection for different mtDNA genotypes in heteroplasmic mice', Jenuth JP, Peterson AC, Shoubridge EA (1997), *Nature Genetics* 16(1), p93-95 – http://dx.doi.org/10.1038/ng0597-93
   - 'Selection of a mtDNA sequence variant in hepatocytes of heteroplasmic mice is not due to differences in respiratory chain function or efficiency of replication', Battersby BJ, Shoubridge EA (2001), *Human Molecular Genetics*, 10(22), p2469-2479 – http://dx.doi.org/10.1093/hmg/10.22.2469
   - 'Nuclear genetic control of mitochondrial DNA segregation', Battersby BJ, Loredo-Osti JC, Shoubridge EA (2003), *Nature Genetics* 33(2), p183-186 – http://dx.doi.org/10.1038/ng1073

   The theory has been explored more recently in the following papers:

- 'MtDNA segregation in heteroplasmic tissues is common *in vivo* and modulated by haplotype differences and developmental stage', Burgstaller JP *et al* (2014), *Cell Reports*, 7(6), p2031-2041 – http://dx.doi.org/10.1016/j.celrep.2014.05.020

- 'Mitochondrial DNA disease and developmental implications for reproductive strategies', Burgstaller JP, Johnston IG, Poulton J (2015), Molecular Human Reproduction, 21(1), p11-22 – http://dx.doi.org/10.1093/molehr/gau090

Authors of these last two papers submitted both written and oral evidence to the *Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception* in 2014.

All of this evidence is assessed on p29-33 of the *Third Scientific Review* – http://www.hfea.gov.uk/docs/Third_Mitochondrial_replacement_scientific_review.pdf

6. Of course, the cell senses the activity of mitochondria, so that it can regulate mitochondrial DNA replication and gene expression to increase or decrease the amount of energy produced.

   But this relies on detection of the products of oxidative phosphorylation (adenosine triphosphate and reactive oxygen species) due to the combined action of nuclear and mitochondrial gene products.

7. The argument is made in the following paper:

   - 'Mitochondrial replacement, evolution, and the clinic', Reinhardt K, Dowling DK, Morrow EH (2013), *Science*, 341(6152), p1345-1346 – http://dx.doi.org/10.1126/science.1237146

   An opposing argument is made in the following paper:

   - 'The challenges of mitochondrial replacement', Chinnery PF *et al* (2014), *PLoS Genetics*, 10(4) – http://dx.doi.org/10.1371/journal.pgen.1004315

   Authors of both papers submitted both written and oral evidence to the *Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception* in 2014.

   All of this evidence is assessed on p30-33 of the *Third Scientific Review* – http://www.hfea.gov.uk/docs/Third_Mitochondrial_replacement_scientific_review.pdf

8. The relevant research is discussed in the following papers:

   - 'Variation in mitochondrial genotype has substantial lifespan effects which may be modulated by nuclear background', Clancy DJ (2008), *Ageing Cell*, 7(6), p795-804 – http://dx.doi.org/10.1111/j.1474-9726.2008.00428.x

   - 'Experimental evidence supports a sex-specific selective sieve in mitochondrial genome evolution', Innocenti P, Morrow EH, Dowling DK (2011), *Science*, 332(6031), p845-848 – http://dx.doi.org/10.1126/science.1201157

   The research is assessed, and the precautionary recommendation made, on p31-33 of the *Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception* – http://www.hfea.gov.uk/docs/Third_Mitochondrial_replacement_scientific_review.pdf

9. Three-year follow-up studies of nonhuman primates conceived via maternal spindle transfer have found no evidence of adverse epigenetic effects. See:

   - 'Towards germline gene therapy of inherited mitochondrial diseases', Tachibana M *et al* (2013), *Nature*, 493(7434), p627-631 – http://dx.doi.org/10.1038/nature11647

10. See p17 of the *Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception* – http://www.hfea.gov.uk/docs/Third_Mitochondrial_replacement_scientific_review.pdf

11. See p21 of the *First Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception* – http://www.hfea.gov.uk/docs/2011-04-18_Mitochondria_review_-_final_report.PDF

12. See p20-21 of the *Second Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception* – http://www.hfea.gov.uk/docs/Mito-Annex_VIII-science_review_update.pdf

13. The additional critical experiment recommended in the 2013 review addressed concerns about carryover of mutant mitochondria.

    See p20-21 of the *Second Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception* – http://www.hfea.gov.uk/docs/Mito-Annex_VIII-science_review_update.pdf

14. The treatment and its implications are discussed in:

    - 'Mitochondria in human offspring derived from ooplasmic transplantation', Barritt JA, Brenner CA, Malter HE, Cohen J (2001), *Human Reproduction*, 16(3), p513-516 – http://dx.doi.org/10.1093/humrep/16.3.513

15. The follow-up research is being led by Serena Chen at the USA's St Barnabas Medical Centre as reported in 'An unplanned experiment' (adjunct to the article 'Reproductive medicine: the power of three'), *Nature*, 2014 – http://dx.doi.org/10.1038/509414a

16. The American clinician in question was Dr Jamie Grifo.

    He and his colleagues discussed the case in their presentation 'Pregnancy derived from human nuclear transfer', at the 59th annual meeting of the American Society for Reproductive Medicine on 14 October 2003.

17. See the transcripts of the 59th Meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee of the Food and Drug Administration.

    - Transcript of proceedings on 25 February 2014: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM390945.pdf

    - Transcript of proceedings on 26 February 2014: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM390947.pdf

18. The first meeting (of an anticipated five) organised by the Institute of Medicine to work on this report took place on 27 January 2015.

    See http://www.iom.edu/Activities/Research/MitoEthics.aspx for further details.

19. See p10-11 of the *Third Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception* – http://www.hfea.gov.uk/docs/Third_Mitochondrial_replacement_scientific_review.pdf

20. This point is discussed by two members of the HFEA's scientific review panel (Professors Peter Braude and Robin Lovell-Badge) in 'Response to open letter on mitochondrial transfer', *BioNews*, 2014 – http://www.bionews.org.uk/page_472827.asp