Preventing Mitochondrial Disease

Mitochondria convert biological fuels like sugars and fats into the energy a cell needs. Women with a disease caused by faulty mitochondria pass their condition on to their children. Researchers are developing treatments to prevent this by using healthy mitochondria from a female donor. This note describes these treatments and looks at the issues raised by their potential use in IVF.

Background
In March 2013, the fertility regulator (HFEA) will publish the findings of a public consultation on the social and ethical implications of mitochondrial replacement. These are treatments that allow women with mitochondrial disease to give birth to healthy children. They are controversial because they involve altering the embryo’s complement of DNA, with the changes made being passed on to future generations. The public consultation was the latest step in evaluating the scientific, social and ethical aspects of these treatments for clinical use:

- in 2011, HFEA published advice on the safety and effectiveness of these techniques concluding that there was no evidence to suggest that they were unsafe but recommending further research.
- in 2012, the Wellcome Trust announced funding for Newcastle University to conduct some of this research.
- in 2012, the Nuffield Council on Bioethics (NCB) concluded that if the treatments were shown to be acceptably safe and effective, it would be ethical for families to use them.

The Human Fertilisation and Embryology Act 1990 (as amended) prohibits the implantation into a woman of eggs or embryos that have had their DNA altered. However, the Act makes provision for regulations, subject to parliamentary consent, to permit this for a single specific purpose: “to prevent the transmission of serious mitochondrial disease”.

Overview
- New treatments are being developed to allow mothers with serious mitochondrial disease to give birth to healthy children.
- These replace the mother’s mitochondria with those of an egg donor, and thus alter the embryo’s complement of DNA.
- Any changes made by such treatments would be passed on to successive generations.
- The law currently prohibits implantation of embryos with altered DNA into a woman. Parliament can consent to this prohibition being waived for a single specific purpose: preventing serious mitochondrial disease.
- Further research is underway to assess the safety and efficiency of such treatments.

This briefing looks at:
- mitochondria and mitochondrial disease
- current options for minimising the risk of children inheriting mitochondrial disease from their mother
- new treatments to prevent such conditions being inherited
- issues raised by these treatments.

Mitochondria and disease

Mitochondria
All cells need energy to function. This energy is provided by structures called mitochondria found in the fluid that surrounds the cell nucleus. Cells can contain many mitochondria, each harbouring small sequences of mitochondrial (mt) DNA. mtDNA contains 37 genes, each of which is involved solely in maintaining mitochondrial function. Over 99% of a cell’s DNA is found inside the nucleus. This nuclear (n) DNA contains more than 20,000 genes, at least 1,100 of which have active roles in mitochondria. Mutations in mtDNA or nDNA can cause mitochondrial disease. While nDNA is inherited from both parents, mtDNA is inherited solely from the mother. This means that any mutations in a mother’s mtDNA will be inherited by her children. It is these types of mutations and their inheritance that are the focus of this note.

The number of mitochondria in cells varies. Primordial germ cells (the cells that develop into eggs and sperm) may have as few as ten mitochondria per cell, whereas adult cells...
Mitochondrial disease

Mitochondrial diseases vary widely in severity, from being life-threatening to having few or no obvious symptoms. They tend to affect parts of the body that use a lot of energy such as the brain, muscle, nerves, liver, kidney and heart. Symptoms vary widely but can include poor growth, muscle weakness, tiredness, poor co-ordination, and sensory, respiratory or cognitive problems. There are no effective treatments available for serious mitochondrial disease.

It is estimated that at least 3,500 women in the UK carry potentially problematic mtDNA mutations. The severity of their conditions not only varies from one individual to another, but also within an individual, from one tissue to another and/or over time. The mitochondria an embryo inherits from its mother may contain a mix of normal and abnormal mtDNA; the greater the proportion of abnormal mtDNA the more severe the disease. The relatively low number of mitochondria in the early embryo (the bottleneck described above) increases the chance of some cells having all, or mostly all, abnormal mtDNA. If such cells go on to develop into important organs or tissue then the resulting child could have a severe (and potentially fatal) disease.

Current options

Women with no noticeable symptoms and no family history of disease can produce eggs with a high load of abnormal mtDNA and vice-versa. Those who know they have a disease caused by mutations in mtDNA can choose to have a baby using donated eggs or opt for adoption. One option that might allow them to be the biological mothers of healthy children is pre-implantation genetic diagnosis (PGD). PGD involves testing embryos to select those with the lowest proportion of abnormal mtDNA for implantation. It can reduce, but not eliminate, the risk of a mother having a baby that is severely affected by mitochondrial disease. However, PGD is not applicable to all women with mtDNA mutations; it can only be used where the exact mutation the mother carries is known. Furthermore, PGD is unlikely to help women with high levels of abnormal mtDNA, and cannot help the small proportion of women with 100% abnormal mtDNA, to conceive a healthy child.

Mitochondria replacement treatments

There are several possible methods for replacing faulty mitochondria. All involve transferring ‘packets’ of the mother’s nDNA to a (donor) cell containing healthy mitochondria. This section describes the two most developed methods, maternal spindle transfer (MST, see Figure 1) and pro-nuclear transfer (PNT, see Figure 2).

Maternal spindle transfer (MST)

The maternal spindle is a structure found in the nucleus of an egg prior to fertilisation. It consists of the chromosomes that carry the mother’s nDNA. In MST (Figure 1), the maternal spindle is removed from the intended mother’s egg and transferred into an egg from a donor that has had its maternal spindle removed. The reconstituted egg would then be fertilised by the intended father’s sperm and the newly formed embryo implanted into the intended mother.

Pronuclear transfer (PNT)

During fertilisation, the sperm’s nucleus enters the egg creating an early embryo containing two pronuclei: one from the egg containing the mother’s nDNA and one from the sperm containing the father’s nDNA. These eventually fuse to form a single nucleus. In PNT (Figure 2) an egg from the intended mother and an egg from a donor are both fertilised. The pronuclei from the donor embryo are removed and replaced with the pronuclei from the intended parent’s embryo. The reconstituted embryo now contains nDNA from both the intended parents and mtDNA from the egg donor.

Key issues

Safety

PNT was developed in the 1980s and has been used to produce many generations of normal mice. Researchers at Newcastle University have used pronuclei from fertilised...
human embryos unsuitable for use in IVF in PNT to create healthy embryos that develop normally.\(^5\) MST is a more recent technique that has been used in a range of animals. For instance it has been used to produce rhesus macaques that developed normally\(^6\) and human eggs (see below).

**The 2011 HFEA expert panel scientific review**

HFEA’s review considered three main safety concerns.

- Whether mutated mtDNA is carried over when the maternal spindle or pro-nuclei are transferred. The panel noted that mutated mtDNA is often undetectable in embryos made using such techniques and that even when detected, it is at too low a level to cause disease.
- Concerns over some of the reagents and procedures used for the transfer and introduction of nDNA into the donor cell. However, the panel considered that there was enough evidence that the techniques could be used safely if appropriate precautions were taken.
- Mitochondria from different people can be classified into different groups according to similarities or differences in their DNA sequence. Concerns have been raised that donor mitochondria of a different group from those of the mother might not interact correctly with the mother’s nDNA, but the expert panel found no evidence for this.

The expert panel concluded that there was no evidence to show that either technique was unsafe, or to favour one over the other. It recommended further research before the methods can be assessed as safe for clinical use:

- MST using human eggs that are then fertilised
- PNT using normally fertilised human embryos
- PNT in non-human primates.

**Progress of the research**

Since the HFEA review, researchers in Oregon have used MST to create 65 reconstituted human eggs, 14 of which developed normally.\(^7\) Extra studies of MST and PNT in human cells are also being conducted by the Newcastle research team. The HFEA expert panel is updating its scientific review and will report its findings in March. The HFEA panel will decide whether further studies of PNT in primates will be necessary.

**Access to treatments**

Parliament will decide in principle whether to allow MST and/or PNT to be used to prevent serious mitochondrial disease. But if Parliament does approve the use of such treatments, it will be for the regulator, clinicians and patients to decide when to use them in individual cases. This section looks at how this might work in practice.

**Moving to clinical use**

The Nuffield Council on Bioethics (NCB) recommended that MST and PNT should initially be offered as part of a research trial in centres specialising in mitochondrial disease. It also noted that parental consent to follow up should be mandatory for participation in the trial and that such follow up should be very long-term, following families over generations. However, this may be difficult to achieve in practice.

**Seriousness**

The current law permits regulations to be made only for the prevention of serious mitochondrial disease. It is not possible to predict the severity of the outcome in a child solely from the mother’s condition. However the vast majority of women seeking such treatments will have affected children or relatives. An experienced mitochondrial clinician can combine this family history with other information to give potential parents an estimate of the risks of having a child with serious disease. The HFEA consultation noted that this should be done on a case-by-case basis. It sought opinions on whether such decisions should be made by the regulator, left to clinicians and patients or a combination of both, with the regulator deciding which diseases were serious enough to warrant use of the treatments and clinicians and patients making decisions for just these diseases.

**The likely number of treatments**

There are three centres in England (London, Oxford and Newcastle) that might offer such treatments if Parliament approves them. Between them they counsel 100-150 families a year on the options open to them. Not all of these families would be offered the new treatments; clinicians estimate that the number of treatments performed each year would be in the tens rather than hundreds.

**The role of the regulator**

Regulation of mitochondria replacement requires expertise in embryo research and assisted reproduction. HFEA has considerable expertise in both areas and already regulates comparable techniques such as PGD. The Government has commissioned a review which, among other things, will look at the scope for a merger of HFEA and the human tissue regulator. Previous attempts to merge HFEA with other regulators have raised concerns about loss of expertise.\(^8\) This raises the question of whether any new body would retain sufficient expertise to regulate this area.

**Affect on future generations**

The mtDNA and nDNA found in an egg constitute the germ line that is passed on via the mother to future generations. Changes made to mtDNA will be inherited by children born as a result of mitochondria replacement and passed on to successive generations of children born to daughters resulting from such treatments. While the aim is to prevent serious disease, any adverse effects associated with the treatments would also affect future generations. This means that any changes made to DNA by using such treatments are essentially irreversible. Ensuring that the treatments produced only boys in the first instance would limit any risk to a single generation, because fathers do not pass mtDNA on to their children. However the reconstituted embryos may not be robust enough to withstand the main method used for sex selection (PGD).

**Changing the germ line**

Over the years a consensus has emerged that no changes should be made to the DNA of the human germ line. This consensus emerged in the context of techniques designed
to alter a cell’s nDNA, such as genetic modification and gene therapy. It has meant that the use of such techniques has been confined to modifying mature cells; no-one has sought to use them to modify the nDNA of human eggs, sperm or embryos to create ‘designer babies’. There is widespread agreement that this should continue to be the case. However, there is debate about whether allowing the replacement of mtDNA would breach the consensus as mtDNA did not feature in the debate leading up to it. Pro-life groups and some academics claim that allowing replacement of mtDNA would lead to:
- the use of similar techniques for other purposes and/or
- pressure to allow changes to be made to germ line nDNA.

**Use of similar techniques for other purposes**

Pro-life groups claim that allowing mtDNA replacement to prevent mitochondrial disease would pave the way to nuclear transfer being used for a host of other purposes. However, prevention of serious mitochondrial disease is the only purpose for which the current law might allow an embryo with altered DNA to be implanted into a woman. Allowing an embryo with alterations to its DNA to be implanted for any other purpose would require the primary legislation to be re-written, a major undertaking.

**Allowing changes to nDNA**

Pro-life groups and some academics suggest that allowing changes to one component of the germ line (mtDNA) will make it more difficult to continue to oppose changes to the other (nDNA). They suggest that the current position - no alteration to the DNA of an embryo, sperm or egg - is easy to defend, and see it as a clear line in the sand for which there is a strong justification. Further, they point out that parliament could approve a regulation allowing changes to nDNA for the purpose of avoiding serious mitochondrial disease under the current law.

In practice however allowing mtDNA replacement may have little effect on the consensus not to alter germ line nDNA. First, NCB noted that there is a “distinct material boundary” between mtDNA and nDNA that allows a “clear legal distinction” to be made that would form a “practical barrier” to any proposals to change germ line nDNA. Second, the changes made to mtDNA in MST or PNT involve swapping one person’s mtDNA for another’s. This is in contrast to techniques for modifying nDNA which involve snipping gene sequences from one cell and splicing them into another. The process can disrupt genes at the site of insertion into nDNA with unforeseen consequences. Any such proposal would likely be rejected on safety grounds by the regulator before it reached Parliament. Finally, some researchers point to differences in the respective roles of mtDNA and nDNA as justification for regulating them differently. mtDNA is thought to perform only a very limited - albeit vital - set of functions in the human body, in contrast to nDNA, which contributes more widely to our identity and predetermined characteristics.

**Egg donors**

**Status of the egg donor**

Any embryo created by MST or PNT will contain DNA from three people. Under UK law the mother is the woman who carried and gave birth to the child and the father is the man who provided the sperm. So what is the status of the woman who donated the egg containing the healthy mitochondria? Mitochondria donors could be considered as having the same status as women donating eggs or embryos for conventional IVF programmes. If so, they would be compensated up to £750 for each donating cycle and the resulting child (on reaching the age of 18) would be able to apply for identifying information about their donor. Alternatively, donors could be accorded the same status as people who donate blood, bone marrow or other tissue. In this case, the donor would not be compensated and the donation would be anonymous.

In practice, mitochondria donation falls somewhere between the two. NCB noted that mitochondria donors have to undergo the same invasive procedures as egg and embryo donors to make their donation and should thus receive the same compensation and be subject to the same safeguards. But it saw no reason why they should be identifiable to the adults born as a result of their donation(s). However, others might argue that a mitochondria-donor conceived child has a legitimate interest in knowing about all of the people who contributed to his or her genetic make-up.

**Demand for egg donors**

Any increase in research or treatments involving MST or PNT would increase the demand for egg donors at a time when donors for reproductive purposes are in short supply. It is not clear whether women would be more or less likely to donate their eggs for mitochondria research/treatment than for reproductive purposes. This may depend on whether mitochondria donors are allowed to donate anonymously: the removal of anonymity from egg and sperm donation in 2005 is widely cited as being a contributory factor to the current shortage of donors for reproductive purposes.

**Identity of the child**

The NCB report and HFEA consultation both identified the effect the treatments might have on the resulting children’s sense of themselves as an issue. NCB concluded that the presence or absence of serious mitochondrial disease could significantly affect multiple aspects of identity but that none of these were unique to the treatments in question.

**Endnotes**

1. Scientific review of the safety & efficacy of methods to avoid mitochondrial disease through assisted conception, HFEA 2011
2. www.wellcome.ac.uk/News/Media-office/Press-releases/2012/WTVM054145.htm
8. See Joint Committee on the Human Tissue & Embryos (Draft) Bill, Vol 1, HL Paper 169-IHC Paper 630-I, 2007; and Consultation on proposals to transfer functions from the HFEA & HTA, Responses, DH, 2013