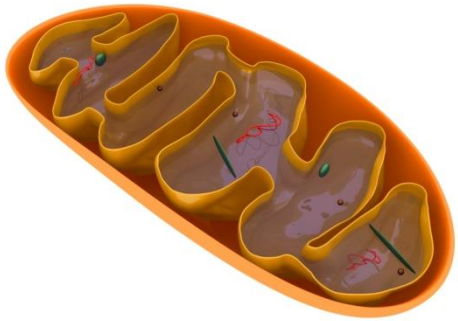
HOUSES OF PARLIAMENT
PARLIAMENTARY OFFICE OF SCIENCE & TECHNOLOGY

POSTNOTE

Number 431 March 2013, Updated October 2014

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.

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.
- The treatments raise ethical, societal and safety issues and the changes made will 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.

Background

Two new treatments may allow women with mitochondrial disease to give birth to healthy children. They are controversial, raising potential safety and ethical concerns. For instance, they involve altering the embryo's complement of DNA, with the changes made being passed on to future generations. The treatments have thus been through a number of reviews to evaluate the scientific, social and ethical issues that they raise. These include:

- HFEA expert panel reviews on safety and effectiveness in 2011, updated in 2013 and 2014. Each review concluded that there was no evidence to suggest the treatments were unsafe but recommended further research[1][2][3].
- An ethical review in 2012 by the Nuffield Council on Bioethics (NCB). This concluded that if the treatments were shown to be acceptably safe and effective, it would be ethical for families to use them.[4]
- A public consultation exercise conducted by HFEA.[5] This reported that "there is general support for permitting mitochondria replacement in the UK, so long as it is safe enough to offer in a treatment setting and is done so within a regulatory framework".

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".

The government recently consulted on such a regulation[6] and will put it before Parliament shortly. This briefing:

- looks at mitochondria and mitochondrial disease
- describes options for minimising the risk of children inheriting mitochondrial disease from their mother
- outlines what the two new treatments entail
- examines the 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 contain a few hundred or thousand depending on their energy requirements. At the top of the list are mature eggs that contain more than 100,000 mitochondria per cell. Eggs need such a high number because the early embryo cannot make its own mitochondria. The early embryo is thus dependent on the mitochondria it inherits from its mother, a bottleneck that keeps the number of mitochondria per cell relatively low in the early stages of development.

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.[7] 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.[1]

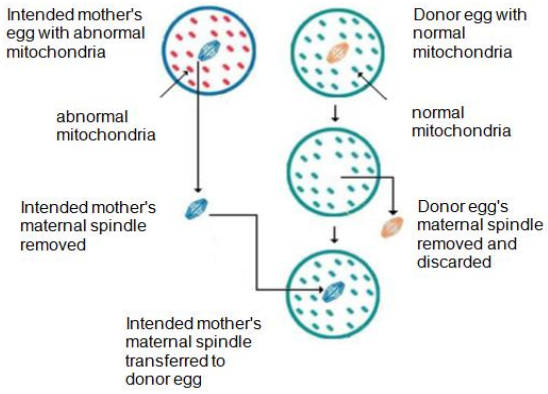
Mitochondria replacement treatments

There are several possible methods for replacing faulty mitochondria.[8] 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.

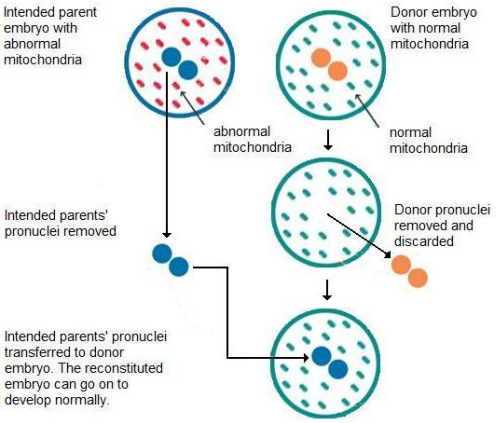
Figure 1 Maternal Spindle Transfer (MST)



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.

Figure 2 Pronuclear Transfer (PNT)



Key issues

Safety

Development of PNT and MST

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.[9] The 2014 expert panel review reported that the group has refined the PNT technique using normal fertilisation to create early (5 day) human embryos.[3]

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 have developed normally[10] to sexual maturity (5 years). Researchers in Oregon have used MST to create 65 reconstituted human eggs, 14 of which developed normally into early stage (5 day) embryos.[11] Human embryonic stem cell lines have been derived using MST and have been shown to have normal chromosomes.

The expert panel has consistently concluded that there is no evidence to show that either technique is unsafe, nor to favour one over the other. The 2014 expert panel review recommended that further research is needed before the techniques can be assessed as safe for clinical use.[3] In particular it recommended research:

- comparing human embryos created using PNT with normal fertilisation with human embryos created using PNT with intra-cytoplasmic sperm injection
- using MST and fertilisation to create human embryos.

Carry-over of mtDNA

Small amounts of the mother's mutated mtDNA may be carried over during the transfer process (MST or PNT). The 2011 review 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.[1] However the 2014 review looked at evidence that different mtDNA variants can become segregated and amplified in certain tissues.[3] It recommended a "critical experiment" to determine the extent to which neighbouring cells in early embryos created using MST or PNT differ in their mtDNA composition. It also recommended research in human stem cell lines (and specialised cells derived from them) created using PNT or MST and designed to contain two different mtDNA variants.[3]

Mitochondrial mis-matches

Mitochondria from different people can be classed into different groups (haplogroups) according to their DNA sequence. There are concerns that donor mitochondria of a different haplogroup from those of the mother might not interact correctly with the mother's nDNA (mis-matches). There is some evidence in mice and fruit flies that experimentally induced mismatches between mtDNA and nDNA can have developmental effects.[12] However the relevance of this research to humans is a matter of debate.[13,14] The 2014 review recommended that "consideration is given to mtDNA haplogroup matching when selecting donors" as a precautionary step.[3]

Access to treatments

If Parliament approves the use of the new 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 NCB recommended that MST and PNT should initially be offered as part of a research trial in centres specialising in mitochondrial disease.[4] It also noted that parental consent to follow up should be mandatory for participation in the trial and extend to future 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 most 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 sought opinions on who should make decisions on clinical use of the new treatments. Its advice to government, based on the consultation, was that the HFEA should license each centre wishing to offer such treatments and approve each use on a case-by-case basis in the first instance.[15]

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.

Effect 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[1] (PGD, see POSTnote 445).

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. It is not clear whether allowing the replacement of mtDNA would breach the consensus not to alter the human germ line as mtDNA did not feature in the debate that led to the consensus being reached. The HFEA consultation[14] identified two main strands of concern about changing the law to allow the new treatments:

- it might inadvertently open the door to similar techniques for other, less desirable, purposes and/or
- it might make it harder to argue against other, more controversial, treatments that alter germ line nDNA.

Use of similar techniques for other purposes

Those who oppose allowing mtDNA replacement to prevent mitochondrial disease claim that it could 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

There are concerns that allowing changes to one component of the germ line (mtDNA) might make it more difficult to continue to oppose allowing changes to the other (nDNA). Pro-life groups and some academics 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.

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[4]. 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 may 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.[16] mtDNA is thought to perform only a very limited - albeit vital - set of functions in the human body (although there is debate over the extent to which mtDNA contributes to identity[17]). In contrast, nDNA is known to contribute 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. Following its public consultation, HFEA advised that mitochondrial donors should have a similar status to that of tissue donors.[14]

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

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2 *Scientific review of the safety & efficacy of methods to avoid mitochondrial disease through assisted conception: update*, HFEA 2013
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5 Medical frontiers: debating mitochondria replacement, HFEA, 2013
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13 Reinhardt K et al, *Science*, 341, 1345-46, 2013
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