Assisted reproductive technologies to avoid the transmission of mitochondrial disease: the UK experience of moving from research towards clinical application

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My talk

• Brief background on mtDNA and disease
• What is mitochondrial donation?
• The HFEA and licensing mitochondrial donation
• Ethical objections
• Scientific assessment – safety considerations
• Future: alternatives and the wider genetic modification debate
Mitochondrial DNA (mtDNA)
Mitochondrial DNA (mtDNA) and disease
Options for women with mitochondrial disease who want to have children

• Do not reproduce
• Adoption
• Egg donation
• Preimplantation genetic diagnosis (PGD)
What is mitochondrial donation?

- Mitochondrial disease caused by faults in the small amount of DNA in the mitochondria, inherited from the mother

- Estimated 1 in 5,000 people affected by mitochondrial disease, around 1 in 6,500 children thought to develop serious mitochondrial disorder

- Maternal spindle transfer (MST) & pronuclear transfer (PNT): techniques to avoid inheritance of affected mitochondria by transferring nuclear material from eggs or early embryos
Unfertilised donated egg with normal mitochondria

Spindle with associated chromosomes removed as karyoplast from donated egg and discarded

PB1T
1st polar body removed from patient’s egg and fused or injected into “enucleated” donor egg

Sperm from patient’s partner

Reconstituted embryos with normal mitochondria from the donor and maternal and paternal genomes from the patient and her partner

AND/OR

Unfertilised patients egg with abnormal mitochondria

1st polar body

Unfertilised donated egg with normal mitochondria

Spindle with associated chromosomes removed as karyoplast from donated egg and discarded

MST
Spindle with associated chromosomes removed as karyoplast from patient’s egg and fused into “enucleated” donor egg

Sperm from patient’s partner

2nd polar body

Reconstituted embryos with normal mitochondria from the donor and maternal and paternal genomes from the patient and her partner
Donated egg fertilised with sperm from the patient’s partner. Normal mitochondria

Fertilised egg (zygote) => Female (maternal) pronucleus removed and discarded.

Both pronuclei removed and discarded.

1st polar body

1st polar body

2nd polar body removed from patient’s zygote and transferred to donor zygote lacking maternal pronucleus = PB2T

AND/OR

Both pronuclei removed from patient’s zygote and transferred to enucleated donor zygote = PNT

Reconstituted embryos with normal mitochondria from the donor and maternal and paternal genomes from the patient and her partner

Donated egg fertilised (with any sperm). Normal mitochondria

2nd polar body of donor zygote

Both pronuclei removed and discarded

+ fusogen

+ fusogen
Timeline

- **HFEA* grants research licence**
- **First scientific review**
- **Public dialogue & second scientific review**
- **Third scientific review**

*Human Fertilisation & Embryology Authority (HFEA)*

Timeline:
- 2005
- 2011
- 2012/2013
- 2014
Conduct a **public dialogue exercise** to explore:

- The **ethical aspects** and issues involved in techniques to avoid mitochondrial disease; and

- The **practical implications** of allowing such techniques within regulation

**Three reviews on the safety and efficacy** of methods to avoid mitochondrial disease (plus addendum on polar body transfer)

**An introductory briefing note** to inform Parliamentary debate
Objections

• Ethical

Women could have children without mitochondrial donation (egg donation, adoption)
Identity concerns (what does mtDNA contribute?)
We are effectively experimenting on humans
We are altering the human germ line – inter-generational justice
It makes nuclear DNA editing more likely (GM babies)
Designer babies (slippery slope etc.)
We are ‘playing God’

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Safety and efficacy

Three reports from the expert scientific panel, over three years

The panel concluded that:

• There is no evidence to demonstrate that mitochondrial donation is unsafe

• Research is progressing well and the recommended further experiments are expected to confirm this view

http://www.hfea.gov.uk/8807.html
What research has been carried out?

- Many experiments conducted using maternal spindle transfer (MST) and pronuclear transfer (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 and human embryos

- The expert panel concluded that these studies have shown that the techniques are effective and ‘not unsafe’
Mito-nuclear incompatibilities

• Experiments in different model organisms have tested compatibility of mtDNA and nuclear DNA.
• Panel felt that these experiments were not an adequate reflection of human mitochondrial donation – risks are theoretical – more research required.
• However, they recommended consideration of haplogroup matching as a precautionary measure.
  - research at time of potential treatment crucial.
What further research is needed?

- Panel has recommended further experiments: necessary to the consideration of the safety and efficacy of the technique before treatment is offered. Expects such research to support the conclusions it has reached so far.

- Main research: observe embryonic stem (ES) cells derived from embryos created by MST and PNT, to examine how mitochondria behave after cell divisions.
DNA from second mothers to help combat ‘cruel’ health risks

3-parent babies ‘safe’ to be born

THREE-PARENT babies could be born within two years after watchdogs gave the go-ahead for the controversial IVF method yesterday.

The techniques used in the procedure were ‘not unsafe’ and ‘potentially useful’, the Human Fertilisation and Embryology Authority confirmed.

But further research, including experiments on human embryos, was needed, it said. So far, only mice and monkeys have been tested.

It is hoped it could help conditions by NICOLE LE MARIE

The panel concluded that two techniques it reviewed ‘had the potential to be useful for all patients with disorders caused by mutated mitochondrial DNA’.

The panel said a ‘waiting list’ of women unable to carry a child has...
Mitochondrial Donation Regulations 2015

- House of Commons debated & approved: 3 February
- House of Lords debated & approved: 24 February
- Regulations officially signed into UK law: 4 March
- Regulations come into force: 29 October
Next steps

• Parliament approved Regulations in February 2015 but it will take some time before a clinic can be licensed to offer mitochondrial donation in treatment

• HFEA is designing a licensing process: safety and efficacy considerations, clinic competency and case-by-case approval of patients – ready for Oct 29th and a subsequent license application

• Alternative techniques: Polar Body Transfer (PBT)? Genome editing?
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Nuffield Council on Bioethics: Working Group on Ethical Issues Arising From Genome Editing

http://nuffieldbioethics.org/project/genome-editing/