

Call for evidence: Scientific review of the methods to avoid mitochondrial disease

1. Scope of review

- 1.1. The Secretary of State for Health has asked the Human Fertilisation and Embryology Authority (HFEA) to co-ordinate a scientific review of the methods to avoid mitochondrial disease. The HFEA has established a core panel (see Annex 1), with broad-ranging scientific and clinical expertise, to collate and summarise wide-ranging evidence from experts in any relevant field.
- 1.2. This paper is calling for any evidence on the safety and efficacy of techniques to avoid mitochondrial disease through assisted conception, to be submitted by **15 March 2011**. This evidence will be considered by the core panel, and select researchers will be invited to attend a workshop in London on Friday 25 March 2011 to discuss further. The core group will submit a report to the Department of Health by mid-April 2011.
- 1.3. The Secretary of State will use this scientific review to inform his decision as to whether to hold a public consultation on introducing the regulations.

2. Legislative framework

- 2.1. In the UK, the Human Fertilisation and Embryology (HFE) Act 1990 (as amended) only permits eggs and embryos that have not had their nuclear or mitochondrial DNA altered to be used for treatment. However, the Act allows for regulations to be passed that will allow techniques that alter the DNA of an egg or embryo to be used in assisted conception to prevent the transmission of serious mitochondrial disease. In introducing this provision into the HFE Act in 2008, the Government gave assurance that the power to make these regulations would only be considered once it was clear that the procedures involved were effective and safe.

3. Methods of avoiding mitochondrial disease through assisted conception

- 3.1. Preimplantation Genetic Diagnosis (PGD) is the only method currently permitted that has the potential to avoid transmitting a serious mitochondrial disease, as it does not alter the nuclear or mitochondrial DNA of the embryo. PGD assesses the mitochondrial DNA content in a polar body or blastomere to estimate whether or not the levels of mutant mitochondrial DNA in the embryo will give rise to a disease. PGD is permitted for treatment in the UK, under close regulation by the HFEA. The HFEA has licensed PGD for a number of mitochondrial diseases.
- 3.2. Pronuclear transfer and spindle transfer are two techniques, currently at the research stage, that have the potential to avoid transmitting a serious mitochondrial disease. Pronuclear transfer involves transferring the pronuclei from an embryo that has unhealthy mitochondria and placing it into an

embryo that has healthy mitochondria. Spindle transfer involves transferring the nuclear DNA from an oocyte with unhealthy mitochondria and placing it into an oocyte with healthy mitochondria. Neither of these techniques is currently permitted for treatment under the HFE Act 1990 (as amended) because each alters the mitochondrial DNA of the egg or embryo.

3.3. Other techniques that have been tried in the past to improve mitochondria function include germinal vesicle transfer and cytoplasmic transfer. Germinal vesicle transfer involves removing the nucleus from an oocyte at the germinal vesicle stage of development and transferring it to an enucleated donor egg. The oocyte is then matured *in vitro*. In cytoplasmic transfer, cytoplasm from an oocyte with healthy mitochondria is injected into an oocyte with unhealthy mitochondria. Again, neither of these techniques is currently permitted for treatment under the HFE Act 1990 (as amended) because each alters the mitochondrial DNA of the egg.

4. Previous consideration of methods to avoid mitochondrial disease

4.1. As part of its remit, the HFEA has a Scientific and Clinical Advances Committee (SCAAC) that reviews developments in techniques that may impact on assisted conception or human embryo research. SCAAC last considered the different techniques to avoid the transmission of mitochondrial disease through assisted conception at its meeting on 13 May 2010¹.

Pronuclear transfer and spindle transfer

4.2. The Committee thought that spindle transfer and pronuclear transfer were both promising methods, although they posed different safety concerns. The Committee agreed that more safety testing is needed before pronuclear transfer could be considered for use in treatment, especially around epigenetics and chromosomal abnormalities. They noted that the environmental temperature needs to be closely regulated during spindle transfer to avoid chromosome abnormalities in the resulting embryo. The follow-up studies of primates created using spindle transfer would be pertinent.

4.3. They suggested the following research to test the safety of pronuclear transfer:

- further animal studies to research development following blastocyst and implantation stages
- further studies using normal human oocytes
- further research on the interaction between mitochondria and the nucleus
- research on the incidence of chromosomal abnormality and array expression analysis of embryos
- research to develop embryonic stem cell lines from blastocysts created using pronuclear transfer. Differentiating cells can then be put in conditions where mitochondria need to function to provide energy, in order to examine mitochondrial activity

¹ <http://www.hfea.gov.uk/5906.html>

PGD to avoid mitochondrial disease

4.4. The Committee noted that PGD reduces the risk of passing a mitochondrial disorder from mother to child but does not eliminate it. It can only be used in heteroplasmic conditions, not homoplasmic conditions. They acknowledged that in heteroplasmy, the levels of affected mitochondria vary between cells in the embryo and from condition to condition, which makes it very difficult to estimate the risk of transmission. However studies of blastomeres from disaggregated embryos suggest that there is less variation between cells than might be expected. The Committee suggested that there should be further research to investigate the effects of the mitochondrial bottleneck and the implications of the reliability of a diagnosis based on preimplantation stages.

Cytoplasmic transfer

4.5. The Committee thought that cytoplasmic transfer is a less preferable method to pursue. The technique was banned in the United States by the Food and Drug Administration. It is also less likely than other methods to adequately replace abnormal with normal mitochondria. One member did raise that it is less invasive and therefore carries a lower risk than pronuclear transfer.

5. Call for evidence

5.1. Since SCAAC's consideration last year, there has been further research in techniques to avoid mitochondrial disease. Though the HFEA has a background understanding in this area, the assessment of these techniques requested by the Secretary of State's requires a broader and more wide-ranging review to collate and summarise the current state of expert understanding.

5.2. The core panel established by the HFEA is therefore calling for scientific evidence from experts in any relevant field on **the safety or effectiveness of methods to avoid the transmission of mitochondria disease through assisted conception**. Evidence can include published studies, unpublished research or statements. It can be submitted from individuals or organisations.

5.3. Because of the tight deadline of this review, please submit any evidence by Tuesday **15 March 2011** to mitochondriareview@hfea.gov.uk or Mitochondria Review, Policy Team, HFEA, 21 Bloomsbury Street, London WC1B 3HF. Please include your name and affiliation.

5.4. The core panel will review the evidence at a workshop on 25 March 2011. Select people who submitted evidence will be invited to attend. The core panel will be submitting a report to the Department of Health by mid-April 2011. This will be copied to all contributors.

Annex 1: Details of Core Panel

Membership

Professor Neva Haites (*Chair*), University of Aberdeen

Professor Peter Braude, Kings College London

Professor Keith Campbell, University of Nottingham

Professor Sir Richard Gardner

Dr Robin Lovell-Badge, MRC National Institute for Medical Research

Professor Anneke Lucassen, Human Genetics Commission

Terms of reference

The group will collate and summarise the current state of expert understanding on the safety and efficacy of methods to avoid mitochondrial disease through assisted conception.