Mitochondrial Donation

Standard Note: SN/SC/6833

Last updated: 29 January 2015

Author: Dr Sarah Barber - Science and Environment Section

Dr Peter Border – Parliamentary Office of Science and Technology (POST)

New mitochondrial donation techniques could provide an option for women with mitochondrial DNA mutations to enable them to give birth to healthy children. They involve using donor mitochondria in an in vitro fertilisation (IVF) treatment.

The techniques (maternal spindle transfer and pronuclear transfer) have been subject to three scientific reviews (2011, 2013 and a further update in 2014) by a Human Embryology and Fertilisation Authority expert panel, an ethical review by the Nuffield Council on Bioethics and a HFEA public consultation.

In 2013, the HFEA advised the Government that there is general support for the introduction of these treatments. They recommended that further research is still needed and the treatment should be offered within a strict regulatory framework.

On 17 December 2014, the Under-Secretary of State for Health announced that the Regulations to allow for the introduction of these techniques had been laid before the House. This followed a consultation on draft regulations and a scientific review update by the HFEA expert panel in 2014. A House of Commons debate on the Regulations has been tabled for 3 February 2015.

A number of safety and ethical considerations have been raised in regard to mitochondrial donation. The treatments involve changing the embryo's mitochondrial DNA prior to implantation. However, the nuclear DNA, which makes up over 99% of our total DNA will not be altered by these treatments. There has been some opposition to their proposed introduction and the media have reported that the techniques will lead to *three parent babies.*

This note provides a summary of the role of mitochondria, mitochondrial disease and the proposed new techniques. It also provides information on the reviews and consultations. The main safety and ethical considerations associated with the introduction of mitochondrial donation into clinical practice are discussed. Overviews of recent Parliamentary debates and a House of Commons Science and Technology Select Committee one off session are included in the note.

The Parliamentary Office of Science and Technology have provided two annexes to this note. They provide further information on other mitochondrial transfer methods and mitochondrial matching.

Contents

1 Mitochondria and mitochondrial disease

1.1 Mitochondria

Mitochondria are found in the fluid surrounding the nucleus of our cells. They are responsible for making energy within the cell, without which the cells would not survive. The mitochondria have their own mitochondrial DNA (mtDNA) which ensures they work properly.

Most of our DNA, (over 99%) is found in the nucleus of the cell and we inherit this from our mother and father. Mitochondrial DNA however, is only inherited from our mother. Any mutations in a mother's mitochondrial DNA, which may cause mitochondrial disease, will be automatically inherited by her children.

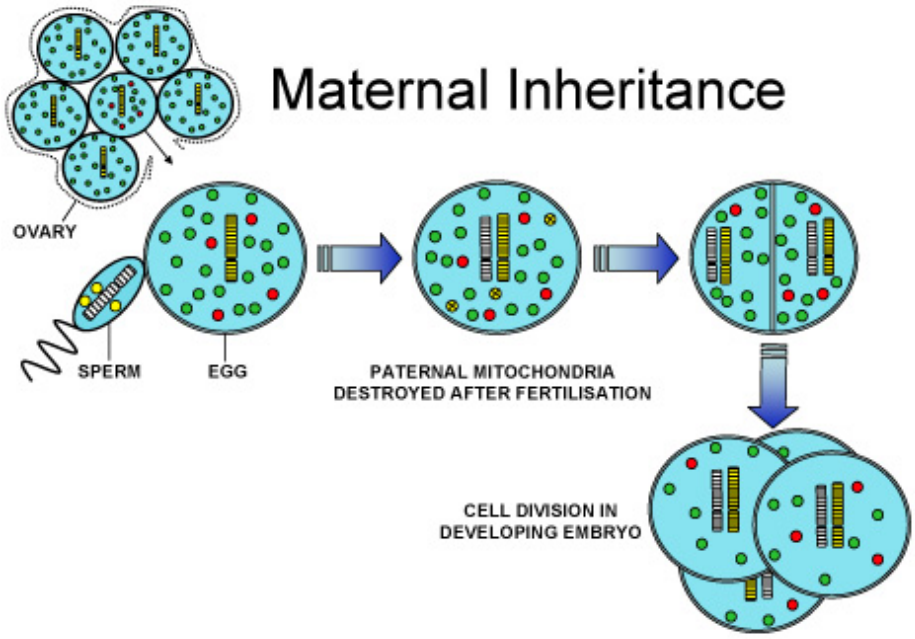


Fig 1. Maternal Inheritance of mitochondria (reproduced with permission from the Rare Mitochondrial Disease Service for Children and Adults, NHS). The small specks in the eggs and sperm represent mitochondria.

1.2 Mitochondrial disease

Mitochondrial diseases are varied, they can be mild with little or no symptoms or can be severe enough to be life threatening.[1] They tend to affect parts of the body that require a lot of energy, like our brain, muscle, kidney and heart. There are no effective treatments available for serious mitochondrial diseases. It is thought that one in 6,500 children born each year will develop one of the more serious mitochondrial disorders.[2]

Mitochondrial disease can be caused by mutations in the mitochondrial DNA (mtDNA) or in the nuclear DNA that affects gene products required within mitochondria. The HFEA provide a list of clinical disorders due to mutations in mtDNA as an annex to their 2011 scientific

---

1 BBC News, Robin Banerjii, The woman who lost all seven children, 20 September 2012

2 Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012. Page 25

review of the safety and efficacy of methods to prevent mitochondrial diseases.[3] These include conditions that cause deafness, diabetes, heart disease, epilepsy and brain disorders.

It is estimated that at least 3,500 women in the UK carry mtDNA mutations that could be potentially problematic to their children.[4] It is possible that women with no symptoms themselves may have mitochondrial DNA in their eggs that carry the potential to cause life threatening disease.

The current options available to women with mtDNA mutations when considering having children are primarily to use donated eggs or to adopt. One option that can be considered is to use pre-implantation genetic diagnosis, where embryos are tested before implantation to look for those with the lowest proportion of mutated mtDNA. This is only useful where the exact mutation is known and it can only reduce, not eliminate the risk of having an affected baby. This technique is more useful in those who have nuclear DNA mutations that cause mitochondrial disease.

Mitochondrial donation could allow women with abnormal mtDNA to give birth to healthy children. The procedures use donated mtDNA whilst also allowing a woman to have babies that are genetically related to her. There are several possible methods for this.

It was initially estimated that the introduction of this treatment could save around 10 lives a year,[5] but recent responses to Parliamentary questions have suggested this number may be much higher, between 10 and 20, and eventually up to 80.[6]

1.3 Methods to prevent mitochondrial disease

As discussed above, preimplantation genetic diagnosis is the only method currently available to attempt to reduce the risk of mitochondrial disorders in children. Those proposed techniques evaluated during the scientific review were pronuclear transfer and maternal spindle transfer.

Preimplantation genetic diagnosis (PGD)

This diagnostic method can be used to test embryos prior to implantation during in vitro fertilisation (IVF) procedures. Cells are removed from an in vitro embryo for testing prior to implantation.

This method is licensed by the HFEA for a number of mitochondrial conditions.[7] For each mitochondrial DNA (mtDNA) condition, an HFEA licence committee must decide whether it can be licensed for PGD.

There are limitations to this method; it cannot be used by all women with mtDNA mutations. Some women have normal and mutated mtDNA in their cells (heteroplasmy) and others have all mutated mtDNA (homoplasmy). PGD can only benefit women who are heteroplasmic.

---

3 HEFA, Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception, Report provided to the Human Fertilisation and Embryology Authority, April 2011 (annex A)

4 The Lancet, Brown DT, Herbert M et al, Transmission of mitochondrial DNA disorders: possibilities for the future, 2006

5 HL Deb 15 July 2013 cWA87

6 HC Deb 10 March 2014 c97W

7 HFEA, PGD conditions licensed by the HFEA

Inheritance can be complex and prognosis for a tested embryo can be unclear. PGD can reduce but not eliminate the risk of a child being affected. The HFEA, in their review of scientific evidence in 2011 outlined the limitations of PGD:

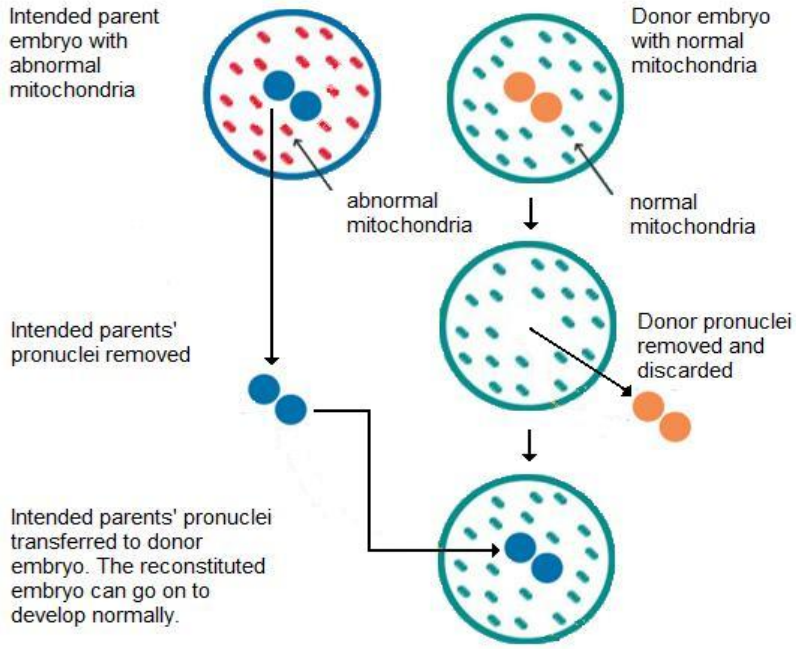
> Preimplantation genetic diagnosis (PGD) can be used to test embryos that might be carrying mutations in their nuclear DNA so that only unaffected embryos are selected for implantation. Unlike most nuclear DNA mutations, mtDNA is solely maternally inherited, and any mutations it acquires are therefore likely to be passed on to all offspring. This presents particular challenges when it comes to avoiding transmission of disease to subsequent generations. For some women who are known to carry mtDNA mutations, current methods of diagnosis including PGD, can reduce, but not eliminate, the risk of a child being born with mitochondrial disease. However, these methods are not applicable to all cases. Moreover, even if unaffected themselves, girls born after the use of this procedure may themselves still be at risk of having affected children, as some abnormal mitochondria may be present in their oocytes (eggs).

Pronuclear transfer (PNT)

Pronuclear Transfer is a technique used following IVF with the parent's sperm and egg. Once a sperm enters an egg, the fertilised egg contains genetic material from both mother and father. These are each enclosed in a separate membrane and are called pronuclei.

The two pronuclei are removed from the egg on day one of development which leaves the vast majority of the mother's mutated mitochondria behind.

Another egg from a donor is fertilised using father or donated sperm. On day one of development, the pronuclei from this egg are removed. The mother and father's pronuclei are then injected into the second egg. This embryo cell now contains pronuclear DNA from the parents and healthy donor mitochondria from the second egg.[8] Once the egg has developed as an embryo, it will be transferred to the mother's womb.



[8] Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012. Page 32

Fig.2 Pronuclear Transfer (reproduced with permission from POSTnote 431 *Preventing Mitochondrial disease*)

Maternal spindle transfer (MST)

Eggs are obtained from the mother's ovaries. These eggs will have mutated mtDNA.

The nuclear DNA will be contained on one side of the cell in a spindle shaped group. This 'spindle' group of nuclear DNA is removed from the eggs.

Donor eggs with healthy mtDNA also have their spindles removed. The spindles from the mother's eggs are then inserted into the donor eggs. These eggs now have healthy nuclear DNA and mtDNA.

The eggs can now be fertilised using the father's sperm and the embryo can be developed in vitro. One or two of these embryos can then be transferred into the mother's womb.[9]

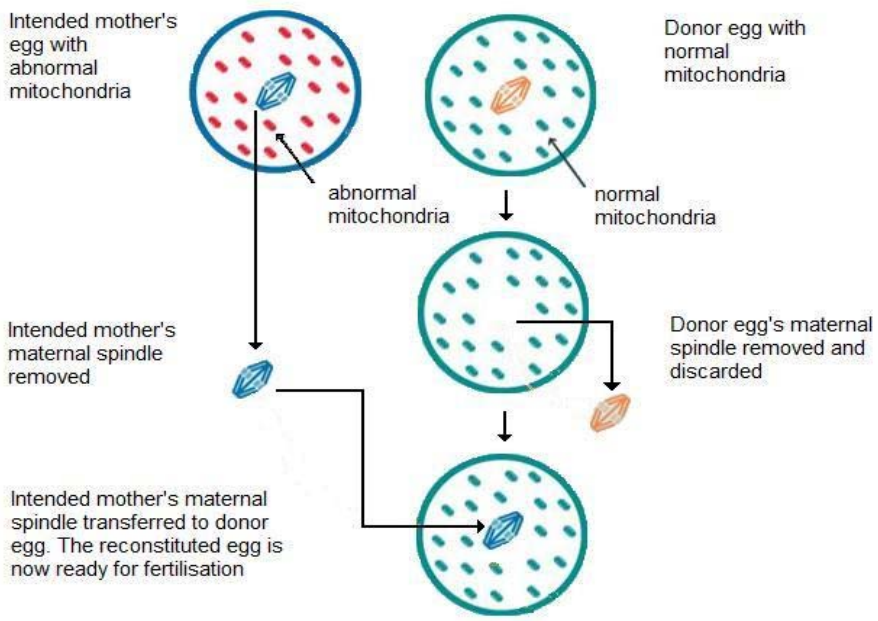


Fig. 3 Maternal Spindle Transfer (reproduced with permission from POSTnote 431 *Preventing Mitochondrial disease*)

[9] Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012. Page 34

2 The Human Fertilisation and Embryology Act 2008

The *Human Fertilisation and Embryology Act 1990*, as amended by the *Human Fertilisation and Embryology Act 2008*,[10] prohibits the implantation of an egg or embryo that has had its DNA altered.

However, the Act does go on to make provision for regulations subject to parliamentary approval to permit this for one purpose "to prevent the transmission of serious mitochondrial disease" under a new section 3ZA (subsection 5):

> (5) Regulations may provide that—
>
> (a) an egg can be a permitted egg, or
>
> (b) an embryo can be a permitted embryo, even though the egg or embryo has had applied to it in prescribed circumstances a prescribed process designed to prevent the transmission of serious mitochondrial disease.

3 Reviewing the techniques for the prevention of mitochondrial disease

These techniques are new and involve changing the mtDNA of an embryo prior to implantation. They have been subject to three scientific reviews, an ethical review and public consultation.

In February 2011, the Secretary of State for Health asked the HFEA to carry out a scientific review of the safety and effectiveness of mitochondrial donation techniques.[11] This review was later updated alongside the public consultation in early 2013.

In 2012 the Nuffield Council on Bioethics conducted a review on the ethical issues surrounding the introduction of mitochondrial donation.[12]

In January 2012, it was announced that, following a request from the Secretaries of State for Health and Business, Innovation and Skills, the HFEA would launch a consultation to seek public views on the introduction of mitochondrial donation.[13]

This section will outline some of the main findings and decisions resulting from these processes.

The expert panel at the HFEA conducted a third scientific review in 2014 alongside the publication of draft regulations, this is discussed in section 4.

3.1 The scientific review 2011 and the 2013 update

Following a request from the Secretary of State for Health, the HFEA undertook a review of the safety and efficacy of the potential methods for preventing mitochondrial disease in 2011.[14]

---

10 *Human Fertilisation and Embryology Act 2008*

11 HFEA, Call for evidence: Scientific review of the methods to avoid mitochondrial disease, 2011

12 Nuffield Council on Bioethics, Mitochondrial DNA disorders, June 2012

13 HFEA, Press release: HFEA launches public consultation, Medical Frontiers: Debating mitochondria replacement, 17 September 2012

14 HFEA, Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception, Report provided to the Human Fertilisation and Embryology Authority, April 2011

The HFEA established a small panel of scientific and clinical experts to look at the current scientific evidence. They assessed PGD, MST and PNT. Their main conclusions and recommendations are outlined here:

- Information about mtDNA has been obtained primarily from animal research. More research on human embryos is needed and should be encouraged.
- PGD for nuclear DNA mitochondrial disorders can only be possible if the nuclear DNA mutation is known. Further work must be done to develop reliable tests to find mitochondrial disease caused by nuclear DNA mutations.
- PGD can only be aimed at risk reduction in cases of varied levels of mutated mtDNA (heteroplasmy). It will not eliminate the risk of transmitting mutated mtDNA.
- Recommendations were provided on the standard of care for centres that offer PGD for mtDNA disorders.[15]
- MST and PNT have the potential to treat all patients with mtDNA disorders. There is currently insufficient evidence to recommend one technique over the other. Further safety research was needed before they could be used in clinical practice.
- The panel strongly recommended that once the techniques have been assessed as being safe, those born as a result of these methods should be followed up over an extensive period.

The HFEA panel recommended a minimum set of experiments which must take place prior to MST or PNT being assessed as safe to use clinically.[16] These experiments were:

- MST using human oocytes (eggs) that are then fertilised
- PNT using normally-fertilised human oocytes and development compared to normal ICSI-fertilised human oocytes (Intra-cytoplasmic sperm injection (ICSI) involves injecting a single sperm into an egg to fertilise it); and
- PNT in a non-human primate model, with the demonstration that the offspring derived are normal.

Following the recommendations of the scientific review, a new mitochondrial research centre was set up in Newcastle, to carry out some of the suggested research as set out by the panel. This centre was funded by the Wellcome Trust and Newcastle University.[17]

This scientific review was updated during the public consultation in 2012-13 following a request from the Secretary of State for Health.

The HFEA panel at this time (March 2013) provided its conclusions. These included that at the current time there is insufficient evidence to prefer one technique over another and that

---

15 HFEA, Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception, Report provided to the Human Fertilisation and Embryology Authority, April 2011 (page 23, 6.5)

16 HFEA, Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception, Report provided to the Human Fertilisation and Embryology Authority, April 2011 (page 21)

17 Wellcome Trust, Techniques to prevent the transmission of mitochondrial diseases to be assessed in £5.8million Wellcome Trust centre, 19 January 2012

permission should be sought for long term follow up of those born following the use of mitochondrial donation:

> There is currently more published work available to support MST than PNT, but there is still insufficient evidence to recommend one transfer technique over the other. Indeed, once an embryo begins to develop normally, the data accumulating from the two methods would appear to be very complementary.
>
> Although the results with the two techniques are promising, further experiments need to be done before introducing either into clinical practice to provide further reassurance with respect to efficiency and safety[.....]
>
> Once assessed as safe to use in clinical practice, the panel strongly recommends that permission is sought from the parents of the children born from MST or PNT to be followed up for an extensive period (then seek permission from the children themselves, when old enough). In the case of females, this ideally should be extended to the next generation. These recommendations should also apply to PGD for mtDNA genetic diseases.
>
> Until knowledge has built up that says otherwise, the panel recommends that any female born following MST or PNT should be advised, when old enough, that she may herself be at risk of having a child with a significant level of mutant mtDNA, putting this child or (if a female) subsequent generations at risk of mitochondrial disease. Thus, we recommend that any female born following MST or PST is advised that, should she wish to have children of her own, that her oocytes or early embryos are analysed by PGD in order to select for embryos free of abnormal mtDNA. This has the potential to eliminate risk in subsequent generations.[18]

The HFEA panel proceeded to recommend that further research was needed to improve the knowledge of basic mitochondrial biology and safety information with regards to PNT and MST.

The panel reviewed the minimum critical experiments as advised in the 2011 review:

1. *MST using human oocytes that are then fertilised*

   Experiments on these have now been carried out and published. It is still important for follow up experiments to take place, especially to improve efficiency.

2. *PNT using normally fertilised human oocytes and development compared to normal ICSI-fertilised human oocytes.*

   Experiments on this appear to be well underway. It will be necessary to see the full results before any assessment can be made.

3. *PNT in a non-human primate model, with the demonstration that the offspring derived are normal.*

   The panel decided that this recommendation was no longer critical or mandatory. Further experiments on non-human primates could provide further information but, many of the important issues have already been addressed by studies involving macaques, rodent and humans.

---

[18] Annex VIII: Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: update, March 2013 (page 17)

They recommended that other studies related to the behaviour of mutant mtDNA may be better performed on mouse models or using human oocytes. They also advised that, '*if there are critical periods where the human is unique, such experiments may even be misleading if carried out in animals.'* The panel expressed concerns that in assessing the efficacy and safety of MST and PNT, the differences between macaque and human eggs will be unhelpful.

There are ethical issues raised by carrying out experiments on animals, especially non-human primates if these are unlikely to be informative.

In addition the panel recommended a number of further studies to be carried out.[19]

3.2 The ethical review

The Nuffield Council on Bioethics (NCB) conducted a review in 2012 of the ethical considerations in the use of PNT and MST.[20]

The NCB concluded that, should the treatments provide a safe and effective form of preventing mitochondrial disease, there would be a strong ethical reason for permitting their use. However, it identified three main areas of potential ethical concern:

- PNT and MST are a form of germline therapy. This could represent problems in itself or could represent a slippery slope to allowing the altering of nuclear DNA
- The knowledge about these techniques is uncertain and could remain so for several generations- their use could potentially harm future persons.
- A person born with genetic material from three people might have a conflicted self identity.

The working group concluded that if PNT and MST techniques are proven safe and effective, it would be ethical for families to use them:

> In light of the health and social benefits to individuals and families living free from mitochondrial disorders, and where potential parents express a preference to have genetically-related children, the Working Group believes that, if the PNT and MST techniques are proven to be acceptably safe and effective, on balance it would be ethical for families wishing to use them to do so. This should, however, be subject to the offer of an appropriate level of information and support.
>
> If the proposed therapies are adequately shown to be safe and effective and patients choose to use them, the Working Group believes that, potentially, these could be of benefit to both prospective parents and the resulting children who might be born free from mitochondrial disorders. This health benefit appears to be likely to extend to descendants of any women born via these therapies, although this would not ordinarily be the primary objective of the treatment.[21]

For further discussion of the main ethical concerns, please see section 5.

---

[19] Annex VIII: Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: update, March 2013 (page 21)

[20] Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012.

[21] Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012. (Page 88)

3.3 The public consultation

Secretaries of State for Health and Business, Innovation and Skills asked HFEA to seek public views on the use of new techniques to prevent mitochondrial disease. This consultation took place in 2012 with the support from the Sciencewise Expert Resource Centre.

A number of methods were used to gather information from the public.[22]

- **Deliberative public workshops**- workshops were held in Newcastle, Cardiff and London, participants were recruited to reflect a broad spectrum of the population. The aim was to explore public attitudes in depth.

- **Public representative survey**- Almost 1000 face to face interviews were carried out with the public in 175 random locations. The aim of the survey was to generally assess public opinion on the issues surrounding mitochondrial donation.

- **Open consultation questionnaire**: A public consultation period of several months allowed responses from self-selected members of the public on seven questions. 1,836 responses were received. Stakeholder organisations, those with personal experience of mitochondrial disease and general members of the public responded.

- **Open consultation meetings**- Two public meetings were held, one in London and one in Manchester. These were open for anyone to attend. The meetings involved talks from a panel of speakers and then small and whole group discussions.

- **Patient focus groups-** One focus group of six participants was held to gather in depth views on mitochondrial donation techniques from those who were affected by mitochondrial disease.

The HFEA advice to the Government, published in March 2013 following the consultation, concluded that there was general support for permitting mitochondrial donation in the UK:

> Our advice to Government, set out in this report, is 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. Despite the strong ethical concerns that some respondents to the consultation expressed, the overall view is that ethical concerns are outweighed by the arguments in favour of permitting mitochondria replacement.
>
> We have therefore framed our advice so as to inform the Government's thinking, should it be minded to put Regulations forward to Parliament to make this possible. The advice we give below addresses the policies and safeguards that might guide those Regulations.
>
> It is worth noting that there are also ethical issues associated with deciding not to seek Parliament's approval to permit mitochondria replacement. Such a move would restrict the reproductive options of people with serious mitochondrial disease, denying them access to a treatment which has clinical promise.[23]

The advice goes on to discuss in more detail a number of safety and ethical issues highlighted by the consultation.

---

[22] HFEA, Mitochondria replacement consultation: advice to Government, March 2013
[23] HFEA, Mitochondria replacement consultation: advice to Government, March 2013

4 Regulations to allow the introduction of mitochondrial donation

Following the advice from the HFEA, the Chief Medical Officer, Professor Dame Sally Davies announced that the Government planned to publish draft regulations for further public and Parliamentary consultation in June 2013:

> Following a public consultation in which there was overall support for the treatment, which could save around 10 lives each year, the decision was taken to publish draft regulations later this year in a further public consultation. The regulations, which would be subject to strict safeguards, would make the UK the first country in the world to give patients the option of using the ground-breaking IVF-based treatment.[24]

On 27 February 2014, the Department of Health launched a public consultation on the newly published draft regulations on Mitochondrial Donation.[25] At this time, the Under-Secretary of State for Health announced a further assessment of safety and efficacy by the HFEA expert panel:

> Consultation on the draft regulations begins today and will run until 21 May 2014.
>
> We welcome responses from everyone with an interest in this area. We have also asked the HFEA to reconvene the Expert panel to review the latest evidence of safety and efficacy. We will consider their advice alongside the responses to the consultation.
>
> Expert briefing meetings for hon Members and Peers will be arranged during the consultation period, and will be an opportunity to discuss issues arising from the consultation document.[26]

The HFEA published a call for evidence on the update to the scientific review.[27]

4.1 The Scientific Review: 2014 update

Alongside the draft regulations and the consultation in February 2014, the Government requested that the HFEA conduct another scientific review of the evidence on mitochondrial donation.

This review involved the consideration of submissions of new evidence and a further review of the literature available in this area. The panel met on three occasions and one of those meetings involved a workshop where people who had submitted evidence could take part in a roundtable discussion.

The conclusions of the panel in 2014 were very similar to those previously expressed. MST and PNT are potentially useful for a specific group of patients who wish to have genetically related children but whose offspring would be at risk of severe or life threatening genetic disease. The panel, as in previous reviews stated that the evidence does not suggest that these techniques are unsafe.

As far as future research needs, the panel agreed that the following studies remain critical, but that progress had been made in these areas:

---

[24] Department of Health, Innovative genetic treatment to prevent mitochondrial disease, 28 June 2013

[25] Department of Health, Mitochondrial donation consultation launched, 27 February 2014

[26] Department of Health, Written Ministerial statement, Consultation on Regulations to allow Mitochondrial Donation, 27 February 2014

[27] HFEA, Call for Evidence: Update to scientific review of the methods to avoid mitochondrial disease,

- **MST using human oocytes that are then fertilised (not activated).** It is still important for some follow-up experiments to be carried out, notably to improve efficiency if possible, and further corroborative experiments would be valuable.

- **Experiments comparing PNT using normally-fertilised human oocytes with normal ICSI fertilised human oocytes.** The method continues to be developed and appears promising. Further work will be published in the near future and those results will need assessing before they can be incorporated into recommendations.

In addition, the panel continues to recommend that:

- PNT in a non-human primate model, with the demonstration that the offspring derived are normal, is not critical or mandatory.

- **MST and PNT should both be explored and that, as yet they do not consider one technique to be preferable to the other.**[28]

Concerns had been expressed about segregation and inappropriate over expression of mtDNA as a result of carryover from mutated maternal mtDNA. In response to this, the HFEA panel recommended a further set of experiments. These would involve the study of the differing genetic make-up of cells in very early stage embryos (morulae) following the use of MST or PNT. They would seek to provide more information on the extent of mtDNA variation within the cells (heteroplasmic mosaicism):

> In 2014, based on concerns about carryover of mutant mitochondria the panel continues to recommend that it is important to demonstrate the degree of heteroplasmic mosaicism[29] in morulae[30], and to provide data to address whether there was any amplification of mtDNA carried over. Therefore the following is also considered to be a critical experiment:
>
> Studies on mosaicism in human morulae (comparing individual blastomeres[31]) and on human embryonic stem (ES) cells (and their differentiated derivatives) derived from blastocysts, where the embryos have (i) originated from oocytes heteroplasmic for mtDNA and (ii) been created through MST and PNT using oocytes or zygotes[32] with two different variants of mtDNA. Although experiments are already reported on ES cells and their derivatives with MST, further corroborative experiments would be valuable to demonstrate the degree of heteroplasmic mosaicism in morulae, and to provide data to address whether there was any amplification of mtDNA carried over.[33]

The panel recommended that consideration should be given to mtDNA haplogroup matching between the donor and mother as a precautionary step. However, they concluded that the risks of not matching would be very low and there may be practical factors preventing it. The panel also recommended that the follow up of children born as a result of the techniques should include assessment of any repercussions of mtDNA haplogroup mismatch:

---

28 HFEA, Third Scientific Review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception:2014 update, June 2014

29 Mosaicism is a condition in which cells within the same person have a different genetic makeup

30 A morula is an embryo at a very early stage of development, around day 3-4 following fertilisation.

31 Blastomeres are cells resulting from the division of an ovum after fertilisation and during early embryonic development.

32 A fertilised egg, the very first stage following fertilisation.

33 HFEA, Third Scientific Review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception:2014 update, June 2014

> In addition, the panel recommends that the follow-up of children born as a result of these new methods should include assessment of whether any preferential expansion of the mtDNA mutations occurs over time, and that correlations are made between the general state of health of the child and degree of haplotype mismatch. This follow-up could help to inform future decisions about matching, in addition to providing information about human mitochondrial biology.

There is further discussion of concerns surrounding haplogroup mismatch in the safety considerations section of this note.

4.2 Government response to the consultation July 2014

Following the twelve week consultation on the draft regulations to introduce mitochondrial donation techniques, the overview of responses and the Government response were published on 22 July 2014. The Government had decided to proceed with the putting the Regulations before Parliament.

It received 1857 responses, which they described as representing a wide spectrum of views. 316 of the responders directed their answers to the questions on the draft regulations, the majority expressed general views in support of, or opposing mitochondrial donation in general. There was evidence of a coordinated campaign approach in some of these responses and of the total, 1,152 were opposed to the introduction of the new techniques, and 700 were in support.[34]

Those responders that were in favour of mitochondrial donation were often those with first-hand experience of the impact of mitochondrial diseases. Others, such as the British Medical Association and the Association of Medical Royal Colleges provided support generally for techniques that would prevent disease or improve life.

Amongst those who opposed the introduction of the treatments, there were a number of issues highlighted. Some were concerned that the safety of MST and PNT had not been proven, others had ethical objections and believed that mitochondrial donation should never be introduced.

Further discussion of the consultation results and the Government response is found in the sections below.

4.3 Regulations laid before the House.

On 17 December 2014, the Under-Secretary of State for Health, Jane Ellison announced that the Regulations to allow for the introduction of mitochondrial donation[35] had been laid before the house.[36] She highlighted the lengthy and transparent process of review of the evidence on safety and efficacy of the techniques, and the consultations that have taken place.

Jane Ellison also stressed that if the regulations were approved the use of mitochondrial donation would fall under the regulatory control of the HFEA. Any prospective provider would need to prove safety and efficacy of the technique in order to be granted a licence.

---

34 Department of Health, Mitochondrial Donation, Government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child, July 2014

35 The Human Fertilisation and Embryology (mitochondrial donation) Regulations 2015

36 Mitochondrial donation: Written statement - HCWS132, 17 December 2014

The Regulations have been considered by the Secondary Legislation Scrutiny Committee in the House of Lords[37] and the Joint Committee on Secondary Legislation.[38] A House of Commons debate on the Regulations has been tabled for 3 February 2015.

It has been reported that Lord Brennan QC had raised concerns over the legality of the Regulations.[39] The House of Lords Secondary Legislation Scrutiny committee commented on this issue. They noted that the JCSI had raised no legal issues relating to the Regulations, and that the Department of Health had provided a response to this legal opinion, stating it was confident that the Regulations were lawful.[40]

4.4 The Regulations

The *Human Embryology and Fertilisation (Mitochondrial Donation) Regulations 2015* allow for the use of mitochondrial donation techniques as part of an in-vitro fertilisation procedure, they apply across the UK. The Government provides information on what the Regulations allow for in its explanatory memorandum to the Regulations.[41] The Department of Health have produced a guide to the Regulations and within this it outlines the effect of each Regulation:

> In summary, each regulation has the following effect:
>
> Regulation 1: determines that, if approved by Parliament, the Regulations will be entitled The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 and that they will come into force on 29th October 2015.
>
> Regulation 2: defines the terms used in the Regulations.
>
> Regulation 3: enables an egg created by the use of a mitochondrial donation technique to be considered to be a "permitted egg" and suitable to be placed in a woman.
>
> Regulation 4: prescribes the donation technique to be used for eggs. No technique that does not match this description may be used.
>
> Regulation 5: prescribes the criteria that must be satisfied before a patient can be treated: that there is a particular risk that the patient's egg will carry a mitochondrial DNA abnormality and that there is a significant risk that a child born from the use of that egg will have or develop a serious mitochondrial disease.
>
> Regulation 6: enables an embryo created by the use of a mitochondrial donation technique to be considered to be a "permitted embryo" and suitable to be placed in a woman.
>
> Regulation 7: prescribes the donation technique to be used for embryos. No technique that does not match this description may be used.
>
> Regulation 8: prescribes the criteria that must be satisfied before a patient can be treated: that there is a particular risk that an embryo created using the patient's egg will

---

37 HOUSE OF LORDS Secondary Legislation Scrutiny Committee,23rd Report of Session 2014–15, 22 January 2015

38 House of Lords House of Commons Joint Committee on Statutory Instruments Seventeenth Report of Session 2014-15, 7 January 2015

39 Steve Connor, *New three-parent baby law 'is flawed and open to challenge', says senior lawyer*, The Independent, 14 January 2014

40 House of Lords House of Commons Joint Committee on Statutory Instruments Seventeenth Report of Session 2014-15, 7 January 2015 (Appendix 2)

41 EXPLANATORY MEMORANDUM TO THE HUMAN FERTILISATION AND EMBRYOLOGY (MITOCHONDRIAL DONATION) REGULATIONS 2015

carry a mitochondrial DNA abnormality and that there is a significant risk that a child born from the use of that embryo will have or develop a serious mitochondrial disease.

Regulation 9: specifies that a clinic already holding a treatment licence from the HFEA, to carry out IVF, cannot provide mitochondrial donation treatment without specific prior approval to do so from the Authority.

Regulation 10: introduces modifications to provisions in the Human Fertilisation and Embryology Act 1990 and the Human Fertilisation and Embryology Act 2008 that will apply where an egg or embryo has been crafted as the result of the application of a mitochondrial donation technique.

Regulation 11: determines what information may be given to a mitochondrial donor-conceived person, on application to HFEA, about their mitochondrial donor. No identifying information may be disclosed.

Regulation 12: clarifies that a mitochondrial donor-conceived person cannot be considered as genetically related to the mitochondrial donor or any person who was born as a result of treatment services using genetic material from the person's mitochondrial donor for the purposes of requesting information about whether an intended spouse, civil partner or person with whom that person has or intends to have an intimate physical relationship is genetically related to them.

Regulation 13: provides that mitochondrial donors must not be informed that a young person born as a result of their donation has sought non-identifying information about them from the HFEA.

Regulation 14: determines what information can be given to a mitochondrial donor, on application to the HFEA, about children born as a result of their donation. No identifying information can be disclosed.

Regulation 15: clarifies that the mitochondrial donor cannot be considered to be a biological parent of a person born as a result of their donation for the purposes of section 31ZE of the Human Fertilisation and Embryology Act 1990, which means that two persons with the same mitochondrial donor are not to be regarded as genetic siblings.

Regulation 16: provides that a mitochondrial donor cannot withdraw their consent to their donated egg or embryo being used in the treatment of the affected patient once it has undergone the MST mitochondrial donation technique, even if the egg or embryo has not yet been placed in the patient.

Regulation 17: ensures that for the purposes of the consent provisions in the Human Fertilisation and Embryology Act 1990, the resulting egg or embryo is not to be treated as the egg or embryo of the person whose mitochondrial DNA was used to create it.

Regulation 18: provides that where a child has been born following treatment services a person who donated mitochondria is not eligible to apply for a parental order on the basis of that donation alone. .

Regulation 19: amends the Human Fertilisation and Embryology Authority (Disclosure of Donor Information) Regulations 2004 so that they do not apply to information

requests under the Human Fertilisation and Embryology Act 1990 about mitochondrial donation.[42]

5 Ethical considerations

5.1 Germline modification and a slippery slope?

The germline refers to the genetic material which is passed down through generations of a family. If a modification to mtDNA is made it will therefore continue down the germline.

In the NCB review on the ethics surrounding the new techniques, it was concluded that they would represent a germline modification. The group advised that because MST and PNT would change the child's mtDNA, and in the case of females, this would also be passed on their children.

Some of the concerns expressed regarding germline modification included, the fact that it may cause health risks, that it is wrong to interfere artificially with the genetic inheritance of future people and that it represents 'tampering' with nature. Others, notably patients and patient groups, highlighted the values of the treatments to those suffering with these conditions:

> Women of child bearing age with these diseases are not asking for designer babies just children who will be able to grow up without devastating mitochondrial disease. The possibility of stopping the disease for the next generation, if the research was allowed to go ahead would be phenomenal. The end of mitochondrial diseases and the suffering it causes is a must for future children.[43]

The NCB review concluded that "*given the seriousness of mitochondrial DNA disorders, it is reasonable that society should permit women seeking to avoid the transmission of mutated mitochondria to access such treatment."*[44]

The NCB review also discussed the legal issues surrounding germline therapies. They drew attention to the *Universal Declaration on the Human Genome and Human Rights* issued by UNESCO in 1997. This document expresses opposition to any treatments that are contrary to a persons' dignity, such as reproductive cloning:

> Practices which are contrary to human dignity, such as reproductive cloning of human beings, shall not be permitted. States and competent international organizations are invited to co-operate in identifying such practices and in taking, at national or international level, the measures necessary to ensure that the principles set out in this Declaration are respected.[45]

However, the working group said that not all international instruments would exclude the introduction of mitochondrial donation techniques:

---

[42] Department of Health, *The Draft Human Embryology and Fertilisation (Mitochondrial Donation) Regulations 2015, A guide on new regulations to enable the use of mitochondrial donation techniques in clinical practice*, January 2015

[43] Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012. (Page 61)

[44] Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012. (Page 61)

[45] University of Minnesota, Human rights Library, Universal Declaration on the Human Genome and Human Rights, UNESCO Gen. Conf. Res. 29 C/Res.16, reprinted in Records of the General Conference, UNESCO, 29th Sess., 29 C/Resolution 19, at 41 (1997) (adopted by the UN General Assembly, G.A. res. 152, U.N. GAOR, 53rd Sess., U.N. Doc. A/RES/53/152 (1999)).

> Some international instruments would not necessarily rule out either nuclear or mitochondrial germline therapies. For example, 1997's UNESCO Declaration on the Responsibilities of the Present Generations Towards Future Generations, Art.6 states: "The human genome, in full respect of the dignity of the human person and human rights, must be protected and biodiversity safeguarded. Scientific and technological progress should not in any way impair or compromise the preservation of the human and other species."
>
> In 2005, the preamble to UNESCO's Universal Declaration on Bioethics and Human Rights, stated that "based on the freedom of science and research, scientific and technological developments have been, and can be, of great benefit to humankind in increasing, inter alia, life expectancy and improving the quality of life." It continues at Art.16: "The impact of life sciences on future generations, including on their genetic constitution, should be given due regard."[46]

The Government responded to concerns about international agreements in the response to the consultation on the draft regulations in 2014, more detail is provided below.

The HFEA consultation in 2012 sought general public views on the germline modification associated with mitochondria replacement techniques.[47] It reported that the public were generally relaxed about changing the germline; the majority felt the benefits would outweigh the risks.[48] Self-selected respondents were more varied in their views. Concerns were expressed on safety and the extent to which the consequences of changing the germline could be predicted. The HFEA responded to these concerns by highlighting the further research that was recommended before these techniques could be used clinically. They also recommended that long term follow up of patients was desirable and could be a formal condition of treatment.

The HFEA reported that the one of the principal ethical concerns raised regarding germline modification is that mitochondrial donation may open the door to further germline modification, for example with nuclear DNA. The authors argued that the technical element of this concern could be addressed through careful regulation and monitoring- if regulations were introduced they would reflect the prohibitions in the parent legislation.[49]

As far as the more conceptual issues are concerned with germline modification, the HFEA advised that these are more difficult to address. The authors said they did not know if there might be a demand in future for nuclear DNA modification but they said it was unlikely, especially as PGD offered a viable existing option for these patients. They also noted that similar concerns had been expressed when somatic cell nuclear transfer (SCNT) or cloning had been introduced for research in 2001- but there had so far been no demand for reproductive cloning following this.

Definition of genetic modification

There have been a number of Parliamentary questions related to concerns on germline modification and genetic modification. The response from the Government has been an acknowledgement that the techniques represent a germline modification but that this does not represent genetic modification.

---

[46] Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012. (Page 50)

[47] HFEA, Mitochondria replacement consultation: advice to Government, March 2013 (page 16)

[48] The methodology of the HFEA consultation is outlined in section 3.3 and detail is provided in the consultation document.

[49] HFEA, Mitochondria replacement consultation: advice to Government, March 2013 (page 19)

There was further discussion of concerns about genetic modification in the 2014 consultation. The Government stated that it has adopted a working definition of genetic modification and that they do not believe that mitochondrial donation fulfils this definition:

> There is no universally agreed definition of 'genetic modification' in humans – people who have organ transplants, blood donations or even gene therapy are not generally regarded as being 'genetically modified'. While there is no universally agreed definition, the Government has decided to adopt a *working* definition for the purpose of taking forward these regulations. The working definition that we have adopted is that genetic modification involves the germ-line modification of nuclear DNA (in the chromosomes) that can be passed on to future generations. This will be kept under review.
>
> On the basis of that working definition, the Government's view is that the proposed mitochondrial donation techniques do not constitute genetic modification.[50]

In response to concerns that these treatments would contravene international conventions and opinions, the Government stated that the UNESCO Universal declaration on the human Genome and Human Rights (DHGHR) is a statement of principle and therefore not legally binding. However, the Government supports good practice in informed choice for all patients to prevent serious illness, and does not support human eugenic practices.

In July 2014, the Independent reported that a number of scientists had criticised the Government's definition of genetic modification in response to the consultation on draft regulations.[51]

There was further discussion on the definition of genetic modification during the House of Commons Science and Technology one-off session on mitochondrial donation in October 2014. The Chief Medical Officer, Professor Dame Sally Davies responded to criticisms of the Government's working definition of genetic modification. She said that the working definition was adopted to provide clarity to the discussion:

> It seemed to us that, in order to have the discussion we were having, it was important to lay down working definitions. Germline is anything that is done to DNA that goes through the generations, and mitochondria go from woman to child through the generations. This is clearly a germline modification because it passes through, but we needed to make the distinction between nuclear DNA, which makes us who we are and how we are—our personalities, heights, weights and whether or not we get baldness—and the 37 genes in the mitochondria which are about energy for the cell, and which we describe as the power pack. That was why we adopted that working definition.[52]

5.2 The role of the mitochondrial donor

There was some consideration of the role of the donor in these new techniques within the NCB ethical review. It stated that decisions had yet to be made about whether identifiable information should be made available about the mitochondrial donor to the child. Some patients who would hope to go on and use the techniques commented that they would tell

---

50 Department of Health, Mitochondrial Donation, Government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child, July 2014

51 The Independent, Steve Connor, Exclusive: Scientists accuse government of dishonesty over GM babies in its regulation of new IVF technique, 28 July 2014

52 Science and Technology Committee, Oral evidence: Mitochondrial Donation, HC 730 Wednesday 22 October 2014, page 25

their children about their genetic connection to a mitochondrial donor, whereas others had said they would not.[53]

In conclusion the NCB group said that in their view *''motherhood' is not indicated biologically or legally by mitochondrial donation.'*[54] It did not think it was appropriate to refer to the mitochondrial donor as a mother or a third parent. It advised that the status of the mitochondrial donor should be carefully considered by regulators and parliamentarians. It did not conclude that it should be compulsory for donors to be identifiable but that there may be a place for a voluntary scheme for contact between donors and people born following PNT or MST.

The HFEA advice to the Government following the 2012 consultation highlighted that media reports had referred to mitochondrial donation as *three parent IVF*. It reported that by a slight majority, the public had not been concerned about this issue.[55]

Some of those asked rejected the idea that a treatment like this would represent three parent IVF: the tiny amount of mtDNA contributes little or nothing to personal characteristics.[56]

In response to questions on the status of a mitochondrial donor, the public held varied views on whether a child should have the right to know about the donor. Some respondents thought that there should be no identifiable information available; those providing this answer saw mitochondrial donation as similar to blood or tissue donation as opposed to sperm or egg donation. Others who favoured the child having access to this information usually expressed stronger views on the consequences of mitochondrial donation. The majority view from health professionals in this area was that there should not be identifiable information available; mitochondrial donors are more like tissue donors than gamete donors.[57]

The HFEA advised the government in their conclusions that children born as a result of mitochondrial donation should not have a right to access identifiable information about the donor but that voluntary schemes, as outlined by the NCB review, should be put in place.

In a Westminster Hall debate on mitochondrial disease in June 2013, the then Under-Secretary of State for Health, Anna Soubry said that the media had been misleading about suggesting mitochondrial donation techniques would result in three parent children:

> When the science and the real benefits are explained to people, and the fact that the child who is born has the same genetic background as their mother, they will see that the press have perhaps been a bit misleading in saying that, if it all goes ahead, some children will have three parents. They really will not: they will have their biological mother and father. It is simply that the batteries have been taken from another woman's egg so that they are sure that any child does not bear some of the very serious diseases that often lead to premature death.[58]

In response to the 2014 consultation on the regulations, the Government again reiterated that it did not accept the idea that the mitochondrial donor is in any way a third parent. They

---

53 Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012. (Page 73-74)

54 Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012. (Page 88)

55 HFEA, Mitochondria replacement consultation: advice to Government, March 2013 (page 21)

56 HFEA, Mitochondria replacement consultation: advice to Government, March 2013 (page 21)

57 HFEA, Mitochondria replacement consultation: advice to Government, March 2013 (page 24)

58 HC Deb 25 June 2013 c67WH

adopt the view that mitochondrial donation would be "*a new and distinct form of donation that falls somewhere between gamete donation and organ/tissue donation*."[59] The Government highlighted the fact that gamete donors are not treated as parents of the child so there is no justification to treat mitochondrial donors as such.

What information should be available about the donors?

The draft regulations on mitochondrial donation set out the kind of information that would be available to children about mitochondrial donors. Regulations 10-14 modify the *Human Fertilisation and Embryology Act* to enable children born as result of mitochondrial donation to access *'limited, non-identifying'* information about the donor. Family medical history and screening test results are examples of the information that could be accessed. And for the same level of information to be available to the donor about the child/children born as a result of their donation.

The consultation responses to these regulations were generally positive. There were some concerns about the age at which this information should be available and whether it should be necessary for the person to apply to the HFEA for this information. The Government decided to retain the original wording of the draft regulations.[60]

5.3 Issues of identity

The NCB considered the ethical issues surrounding identity for the children conceived from these procedures.

They said that some respondents to the review did not recognise any contribution of mtDNA to identity at all. The authors highlighted the submission from the Wellcome Trust and the Medical Research Council:

> We do not believe the transfer of mtDNA raises issues around identity, since it does not carry any genetic data associated with the normally accepted characteristics of identity. An analogy could be drawn with replacing the battery in a camera – the brand of the battery does not affect the functioning of the camera.[61]

However, the NCB working group concluded that it was difficult to draw a distinction between the impact of nuclear or mitochondrial DNA therapy and the effect on identity. If a person benefited from mitochondrial donation so that they were born without the risk of mitochondrial disease this may impact significantly on their idea of self conception of identity and genetic identity.[62]

The HFEA public consultation gathered information on public views on the impact of mitochondrial donation on identity. Those who expressed concerns suggested that children might be confused by the fact that they carry DNA from three people, that they may be

---

59 Department of Health, Mitochondrial Donation, Government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child, July 2014

60 Department of Health, Mitochondrial Donation, Government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child, July 2014

61 HFEA, Mitochondria replacement consultation: advice to Government, March 2013 (page 53)

62 Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012. (Page 56)

unhappy knowing about the creation and destruction of embryos for PNT, and that there may be potential emotional or psychological damage experienced.[63]

Those who considered there would be less of an impact on identity, if any at all, thought there was no connection between mtDNA and identity and that genes important for identity are found in nuclear DNA. Mitochondrial donation was similar to tissue or blood donation and that the impact on the child would be similar or less than those born following sperm or egg donation.[64]

6 Safety considerations

The 2011 HFEA scientific review considered safety issues relating to the use of MST and PNT:[65]

- Carryover of abnormal mtDNA from the mother's egg during the procedure might be expected. However, evidence showed that this carryover was usually less than 2% of the total mtDNA in the final embryos from both MST and PNT.

- The substances used in the processes of MST and PNT have not previously been used in conventional reproductive treatments. However the panel were reassured that these substances wash out easily and should not persist to the later stages of the treatment. They stated that as with other similar procedures, all processes involved in PNT and MST would need to be assessed for safety.

- The panel also discussed a concern about the interaction between mtDNA from the donor and nuclear DNA from the mother-haplogroup mismatch. They said there was no evidence for any mismatch between the nucleus and any mtDNA, but if this proved to be an issue it would be possible to match mtDNA from a similar ancestry to the mother's mtDNA.[66]

The NCB review echoed the concerns mentioned by the scientific review and highlighted the experimental nature of the proposed treatments. Adverse effects are unlikely to be either reversible or treatable.[67]

The NCB also reported that previous novel reproductive technologies had been introduced without extensive testing, and in this respect the approach to the potential introduction of PNT/MST represents a welcome departure. It has been the subject of scientific review following which, a programme of critical experiments had been advised. Funding has been allocated to conduct that research and this evidence can be used to inform regulation and clinical practice if this is introduced.[68]

The working group also considered the risks if regulations to allow these techniques were not introduced. It was likely children would continue to be born with mitochondrial disorders

---

63 HFEA, Mitochondria replacement consultation: advice to Government, March 2013 (page 22)

64 HFEA, Mitochondria replacement consultation: advice to Government, March 2013 (page 22)

65 HEFA, Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception, Report provided to the Human Fertilisation and Embryology Authority, April 2011

66 For further information on this- please see HEFA, Scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception, Report provided to the Human Fertilisation and Embryology Authority, April 2011 (page 28 4.3.3)

67 Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012. (Page 65)

68 Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012. (Page 66)

which may be very serious or life threatening and a group of patients would have no option available to them to have healthy children who were genetically related to them.

In their report to the Government following the public consultation and the 2013 update to the scientific review, the HFEA made several conclusions and recommendations regarding safety. With regards to the public consultation, the authors say that they attempted to gather views on social and ethical matters independent of concerns regarding safety but in practice most of the expressed views made some reference to safety.

The HFEA stated that safety was an uncertain issue in this area, which they believed the public understood:

> The public expects questions of safety to be settled by the experts and that new treatments will not be made available until there is a consensus that it is safe to move from the laboratory to the clinic. The vast majority of people trust that someone will have the expertise to decide when the techniques are safe enough to use in humans and that mechanisms for robust follow-up research will be put in place.[69]

In their report to the Government the HFEA addressed concerns relating to the safety of the new techniques. As previously mentioned in this note, the HFEA proposed two methods of addressing safety concerns:

- a set of experiments (critical and recommended) to be undertaken before the techniques can be deemed safe enough for use in human treatment.
- long-term follow-up studies in order to monitor any possible effects on children born and future generations.

They also considered the possibility of using sex selection to choose male only embryos following mitochondrial donation. This would serve as a means to avoid the effects of mitochondrial donation on any future generations. It was advised that this would involve too much manipulation of the embryo and would not be a practical option.[70]

The safety of mitochondrial donation was again discussed during the Science and Technology Select Committee One-off session. Professor Braude from the HFEA expert panel reiterated that they had not seen anything in the evidence that says that these processes are fundamentally not safe. In the next stage it is up to the regulators to ask if there is enough information.[71]

6.1 Haplogroup matching

As mitochondrial DNA is inherited maternally and passed down through generations, harmless mutations can develop that are also passed down. These mutations can form genetic patterns that are characteristic of a certain genetic lineage and are referred to as haplogroups. Concerns have been raised that a mismatch of these haplogroups could cause abnormal interactions between the mtDNA and nuclear DNA.

In the 2011 and 2013 scientific reviews the interaction between mtDNA and nuclear DNA was discussed and it was concluded that mismatch would be unlikely.

---

69 HFEA, Mitochondria replacement consultation: advice to Government, March 2013(page 15)
70 HFEA, Mitochondria replacement consultation: advice to Government, March 2013(Annex vii, page 10)
71 Science and Technology Committee Oral evidence: Mitochondrial Donation, HC 730 Wednesday 22 October 2014

A paper on mitochondrial donation was published in *Science* in September 2013, *Mitochondrial Replacement, Evolution and the Clinic.*[72] The authors expressed concerns that the interaction between mismatched nuclear and mtDNA in MST and PNT may cause more adverse health problems in children than the HFEA had addressed. The authors suggested that the possibility of matching DNA types as a way to improve outcomes should be explored by further research and that the sexual maturity of the macaques that had been born as the result of mitochondrial donation should be awaited.

The HFEA responded to the paper. It said that it had carefully considered the interaction between nuclear and mtDNA during its 2013 scientific review. It had advised that nuclear and mtDNA interaction would not be a problem- this was based on the fact that 50% of a person's nuclear DNA is inherited from the father and therefore alien to the mtDNA. Also, if this was the case, it would be expected that mitochondrial disease would be more frequent in mixed-race children as mismatch would be more likely where there is a larger variation between the parents' haplogroups. This was not the case.

The HFEA also addressed the paper's assertions that the studies on macaques had been with animals with similar DNA- the HFEA stated that the animals from two different sub-species had DNA from different lineage and the male monkeys had developed normally. However, there was still work to be done before the techniques could be used in the clinical setting.[73]

Professor Doug Turnbull, the Director of the Wellcome Trust Centre for Mitochondrial Research, also responded to the criticisms in the paper. He said that he welcomed discussion of the risks involved in the new techniques and agreed that families should be fully informed of all the science to make the best decisions. However, he did question some of the suggestions made in the paper. Professor Turnbull said the concerns had not been overlooked and the experiments cited by the authors of the report had limited relevance to humans.[74]

Two concerns were raised as potential issues during the scientific review 2014 update. Firstly, that carryover of mutated mtDNA (from the mother) during the PNT or MST process may result in some cells acquiring higher levels of mutated mtDNA than others. It was suggested that this may lead to mitochondrial disease in the child and, if female, in her offspring. The panel advised further research into early stage embryos with heteroplasmic mtDNA to look for differences in expression of the mtDNA in neighbouring cells and whether carryover of maternal mutated mtDNA resulted in this amplification.

Secondly, as highlighted in the 2013 paper above, *Mitochondrial Replacement, Evolution and the Clinic*, mito-nuclear interactions that have co-evolved may be disrupted by MST and PNT. The panel decided that the haplogroup matching of donors could be a precautionary step but it might not always be possible. They advised that this may be considered when selecting donors but that the risks of not doing so were very low:

> In conclusion, the panel considered the evidence presented concerning the two issues relating to mtDNA haplotypes: (i) that mito-nucear mismatch as a result of MST or PNT might lead to unexpected adverse effects on the offspring - albeit that this does not

---

[72] Reinhardt K, Dowling D, Morrow E, *Mitochondrial Replacement, Evolution and the Clinic,* Science 20 September 2013: Vol. 341 no. 6152 pp. 1345-1346

[73] HFEA, HFEA statement regarding the Klaus Reinhardt et al Science paper 'Mitochondrial replacement, evolution, and the clinic' 19 September 2013

[74] Science Media Centre, Expert reaction to mitochondrial replacement and evolution, 19 September 2013

> seem to occur naturally, and (ii) possible segregation in favour of any carried-over mutant mtDNA, exacerbated by unusual nuclear mitochondrial interactions. Whilst the panel acknowledges the haplogroup matching of donors could be a possible precautionary step that might ameliorate such effects should they operate in humans, they appreciate that it may not always be possible, especially when close relatives might also be at risk of transmitting the mtDNA mutations, or when the patient has an unusual haplotype compared to the possible donor population. Further evidence is needed to understand whether and how the proposed effects might be operative.
>
> The panel thus recommends that consideration is given to mtDNA haplogroup matching when selecting donors, although the panel considers that the risks of not doing so will be very low, and that there may be practical factors preventing it. In addition, the panel recommends that the follow-up of children born as a result of these new methods should include assessment of whether any preferential expansion of the mtDNA mutations occurs over time, and that correlations are made between the general state of health of the child and degree of haplotype mismatch. This follow-up could help to inform future decisions about matching, in addition to providing information about human mitochondrial biology.[75]

It was also noted during the HFEA scientific review that the macaques born as result of MST techniques had reached sexual maturity and had shown no sign of abnormality. They are to be entered into a breeding programme to assess their fertility.[76]

Following the publication of the Government response to the consultation on draft regulations to introduce mitochondrial donation, Dr Morrow wrote in the Guardian that he believed "*a number of important safety concerns remain unresolved."* He highlighted that no further research had been recommended to look at mtDNA mismatch and that he believed this represented a reasonable safety concern that was being ignored.[77]

Dr Greenfield, the chair of the HFEA panel responded to this article. He stated that Dr Morrow's submissions had been considered. It was decided that the views submitted on mismatch were not sufficiently established to justify a reassessment of other scientific views on the safety of mitochondrial donation:

> Among other things, the panel felt that the data he submitted related to inbred mice and *Drosophila* in a way that did not materially contribute to an understanding of a predominantly outbred human race, and also noted that data obtained in large-scale human genome projects looking for disease associations have not found any consequences due to the exchange of mitochondrial DNA (mtDNA) haplogroups by reproduction. The panel also consulted other scientists with expertise in evolutionary biology, who, while also raising the hypothetical issue of mismatching, assessed the situation differently from Dr Morrow.[78]

He emphasised that "*safety is and always will be of paramount importance*."

During the Science and Technology Select committee one-off session on mitochondrial donation, Dr Morrow again reiterated his concerns about mtDNA mismatch. He said that he believed the HFEA expert panel had not taken the risks seriously and he thought it was a risk

---

75 HFEA, Third Scientific Review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception:2014 update, June 2014

76 HFEA, Third Scientific Review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception:2014 update, June 2014

77 The Guardian, Safety concerns remain over three-person IVF, 22 July 2014

78 The Guardian, HFEA panel on mitochondrial replacement considered all submissions, 24 July 2014

that parents should be made aware of. Professor Braude, a member of the expert panel, stated that they had spent an inordinate amount of time considering mitochondrial interactions. In the end, they had recommended that consideration be given to mtDNA haplogroup matching, bearing in mind the practicalities of doing it.[79]

For more detailed information on haplogroup matching please see Annex B

7 How would these treatments be regulated?

Regulation has been an important consideration throughout the stages of review for these new techniques.

The NCB in its report on the ethical review recommended that those who have a child using the new procedures should be encouraged to commit to very long term follow up of their children. In order to facilitate this, they proposed that a centrally held comprehensive register of all such procedures be maintained and kept with access allowed for researchers. The Department of Health should confirm that funding would be available for such a register.[80]

The NCB working group advised that all previous regulations for egg donors should apply to those donating eggs for MST and PNT. With regard to sperm donors, the NCB did not think that those who donate sperm to fertilise an egg to be used for its mitochondria should be subject to the same regulation as sperm donors who fertilised eggs in order to create embryos. Primarily, he should not be required to be identifiable.

The NCB also advised that counselling should be provided to all those who hoped to use mitochondrial donation techniques in future. It said, in their experience, counselling for those who now sought PGD was variable and with the new procedures there should be extra opportunities available. It advised that patients should have access to a counsellor with specific training within a specialist unit in order to discuss options in a thorough way.[81]

The HFEA's advice to Government in March 2013 provided recommendations on the regulation that these techniques should be subject to, if they were to be introduced into clinical practice. Under models currently in place, the HFEA would only allow certain specialist clinics to offer these treatments.

Following consideration of a number of options for accessing treatments the HFEA concluded that regulation of mitochondrial donation should:

- ensure the techniques are only used to avoid serious mitochondrial diseases in cases where clinical specialists have deemed it to be appropriate
- require the HFEA to approve each licensed centre wishing to offer mitochondria replacement as a clinical treatment

In order to future-proof the Regulations, they should provide flexibility for the HFEA to design a process for approving the use of mitochondria replacement in individual cases. Given the novel nature of these treatments, we recommend that the HFEA

---

[79] Science and Technology Committee Oral evidence: Mitochondrial Donation, HC 730 Wednesday 22 October 2014

[80] Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012. (Page 90)

[81] Nuffield Council on Bioethics, Novel Techniques for the prevention of mitochondrial DNA disorders: an ethical review, June 2012. (Page 89)

> approves the use of mitochondria replacement on a case-by-case basis. It may be appropriate in the future to move to a more localised, clinic-based approval process.[82]

The mitochondrial donation draft regulations for consultation provide information on how these services would be regulated by the HFEA:

> Regulations 5 and 8 provide that the Human Fertilisation and Embryology Authority must have issued a determination there is a particular risk that egg or embryo A may have a mitochondrion abnormality caused by mitochondrial DNA, and that there is a significant risk that a person with that abnormality will have or develop a serious physical or mental disability, a serious illness or other serious medical condition.
>
> Regulation 9 makes supplemental provision to provide that existing treatment licences do not enable the use of embryos and eggs permitted under the regulations and to clarify that any new licence issued will require express provision to enable the use of such eggs or embryos.[83]

Comments from the consultation tended to agree that the HFEA should have this regulatory role. Some said that this approval process could be relaxed with time and this would prevent it becoming overly burdensome and slow. Some proposed that further down the line a condition by condition framework could be used, and others, including the Medical Research Council suggested that it may be appropriate for the HFEA, in future, to assess a particular centres ability to evaluate patients.[84]

Some respondents, including the Nuffield Council on Bioethics, thought that decisions on a case by case basis should be made by the clinicians that were closer to the patients and better placed to make an assessment.

The Government response to the consultation confirmed their intention to stick to the regulatory approach as set out in the draft regulations:

> The Government is firmly of the view that there must be strict regulatory controls on the use of the mitochondrial donation techniques in treatment so that an assessment must be made of the cases for which approval is sought to ensure they fulfil the requirements with regard to the risk of an embryo or egg having an abnormality and the severity of the likely condition arising from that abnormality. The Government acknowledges the very important points made by respondents in respect of ensuring that the process of assessment of risk is kept under review as the technique develops. However the Government does not believe that the consultation has identified any viable alternative approach to assessment that would ensure the necessary level of safeguards and consistency of approach and has therefore concluded that Regulations 5 and 8, as currently drafted, with the HFEA as the assessing body, will provide for the most robust and effective regulation.[85]

The detail of the current draft Regulations laid before Parliament is provided in Section 4 of this note.

---

82 HFEA, Mitochondria replacement consultation: advice to Government, March 2013 (page 33)

83 Department of Health, Mitochondrial donation: Consultation on draft regulations, February 2014 (page 35)

84 Department of Health, Mitochondrial Donation, Government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child, July 2014

85 Department of Health, Mitochondrial Donation, Government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child, July 2014

The issue of follow up for those born following the use of these techniques was discussed during the House of Commons Science and Technology Select Committee one-off session on mitochondrial donation. There was a consensus from scientists, regulators and the Minister that follow up was very important. It was hoped that it would be generational so that children could be monitored. Peter Thompson, the Chief executive of the HFEA said that he did not think that ethically follow up could be compelled but that a clinic should have all the processes in place to ensure follow up and that the benefits of this should be explained to patients.[86]

Overseas patients seeking treatment with these techniques were also discussed at the session. Peter Thompson said that if someone came to the UK to use a clinic licenced here then the processes would be the same. The Under Secretary of State for Health reported that NHS patients would be the priority and the Chief Medical Officer, Professor Dame Sally Davies stated that overseas patients would pay the full cost for treatment, the NHS would not be subsidising it.[87]

8 Opposition to the proposed techniques

This section does not provide a comprehensive list of all those that have expressed opposition to mitochondrial donation techniques, but provides an overview of some of them.

These techniques are new and propose a change to an embryo's DNA prior to implantation. As such, they have been the subject of some opposition and controversy. Opposition to the techniques was expressed during the HFEA consultation by a number of organisations, including faith and pro-life groups. A detailed consideration of responses to the open questionnaire, which outlines the views of stakeholders, is provided by the HFEA alongside their advice to the Government in 2013.[88] Some of the ethical and safety concerns that have been raised are discussed in more detail earlier in this note.

The Government reported in July 2014 that they received a number of responses to the consultation on draft regulations that were opposed to the introduction of mitochondrial donation. Most of these respondents believed that the techniques crossed unacceptable ethical lines and should never be allowed. They also believed that mitochondrial donation would lead to three parent children.[89]

Dr David King, Director of Human Genetics Alert (an independent watchdog organisation) has been a vocal opponent of the new techniques. He has said that they are dangerous and unnecessary.[90] In June 2013, Dr King criticised the advice provided by the HFEA to the Government as being based on a '*biased and inadequate consultation.'* He said that the majority of views in the consultation were actually against the introduction of mitochondrial

---

86 Science and Technology Committee Oral evidence: Mitochondrial Donation, HC 730 Wednesday 22 October 2014

87 Science and Technology Committee Oral evidence: Mitochondrial Donation, HC 730 Wednesday 22 October 2014

88 HFEA, Medical frontiers: debating mitochondria replacement. Annex IV: Summary of responses to the open consultation questionnaire, 2012

89 Department of Health, Mitochondrial Donation, Government response to the consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child, July 2014

90 BBC News, James Gallagher, Three person IVF is 'ethical' to treat mitochondrial disease, 12 June 2012

donation techniques.[91] The HFEA strongly refuted his suggestions, noting that the consultation was made up of a number of strands:

> One strand of the consultation showed a small majority against mitochondria replacement and those people tended to have broader concerns about IVF.
>
> In all the other public engagement strands a majority of respondents and participants supported the use of mitochondria replacement.
>
> We used a range of methods to explore these complex issues. Our consultation was a more nuanced exercise than simply counting up votes for and against the techniques.[92]

In October 2013 a group of 34 Members of the Council of Europe (including 8 British MPs and peers) signed a declaration against the introduction of mitochondrial donation.[93] The declaration was submitted by the Labour MP, Mr Jim Dobbin, and stated that mitochondrial donation techniques were incompatible with human dignity:

> The undersigned members of the Parliamentary Assembly affirm that the creation of children with genetic material from more than two progenitor persons, as is being proposed by the United Kingdom Human Fertilisation and Embryology Authority, is incompatible with human dignity and international law.[94]

9 Parliamentary activity

9.1 Westminster Hall 12 March 2014

Mr Jacob Rees-Mogg MP tabled a 30 minute Westminster Hall debate, *Mitochondrial Transfer (Three-Parent Children)*.[95]

Mr Rees-Mogg expressed concerns about a number of issues related to mitochondrial donation. He said he believed that the techniques amounted to eugenics and that their use could lead to a slippery slope:

> Many of us have imperfections, but they make up humanity, and the mixed variety of interest, thoughtfulness and development that is humanity often comes from our faults, as well as our abilities. It is a fundamentally dangerous road to start down because, although the technique cannot at this stage affect eye colour, some clever scientist will eventually work out how to ensure that babies have blue eyes and blonde hair, or whatever people want. Every time something like this happens, we go to the next stage and the argument becomes, "Well, we've done this, so it is logical to continue." When that line has been crossed, the argument against going further is merely a matter of degree; it is not absolute.[96]

Mr Rees-Mogg stated that there were three main categories of risk involved with the techniques. Firstly, he identified practical risks relating to the long term efficacy and safety of the techniques. He also said that there were moral and ethical concerns related to the dignity of the human being. Finally he highlighted a legal risk- that use of the techniques

---

91 Human Genetics Alert, Decision to allow human genetic manipulation is not supported by the public, 28 June 2013

92 HFEA, HFEA refutes David King's suggestion that public opinion in the 'Medical Frontiers: Debating mitochondria replacement' consultation was misrepresented, 28 June 2013

93 Three parent babies 'incompatible with human dignity', The Telegraph, 4 October 2013

94 Creation of Embryos with Genetic Material from More than Two Progenitor Persons, Written declaration 557, Council of Europe, 3 October 2013

95 HC Deb 12 March 2014 c164WH

96 HC Deb 12 March 2014 c169WH

would be in infringement of the European Union Charter of Fundamental Human Rights. A number of other Members also expressed concerns about the proposed techniques.

In response to the debate, the Under-Secretary of State for Health, Jane Ellison outlined that the regulations will be subject to the affirmative procedure and that the matter would be debated on the floor of the House. She also said that she was sure that this would be the subject of a free vote.[97]

Jane Ellison said that parliamentary briefings would be arranged with some of the scientists involved and the Chief Medical Officer. She said the views expressed in the debate had served to identify some areas of particular concern and would help direct preparation for future debates.

9.2 Backbench Committee Debate 1 September 2014

A group of MPs tabled a Backbench Committee debate on 1 September 2014 on mitochondrial donation. The motion highlighted public safety issues around the techniques:

> That this House has considered the Human Fertilisation and Embryology Authority's most recent scientific review into the safety and efficacy of mitochondrial replacement techniques which highlights concerns for subsequent generations of children born through maternal spindle transfer and pronuclear transfer; welcomes the recent comments of scientists including Professor Lord Winston that, prior to the introduction of such techniques, more research ought to be undertaken and a full assessment conducted of the potential risk to children born as a result; and calls upon the Government, in light of these public safety concerns, to delay bringing forward regulations on mitochondrial replacement.[98]

In the Times on 25 August 2014, Lord Winston had expressed his support for the introduction of mitochondrial donation techniques. He said he would vote for them and criticised MPs opposing the regulations for '*quoting him out of context*.'[99] He believed this had led to the impression being given that the medical establishment had serious concerns about the regulations. In June 2014 in the Independent, Lord Winston had suggested that there probably needed to be more research to help ensure safety:

> "The idea of replacing [defective] mitochondria with mitochondria that don't have the defect is a wholly good thing to do," Lord Winston says. "The problem is that I don't believe there has been enough work done to make sure mitochondrial replacement is truly safe. There probably needs to be a great deal more research in as many animal models as possible before it's done." [100]

Numerous Members spoke during the debate on 1 September 2014, and expressed views both supporting and opposing the motion. A brief overview is included here.

Fiona Bruce MP introduced the motion and outlined concerns about the safety of the mitochondrial donation procedures. She suggested that to allow the procedures at present

---

97 HC Deb 12 March 2014 c170WH

98 Future Business for 22 July 2014

99 The Times, Hannah Devlin, Three-parent IVF 'will stop diseases being inherited', 25 August 2014

100 The Independent, Steve Connor, Lord Winston criticises 'jungle' world of British fertility treatment, 15 June 2014

would be "*tantamount to experimentation*[101]*."* She said that it would be wrong for parliament to agree to the regulations before safety had been established:

> It is vital that, taking advice from scientists, the decision about whether to proceed down this road is made by this House and is seen to be made by the public. It would be wrong for Parliament to pre-emptively sign off the legislation even if there were a provision in the regulations saying that the Government would not move to implementation until such time as the HFEA said it was content with the outcome of the pre-clinical report. That would be to outsource the final decision to technocrats, possibly behind closed doors, rather than in the transparent environment of this Chamber, in full public view. Parliament cannot be seen to provide pre-emptive mandates in relation to a subject on which there are such significant public safety concerns. We need scientists and experts to conduct the research but we must make the final decision.[102]

A number of Members spoke in support of these views, and others expressed ethical concerns regarding the new techniques. Sir Edward Leigh stated there was an almost universal international consensus rejecting germline modification, and to proceed with the regulations could be making the UK a rogue state. [103]

A significant number of Members spoke in favour of the introduction of mitochondrial donation, David Willetts, amongst others, said it was a "*great piece of British scientific advancement*" and addressed some of the concerns raised by other Members. He said this was not a technique that would affect human identity, it would not lead to a slippery slope, and it did not represent eugenics.[104]

Dr Sarah Wollaston spoke in support of the new techniques, she said it was right that the House debates the ethics, but that some of the language used had clouded the arguments. It was the place of the expert panel and the HFEA to examine the evidence and advise on these matters and that the treatments were about wanting to save people from serious medical problems:

> Of course it is absolutely right that the House debates the ethics, as so many Members have pointed out, but at times the language used has clouded those arguments. We have heard terms such as "eugenics", "three-parent babies", "designer babies". This is not about wanting to create a child who is more beautiful or more intelligent. This is about wanting to spare families and children from a lifetime of devastating medical problems. We have the potential to do that. I fully respect those who oppose this on ethical grounds—they are entirely consistent in their view—but I am concerned that there has been selective misquoting from the scientific evidence. The House is not really qualified to examine the evidence in detail, and that is why we have expert panels, and bodies such as the HFEA, to advise and regulate this, and they do so with a great deal of thoughtfulness and expertise.[105]

Jane Ellison, the Under-Secretary of State for Health responded to the debate. She denied that the process of reviewing mitochondrial donation had been rushed. She outlined the stages that had been gone through so far. However, she did note that research cannot

---

[101] HC Deb 1 September 2014 c93
[102] HC Deb 1 September 2014 c96
[103] HC Deb 1 September 2014 c112
[104] HC Deb 1 September 2014 c97
[105] HC Deb 1 September 2014 c112

answer all the questions and the decision about whether a new technique can be called safe is never absolute.

In response to a number of Members raising concerns about three parent babies, she said that parenthood could not be reduced to a matter of genes, it is about so much more than that. Parliament must consider all the issues, and the Government will continue to consider the expert advice it has received:

> This has been a thoughtful debate, and it is vital that Parliament discusses such matters openly and considers all the issues. For those who are not opposed in principle, we must consider all the evidence alongside the benefits that this treatment can bring, and make that consideration in a rational way. The Government will, of course, continue to consider the expert advice we have received and how that influences regulations before they are brought before Parliament for further debate. We believe that this is an important scientific advance that holds out great hope for families in this country and around the world.[106]

The motion was put to the House and agreed to.

9.3 House of Commons Science and Technology Select Committee session

The House of Commons Science and Technology Select Committee held a one off evidence session to consider the science of mitochondrial donation on 22 October 2014. The Committee heard from scientists in the field, the chief executive of the HFEA and the Under-Secretary of State for Health, Jane Ellison amongst others. A full transcript and video of the session are available on the Committee webpage.

Following the session, the Chair of the Committee, Andrew Miller MP wrote to the Under-Secretary of State for Health.[107] He said that following hearing from the scientists, regulators, the Minister and considering all the other information received by Committee, the Committee had concluded that '*there is sufficient information for Parliament to come to a rational conclusion about these technologies.'* The letter urged the Minister to lay the Regulations before Parliament as soon as possible to provide good time for all MPs and Peers to consider the details ahead of the debate.

---

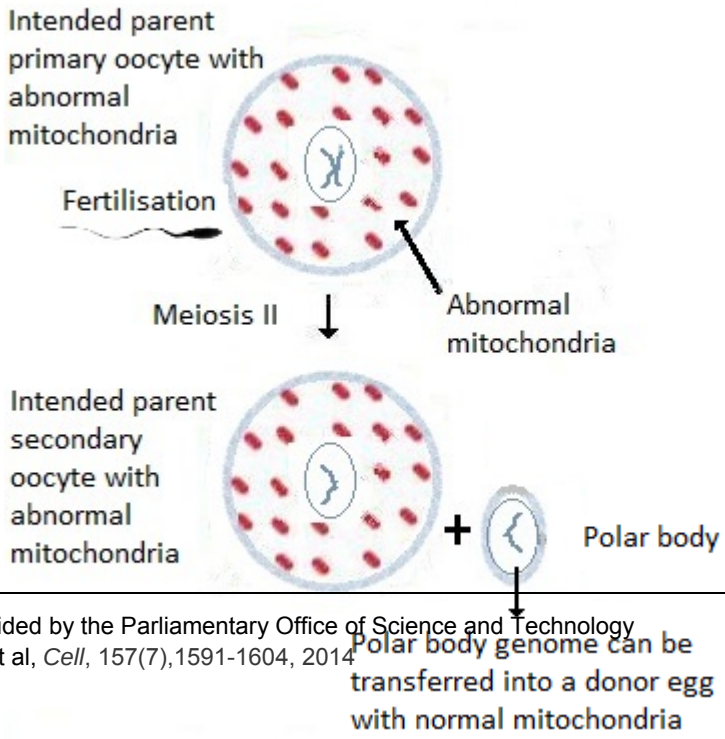
[106] HC Deb 1 September 2014 c122

[107] Science and technology Committee, Letter to Jane Ellison, 30 October 2014

10 Annex A: Other mitochondrial transfer methods[108]

10.1 Polar body genome transfer

In June 2014, a paper published in the Journal *Cell* described a new technique for mitochondrial replacement in mice.[109] Known as polar body genome transfer, the technique is similar to MST and PNT insofar as it involves transferring a 'packet' containing the intended mother's nDNA to a donated egg with normal mitochondria which has had its nucleus removed. The difference is that the source of the maternal nDNA is not from one of the intended parent's eggs, but rather from the polar body that is formed as part of the cell division that gives rise to the mature egg (secondary oocyte, see figure below). As shown in the figure below, the primary oocyte has two copies of every chromosome. A reductive cell division called meiosis results in the formation of the secondary oocyte plus a polar body, each of which contain just a single copy of each chromosome. This division is asymmetric – virtually all of the cytoplasm and mitochondria end up in the secondary oocyte, with very little in the polar body. This lack of mitochondria is seen as one of the potential advantages of using the polar body as the source of maternal nDNA, as it may reduce the chance of carry-over mtDNA being associated with the transfer.



[108] Kindly provided by the Parliamentary Office of Science and Technology

[109] Wang T et al, *Cell*, 157(7),1591-1604, 2014

To date, no research has been reported using polar body genome transfer in human eggs. Human polar bodies have been used as a source of DNA for diagnosing whether an egg is likely to have chromosomal abnormalities and to screen for genetic diseases such as cystic fibrosis.[110]

In October 2014, following a request from the Department of Health, the HFEA expert panel reviewed the safety and efficacy of polar body transfer and published a report of its findings and recommendations in October 2014.[111]

The panel concluded that developments in this area are likely to be rapid in the coming years. Its recommendations as regards critical required experiments on polar body transfer are similar to those required for MST and PNT:

- Polar body 1 transfer (PB1T) using human oocytes that are then fertilised (not activated), and comparative follow up of development in vitro. *This could include a molecular karyotype analysis of PB2T.*

- Polar body 2 transfer (PB2T) using normally fertilised human oocytes, from which the maternal pronucleus has been removed, and development compared to normal ICSI-fertilised human oocytes. *The panel highlighted the importance of demonstrating a robust method for distinguishing the maternal and paternal pronuclei, such that the maternal pronucleus can be reliably selected for removal.*

They also recommended further experiments as desirable. However, the panel reported that, even though this technique might be at early stages there may offer advantages over MST and PNT. Some of those possible advantages included, a reduced chance of carryover and a reduced risk of leaving chromosomes behind compared with MST.

10.2 Cytoplasmic transfer

Cytoplasmic transfer was developed as a fertility treatment in the USA in the early 1990s. It is not a technique that is permitted under UK regulations, nor can it be used to avoid mitochondrial disease. It was used as a treatment for women who repeatedly failed to produce healthy embryos following IVF treatments. The treatment involves transferring cytoplasm from an egg of a fertile donor into an egg from the woman receiving IVF. In the most common form of the treatment, cytoplasmic transfer was combined with ICSI (intra-cytoplasmic sperm injection) with the intended mother's egg being injected with a single sperm from the intended father along with 5-15% of the donor egg cytoplasm.[112]

Cytoplasmic transfer has proved successful in some cases. For instance, in one US clinic, 30 fertilisations were reported, leading to 13 pregnancies among women who had previously

---

[110] Griesinger G et al, *Deutsches Arzteblatt International*, 106 (33), 533-38, 2009

[111] HFEA, Review of the safety and efficacy of polar body transfer to avoid mitochondrial disease: Addendum to 'Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2014 update, October 2014

[112] Barritt JA et al, *Human Reproduction Update*, 7, 428-35, 2001

been unable to produce healthy embryos. Two foetuses had chromosomal abnormalities (a missing X chromosome); one spontaneously aborted, the other was terminated at 16 weeks.[113] It is not known whether these abnormalities were related to the treatment, nor what active component or components of the treatment resulted in successful pregnancies. It is thought likely that factors in the donated cytoplasm such as mitochondria, nucleic acids or proteins increased the chances of normal embryo development. It has been shown that embryos resulting from the treatment contain mtDNA from both the mother and the egg donor.[114]

An estimated 30-50 babies have been born worldwide following cytoplasmic transfer, mainly in the USA. In 2001, the US Food and Drug Administration wrote to fertility clinics and practitioners offering the treatment advising them that it had jurisdiction over treatments that alter the DNA of human cells. This had the effect of banning cytoplasmic transfer in the USA, since the treatments could only be offered as part of an FDA sanctioned investigational new drug programme. The FDA's intervention was based on ethical and safety concerns. Fertility clinics elsewhere in the world (for example in Cyprus, Dubai and the Czech Republic) continue to advertise cytoplasmic transfer as an available option.

10.3 Mitochondria transfer

Mitochondrial transfer is a treatment that involves purifying mitochondria from a patient's own ovarian cells, and transferring the purified extract into one of her eggs in an attempt to enhance fertility. There is evidence from animal studies that such an approach can lead to beneficial effects on early embryo development in species such as pigs, cows and mice. A briefing paper for the US Food and Drug Administration refers to a single trial in humans among 20 female patients with a history of IVF failure in Taiwan in the early 2000s.[115] The technique increased pregnancy rates and resulted in 20 live births. No follow up study has been published to date. The technique is not permitted under UK regulations, nor would it be effective in preventing mitochondrial disease.

[113] *Ooplasm transfer as a method to treat female infertility*, US FDA, May 2002
[114] Brenner CA et al, *Fertility and Sterility*, 74, 573-78, 2000
[115] Cellular, Tissue, and Gene Therapies Advisory Committee, FDA briefing document 59, February 2014

11 Annex B: Mitochondrial matching[116]

The government has announced its intention to put regulations before Parliament to allow the use of the new treatments to prevent serious mitochondrial disease. No timetable for this has been published, but the government has said that the timing will take account of discussions with HFEA about an appropriate approval process and progress towards additional research recommended by the HFEA expert panel. This briefing examines whether there is a need to match the genetic lineage of the donor mtDNA (haplogroup or haplotype, see Box 1) to that of the mother. This has been the subject of considerable debate in recent academic literature[117,118]. The HFEA expert panel considered two potential concerns in its 2014 report[119]:

- mismatches – the idea that changing the haplotype (Box 1) of mtDNA through PNT or MST may interfere with the mtDNA-nDNA interactions needed for energy production

- segregation – concerns that a small amount of the mother's faulty mtDNA may be carried over with the transfer of the nDNA and might become segregated amplified in certain tissues or organs in the resulting child.

11.1 Mismatches between mtDNA and nDNA

Mismatches between mtDNA and nDNA have largely been studied in fruit flies and mice. Researchers have made hybrid fruit flies that contain nDNA from one sub-species and mtDNA from another. They have identified several mtDNA/nDNA combinations that resulted in effects such as developmental problems, infertility, accelerated ageing and impaired mitochondrial function in males.[120] In mice, experimentally induced mtDNA/nDNA mismatches have been linked to a range of effects including impaired physical performance[121] and modified cognition[122] and respiration[123.]

Such findings have led some researchers to suggest that replacing mtDNA using MST or PNT could disrupt the subtle mtDNA/nDNA interactions that have co-evolved over many generations. However others question the significance of the findings to MST or PNT use in humans. They suggest that the findings are of limited significance because:

- the strains of fruit flies and mice used in the studies were highly inbred to ensure uniformity of the nDNA between individuals whereas most human populations are outbred

- the mtDNA/nDNA combinations came from different strains or sub-species – it is unclear whether the genetic variation between these is representative of the variations seen in human populations

- there is no evidence of adverse health effects in children born to couples with divergent haplogroups such as those born to mixed race couples

---

[116] Kindly provided by the Parliamentary Office of Science and Technology
[117] Reinhardt K et al, *Science*, 341, 1345-46, 2013
[118] Chinnery PF et al, *PLoS Genet* 10(6): e1004472, 2014
[119] *Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception,* HFEA, 2014
[120] Innocenti P et al, *Science* 332845-48, 2011
[121] Nagoa Y et al, *Genes and Genetic Systems*, 73 (1), 21-27, 1998
[122] Roubertoux PL et al, *Nature Genetics*, 35, 65-69, 2003
[123] Moreno-Loshuertos R et al, *Nature Genetics*, 38, 1261-68, 2006

- no mismatches have been observed in the animal model that is closest to humans (a study of four macaques born following MST that have now reached sexual maturity)[124].

Box 1. Variations in mtDNA sequences
mtDNA has a relatively high mutation rate compared to nDNA. Any changes that arise in the mother's mtDNA are passed directly on to the next generation. Those changes that confer an advantage in a particular place are likely to be retained over time, while those that are disadvantageous are more likely to be lost. This means that different patterns of mtDNA sequence have emerged that are characteristic of different geographical locations. The main classes of such patterns are known as haplogroups. Within these main groups there are other mtDNA variations that are known as haplotypes.

11.2 Segregation of mutated mtDNA

Small amounts of the mother's mutated mtDNA may be transferred to the donor egg along with the structure containing the mother's nDNA. The levels of mutated maternal mtDNA detected are too low (less than 1-2% of total mtDNA)[9] to cause mitochondrial disorders provided that the mutated mtDNA is evenly distributed in all tissues and organs. However, there are two possible ways that the mutated mtDNA might be segregated into specific cells:

- if the mtDNA haplotype that carries disease mutations has a competitive advantage in some types of tissue compared to the donor mtDNA haplotype. Research in mice that have two distinct mtDNA haplotypes has shown that segregation can occur; one distinct mtDNA haplotype was found in high levels in liver and kidney tissue, with the other predominating in blood and spleen[125].

- because of the bottleneck effect.[9] Mitochondria are in very short supply/high demand in the early embryo. This means that, following cell division, each daughter cell is allocated a relatively small number of mitochondria, which it then uses as templates for making more. If a cell is randomly allocated a disproportionately high number of mutated mitochondria during cell division, then it - and the cells that develop from it - may contain high enough levels of mutated mtDNA to cause disease.

In order to address these potential concerns the HFEA expert panel made a number of recommendations for further research in its 2014 report[9]. In particular it recommended that research on early stage (8-16 cell) human embryos containing two different variants of mtDNA should be conducted as "a critical experiment" to investigate the extent to which neighbouring cells' mtDNA composition varies. It also recommended further research using human embryonic stem cells and specialist cells derived from them which had: a) been created using MST or PNT and b) contained two different types of mtDNA to investigate the extent of mtDNA carry over/amplification. Finally, the expert panel is currently considering another potential treatment (polar body genome transfer). This is similar to MST and PNT but the maternal nDNA is taken from a polar body, a residual cell formed during the development of oocytes (eggs) that contains few mitochondria and may thus minimise mtDNA carry-over.

[124] Tachibana M et al, *Nature*, 367-72, 2009
[125] Jenuth JP et al *Nature Genetics*,.14, 146-51, 1996

11.3 Matching haplogroups

The most recent report from the HFEA expert panel[9] considered the evidence on mismatches and segregation. It recommended that "consideration is given to mtDNA haplogroup matching when selecting donors". However it considered the risks of not doing so as being "very low" and noted that there may be "practical factors preventing it". In practice, close female relatives of the mother might be approached as potential egg donors, as they are likely to have the similar haplogroup and haplotype. Mothers who have no suitable female relative to act as a donor, or those with a less common haplogroup may face a long wait to find a suitable donor.

The expert panel also recommended[9] the follow-up of any children born as a result of the new methods. It noted that this should include the following:

- assessment of whether any preferential expansion of mtDNA mutations in the children occurs over time
- correlations between the general state of health of the child and degree of haplotype mismatch

- testing the eggs of females born as result of the treatments who wish to have a child of their own for signs of mutated mtDNA.

Such follow up could help to inform future decisions about haplogroup matching. Further research might allow donors to be screened for advantageous traits with respect to the mother's nDNA. For instance, it might one day be possible to deliberately choose a donor carrying a haplogroup that has a selectable advantage and which would thus out-compete any mutated mtDNA carried-over from the mother[9].