

Mitochondrial Donation

Response to a Department of Health 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

**from
Christian Medical Fellowship**

The Christian Medical Fellowship (CMF) has over 4,000 doctor members and around 1,000 medical student members and is the UK's largest faith-based group of health professionals. A registered charity, it is linked to about 70 similar national bodies in other countries throughout the world.

Question 1: Regulation 2 defines the removal or insertion of nuclear DNA involved in mitochondrial donation. Do you agree with this definition?

Maternal Spindle Transfer (MST) and Pronuclear (PNT) techniques are usually described as forms of 'mitochondrial replacement' or 'donation', or are sometimes referred to as nuclear replacement techniques.

However, as made clear in the more detailed biological description of both these procedures provided by the HFEA as part of its public consultation, it is the entire cytoplasm that is transferred during both procedures along with the actual mitochondria containing the chromosomes.

It is not just new mitochondria that are being harvested from a defective unfertilised or fertilised egg but the whole new unfertilised or fertilised egg which has been emptied of its maternal spindle or pronuclei, respectively. Mitochondria only form a tiny part of this new egg.

The mitochondria are certainly not taken out of one egg and safely transplanted into another egg, from which all or most of the latter's mitochondria have already been removed. This is in reality cell nuclear replacement.

It is unfortunate and somewhat disingenuous that the DH, HFEA, Government ministers and MPs are using the technically inaccurate and highly misleading term 'mitochondria replacement'. Presenting MST and PNT as 'mitochondrial replacement' misrepresents reality while making it difficult for the general public to make an informed decision about the procedures and the grave ethical difficulties which they raise for both individuals and the whole of society.

Question 2: Regulations 4 (eggs) and 7 (embryos) only allow mitochondrial donation where all the nuclear DNA is transferred from an egg or embryo to another egg or embryo from which all the nuclear DNA has been removed. Do you agree with this description and restriction?

As explained above, the process described is not *mitochondrial donation*. It is, more

accurately, the entire cytoplasm that is transferred during both procedures along with the actual mitochondria containing the chromosomes.

It is not just new mitochondria that are being harvested from a defective unfertilised or fertilised egg but the whole new unfertilised or fertilised egg which has been emptied of its maternal spindle or pronuclei, respectively. Mitochondria [only form a tiny part](#) of this new egg.

Question 3: Regulations 5 (eggs) and 7 (embryos) require that, in order to agree that mitochondrial donation can go ahead, the HFEA must decide if there is both a particular risk that the egg or embryo of the patient has a mitochondrial abnormality and a significant risk that a person with the particular mitochondrial abnormality will have or develop a serious physical or mental disability, a serious illness or other serious medical condition. Do you agree that the HFEA should have this role?

We question how any organisation or body, including the HFEA, will be able to assess and weigh up the risk of a child perhaps developing a 'serious' (currently undefined) mitochondrial disorder at some point, against the unknown health risks that these new techniques will *themselves* raise for the child.

We suspect that the HFEA will not be in a position to do so, and nor will it have the expertise to define and decide what is the meaning of 'significant' risk or 'serious medical condition'. The lack of definition of the terms 'substantial' and 'seriously' in the Abortion Act 1967 has put doctors in the unenviable position of deciding what degree of handicap qualifies for legal protection and what does not. There is no consensus. These highly subjective terms are commonly given a wide scope of meaning, often beyond the original legislative intention.

We do not believe it will ever be safe or justified (or indeed ethically acceptable) to permit what is effectively a set of experiments to create human life, making irreversible genetic changes that will pass down generations, even if there is a risk that a mother will otherwise have a child who develops a mitochondrial disorder.

The Regulatory Triage Assessment, states that a basis for the rationale for intervention is that research has advanced to a point where it is suitable for clinical use (p36).

We strongly disagree with the Regulatory Triage Assessment. These 'therapies' are not proven to be suitable or safe enough for clinical use. Indeed, they are not 'mitochondrial donation *therapies*' (p36) but are mitochondrial donation techniques used to create a new embryo.

The HFEA proposed that a series of critical tests be conducted prior to proceeding with PNT and MST (*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. Paragraph 5.4*). Rather than awaiting the publication of the tests and their findings, however, the Government has proceeded to publish draft regulations before knowing these techniques are safe to use to create humans.

Evidence presented to the HFEA suggests that the application of this technology may well be more unpredictable, complex and limited (to certain combinations of haplogroups) than is now being claimed by the HFEA (Non-confidential evidence to Mitochondria Review, HFEA, 2011.).

Nuclear-mitochondrial compatibility is essential for nuclear transfer. Several scientific journal articles have highlighted concern that disrupting the 'fine-tuned' relationship between the nuclear and mitochondrial gene complexes will adversely affect health of the offspring (For example, Klaus Reinhardt, Damian K. Dowling, Edward H. Morrow. Mitochondrial Replacement, Evolution, and the Clinic. *Science*. 20 September 2013: Vol. 341 no. 6152 pp. 1345-1346. See also http://www.hfea.gov.uk/docs/Mito-Annex_VIII-science_review_update.pdf).

The macaque study by Tachibana et al, reported in Nature in 2009, has provided critical justification for the HFEA to recommend to the UK Government that the procedure should be safe for human trials to proceed and that regulations should be introduced to permit their use to create new humans (HFEA, Mitochondria public consultation 2012). The HFEA has also relied on limited evidence presented by the 'Newcastle group' who will inevitably be advocates of the research, as they are the primary centre in the UK where the research is being carried out. It is thus in their interests to be permitted (and funded) to continue with it.

We do not concur with the HFEA's recommendation.

The HFEA has admitted that '*Current research using PNT in Macaques has yet to be shown to be successful.*' However they have consequently stated that safety tests are no longer required to be carried out on non human primates. (http://www.hfea.gov.uk/docs/Mito-Annex_VIII-science_review_update.pdf)

'...studies in humans have only tracked health through to the blastocyst stage and in macaques to three years of age. The results from mice and invertebrates suggest that many deleterious effects of MR would not be revealed until adulthood.' The same researchers note that studies on other organisms have found that mitochondrial replacement does indeed have a big (adverse) effect on genetic expression, but this has received little profile. (Klaus Reinhardt, Damian K. Dowling, Edward H. Morrow. Mitochondrial Replacement, Evolution, and the Clinic. *Science*. 20 September 2013: Vol. 341 no. 6152 pp. 1345-1346).

Earlier adverse experiences with germ line modification and somatic gene transfer should serve as a warning for the enormous challenges that await mitochondrial gene replacement. (Bredenoord, A., Braude, P. Ethics of mitochondrial gene replacement: from bench to bedside. *Br. Med. J.*. 2011;342:87-89).

Even those who are involved closely in this research acknowledge that there may be significant incompatibilities, causing abnormalities: '*In addition to the risk of aneuploidy and other effects of the technical procedures, concern has been raised about the implications of possible incompatibilities between the nuclear genotype of the parents and the donor mitochondrial genomes. The potential biological significance of this stems from the fact that the majority of proteins involved in mitochondrial metabolism are encoded by the nuclear genome.' 'The question of whether the manipulations associated with nuclear genome transplantation might induce epigenetic anomalies remains to be resolved'.* (Craven, Murdoch,

Herbert, Turnbull et al, Mitochondrial DNA disease: new options for prevention. Hum Mol Genet. Oct 15 2011; 20(R2): R168–R174. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3179382/>)

The HFEA have been provided with evidence that nuclear-mitochondrial interactions are disrupted following nuclear transfer, leading to ‘unhealthy’ mitochondria and compromised cell function.’ (eg. See St. John, J. C., R. E. Lloyd, et al. The consequences of nuclear transfer for mammalian foetal development and offspring survival. A mitochondrial DNA perspective. *Reproduction* 2004; 127(6): 631-41. St. John, J. C., R. E. Lloyd, et al. The potential risks of abnormal transmission of mtDNA through assisted reproductive technologies. *Reprod Biomed Online* 2004 Jan; 8(1): 34-44).

As a result of these unknown long-term health and safety concerns, the HFEA recommends that:

‘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’. http://www.hfea.gov.uk/docs/Mito-Annex_VIII-science_review_update.pdf

The only justification offered for creating and thus submitting a human child to such serious risk is that the mother wishes to be the nuclear genetic parent of a child. However the **risks to the child** created using these experimental techniques can never be justified by this desire, and alternative options should be considered for prospective parents (see Q9 below).

Question 4: Do you agree with the principle that centres should not be permitted to undertake mitochondrial donation without first obtaining authorisation to do so from the HFEA?

As we have made clear above, the safety concerns are such that no clinics or any other body should be permitted to undertake these techniques in the UK and put the lives of future children, and subsequent generations, at such risk.

Question 5: Do you agree that people donating eggs and embryos for the purposes of mitochondrial donation should *not* have the same status as those donating eggs and embryos for use in fertility treatment but rather regarded more like organ or tissue donors?

We disagree.

If this procedure was ever allowed – which should not be the case – the donor should be regarded as a parent, not a tissue donor.

As we explain at Q1, a whole new unfertilised or fertilised egg is emptied of its maternal spindle or pronuclei. Thus the second mother provides the bulk of the biomass of the embryo without which the three-parent child could not have life. The second mother also

provides identifiable genetic material which will be passed down the generations through female offspring.

An individual's biological heritage is different to organ or tissue transplantation in that it holds their genetic identity and links to their wider biological family, past, present and future. It is also generationally transmissible. The few studies that have asked donor offspring about their conception commonly reveal frustration and anger at the lack of information about gamete donors and a desire to know more about their genetic heritage, including any donor siblings. This is an important part of a person's identity and is a right already granted to children who are adopted.

Furthermore, organ donors do not enable a person to come into existence but instead enable an existing person to stay alive. By contrast, three parents create a new child by MST or PNT. They would all be biological parents, albeit playing different roles.

Question 6: Regulation 10 provides that the HFEA should tell a person aged 16, on request, if they were born following mitochondrial donation. Do you agree with this?

This question is highly revealing.

Clearly Government, in drafting these regulations, recognises that there would indeed be three parents of any child created using these techniques. It is therefore not possible to deny that 'three parent children' could potentially become a reality for the first time in history (by this we mean three genetic parents, not social parents).

Advocates of these techniques may try to downplay the relevance of the mitochondria in the individual's genetic make-up, yet we do know that there will be three adults with whom a baby shares a parental genetic connection, and there will be identifiable genetic material from a second female parent which will be passed down the female generations. An extra individual would join the family tree.

So all three parents play some role in the child's biological and genetic heritage, therefore the question here is how much should that be recognised?

We concur with Bayliss that the contribution of the mtDNA is important in shaping a person's narrative and determining who a person will be. (Baylis F. The ethics of creating children with three genetic parents. *Reproductive BioMedicine Online* 2013;26:531-534).

A child has the right to know about the existence and identity of all of their three parents, and their genetic heritage, as well as how they came into being.

Therefore we agree that the HFEA should inform a person if they were born (created) using mitochondrial donation techniques (see also Q7).

Indeed, we consider this to be essential. We note that the HFEA has warned that:

'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'. http://www.hfea.gov.uk/docs/Mito-Annex_VIII-science_review_update.pdf

Clearly if any female born of these techniques is not informed of that fact, she will be at risk that her own daughters will have significant levels of mutant mtDNA. Information about her birth, and the subsequent risks it entails, must be given to her.

Question 7: Regulation 10 also provides that the information that the HFEA should provide in response to such a request should not identify the mitochondrial donor and be limited to screening tests carried out on the donor and about her family medical history, and any other non-identifying information that the donor has provided with the intention that it is made available in these circumstances. Do you agree with this approach?

We strongly disagree.

As above, this question and the draft regulation are highly revealing in acknowledging that 'three parent children' would be a reality if these techniques are permitted. The contribution of the mtDNA to a person's biological and genetic heritage cannot be ignored and should not be downplayed. The mtDNA plays a part in the shaping of a person's narrative and in determining who a person will be (Baylis F. The ethics of creating children with three genetic parents. Reproductive BioMedicine Online 2013;26:531-534).

A child has the right to identify and know who his/her three genetic parents are. Denying such knowledge may not be compliant with their human rights. This is already a right granted to children who are adopted so would create a situation where children resulting from three parent embryos techniques are being discriminated against. This may well be illegal under existing equality legislation.

Question 8: Regulation 13 provides that the HFEA should tell a mitochondrial donor, on request, when a child has been born from their donation, how many and their sex. Do you agree with this approach?

Whilst fundamentally disagreeing with creating human children using these techniques, were they to be permitted, we agree that the second mother should be aware of the birth of any child she has co-mothered.

We question what the rights of the donor will be if one day she applies for contact or even a parental order for the child? What rights will be granted to her as a genetic parent?

Question 9: Do you have comments on any other aspect of the draft regulations?

The Regulatory Triage Assessment (Annex C)

Regarding the Regulatory Triage Assessment, we question the basis for the rationale for intervention.

As we have stated above, Q3, **we strongly disagree with the Regulatory Triage Assessment** that these ‘therapies’ are proven to be suitable and safe enough for clinical use.

Lack of proven safety also undermines the claim that the public are supportive of the techniques, as this support was on the basis that they are safe. (In fact, the public ‘support’ from the HFEA consultation was highly questionable anyway).

A further rationale for permitting these techniques is to reduce harm to patients and reduce incidence of mitochondrial disease. Yet as we have noted in Q3 there is a high likelihood that children created using these new experimental techniques will be put at **greater risk themselves**, and any abnormalities and problems will be **generationally transmissible**, and thus affect even more children.

Yet there is not an unmet clinical need for these techniques.

Government claims that ten or so lives may be saved each year are based on unproven estimates by the Wellcome Foundation that have not been verified. Earl Howe, Health Minister, admitted recently that: *‘Numbers are based on advice from the Wellcome Centre for Mitochondrial Research at Newcastle University ... the potential for new mitochondrial donation techniques is based on the numbers of patients already undergoing some form of reproductive assistance each year in the United Kingdom in the form of either pre-implantation genetic diagnosis or prenatal testing...**The Department of Health has no written calculations that can be placed in the House of Lords library.*** (House of Lords Answers to Written Parliamentary Questions, Hansard. 6th May 2014).

The reality is, very few women would be candidates for even considering these techniques, as is briefly noted p39 of the Assessment.

Only about 15% of mitochondrial diseases are even caused by mitochondrial DNA. In other words, these techniques would not help 85% of the women with mitochondrial diseases. Moreover, mothers can pass on disorders without being clinically affected themselves.

In other words, these techniques will not be of any benefit to most children or parents. Children will still be born with mitochondrial disorders. **Therefore funding would be more effectively invested into researching treatments for those living with mtDNA disorders.**

If the clinical need is to be expected to be very low, we question the justification of permitting, for the first time ever, techniques that are: *‘... a form of germline modification or germline gene therapy, as respectively recognised by the HFEA and the Nuffield Council on Bioethics.’* (Earl Howe, 18 December, Hansard).

As an aside here, we note mention in the Regulatory Triage Assessment of the expected benefit from the inflow of foreign investment into the industry and the stated: *‘desire to be at the forefront of cutting edge of medical techniques’* in the Supporting Evidence. We would welcome reassurance that these hoped for benefits do not in anyway put at risk the health and well-being of future children, by encouraging experimentation for research purposes rather than genuine therapy, or by investing in these techniques instead of investing in research for treatments for those who are already born, or will be born, with mitochondrial disorders.

Supporting Evidence (Annex C)

The 'Supporting Evidence' paper in the consultation fails to offer any acceptable alternatives.

This is a clear omission.

For women who know that they are carriers and who want to have a healthy genetically related child, pre-implantation genetic diagnosis (PGD) is an alternative that does not require the use of unproven techniques.

In fact, as noted above, PGD is recommended by the HFEA for any females who might be born following MST or PNT, because of the risk that they will have a child of their own with mutant mtDNA (http://www.hfea.gov.uk/docs/Mito-Annex_VIII-science_review_update.pdf). So by attempting to bypass the risk for prospective mothers now, the risk of having a child with mutant mtDNA is heightened for their own daughters.

For women known to have mitochondrial diseases who want to have a healthy child, adoption or IVF with the use of a donor's egg are available alternatives. The child would not be genetically related to either both or one of its parents but neither would the child or his/her children be put at grave risk by an experimental, irreversible procedure.

The 'Supporting Evidence' in the consultation is also misleading in stating that an intended effect is: *'To enable safe and effective treatment for mitochondrial disease'* (p40).

The reality is, this technology will not treat or save lives, as it purports to do. It will use experimental techniques to create *new* lives. The research is not about treatment of affected individuals but about trying to create unaffected individuals through genetic manipulation of the germline, for women at risk of having a child with a mitochondrial disorder who want their child to be genetically related to them.

Jeffrey Kahn of Johns Hopkins University rightly acknowledges that: ***'We're not treating humans. We're creating humans.'*** (<http://www.sciencemag.org/content/343/6173/827.full>).

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