Mitochondrial Donation

A 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

Response Form

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

Current research does not unanimously support the view that nuclear and mitochondrial DNA can be clearly delineated. The problems in this area have been well explained by Human Genetics Authority[1].

Their useful summary is this:

"We argue that the HFEA should take a precautionary approach to the safety of MST/PNT, since the HFE Act insists that the welfare of the child is the most important consideration. The existence of a safe alternative technique, ie egg donation means that it would be unacceptable not to take such an approach to the safety of MST/PNT. We list research that should be undertaken before approving MST/PNT, notably studies on epigenetic changes in embryos produced by them."[2]

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

[1] http://www.hgalert.org/Report%20on%20the%20safety%20of%20mitochondrial%20transfer.pdf
[2] Ibid.

another egg or embryo from which all the nuclear DNA has been removed. Do you agree with this description and restriction?

There is a severe potential problem here. As noted above, the strict delineation between genomic and mitochondrial DNA presupposed by the authorisation process may not be supported in the scientific literature. Some researchers have pointed to the data on the human genome available in the ENSEMBL[3] and OMIM[4] databases as a possible contradiction of the view that this distinction may not be absolute.

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?

It seems appropriate that the HFEA should have this role if the proposed regulatory regime is to go ahead. Nevertheless, it is extremely important the HFEA make publicly available the criteria that they intend to use to make this decision. There must be full transparency in how the decisions are made and who is making them, and there should be mechanisms for reviewing and altering the criteria. It is vital that the decision process not simply become, or be perceived as, a rubber-stamping exercise, and any liberalisation or loosening of the criteria must be preceded by full and detailed public consultation.

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 ?

The HFEA should absolutely be the first line of authorisation. However, further liberalisation must be avoided, that is to say that once the principle of the permissibility of mitochondrial transfer has been admitted into regulation, the door is open to far-reaching manipulation of the human genome. The The HFEA's regulatory regime has clearly drifted in this direction over recent times, for example in their assessments of eligibility for fertility treatment, and also with amendments to embryo research regulation since 1990. Mitochondrial transfer is a significant ethical barrier – which, once crossed,

[3] http://www.ensembl.org/index.html
[4] http://www.ncbi.nlm.nih.gov/omim

opens many new doors.

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?

LIFE cannot agree with this. Donors are intrinsically genetically related to the resulting child, and some research suggests that they may be more "genetically involved" that the HFEA guidelines accept.

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?

See reply to Q8

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?

See reply to Q8

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?

Most of the provisions in Questions (6), (7) and (8) above are good. We object however to the denial of detailed and complete information to children about their genetic past[5]. It is not yet clear that these techniques will ensure total removal of genomic DNA from the mitochondrial donor in the implanted embryo. Mitochondrial donors may therefore have a more substantial connection to the resulting offspring than the guidelines currently suggest.

The end of donor anonymity in conventional fertility treatment some years ago[6] was a recognition that for children born as a result of those treatments, curiosity about their genetic ancestry was entirely natural. This reform is an excellent model for regulations concerning mitochondrial donors.

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

LIFE is opposed, in principle, to mitochondrial transfer. We will not lay out our arguments in great detail, but the baseline of our view is that it is wrong to use human embryos as means to ends, and we have deep ethical concerns about the permanent modification of the human germline.

There are two main areas of concern, in our view.

- The proposal that donors of gametes for use in mitochondrial transfer be treated like donors of organs and tissue rather than like donors in conventional fertility treatment is unfair and a denial of the fact that even someone who has only contributed a small amount of genetic material is a relation of the child resulting from the treatment.

- It is too soon to be going ahead with authorising mitochondrial transfer when many safety

[5] For information and background about how donor insemination affects those born as a result, see e.g. the Donor Conception Network http://www.dcnetwork.org/

[6] The new rules came into force in April 2005.

concerns remain to be satisfactorily resolved. The overall state of the scientific evidence about the efficacy and long-term effects of mitochondrial transfer remains uncertain. The logic of the proposed regulatory regime for mitochondrial donation leaves the way open for much less strict rules on germline modification and modification of the human embryo. This is especially worrying as the UK policy is arguably already in contravention of Article 13 of the European Convention on Human Rights and Biomedicine, which states that "an intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants"[7]. Although the UK is not a signatory to this Convention, it does represent an important statement of the international consensus on bioethics and biomedicine.

The United States Food & Drug Administration, the FDA, has expressed considerable reservations about these techniques, most recently in February 2014. An advisory panel to the FDA – the Cellular, Tissues and Gene Therapies Advisory Committee – held several evidence sessions to look into mitochondrial transfer. Many of those giving testimony to this committee were unsatisfied with the research into the long-term safety and possible health consequences of these techniques[8]. Dr Michelle Huckaby of the Genetics and Public Policy, for example, stated that "the potential benefits are huge, but the potential harms are also huge". The head of the committee, Evan Snyder, stated that there is just not enough preclinical data to suggest how to carry out mitochondrial transfer safely[9].

It is clear that the FDA is quite rightly taking a wisely cautious approach to the authorisation and regulation of mitochondrial transfer, waiting for much more data to be published and safety concerns to be addressed. There is a clear lesson here for our own regulators. Permanent alteration of individual DNA, and transfer of genetic material, is a momentous step, and we simply do not know yet whether it is safe.

Research carried out at Newcastle University intended designed to check whether it was actually possible to remove all faulty mitochondrial found that the average amount of defective mDNA left after transfer was not significant enough to cause disease. Nevertheless, this provides little indication of the likelihood of complications manifesting at a later stage of development.

There remain considerable grounds for concern about the long-term safety of mitochondrial transfer. A research project using macaque monkeys at Oregon Health and Science University has yet to establish how whether future generations will be affected by mitochondrial tinkering with an ancestor. Dr Shoukhrat Mitalipov, the lead researcher on the project, has noted that half of the fertilised human eggs that had been through mitochondrial transfer showed abnormalities that did not appear in the macaque fertilised eggs at the same stage, and it was not even clear whether all faulty mitochondrial DNA had even been removed. In an interview with Nature magazine, Dr Mitalipov stated "It looks like human oocytes are more sensitive"[10].

It is striking that there seems to be remarkably little confidence in the Department about the current

[7] http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm
[8] The sessions of the committee are available to watch online:
http://fda.yorkcast.com/webcast/Viewer/?peid=20822bb6fae04813affd80d5c6853cb41d
http://fda.yorkcast.com/webcast/Viewer/?peid=9aa28d9585104c78bc4404188622e9901d
[9] http://www.usatoday.com/story/news/nation/2014/02/26/three-parent-dna-embryo/5837783/
[10] http://www.nature.com/news/dna-swap-technology-almost-ready-for-fertility-clinic-1.11651

research base for policy. The call for more evidence and research issued by the HFEA as recently as 21st March 2014[11] suggests that the knowledge base is not as settled and comprehensive as other documents have made it appear. There is also considerable uncertainty about the number of people born with mitochondrial disease each year. The document issued with this consultation gives a figure of 1 in 200[12], but other estimates are much higher – as high as 1 in 4000[13]. Clarity is needed on this issue.

Human Genetics Alert, the biotechnology thinktank, note that:

"Even basic IVF is now known to increase the incidence of certain disorders, and there is a general correlation between the degree of manipulation and the severity of the side-effects. For example, with the very invasive nuclear transfer techniques used in animal cloning, the effects are very obvious and severe. Although this is probably largely due to errors in reprogramming, it is also likely, in part, to be due to embryo manipulation. The Newcastle techniques involve nuclear transfer as well as enucleation (or removal of the spindle) of the donor egg. A further reason for concern is the problems observed using a much less invasive technique, 'ooplasm transfer', in which mitochondria rather than nuclei are transferred between eggs. This was observed to result in chromosomal abnormalities and developmental disorder in a child born through the use of the technique. The HFEA report tries to minimise concerns about this technique, by suggesting alternative explanations of the problem, and fails to mention the case of developmental disorder. This technique has now been discontinued because of these safety concerns, yet the proposed Newcastle techniques are considerably more invasive."[14]

Mitochondrial transfer is not the only way for women with faulty mitochondrial DNA to have healthy children. It is already possible for them to have conventional fertility treatment using donor eggs free of mitochondrial disease. What mitochondrial transfer does is enable them to have their own genetic children free of these diseases. It is debatable, therefore, whether allowing mitochondrial transfer meets the HFEA's high bar of necessity for controversial and ethically dubious fertility treatments. The desire to one's own children is, of course, a deep, profound and entirely understandable human need. But meeting that desire through mitochondrial transfer comes at a very high cost. We must be careful that we are not simply pressing ahead with research "because we can" and because we want to be the world leaders, the cutting edge, without any thought as to whether we ought to take this step or whether we really need to.

In the long-term, we can only know the full consequences of interfering with the human germline if we monitor not just children born from these techniques, but also several generations of their descendants. However, once they reach the age of 16, it is impossible to guarantee that they will stay within clinical studies. Individuals cannot be compelled to continue to take part in research, and neither can their descendants. Centres carrying out mitochondrial transfer can encourage such participation, and make it easy for individuals to take part, but there is no obligation on those born through this technique to do so, and nor are they obliged to inform future partners of the circumstances of their conception. The proposed guidelines for regulating mitochondrial transfer do not pay close enough attention to these pitfalls.

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[11] http://www.hfea.gov.uk/docs/mitochondria_scientific_review_update_-_call_for_evidence_2014.pdf
[12] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/285251/mitochondrial_donation_consultation_document_24_02_14_Accessible_V0.4.pdf
[13] http://www.newcastle-mitochondria.com/mitochondria/what-is-mitochondrial-disease/
[14] http://www.hgalert.org/Mitochondria%20briefing.pdf

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It cannot be stated clearly enough that the techniques under consideration are not cures. They will not benefit those already suffering from mitochondrial disease, or those whose condition is not identified until after birth. It is estimated that this technique will only be used about 10 times per year. That leaves several hundred people being born each year with mitochondrial conditions who need treatment, care and support. Nor will these techniques help those whose medical conditions which are only partially caused by defective mitochondria. This raises the question of funding priorities. A three-year mitochondria research project at Great Ormond Street Hospital, for instance, requires £394,000 of funding which will be used to classify and identify genes and map disease progression as a means to further develop treatments[15]. Yet more than ten times that amount - £5.8m – has already been committed to research into mitochondrial transfer procedures at Newcastle University[16]. Is this the best way to use scarce research money? We must be very careful that prestigious and extensively hyped research that helps a relatively small number of patients is not prioritised over less glamorous, but equally valuable, research which might help hundreds or even thousands.

[15] http://www.gosh.org/mgf/events-and-appeals/appeals/bringing-research-to-life/new-research/mitochondrial-diseases/

[16] http://www.thejournal.co.uk/news/north-east-news/newcastle-university-experts-58m-funding-4416844