

Mitochondrial Dna Transfer. Some Reflections From The United Kingdom

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MITOCHONDRIAL DNA TRANSFER. SOME REFLECTIONS FROM THE UNITED KINGDOM

ABSTRACT: Recent medical advances and subsequent law reform in the United Kingdom have reignited debate about the ethics of mitochondrial DNA donation and transfer. The potential personal and societal benefits of permitting such practices must be considered against the ethical issues raised by them. It is argued that each objection is defeasible, assuming that safety and efficacy issues can be resolved. A brief description of the new provisions in the UK is provided.

KEYWORDS: Mitochondrial DNA donation and transfer; reproductive liberty; genetic identity; law reform

SUMMARY: 1. Introduction. – 2. Some Ethical Considerations. – 3. The UK Position. – 4. Conclusion.

1. Introduction

As genetic medicine continues to advance, therapeutic developments, while sometimes lagging behind our capacity to identify genetic problems, nonetheless become increasingly feasible. One area of increasing contemporary relevance relates to the human toll generated by disease that can be directly linked to mitochondrial DNA (mtDNA). Mitochondria «are small structures present in cells that produce much of the energy required by the cell. They contain a small amount of DNA that is inherited exclusively from the mother through the mitochondria present in her eggs. Mutations in this mitochondrial DNA...can cause a range of rare but serious diseases, which can be fatal»¹. While relatively rare, it is still estimated that around 3,500 people in the United Kingdom are affected by mitochondrial disease². Equally, it has been said that «[a]round 1 in 6500 children is thought to develop a serious mitochondrial disorder. There is no cure and our current treatments only focus on managing the symptoms»³.

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¹ Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2014 update. Report provided to the Human Fertilisation and Embryology Authority (HFEA), June 2014, p. 3.

² K. ELVIDGE, *Why we should back a law change to allow mitochondrial transfer into the clinic*, in *BioNews* 644, available at http://www.bionews.org.uk/page_124860.asp (accessed 28/04/2015).

³ Wellcome Trust (London), *Q&A: Mitochondrial donation*, available at http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/wtp057782.pdf (accessed 28/04/2015).

While relatively small numbers may be involved, the severity of mitochondrial disease and the human suffering associated with it means that therapeutic progress has the capacity to reduce the overall costs – both human and financial – of mere management of symptoms, where that is even possible. In 2008, scientists at the University of Newcastle announced a potential breakthrough that holds out the possibility that mitochondrial disease could become a thing of the past.

There are two different techniques that could ensure that in the future, where intending parents are aware of the potential that the mother may pass on faulty mtDNA to her offspring, they can, in conjunction with the use of in vitro fertilisation (IVF) choose to avoid this. Essentially, the techniques are designed to replace the faulty mtDNA by using mitochondria from an unaffected donor to replace the mtDNA of the woman intending to become pregnant. These techniques are known as maternal spindle transfer and pronuclear transfer. The former, as the Wellcome Trust explains:

...involves removing the nuclear DNA (which amounts to 99.9% of the total cell DNA) from the donor egg, leaving the part of the cell containing the healthy mitochondria. The nuclear DNA from the mother's egg is then inserted into this cell. The healthy egg is fertilised and is then implanted into the mother's uterus in the same way IVF is carried out already⁴.

The latter, «involves fertilising the mother's egg with the father's sperm first and then transferring the nuclear DNA to the donor egg containing healthy mitochondria, which has had its nuclear DNA removed. The healthy fertilised egg is then implanted into the mother's uterus in the same way as in maternal spindle transfer»⁵. It should be noted here that pronuclear transfer is arguably the more controversial of these options, given that it involves the creation, and potential destruction of embryos. For some, this is sufficiently ethically troubling that no further debate is necessary. However, in most (albeit not all) countries where IVF is permitted, "spare" embryos – that is those not destined, for whatever reason, for implantation – will, after a period of time, be destroyed, so this is not novel to pronuclear transfer. The UK legislation also permits the creation of embryos specifically for research, and these too will inevitably be destroyed⁶.

While positive results have been obtained in animal experiments in the laboratory, the possible successful translation of either of these techniques into human medical practice has proved to be, as one commentator puts it, «immediately controversial»⁷. Few advances in reproductive medicine have proved to be anything else. Forty years ago, debate raged about the ethics – and even the propriety – of IVF. Now, it is widely accepted as essentially standard medical practice, albeit often controlled by a legislative framework which builds in procedural safeguards. Despite the promise of these new techniques, it is unsurprising that a fierce debate has been generated, with polarised posi-

⁴ Wellcome Trust (London), Q&A: *Mitochondrial donation*, available at: http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/wtp057782.pdf (accessed 28/04/2015), para 7.

⁵ Wellcome Trust, *op cit*.

⁶ It is worth noting that the UK did not sign up to the Council of Europe's Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: convention on human rights and biomedicine (1997) precisely because it prohibits the creation of embryos for research. The Convention is available at <http://conventions.coe.int/Treaty/en/Treaties/html/164.htm> (accessed on 23/04/2015).

⁷ K. ELVIDGE, *op. cit*.

tions adopted on each side. Interestingly, there are clear echoes of the very same debate that surrounded IVF in its early days, and by and large those opposing the introduction of these techniques tend to be those who also argued against many of the other advances in reproductive medicine. This is not to malign or denigrate their position, but rather to show how fundamental moral or ethical concerns do not disappear simply because we have become more tolerant of some innovations.

Broadly, the concerns expressed by those who either oppose the further development of these techniques, or who urge extreme caution, involve matters of both a practical and a philosophical type. Practically, there are concerns about the safety of the procedures. Manifestly, were there risks to the future child as a result of the application of these techniques then a powerful argument could be made that they should not be attempted. It could, and possibly should, be argued that we have an obligation not deliberately or knowingly to generate such a risk, potentially causing more harm to future children than their mitochondrial disease would. However, this position makes some assumptions that are susceptible of challenge. First, and arguably convincingly, a number of reviews – including one highly commended series of reports from the Human Fertilisation and Embryology Authority (HFEA)⁸ concluded that «[a]t each review, the panel has reached a view that the evidence it has seen does not suggest that these techniques are unsafe. That remains the panel’s current view»⁹. Second, even if some level of risk were identified, it would be necessary to balance that against the certainty of the suffering caused by mitochondrial diseases which «are progressive and can cause a wide spectrum of severe health problems including heart and other major organ failures, stroke, dementia, blindness, deafness and premature death»¹⁰.

2. Some Ethical Considerations

At a more philosophical level, concern relates to the extent to which manipulating DNA may have an effect on the born child’s identity. The assumption here is that, because additional genetic material will be present in the child, this will affect the child in ways that *prima facie* threaten his or her identity. Murdoch, however, argues that while substitution of faulty by healthy mitochondrial DNA will affect a future child’s health (beneficially), this will not «influence a person’s characteristics»¹¹. Rather, a different child is born – one without disease. An argument along similar lines concerns what is known as denial of an “open future”. On this argument, by deliberately manipulating the child’s genetic makeup we are denying in some way the opportunity for that child to make free, authentic choices in the future. Of course, the same could be said of any selection procedure – whether it is as simple as a choice of mate to co-parent a child, or the use of preimplantation genetic diagnosis (PGD)

⁸ The statutory body which regulates assisted reproduction in the United Kingdom, established by the Human Fertilisation and Embryology Act 1990.

⁹ Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2014 update: Report provided to the Human Fertilisation and Embryology Authority (HFEA), June 2014, p. 4.

¹⁰ *Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review*, London, Nuffield Council on Bioethics, 2012, p. xv.

¹¹ A. MURDOCH, *IVF and the prevention of mitochondrial DNA disease: the moral issues*, in *Bionews* 605, available at http://www.bionews.org.uk/page_01423.asp (accessed 28/04/2015).

to select healthy embryos for implantation. In addition, as Bredenoord, Dondorp, Pennings and De Wert argue, «[a]s health is a *sine qua non* for many plans in life, modification of the mtDNA would establish a more open future»¹².

In a related concern, it is argued that the introduction of a third party's genetic make-up into the future child is likely to be confusing for the child; effectively, it is said, we are creating 3-parent families. Several points can be made about this concern. First, and although for some people knowledge of one's genetic inheritance is a matter of great concern, the amount of "foreign" DNA introduced is tiny and scarcely likely to cause confusion. Only about 0.1% of the child's DNA would come from the donor, and «these genes would only be involved in energy production via the mitochondria, and nothing else»¹³. In any event, it is not solely techniques like this that can introduce third party DNA. As has been said, «[c]omparisons have been made between the genetic significance of donated mitochondria on a person's identity to that of receiving a kidney or bone marrow transplant»¹⁴.

One further aspect of this objection relates to the fact that, as some newspaper headlines would have it, use of the procedures would result in the creation of «3-parent families». However, in a world in which the nuclear family is no longer necessarily the norm – with same sex couples using donated gametes to build families, for example – even if the mitochondrial donor actually made a major contribution to the child's DNA (which we have already seen is not the case) – the law is well-equipped to negotiate the question of parentage even where much more of a genetic contribution is made.

As ever, questions about consent are also raised. Given the uncertainty – particularly in the early days of human trials – as to the safety and/or efficacy of the new techniques, is it possible that a true, informed consent could actually be given? Obviously, were uncertainty of outcome a barrier to the provision of a legally valid consent, then *ex hypothesi* clinical research would grind to a halt; a conclusion that is manifestly not only a threat to medical advance, but counter-intuitive for those who defend an individual's right to make authentic choices for themselves. Of course, taking this argument a little further, it might be argued that while adult human beings have the right to make decisions for themselves, even if they are harmed as a result, they do not have a similar right to make such decisions on behalf of someone else – in this case, their prospective child. Leaving aside the complex question as to whether or not it makes sense to talk about non-conceived future children as having rights or interests worthy of protecting (and some would argue that they do), manifestly parents of born children make innumerable decisions on their behalves on a daily basis, some of which (however inadvertently) cause harm, yet we do not – except in extreme circumstances – remove decision-making authority from them.

Perhaps inevitably, when reproductive medicine is combined with genetic science, the spectre of eugenics raises its ugly head. For example, opponents of PGD argue that "preferring" healthy to affected embryos is a form of negative eugenics and will affect not only the social order but also the self-

¹² A.L. BREDENOORD, W. DONDORP, G. PENNING, G. DE WERT, *Ethics of modifying the mitochondrial genome*, in *J. Med. Ethics*, 2011, 37, 97-100, at p. 100.

¹³ K. ELVIDGE, *op. cit.*

¹⁴ *Ethical issues of new techniques to avoid mitochondrial disease*, Human Fertilisation and Embryology Authority, ELAC (06/11)1, June 8 2011, para 6.1.

esteem and sense of worth of those who live with genetic difficulties. To take the latter example first, this is a view often posited by some of those in the disability rights lobby who fear that making it possible to screen out those who would otherwise be born with a genetic predisposition to or actual disability both demeans the entire disabled population and adds further stigmatisation to the already existing lack of concern and compassion. This is an argument not easy to dismiss, based as it is in the reality that people with disabilities are often unequally treated and sometimes ignored when important social decisions are made. For example, without legislation to enforce it, how many architects would design buildings which are user-friendly for wheelchair users? However, while it is deplorable that people with disabilities may be treated as “second class” citizens, this does not necessarily translate into an argument to prevent intending parents from making decisions that avoid suffering for future children and exercising their reproductive autonomy. Interestingly while it is often the case that spokespersons for the disability community condemn selection based on disability, Shakespeare, one of the disability rights lobby’s most expert and thoughtful commentators, accepts that «there are reasons to want to prevent the birth of a child affected by impairment which do not reflect discrimination against disabled people....»¹⁵.

On the former point, the impact of selection on the “social order” is arguably a hangover from the negative eugenics most dreadfully espoused by Nazi Germany, but also endorsed in a more limited version by countries such as the USA and others¹⁶. It must, however, be borne in mind that one of the most offensive aspects of (negative) eugenic policies was that it was mandated state policy; not the free choice of individuals to make authentic decisions. In no way can individuals exercising free reproductive choices be compared to the policies of hatred and genocide.

This leads in this necessarily brief tour of some of the ethical issues raised by this medical advance to one important consideration; namely, that of reproductive liberty. There are few values of more importance to individuals and couples than the right to make free and authentic decisions about reproduction. In the 20th Century in particular, this became an issue of overwhelming concern for many, given not only the egregious compulsory sterilisation programmes in Nazi Germany, but also programmes conducted on a lesser scale in countries such as the United States where, in authorising the compulsory sterilisation of one Carrie Buck, Judge Oliver Wendell Holmes famously remarked that «three generations of imbeciles are enough»¹⁷. Recognition of the importance of choice in human reproduction is a direct challenge to eugenic or discriminatory policies and is, therefore, important not just for individuals but also for the moral tone of society as a whole. Naturally, no right is absolute and the claims made for reproductive liberty do not require supporting *any* choice; rather, they mandate the default position as being liberty. Evidence of harm may negate the presumption in favour of freedom, but absent that we should be as free as possible to fulfil our reproductive aspirations whether they be to reproduce or not to do so. Permitting mtDNA donation and transfer would

¹⁵ T. SHAKESPEARE, “Losing the plot?” *Medical and Activist Discourses of Contemporary Genetics and Disability*, in *Sociology of Health and Illness*, 1999, 21(5), 681. For further discussion of this issue, see S.A.M. MCLEAN, L. WILLIAMSON, *Impairment and Disability: Law and Ethics at the Beginning and End of Life*, Abingdon, 2007.

¹⁶ For a more in-depth discussion of reproductive liberty see S.A.M. MCLEAN, *Modern Dilemmas: Choosing Children*, Edinburgh, 2006.

¹⁷ *Buck v Bell* 274 US 200 (1927), at p. 207.

support reproductive liberty in that this «would offer women who carry such disorders, or who are affected by them, the chance to have healthy children who are also genetically related to them»¹⁸.

There are potentially endless arguments surrounding the novel techniques proposed to eradicate the suffering caused by the transmission of faulty mtDNA, but perhaps the one that differentiates this debate from those that arise in other areas of reproductive medicine concerns the fact that the treatment can be defined as involving germ-line rather than somatic therapy. While somatic treatment is designed to target a particular symptom without modifying the individual's DNA, germ-line therapy «introduces new genetic material into the gametes. The genetic change would be reproduced in each cell of the developing individual as well as in each subsequent generation»¹⁹.

It is the fact that the individual's DNA would be modified and that this modification would be present for all future descendants that raises the major concern about the proposed techniques. Either of the two methods referred to earlier would result in permanent genetic modification. For the moment, we do not fully know or understand what the consequences of this would be. Might we, for example, lose something beneficial by wiping out certain genetic traits? For example, it is known that people with Tay-Sachs have an inherently higher resistance to malaria. What if similar protections are provided by otherwise harmful genes? As with many medical advances, of course, the answer to this question will only become clear after use and experience.

However, we must also balance the possible risk of losing beneficial protection from something else with the known and often acute harms caused by mitochondrial disease. As the Wellcome Trust has said:

It is never possible to answer every safety question before new medical procedures are used in people, but the scientific evidence suggests that any risks of mitochondrial donation are proportionate to the severity of mitochondrial disease and the well-recognised significant risk that children will continue to be born who will die in infancy if these techniques are not used²⁰.

Nonetheless, germ-line treatment has been and remains controversial if not outright banned. For example, The Council of Europe's Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: convention on human rights and biomedicine (1997) states at Art.13: «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»²¹. Although this Convention has been ratified by many European jurisdictions, the UK is not a signatory which, in light of what has recently taken place in the UK, is of more than passing interest.

UNESCO's International Bioethics Committee also disapproves of what it calls predetermining the genes of future children, calling in aid the principle of intergenerational justice, saying that genetic

¹⁸ Nuffield Report, *op. cit.*, at p. 52, para 4.1.

¹⁹ D.S. RUBENSTEIN, D.C. THOMASMA, E.A. SCHON, M.J. ZINAMAN, *Germ-Line Therapy to Cure Mitochondrial Disease: Protocol and Ethics of In Vitro Ovum Nuclear Transplantation*, in *Cambridge Quarterly of Healthcare Ethics*, 1995, 4, 316-339, at p. 317.

²⁰ Wellcome Trust, *loc. cit.*

²¹ Available at: <http://conventions.coe.int/Treaty/en/Treaties/html/164.htm> (accessed on 23/04/2015).

technologies should not «become instruments for intergenerational tyranny»²². Indeed, the Committee believed that «the most elementary prudence requires that germ-line intervention should not be undertaken on the basis of the “precautionary principle”»²³. However, both science and, to an extent, evidence have changed since this recommendation was made, coming as it did at a time when research into the possibility of germ-line interventions was at best in its infancy. Since then, we must ask whether the precautionary principle should or does apply. Successful animal experiments seem to demonstrate both the likely safety and efficacy of the procedures under consideration here. Indeed, some would argue that «...the fact that nuclear transfer with the aim of preventing the transmission of mtDNA disease would involve germ-line modification cannot convincingly be construed as a categorical moral objection against the possible use of this technology»²⁴.

Times and attitudes move on. In its survey of public attitudes to mtDNA transfer, the HFEA found that there was broad public support for its carefully regulated use. Nor is the United Kingdom alone in re-evaluating its approach to mtDNA replacement therapies. In the United States, for example, an *ad hoc* committee of the Institute of Medicine is currently undertaking a project entitled «Ethical and Social Policy considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Diseases». The project is sponsored by the Food and Drug Administration and is expected to report some time in 2016²⁵.

3. The UK Position

In February 2015, the United Kingdom became the first country to legislate to permit – under careful regulation by the Human Fertilisation and Embryology Authority – mtDNA replacement. Interestingly, given the controversial nature of the subject, the votes in both Houses of Parliament were not as close as might have been anticipated. In the House of Commons (the elected House), the voting was 328 in favour to 128 against; in the House of Lords, the vote recorded was 280 in favour, with 48 opposed²⁶. The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 will come into effect on 29 October 2015. Under the present legislation (the Human Fertilisation and Embryology Act 1990, as amended in 2008), no licence could be issued to perform mitochondrial donation. However, following the passing of these regulations, it will now be possible for such procedures to be carried out, provided that the HFEA determines that there is a risk that a particular woman may have mitochondrial abnormalities in her eggs (where the technique contemplated is maternal spindle transfer). Where pronuclear transfer is contemplated, a similar finding has to be made in respect of the embryo. Finally, as the Explanatory Note to the regulations states, «[t]he HFEA must also be satisfied that there is a significant risk that a person with these abnormalities will have or develop serious mitochondrial disease».

²² Report of the IBC on Pre-implantation Genetic Diagnosis and Germ-line Intervention, (SHS-2003/WS/26), Para 97 (2003).

²³ Para 81.

²⁴ A.L. BREDENOORD *et al.*, *op. cit.*, at p. 100.

²⁵ See <http://www8.nationalacademies.org/cp/projectview.aspx?key=49648> (accessed on 27/04/2015).

²⁶ See Z. KMIETOWICZ, *UK becomes first country to allow mitochondrial donation*, in *BMJ*, 2015,350, h1103.

It was explained earlier that questions as to genetic identity/parenthood have also concerned some commentators. In this respect, the Regulations make it clear that the donor is not legally related to any subsequent child, nor is the donor entitled in law to apply for a parental order in respect of that child. To further distinguish children born following mtDNA transfer and donors, the regulations modify the provisions of the 1990 Act (as amended) in respect of the obtaining of identifying information about the donor. While the UK has adopted an approach that allows for the identification of gamete donors, the Regulations specifically permit children or donors only limited, non-identifying information, thus further emphasising the almost total lack of genetic relationship between child and donor.

4. Conclusion

The HFEA is widely regarded as an efficient and effective regulatory body and doubtless it will continue to regulate in this novel area with its customary diligence. Meantime, research will continue in order to evaluate the safety and efficacy of each of the proposed methods to effect the eradication of mitochondrial disease through the generations. For individuals who risk having children suffering from such conditions, and who wish to have a child genetically related to them, this is surely preferable to the options currently available, which include remaining childless or undergoing IVF with pre-implantation genetic diagnosis.

Without being overly optimistic, it is certainly plausible that if any residual safety and efficacy concerns can be removed by further research «hundreds of genetic diseases might be eliminated from families»²⁷. And it is here that we see one critical reason why germ-line therapy might, in fact, be preferable to somatic therapy, at least in these cases. Simply put, rather than waiting to treat generation after generation for recurring problems, at a stroke they can be eradicated. Further, for some, the question is not so much whether we should use such therapeutic options; rather, this is an «ideal that medicine is obligated to pursue»²⁸. Murdoch further argues that «[I]ike PGD, preventing mitochondrial DNA disease falls within the good medical practice of preventing serious illness, not eugenics»²⁹.

This short discussion has attempted to evaluate some of the issues surrounding mtDNA donation and transfer, and has briefly explored the radical changes recently made in the United Kingdom. While the UK position is currently unique, doubtless it will be watched with some interest by other countries primed to tackle this complex subject. While it may never be possible entirely to convince doubters of the ethical probity of mtDNA transfer, even if safety and efficacy can be reliably assured, it can be argued that – while free to continue to express their concerns – their views cannot, and arguably should not, pre-empt the interests and rights of those who are willing to support what may turn out to be another “medical miracle”; the avoidance of the predictable suffering of future generations and the emotional pain for potential parents.

²⁷ R. MUNSON, L.H. DAVIS, *Germ-Line gene Therapy and the Medical Imperative*, in *Kennedy Institute of Ethics Journal*, 1992, 2(2), 137-158, at p. 139.

²⁸ R. MUNSON, L.H. DAVIS, *op. cit.*, at p. 155.

²⁹ A. MURDOCH, *op. cit.*