Viewpoint

Mitochondrial donation: the slippery slope to genetic engineering?

Jackie Leach Scully[a]

a Policy, Ethics and Life Sciences (PEALS) Research Centre, Newcastle University, UK

Genetic testing in reproductive medicine

Genetic testing is routinely used in today's reproductive medicine and assisted reproductive technologies (ARTs). Prenatal diagnosis (PND), preimplantation genetic diagnosis (PGD), and potentially preconception genetic testing, are now accepted parts of the clinical repertoire alongside more traditional forms of pregnancy screening and testing. One of the many ethical questions these techniques raise is whether it is ethically permissible to go further, that is to use genomic knowledge not just to identify and select against genetic disease and disability, but to deliberately engineer human genomes to control these and other traits by introducing changes that are permanent and passed on to future generations. So far, the ethical and legal consensus has been against such germline manipulation. A recent proposed change in the law governing reproductive medicine in the United Kingdom has unexpectedly returned this question to the foreground. In this Viewpoint I do not give an in-depth analysis of the issue but outline some of the still ongoing professional and public debate.

Treating mitochondrial diseases by donation

In the UK, ARTs are regulated by the Human Fertilisation and Embryology Act 2008, and the main regulatory body involved is the Human Fertilisation and Embryology Authority (HFEA) which is responsible for licensing fertility clinics. Under existing UK law, while a range of prenatal genetic testing techniques including PGD are permitted, anything that changes the DNA of an embryo in clinical practice is not (the DNA of research embryos can be manipulated, but these embryos cannot then be used for pregnancies).

The discussion of a change in the law has been prompted by technical advances towards preventing mitochondrial diseases. These relatively rare conditions are caused by mutations in the mitochondria, subcellular organelles responsible for energy metabolism. Abnormally functioning mitochondria are particularly problematic for organs with high energy demands such as muscles, the nervous system, the liver and the brain.

Crucially, affected mitochondria are passed only along the maternal line in the mother's ova; paternal sperm

do not transfer their mitochondria to the fertilised egg. For reasons to do with the distribution of mitochondria in fertilised eggs, symptoms can vary hugely in severity, and this means that an affected but virtually symptomless woman can go undiagnosed until she has had several affected children. It also makes it impossible to predict how ill a child will be, which for many parents makes the option of prenatal diagnosis and termination ethically problematic. About 200 children are born each year in the UK with mitochondrial disease.

Two techniques are under development in research centres in Newcastle, UK, and in Oregon, USA. In pronuclear transfer (PNT), the pronucleus from a fertilised egg from the (affected) mother and the father is removed and inserted into an enucleated fertilised egg from an unaffected donor, which therefore contains normally functioning mitochondria. In maternal spindle transfer (MST), the nuclear genetic material from the affected mother's egg is removed and placed within an enucleated donor egg, before fertilisation with the partner's sperm. Either way, the resulting embryo has a nuclear genome of around 25,000 genes from the original mother and father, and mitochondria, which contain 13 genes or 0.06% of the total genetic material, from a donor.

Public and professional debate

Neither technique is yet ready for clinical use. To go any further with development will involve the first attempts in humans, and this would require secondary legislation to deal with the current legal block to changing the DNA of an embryo. Before taking this step, which most commentators recognise is a significant one, the UK government asked the Nuffield Council on Bioethics (the nearest equivalent to a national ethics advisory committee) to report on the ethics of mitochondrial donation [1]. In preparing that report, the Council called on evidence and information from a range of perspectives including affected families, clinicians, and bioethicists.

In September 2012 the HFEA was then asked to undertake an extensive public consultation exercise; I was a member of the Oversight Group that managed the process. The consultation ran telephone interviews with 1000 people, received submissions to an online questionnaire from approximately another 1800, ran public engagement events and workshops around the country, and held discussions with affected individuals. The results were published in March 2013 [2]. The overall message was of broad support for the aims of mitochondrial donation, but with a significant minority of responses expressing some reservations, and moreover very little understanding of the biology involved.

The professional and public debate raised a number of ethical issues, which I will only outline here. Chief among these were concerns about the safety of an innovative technique, emphasizing the need for parents to be fully informed of the risks and for long-term follow-up of the health of the child. More speculatively, a large part of the debate focused on the consequences to the child of having DNA from more than the standard 2 parents. Would the child's identity be in some way adversely affected? Exactly what people meant by this was not always clear. In terms of *genetic identity*, the facts that mitochondrial DNA represents only a tiny proportion of the total genetic material, and that it codes for cell structures not normally thought of as having much to do with identity-forming traits, suggest that altered genetic identity is not a serious ethical concern. Worries about *social identity* are rather more plausible, especially given that the media reporting has consistently, and wrongly, described the process as 3-parent IVF.[1] Clearly, if this is the public perception of it, then a child resulting from mitochondrial donation might well suffer stigmatisation. Against this, it is also true that similar sorts of fears were expressed about the acceptance of the first ‹test tube babies›, but in practice society has proved perfectly able to adapt to novel forms of making babies.

A related discussion centres on the identity of the mitochondrial donors, and especially on what kind of legal status – and therefore what kind of parental rights and obligations – they would have. Are they equivalent to gamete donors or are they more like kidney or blood donors? This question remains unanswered at the moment, though the trend of the debate and the public consultation is towards the latter. From the perspective of feminist bioethics, it is striking (and worrying) how little attention has been paid to other aspects of donor egg provision: who will provide them, what sort of compensation if any would be appropriate, and what sort of protections would be needed to prevent any possible exploitation of the women who donate their eggs for the first steps in clinical research and ultimately in clinical practice too.

The most ethically (and politically) contentious area remains the question of mitochondrial donation as a form of germline genetic modification. The 2008 revised law is quite clear that *any* change in the DNA of an embryo is forbidden, but it also contains a provision for secondary legislation to cover future developments in mitochondrial manipulation, and it does this because of the ambiguous status of mitochondrial DNA. There has been intense debate within the bioethics and policy communities as to whether changing the mitochondrial complement actually counts as germline modification. Those in favour of the techniques tend to argue that although it is a permanent and heritable

1 See, for example, these reports by The Independent (http://www.independent.co.uk/life-style/health-and-families/health-news/three-parent-babies-one-step-closer-survey-reveals-support-for-radical-ivf-therapy-8542476.html) and The Guardian (http://www.guardian.co.uk/science/2013/jun/28/uk-government-ivf-dna-three-people), both of which should have known better.

genetic change, it is not ‹germline› in the way that term is normally understood, i.e. it does not involve changes in the nuclear DNA likely to affect the resulting individual's identity and characteristics. Those arguing against are more likely to reject this as biological hair-splitting. They say that allowing mitochondrial donation is the first step on the slippery slope to overt, targeted, deliberate germline modification of characteristics. Against this, proponents point out that any new legislation will specifically refer to mitochondrial donation only; it will, they say, retain a firm distinction between mitochondrial and nuclear genetic modification.

While any revision of the law will indeed retain that distinction, I am reasonably confident that, once mitochondrial donation is allowed, there will soon be public pressure to go further. Slippery slope arguments are often plausible in theory but less inevitable in practice, particularly when there is a legislative barrier in place. But in order for such a barrier to hold, it needs to be one that the population understand and endorse. To grasp the significance of the difference between nuclear and mitochondrial DNA requires a fairly sophisticated level of biological knowledge, and the public consultation gave no indication that most people grasped the *qualitative* rather than *quantitative* distinctiveness of mitochondrial DNA. Moreover, much of the case for mitochondrial donation rests on the severe suffering experienced by affected families. It may be hard in the future to resist arguments where individual and family suffering is just as great but where treatments involve nuclear genetic manipulation. If mitochondrial donation is permitted, there will almost inevitably be a case in which potential parents with a condition that might be prevented by intervention in the nuclear DNA will argue that there really is no significant difference between that and (permitted) intervention in mitochondrial DNA. For them, and many others, the legislative bar and the reasoning behind it will be meaningless.

On 27 June 2013 the UK Department of Health announced that it would begin drawing up guidelines that will enable further research and, if that is successful, to go ahead with first treatments [3].

Whether mitochondrial donation really does turn out to be the start of a slippery slope is far from certain, but what *is* clear is that it has opened up a whole new set of questions.

Correspondence
Prof. Dr. Jackie Leach Scully
PEALS (Policy, Ethics & Life Sciences) Research Centre
Newcastle University
4th Floor Claremont Bridge
Newcastle upon Tyne
NE1 7RU
United Kingdom

E-Mail: jackie.scully[at]newcastle.ac.uk

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