Human Genetic Engineering on the Doorstep

The threat of 'mitochondrial replacement' techniques

Summary

The British government is currently proposing to legalise a new technique for treating certain genetic diseases that would, for the first time, allow the creation of babies whose genes have been intentionally altered. Although food crops, bacteria and animals have been genetically engineered for the last 20 years, there has been a worldwide consensus, embodied in legislation in over 60 countries, that we should not attempt to do the same with human beings. This is because crossing this line would lead inevitably to a future of 'designer babies' and a new consumer-driven eugenics. These techniques are not strictly speaking genetic modification, but involve cloning-type manipulation of eggs that result in an embryo with altered DNA in its mitochondria (small 'organelles', responsible for energy production that are found in all cells). These changes would be passed down the female line to all descendants. Under the Human Fertilisation and Embryology Act 2008, the next step, genetic modification, could happen with no significant public or Parliamentary debate.

The techniques pose significant health risks to the children involved. Advocates of the new techniques argue that they would help prevent severe suffering, but in fact there are already perfectly safe and reliable alternatives: adoption, or the donation of eggs by another woman. Thus the only benefit gained by these techniques is that the mother is genetically related to the child in the normal way. Such a social, rather than medical, benefit in no way justifies dragging humanity across this 'bright line' of profound importance.

The Human Fertilisation and Embryology Authority is currently consulting the public on these proposals and it is imperative that there is a strong response. Their online consultation can be filled in at http://mitochondria.hfea.gov.uk/mitochondria/, before December 7th.

1. Introduction.

In response to requests from scientists at Newcastle University, the British Government is currently proposing to legalise a new technique for treating mitochondrial genetic diseases. If agreed, this would, for the first time, allow the creation of babies whose genes have been intentionally altered. Although food crops, bacteria and animals have been genetically modified for the last 20 years there has been a worldwide consensus, embodied in legislation in over 60 countries, including the UK, that we should not attempt to do the same with human beings. These techniques are not, strictly speaking, genetic modification, but involve cloning-type manipulation of eggs that result in an embryo with altered DNA in its mitochondria (small 'organelles', responsible for energy production that are found in all cells). These changes would be passed down the female line to all descendants. They can be included in the definition of genetic engineering, although they are not genetic modification. These changes would be present in every cell of the person's body. The only benefit of the new techniques over existing methods is that they allow mothers to be genetically related to their child.

The main concern is that once this technique has been legalised and the international prohibition on altering the human germ line (the DNA that is passed down the generations)

has been overturned, it will become difficult to prevent human genetic modification, first to prevent genetic conditions and then in order to produce "designer babies" with enhanced capabilities. HGA has campaigned against the possible creation of such genetically modified human beings for the last twelve years, and we are extremely concerned that this line will be crossed, without appearing to do so, and with little public awareness.

2. What are mitochondrial genetic diseases?

Nearly all cells of higher organisms contain hundreds or thousands of mitochondria, small 'organelles' whose function is to create energy for the cell, in the form of a molecule called ATP. These organelles contain their own DNA, which codes for a number of proteins and RNAs that are part of the mitochondria. Most of the proteins in mitochondria are coded for by nuclear genes.

Mutations in the mitochondrial DNA can cause genetic diseases. Because the child inherits its mitochondria almost entirely from his/her mother's egg, these diseases are passed from mother to child.

There is great variation in the severity of such conditions and in some cases it can be difficult to predict from testing the mitochondrial DNA whether the child will suffer from the condition. The birth frequency of children with mitochondrial conditions is 1 in 5000.

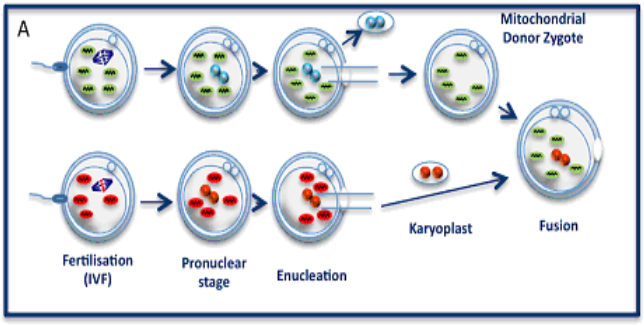
2.1 Existing options to avoid passing on mitochondrial genetic conditions caused by mitochondrial mutations

Until now, mothers at risk of passing on mitochondrial genetic conditions have used the following options:
1. Avoid having children.
2. Have children and take the risk that they will be affected.
3. Adoption.
4. Get pregnant and use prenatal genetic testing to see whether the child is likely to be affected, with the option of terminating the pregnancy.
5. PGD: create embryos using IVF and do genetic testing; implant only embryos likely to develop into a healthy child..
6. Egg donation: use an egg donated by another woman.

The new 'mitochondrial replacement' techniques

Pronuclear Transfer (PNT):

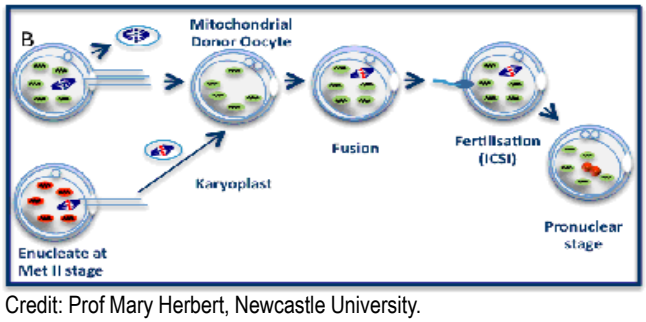
This technique uses IVF to create an embryo using the intending parents' sperm and egg. When it is one day old, the two pronuclei from the parents are removed from the embryo, leaving behind the majority of the mother's mutated mitochondria with the cell, which is then discarded. A second embryo is created from the egg of a donor with healthy mitochondria, fertilized with the father's or donor sperm. After one day, the pronuclei of this embryo are removed and discarded. The parents' pronuclei are then placed into the second embryo, which has maintained the healthy mitochondria from the donor's egg. This embryo can continue to develop and then be transferred into the mother.



Credit: Prof Mary Herbert, Newcastle University.

Maternal Spindle Transfer (MST):

In this technique, the nuclear DNA is removed from the mother's egg and the rest is discarded, including the unhealthy mitochondrial DNA. The chromosomes of a donated egg from a woman with healthy mitochondria are taken out at the same time, leaving the healthy mitochondria in the cytoplasm. The mother's chromosomes are placed into the enucleated donor egg, which can then be fertilized with sperm from the father. The resulting embryo can then be transferred into the mother.



Credit: Prof Mary Herbert, Newcastle University.

These techniques are being referred to as 'mitochondrial replacement'. Both of them are, in essence, an extension of egg donation, with the difference that the donor egg's nuclear DNA is removed and substituted with the mother's nuclear DNA.

3. Legal Loopholes.

The possible legalisation of the techniques was envisaged during the revision of the Human Fertilisation and Embryology Act in 2008. The Act contains rules which effectively prohibit genetic modification of embryos for treatment purposes (Section 3ZA(2)). This is qualified by a power of the Secretary of State for Health to make regulations to allow the creation of an embryo whose nuclear or mitochondrial DNA has been altered if the purpose is to treat mitochondrial diseases (Section 3ZA (5)). This means that rather than there being a full parliamentary debate on the issue, it would be discussed by a small committee of MPs, with very little time given. This procedure is little better than a rubber stamp.

Once the 'mitochondrial replacement' techniques were permitted it is very likely that there would be pressure to allow genetic modification, in order to treat conditions caused by mutations in nuclear genes. Proponents would argue that since the line had been crossed already, it would be illogical and unfair to families affected by mitochondrial conditions caused by nuclear mutations not to receive the same benefits as those whose conditions are caused by mitochondrial mutations. It would be argued that there was no need for further public debate, since the principle of allowing germ line changes had been agreed in 2012. The preparatory research on the genetically modifying embryos is already legal under the HFE Act. Although Human Genetics Alert and the then Liberal Democrat MP, Evan Harris, pointed out to the Government during the debates on the Act in 2008 that the use of genetic modification to prevent the transmission of mitochondrial diseases originating in nuclear genes, could be legalised without proper public and Parliamentary debate, the Labour Government refused to amend the wording.

4. What's wrong with 'mitochondrial replacement'?

There are three main reasons for not using these techniques: i) to do so would contravene the international consensus against modifying the human germ line, and that the consequences of doing so would be socially and ethically disastrous; ii) the technique poses significant risks to the child, and possibly to their descendants; iii) the children created would have three different genetic parents.

Proponents argue that the techniques would allow families to have children unaffected by mitochondrial conditions, and that this is a major medical benefit; however, what they rarely acknowledge is that there already exist a variety of ways of achieving this, including conventional egg donation: thus the only benefit of this technique beyond what can be achieved through adoption or egg donation is that the mother is genetically related to her child. **In our view such a benefit does not outweigh the severe risks to society and to the child from permitting the use of these techniques.**

4.1 The risks of human genetic modification

If we wish to avoid a future of GM 'designer babies', we must preserve the ban on all germ line engineering

Other briefings and documents from Human Genetics Alert available on our website argue the case against allowing human genetic modification, and we will not reproduce these points in detail here. Once genetic modification was allowed for the purposes of avoiding disease, it would be impossible to restrict its use to such purposes, as has already been seen with drugs, surgery, and genetic testing. The case against allowing genetic modification is therefore based upon its use for purposes of 'enhancement'.

Proponents of new reproductive technologies tend to disparage such arguments as 'slippery slope arguments', and some bioethicists have built their careers upon demonstrating that such arguments are logically invalid. Yet in the real world, it is obvious that such a step-by-step progression is happening all the time, and always moving in the same direction. In our society this is called 'progress'. There are a number of problems with the term 'slippery slope', one being that it underestimates the downward forces. There are multibillion dollar industries, non-governmental organisations and teams of PR people who are paid well to constantly push us down the slope. The proponents argue that the further steps would not necessarily take place because there are regulations that require further consultation at each stage, and we can therefore decide to stop. However, when we come to the second step

such proponents invariably argue that since we have already taken the first step, it would be illogical and unfair, even discriminatory, not to continue. **Thus the burden of proof is on them to explain why that this will not happen yet again.** Appealing to the existence of the HFEA reinforces our own arguments since that body, in its 22 year history has only once refused to keep sliding: in 2003 when it tried to legalise social social sex selection but could not override very strong opposition from the British public.

As we have noted above, there is a very clear legal path mapped out, which, once mitochondrial replacement is legalised, would be very difficult to avoid. Here, the slope has been carefully greased, several years in advance. The citation by the HFEA of the frequency of mitochondrial diseases as 1 in 200, which includes cases caused by nuclear genes, shows that they are already envisaging the use of genetic modification.

It is inconceivable that the UK should unilaterally cross this line and decide for the whole of humanity

Thus, when considering whether to allow mitochondrial replacement, it is inescapable to consider the medium-term consequences, ie. genetic 'enhancement'. **If we wish to avoid that result, there is no alternative to preserving the prohibition against germ line engineering, and it is a neglect of our moral and social duty to pretend that that line can be crossed now, because we can safely leave the inevitable consequences to the future.**

In brief, there are two main reasons that we should avoid human genetic modification:

(i) genetically modifying a child's characteristics turns the child into just another designed commodity, and that this will have profoundly negative effects on the relationships between children and their parents;

(ii) creating enhanced GM children would be a form of consumer eugenics that would be disastrous for our society as a whole.

What links these two points is that this will be the moment at which people, like microorganisms, plants and animals before them, finally become fully integrated into the industrial capitalist system of production and consumption of commodities, and become subject to its logic. We already know how in the eugenic egg donor market in the USA the logic of eugenics is identical to that of the free market: those who have a supposedly superior genetic product to sell, such as women from Ivy League universities, can demand higher prices for their eggs.

Until now, religious cultures and secular humanism have dictated that humans are a separate category from designed consumer commodities. I must regard humans as my equal: they are to be accepted and respected as they come, not moulded and selected at the most basic biological level in order to become useful tools for me, according to my whims. Humans, including my future children, are not consumer goods, or 'factors of production'. We must not do this even if such so-called enhancements can be argued to be in their interests. It is not an accident that a recent report on human 'enhancement' focuses on how people's capabilities as workers are to be improved.[1]

As noted above, it is for these compelling reasons that there has been an international consensus against permitting genetic modification of human beings, comparable to the consensus against human cloning. In Europe, nearly all countries except Britain have signed the Council of Europe Convention on Biomedicine and Human Rights, which prohibits the alteration of the human germ line by any methods. It is extremely unusual for governments around the world to create outright bans on specific scientific techniques, and this underlines the seriousness of the reasons against allowing genetic modification. Any decision to cross this line is a matter for the whole of global society, and it is inconceivable that the UK should be allowed to make this decision on behalf of the rest of humanity.

4.2 Risks to the child

In 2011 the HFEA conducted a review of safety issues connected to these techniques and produced a report[2] requiring the scientists to conduct further experiments, which have only just begun. Since there is not nearly enough research evidence, it is hard to reach a firm conclusion on whether these techniques are safe or not. However, there is plenty of background evidence from experience with other reproductive technologies to suggest that there may well be a problem. 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[3]. 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.

There is plenty of reason from experience with other invasive reproductive technologies to believe that there are severe risks to the child

Further evidence of likely safety problems is the fact that in the Newcastle team's published paper the rate of production of blastocysts (a stage of embryo development reached after a few days) from embryos created using the techniques was half that of the control embryos. It seems reasonable to assume that if the manipulations make half the embryos non-viable at such early stages, there will be more subtle effects on the remaining embryos. The opposite assumption, that the remaining embryos are healthy, seems extremely risky.

The only significant evidence of safety of these techniques is a study involving the creation of only four monkeys, which were followed up for only 4 years. The HFEA panel barely considers the likely damage to embryos from these manipulations, yet it suggests experiments designed to test that issue, which shows that this is a significant concern. A recent paper showed that simply manipulating embryos in this way causes significant damage[4]. The HFEA report states that 'The evidence currently available does not suggest that the techniques are unsafe', a phrase carefully crafted for repetition in the media. **But as the HFEA well knows, lack of such evidence does not mean the techniques are safe.**

Overall, it seems that there is not nearly enough evidence to justify beginning clinical trials, and the HFEA panel was right to insist upon further safety research. Until the results of this research are available, and conclusions can be drawn about the likely risks to the child, launching a public consultation on the techniques' acceptability is highly premature.

4.3 'Three parent babies'

Embryos and children produced by these techniques will contain genetic material from three people: nuclear DNA from the child's parents and mitochondrial DNA from the egg donor. For many people the idea of a child with 3 genetic parents is disturbing, and offensive because it contradicts traditional ideas about parentage and inheritance. In our view, however, it is not the issue of parentage, in itself, which is important.

What worries many people about constructing a person in this way is the same thing that worries them about GM foods or human-animal hybrids: the way that scientists treat nature as a set of infinitely exchangeable parts to be mixed and matched as necessary. Just as Frankenstein's creation was produced by sticking together bits from many different bodies, it seems that there is no violation of the norms of nature or human culture at which scientists and their bioethical helpers will balk. Such an attitude ignores the importance of the integrity of biological wholes, and the barriers between them, such as species, despite their deep significance in human psychology. Molecular biology does not tend to recognise the significance of qualitative difference in nature: humans and cauliflowers are described as 40% genetically homologous. Their differences are thereby reduced to quantitative measures, which do not admit of any clear line drawing. Scientists do not understand, and dismiss as 'irrational', people's protests about the integrity of nature, even when the objects they construct are of such profound ethical and psychological sensitivity as a human baby.

There are extensive efforts being made to

minimise the significance of the mitochondrial DNA for the child's parentage. It is pointed out that mitochondria contain only 37 genes and that these are 'only' involved in energy production: they do not contribute to visible characteristics of the child. The same, of course, can be said for many nuclear genes, and it is not clear why energy production is to be considered an unimportant physiological function. It is through variations in mitochondrial DNA that people trace their maternal genetic heritage. But the most obvious problem with these arguments is that it is precisely for the sake of altering these few genes that the whole complex process would be undertaken.

5. What are the benefits of the techniques?

These techniques have been presented as if they are the only solution to mitochondrial genetic diseases, and thus the choice is between permitting them and continuing to allow the suffering associated with the diseases. This is an example of the way in which these debates are always intentionally framed in order to put critics on the defensive. As noted above, the techniques are an extension of egg donation, which allow the mother's nuclear DNA to be passed onto the child. **Egg donation, by itself, and in a safer and more reliable fashion than the new techniques, can guarantee that the parents have a child that will be safe from the threat of mitochondrial disease.** It should also be noted that in many cases of mitochondrial disease, prenatal or preimplantation genetic diagnosis can provide an alternative means of having a healthy child.

The benefits of these techniques over existing options are social, not medical

Thus, the only benefit of MST and PNT is that they allow the mother to be genetically related to the child (the father will be genetically related as normal, whilst the mother will be pregnant and give birth to the child). Of course, anyone can understand and sympathise with a mother's desire to be their child's genetic parent, but this does not confer any medical benefit upon the child or parents. It is, in fact, a social benefit. While such benefits do need to be considered, they are very clearly not comparable to the medical benefits that would be gained if there were no alternative ways in which these families could have healthy children.

Such social benefits are significant but must not be overstated. Adoptive children and parents, and those where egg or sperm donation have taken place will tend to insist that their relationships and status are not inherently 'less than' those of biological parents and children. In conventional medical ethics, social benefits are generally seen as of considerably smaller importance than medical benefits, and where there is competition for limited money, medical benefits will win. Even in the case of a social benefit with an arguably strong medical component, such as access to IVF, such services have been first to be cut in the current austerity measures. The reason that the British NHS does not include cosmetic surgery services is because that is a social benefit. In some cases, such as sex selection, performing a procedure for social purposes is regarded as inherently wrong and is therefore banned.

It is, in fact, difficult to see why millions of pounds of taxpayers' and charitable funds have been invested into this research. In our view, this has much more to do with scientists' tendency to value the high-tech and cutting edge and its associated career advancement, than with genuine medical need. We cannot help noting that these proposals emanate from the same research centre that previously brought us 'therapeutic cloning' and human-animal hybrid embryos. At the time we were told that these were vital medical research, which required changes in the law. Later, as HGA predicted, they were quietly abandoned as impractical and impossibly expensive, and in the case of hybrids, rejected as of little scientific merit by the Medical Research Council.

6. Conclusion: a simple matter of weighing risks and benefits

In order to decide whether is it ethically or socially acceptable to allow clinical trials of the mitochondrial replacement techniques we need to weigh the risks of the techniques versus its claimed benefits.

In our view, the social benefits for a relatively small number of women of being genetically related to their child do not come near to justifying the potential health risks from these techniques to the child and the risks to

global society that stem from human genetic engineering. In fact, even if the latter consideration were not in play, it would be difficult to justify using the techniques. But it is truly inconceivable that the whole of humanity should be unilaterally dragged across one of the few 'bright lines' that have been agreed around the world, a line of such profound significance for the human future, for the sake of a small number of women who wish to be genetically related to their child.

Human Genetics Alert urges all people of goodwill to send a clear message to the HFEA and government, insisting thatlegalisation of these techniques is not approved. The HFEA online consultation is at http://mitochondria.hfea.gov.uk/mitochondria/, and must be completed by December 7th 2012.

References

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The benefits of these techniques do not begin to justify the risks to children and global society

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