



Three-parent embryos for mitochondrial disorders

By Philippa Taylor

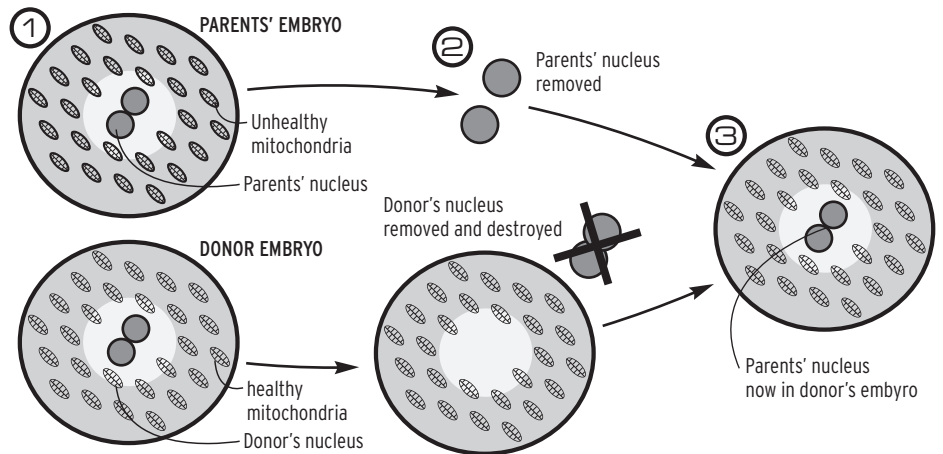
New 'three-parent' IVF techniques have been developed which researchers claim could enable women to avoid passing mitochondrial diseases on to their children. Mitochondrial disease is unusual in that it is transmitted through DNA in the mitochondria (cell 'powerhouses') in the cell cytoplasm rather than through DNA in the cell nucleus.

There are 37 genes in the mitochondria, compared to 20,000-30,000 genes in the cell nucleus.¹ Mitochondrial genes operate differently to nuclear genes and their activities and relationship to the nuclear genome is complex and not yet well understood. Their role, as far as is known, is mainly in generating cellular energy and proteins but it is possible they may play other roles as well. mtDNA is passed down the generations via the mother.

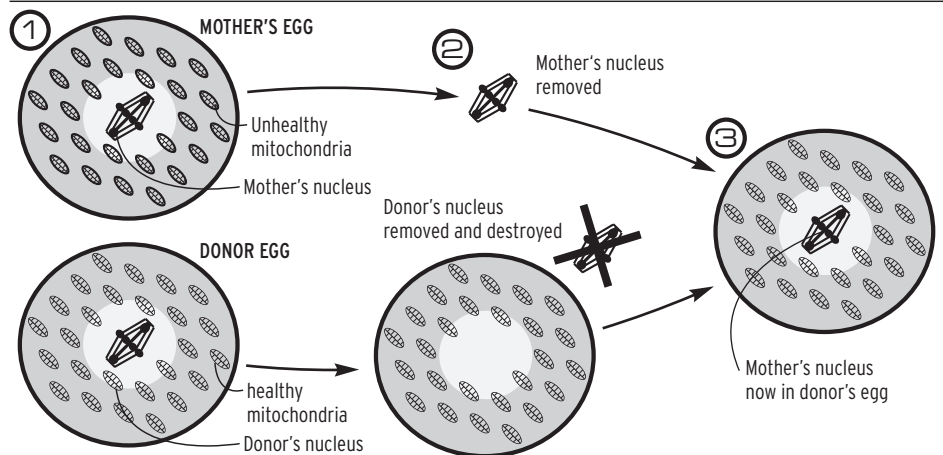
When the mitochondria do not function properly they cause diseases affecting many of the body's organs, usually organs with the highest energy needs, such as muscle, brain, eyes and heart. Mitochondrial disorders are progressive and can be very disabling. They can cause stillbirth, death in babies and children, or may onset with severe effects in adulthood, such as blindness or heart failure. It is difficult to predict how severely a child will be affected because abnormal mtDNA has to pass a certain threshold in order to cause severe mitochondrial disease, and it also depends on the mutation and age it manifests. Moreover, mothers can pass on disorders without being affected themselves.

Mitochondrial disorders are relatively rare. Perhaps 1 in 200 children are born each year with abnormal mtDNA but only 1 in 10,000 are severely affected.² It is suggested

Pronuclear transfer (PNT)



Maternal Spindle Transfer (MST)



that the proposed techniques could 'save' around ten lives each year.³

The 'three-parent' IVF technique can be carried out in two different ways. Both aim to create an embryo that does not carry a mitochondrial disorder by replacing the cytoplasm containing the abnormal mitochondria from an affected mother with cytoplasm and mitochondria from an unaffected woman.

The first technique, called *pronuclear transfer* (PNT), involves fertilising an egg of a woman who has mitochondrial disease and then removing its nucleus. At the same time the nucleus is removed from an egg taken from a donor who does not have this condition. The nucleus from the woman's fertilised egg is then placed in the donated egg (see diagram).

In the second technique, called *maternal spindle transfer* (MST), the nucleus is removed from the mother's unfertilised egg and inserted into an enucleated egg from a 'healthy' donor, before this new composite egg is fertilised.

Regardless of which of the two techniques is used, the resulting embryo will have DNA from three people: nuclear DNA from the sperm of the male father and egg of the prospective mother and mitochondrial DNA (mtDNA) from the egg of a second 'mother', although the contribution from the second woman is very small (just 37 of 20,000-30,000 genes).

A child born following mitochondrial replacement would therefore effectively have one biological father and two biological 'mothers'.

The UK regulator of fertility treatment and research, the Human Fertilisation and Embryology Authority (HFEA), recommended that these techniques should be used for treatment providing: *'it is safe enough to offer in a treatment setting and is done so within a regulatory framework...ethical concerns are outweighed by the arguments in favour of permitting mitochondria replacement'*.⁴ As a result, the Government intends to permit this treatment through new Parliamentary regulations.

In the biblical creation narrative of Genesis 1, human beings are instructed by God to: *'Be fruitful and increase in number; fill the earth and subdue it'*.⁵ So the wise use of technology is to be supported and encouraged by Christians.⁶ Humans have always striven to tame or even transcend nature through technology, which has resulted in great improvements for humanity.

However, if any medical technologies with their enormous potential for benefit are to be used wisely, we need to pay attention both to the *ends* (ie goals) being pursued (for individuals and for society) and the *means* of obtaining those ends. How do mitochondrial replacement techniques measure up when both ends and means are considered?

Is it necessary and effective?

It is important to understand that this technique will not 'save the life' of any child already born with a mitochondrial disorder. Moreover, children will *still* be born with mitochondrial disorders because it is not always possible to know whether a mother is a carrier or, if so, whether, when or how severely her child (embryo) will be affected. The distribution of mutant mtDNA can be different in different tissues and may also change with time. There can be wide variation in the level of abnormal mtDNA between mother and baby.

This research is therefore 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.

For the very small number of women who find themselves in the tragic position of carrying genes for mitochondrial disease, there are the alternative options of egg

donation and adoption (although there are still ethical issues with using the former⁷). It is the desire (not need) of prospective parents for a genetic link to their child(ren) that stops them using alternatives.

Could not the focus and investment of resources be better directed to finding treatments for those affected, including research into the cell's own way of controlling mitochondrial quality, and towards linking couples to children needing adoption, rather than preventing ten or so affected individuals from being born or conceived each year?⁸

What will be the psychological effect on any child knowing that their DNA is derived from three separate genetic 'parents'?

Is it safe?

Scientists have not yet shown that mixing nuclei and cytoplasm from different individuals is safe for the recombined embryo and does not affect normal development. A number of studies have found that some unhealthy mitochondria from the affected mother could still be carried over into the embryo and occasionally amplified to levels that could cause mitochondrial disease in 'mitochondrial-replacement' babies.⁹ Others have expressed concern about disrupting the nuclear-mitochondrial DNA interactions following nuclear transfer, compromising cell function.¹⁰

There are residual health risks to children in the long-term from genetic reprogramming and no long-term safety data to assess these. Embryos can only be grown to the blastocyst stage, but many of the expressions of genetic abnormalities do not manifest themselves until much later in gestation or after birth.¹¹

Testing the safety of new reproductive technologies such as this can only be achieved by actually creating new human individuals. So the first attempts to create children using these techniques will be experiments involving an element of risk. It might be argued that other reproductive technologies do the same, but mitochondrial

replacement techniques involve much more physical disruption to the embryo than, say, IVF or ICSI. It does not follow that because concerns about the health risk to the child are not new, that they are therefore no longer of concern. The same concerns should hold for all reproductive technologies that provide a potential risk to the life and health of children.

The techniques being proposed in the UK are prohibited under international law.¹² The reason is that altering the germline of future children raises profound safety and ethical concerns.¹³ Mistakes and unpredictable consequences would transmit to subsequent generations and become irreversibly part of their genome. There are serious concerns that this would set a precedent for further genetic alterations of human beings.

Is it ethical?

*'It is simply that the batteries have been taken from another woman's egg so that they are sure that any child does not bear some of the very serious diseases that often lead to premature death.'*¹⁴

While some thus argue that the ethical issues are minor and are justified by the benefits, there are a number of ethical concerns with both techniques. First, the research required for both PNT and MST involves the creation and destruction of human embryos. Also, even if the technique is perfected, PNT will necessitate the destruction of one human embryo in order to create a second, reconstituted embryo. Some may consider that because human embryos are small, weak and physically insignificant they are expendable. However, others argue that we owe these most vulnerable of human lives the utmost respect and protection.

Second, little public attention is paid to the need to increase the supply of donated eggs to generate embryos for both the research and treatment. The mitochondria cannot be taken out of the affected mother's egg, hence the need for a donor egg. The demand for donor eggs of course comes to women. Egg extraction requires high doses of drugs and involves risks and often pain for donors.¹⁵ Some eggs may be freely and willingly donated but the risks involved mean that women often have to be offered inducements to 'donate' their eggs, through cut-price fertility treatment or financial 'compensation' (£750 per cycle of donation). Invariably, these will not be wealthy women

but economically disadvantaged and vulnerable women who are more willing to risk harm to their own health, not for their own benefit but for for ethically questionable research.

Third, the outcome of the technique is the creation of an embryo with two 'mothers' and one father. It may not be clear exactly *how* mtDNA will be associated with a person's identity and advocates of the technique can downplay the relevance of the mitochondria in the individual's genetic make-up, yet we *do* know there will be three adults with whom the baby shares a parental genetic connection, and there will be identifiable genetic material from a second female genetic parent which will be passed down the female generations.¹⁶ An extra individual would join the family tree. Baylis argues strongly that the contribution of the mtDNA is important in shaping a person's narrative, and determining who a person will be.¹⁷

The issue of parenthood is complex. The HFEA recommends the status of mitochondrial donors in the child's life should be similar to tissue donors and children should have no right to *identifying* information about them. However children could instead find out *non-identifying* information about the mitochondrial donor at age 16.¹⁸ Other jurisdictions have moved closer to permitting a child to have three legal parents, so it is not inconceivable that a donor may one day apply for contact or even a parental order.¹⁹

What will be the psychological effect on any child knowing that their DNA is derived from three separate genetic 'parents'? Will it affect their sense of personal identity? Indeed, what is a 'parent'? Is the parent genetic, gestational, or social and psychological? There is no obvious answer as we have no experience of this situation, illustrating that this experimental process is proceeding far ahead of any research into the social and psychological implications for those who may be born from such experiments.

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 their

donor and a desire to know more about their genetic heritage, including any donor siblings.²⁰ The warnings from anecdotal testimonies about the damage that the manipulation of genetic heritage, parental bonds, identity and self-understanding can have in the long-term should be heeded.

Fourth, once germline genetic manipulation of a human life is permitted, even if just for rare mitochondrial disorders, an ethical boundary will have been crossed towards allowing germline therapy for other conditions as well, starting with permitting alterations to the nucleus of the human egg, in addition to the mitochondria. For how long would it be possible to say to patients that their condition is in the 'wrong' DNA to be able to intervene? *'The much debated 'designer baby' would become a reality.'*²¹

Several academics in the UK and US have warned that both PNT and MST cross an ethical line and will lead to a future of genetically modified 'designer' babies.²² Genetic reconstruction of this sort moves us beyond selecting certain children to modifying and manufacturing them. Genetically engineering a human person – however little or much – turns that human into a designed product, modifiable at will, without consent. Hence IVF pioneer Lord Winston warns about the future implications of this research:

*'Genetic technologies could be exploited in the future to produce more intelligent, stronger and attractive offspring...a form of eugenics could lead to people wanting to modify their children to enhance "desirable characteristics" such as intelligence and beauty.'*²³

Professor of Cell Biology, Stuart Newman, also warns: *'This attempt to improve future people is not medicine but a new form of eugenics. In its willingness to risk producing damaged offspring by modifying embryos' genomes, this "correctionist" eugenics goes even beyond the "selectionist" version.'*²⁴

This new form of 'eugenics' (the improvement of humans by deliberately choosing their inherited traits) uses a kinder, gentler language, clothed with words such as choice, freedom and 'avoiding suffering', simply to enable the same discriminatory distinctions that used to be made between the so-called 'fit' and 'unfit'.

Technology feeds many people's belief today that they have not just a 'right' to a child but also a right to choose a particular *kind* of child. Greater access to new genetic technologies now is coupled

with more willingness by scientists and parents to take risks with future lives and to pick and choose other characteristics. Yet is it really possible to tamper with the genetic makeup of our fellow human beings without deep long-term harm to both individuals and society?

Biblical reflections

Is there any justification in Scripture to pursue this technology? Developing treatments for terrible illnesses is undoubtedly a worthy aim and Christians have a duty of compassion and care for their fellow humans (neighbours). If this new technology employs the God-given creative gifts and freedom that humans have at our disposal, why are we not justified in developing and using it? May it be argued that the use of this research is to be encouraged if it will (purportedly) save lives and end suffering, for both parents and child?

Ends and means

The argument that the end justifies the means is morally flawed. Romans 3:8 asks: *'And why not do evil that good may come? – as some people slanderously charge us with saying'* (ESV). Using technology responsibly is part of good Christian stewardship, but we must do God's work in God's way. We are not permitted to use immoral means to achieve good ends. We must also ensure that any harm caused to an affected individual, to another child (including those as yet unborn), to a (potential) mother or indeed to any other fellow humans is justified by the good achieved.

The value of early human life

Christians have expressed a range of views on the status of the human embryo, but most consider that human embryos are fully human, made in the image of God and therefore worthy of the utmost respect.²⁵ Their value is not a consequence of human actions, capacities or any abilities but simply because, by virtue of being made in God's image, they are in some way, like God. The Bible teaches that taking the life of another human being is wrong.²⁶

The gift of a child

Psalm 127 reflects that children are a blessing and a gift from God, not a right nor an exercise in self-fulfillment. The Psalmist does not say that only *some* children are a

gift. The parental relationship is not the acquisition of a commissioned 'artifact', which is why theologian Oliver O'Donovan says that children should be 'begotten' not 'made'.²⁷ In other words, there is a boundary that should not be crossed between receiving a baby as God's gracious gift and fashioning a baby, or making him or her, as a product to someone else's specification.

Kinship and adoption

Genealogies in the Bible – family trees – reflect the importance of the network of genetic relationships at the heart of families and communities. Matthew 1 and Luke 3 detail Jesus' human family lineage and there are references throughout the Gospels and Epistles to people's blood relatives as part of defining their identity. The genetic relationship is deeply bound in with the fundamental aspects of human existence: conception, birth, nurture, sex, death and generational replacement.

Interfering with the genetic relationships between a child and his or her parents and, in this case, creating a child with a link to three genetic 'parents', would knowingly disrupt the biblical symmetry of family relationships and the complex interrelatedness of the extended biological family. This would be no one-off experiment as it would impact the child's own female descendants for generations to come. There are similar effects with surrogacy and use of donor gametes,²⁸ however the concerns in this case are compounded by the deliberate manipulation of the inherited germline.

While genetic parentage, identity and family lines are important biblically, the idea of adoption is also a significant theme.²⁹ Adoption is a mutually beneficial act and a different kind of family arrangement that provides a child for a childless couple and a loving home for a child who is already in need. It makes the best of a difficult situation, whereas creating children with DNA from three different 'parents' would knowingly and intentionally create identity problems and confusing parentage for the child.

Tampering with human life

For many, the human body is regarded as dispensable and open to manipulation. Biotechnology can tempt us not just to *accept* a child, but to *transform* the child, in this case, through changing the germline.

1. [bit.ly/AxPler](#)
2. Nuffield Council on Bioethics. Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review. 2012
3. Government press release. Innovative genetic treatment to prevent mitochondrial disease. 28 June 2013. [bit.ly/1714Q8n](#)
4. HFEA. Mitochondria replacement consultation: Advice to Government. March 2013. [bit.ly/12Gg9YT](#)
5. Genesis 1:28
6. *CMF File 49*, Winter 2012
7. *CMF File 47*, Spring 2012
8. Baylis asks if there is justification for investing resources into research on avoiding the vertical transmission of mtDNA disease when there are much greater reproductive health needs for women in developed and developing countries. Baylis F. The ethics of creating children with three genetic parents. *Reproductive BioMedicine Online* 2013;26:531-534. [bit.ly/1b79NKf](#)
9. Takeda K, Akagi S *et al*. Proliferation of donor mitochondrial DNA in nuclear transfer calves derived from cumulus cells. *Mol Reprod Dev* 2003;64(4):429-37
10. Mitochondria are not autonomous organelles but are under the influence of the nucleus. 1,500 nuclear genes are needed for mitochondrial function. HFEA. Evidence to mitochondria review. 2011. [bit.ly/14Nbbgf](#) also [bit.ly/1714Q8n](#)
11. HFEA. Non-confidential minutes of scientific review workshop. 25 March 2011. [bit.ly/14Nbbgf](#) and HFEA. Non-confidential written evidence submitted to the panel. 2011. [bit.ly/1714Q8n](#)
12. In Europe most countries except Britain have signed and ratified the Council of Europe Convention on Human Rights and Biomedicine which prohibits germline interventions under article 13. A UNESCO declaration in 1997 similarly prohibits germline interventions. Mackellar C. GM babies with 3 or 4 parents. The Christian Institute. 2012. [bit.ly/1aBTbvi](#)
13. The germline of a mature or developing individual is the line (sequence) of germ cells that have genetic material that may be passed to a child.
14. Soubry A. 25 June 2013. HC Hansard, Column 64WH. [bit.ly/1652cWQ](#)
15. Ovarian hyperstimulation syndrome. [1.usa.gov/LOAG7N](#)
16. There is still much that is unknown about the role of mtDNA but currently the scientific consensus is that it does not have an influence on the personal characteristics of a child.
17. Baylis F. *Op Cit*
18. Although the HFEA suggests that voluntary information exchange and contact could be arranged by mutual consent, thus clinics should keep records so that donors may be identified. [bit.ly/12Fex6d](#)
19. Nuffield Council on Bioethics. *Op Cit*
20. McWhinnie A. *Who Am I? Experiences of donor conception*. Leamington Spa, Warwickshire: Idreos Education Trust. 2006; Jadva V *et al*. Experiences of offspring searching for and contacting their donor siblings and donor. *Reproductive BioMedicine Online*. 2010;20(4):523-532; Turner and Coyle. What does it mean to be a donor offspring? *Human Reproduction*. 2000;15(9):2041-2051. [bit.ly/12FJwir](#)
21. Almond B. Evidence to Nuffield consultation on preventing mitochondrial DNA disorders.
22. King D, Darnovsky M, Newman S *et al*. Letter to the editor: Eugenics fear over gene modification. *Guardian*, 15 March 2013. [bit.ly/Wtp2Xj](#)
23. Lord Robert Winston warning over child 'eugenics'. *Scotsman*, 18 March 2013. [bit.ly/12dGZb6](#)
24. Newman S. The British embryo authority and the chamber of eugenics. *Huffington Post*, 11 March 2013. [huff.to/Y66e0M](#)
25. Genesis 9:6. See also [cmf.li/165Ah9a](#)
26. Genesis 1:27, 9:5,6; Exodus 20:13
27. Waters B. Reproductive technology. *DLT*, 2001:48, citing O'Donovan O. *Begotten or Made?* Oxford: Clarendon Press, 1984
28. *CMF File 47*, Spring 2012
29. See eg Romans 8:15, 23; Galatians 4:5; Ephesians 1:5
30. Wyatt J. *Matters of life and death*. Leicester: IVP, 1998:69-70
31. Grudem W. *Bible Doctrine*. Leicester: IVP, 1999:263. Cited in Barratt H. Regarding the Image. *CMF File 46*, Christmas 2011
32. Meilaender G. *Bioethics: a primer for Christians*. Carlisle: Paternoster Press, 1997:43

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Yet Professor of Neonatology John Wyatt writes that: '*when Christ is raised as a physical human being, God proclaims his vote of confidence in the created order*'.³⁰ Jesus' physical body after the resurrection affirms two things: the goodness of God's original creation, and that mankind, created in God's image, is the climax of creation. Genesis 1:31 describes the physical body as 'very good'.³¹

Humans, at whatever stage of life or ability, are not to be selected or designed to fit another's whim or will. Once human value becomes dependent on acquiring some particular level of enhanced biological, genetic or cognitive capacity we begin to create a society in which some human beings are more valued than others. This was the foundation of the eugenics movement. Theologian Gilbert Meilaender warns that when we take up the project of shaping future generations in so fundamental a way, we cannot really know what good or ill we will accomplish. We can guess, but we cannot really know what project we are undertaking, nor its outcome.³²

The project to manipulate the human germline is certainly alluring, and may be moved by compassion for the sick as well

as the desire for knowledge, power and, for some, fame. But the most truly human exercise of our freedom will be the courage to say no when asked to master and control nature in this way. Back in 1947 CS Lewis foresaw exactly the sort of advance and dreams of mastery that germline therapies would one day offer us, hence the choice of the stark but powerful title for his book: '*The Abolition of Man*'. The Bible teaches that there are limitations in what we can hope for in this life. Biological perfection and the absence of suffering are a part of the new heaven and new earth, but not possible in this fallen world.

It may be that one day some children might be born with three genetic parents. If so we must treat them with the compassion we would treat any other human beings. But it would seem wiser, given the scientific uncertainty, ethical problems and availability of alternative approaches, if we did not take a further step down that road.

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