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"Three Parent Babies": Techniques Explained, Objections Examined

Rebecca Carr
“THREE PARENT BABIES”: TECHNIQUES EXPLAINED, OBJECTIONS EXAMINED

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The UK Parliament has approved regulations, which come into force in October 2015, that permit the use of new treatment techniques to prevent the transmission of serious mitochondrial diseases from women to their children.1 The introduction of these techniques—which are not currently carried out in any country in the world—will fly in the face of the opposition that has been raised since discussions to permit clinical applications of the techniques first arose. After outlining some background to the techniques, this article briefly examines three of the objections that have been made against them: that the safety and effectiveness of the procedures have yet to be proven; that the procedures would have an adverse socio-ethical impact; and that the procedures are prohibited in international law. None of these objections are as strong as they appear to have been suggested. Indeed, the UK Parliament’s approval of the regulations should be welcomed.

I. MITOCHONDRIAL FUNCTION AND DISEASES

Mitochondria are the energy-producing organelles found in the cytoplasm of every human cell.2 Any nutrition received by the body is converted into cellular energy by the enzymes contained in these mitochondria,3 this energy being essential for the functioning of cells. In particular, energy is required for cell proliferation, movement, contraction, and the generation and processing of signals for organ and tissue functioning.4 Furthermore, mitochondria also play a role in the maturation of human gametes, embryonic development, and programmed cell death.5

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In humans, mitochondria are inherited maternally as individuals’ mitochondrial makeup derives entirely from the cytoplasm of their mother’s egg. Mitochondrial diseases, therefore, are also inherited maternally. The genetic structure comprising each mitochondrial DNA variant may differ and can be defined as either homoplasmic or heteroplasmic. Where the mother’s mutated mitochondrial DNA variant is homoplasmic, all her eggs will inherit identical mitochondrial DNA. However, where multiple sequence variants exist:

[T]here is a possibility of unequal partitioning among oocytes, a phenomenon known as the mitochondrial bottleneck, where a small number of founder mtDNAs ([mitochondrial DNA]) can be over-represented in the pool of mtDNAs of subsequent children, both because some mitochondria may be transmitted preferentially and because of the small sample size imposed by the bottleneck. Thus a heteroplasmic mother with low to medium amounts of mutant mtDNA can give birth to children with significantly higher levels of mutant mitochondria.

This makes it difficult to determine the true likelihood of a mother passing on a heteroplasmic variant-derived mitochondrial DNA disease to her child, and renders the clinical prognosis for the child uncertain. To this extent, mitochondrial DNA diseases have been described as “a cruel class of inherited disease, because serious, even life-threatening conditions are coupled with great unpredictability about how future children will be affected.” The clinical symptoms of a mitochondrial disease are similarly diverse, owing to the manner in which the disease may be inherited and to the often unique distribution of

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6 U.S., Food and Drug Administration, Cellular, Tissue, and Gene Therapies Advisory Committee, FDA Briefing Document: Oocyte Modification in Assisted Reproduction for the Prevention of Transmission of Mitochondrial Disease or Treatment of Infertility (2014) at 6, online: FDA <www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/cellularartissueandgenetherapiesadvisorycommittee/ucm385461.pdf> [FDA, Briefing Document]. The report notes, “[t]he sperm mitochondria are actively degraded by ubiquitination” per Peter Sutovsky et al., “Ubiquitinated Sperm Mitochondria, Selective Proteolysis, and the Regulation of Mitochondrial Inheritance in Mammalian Embryos” (2000) 63:2 Biology Reproduction 582. Note that the process of ubiquitination is one which oversees the degradation of cellular proteins—in this case of the sperm’s mitochondria which is used only in the process of fertilizing the egg, upon which it degrades. In rare circumstances, male mitochondrial DNA may enter the egg; however, this is very rare. See NCB, Ethical Review, supra note 3 for more information.

7 FDA, Briefing Document, supra note 6 at 6.

8 Ibid [citations omitted].

9 Ibid at 6.

affected genes within each cell. Known symptoms tend to become progressively debilitating and include “poor growth, loss of muscle coordination, muscle weakness, visual problems, hearing problems, learning disabilities, heart disease, liver disease, kidney disease, gastrointestinal disorders, respiratory disorders, neurological problems, autonomic dysfunction and dementia.”

Currently, there is no cure for mitochondrial diseases, with most clinical interventions aiming to manage the diseases’ unforgiving symptoms. For heteroplasmic women, pre-implantation genetic diagnosis (PGD) sampling methods detect which, if any, of their eggs appear to contain a lower level of mitochondrial DNA mutations before implantation via in vitro fertilization (IVF) techniques in order to minimize the risks of passing on a mitochondrial DNA inherited condition. This option would not, however, guarantee the non-transmission of a mitochondrial disease to the child (and if the child is female, to her own future children), or be appropriate for women with homoplasmic mutant mitochondrial DNA variants who necessarily transfer the genes that result in disease.

II. NEW MITOCHONDRIAL GENE TRANSFER TECHNIQUES

In light of these factors, researchers have sought to find a way to prevent transmission of mitochondrial DNA diseases in their entirety—two new experimental techniques have been put forward. The first, metaphase spindle transfer (MST) “is the transfer of female nuclear genetic material from an oocyte into an enucleated donor oocyte, containing normal mitochondria, followed by IVF.” The second, pronuclear transfer (PNT) “is the transfer of the male and female pronuclei from a fertilized oocyte (zygote) into a stage-matched enucleated donor zygote, followed by IVF.” Either technique, if successful, would prevent the transmission of mitochondrial DNA diseases from a woman to her child, and would contain genetic material from three people—the mother’s nuclear DNA, the father’s nuclear DNA, and the donor’s mitochondrial DNA.

If the proposed MST and PNT DNA transfer techniques are shown to be successful in humans, their introduction into the clinical setting would represent a scientific breakthrough for the families affected by these diseases. Children who would have otherwise developed inherited mitochondrial DNA disorders will be spared a lifetime of suffering and women carrying mutant mitochondrial DNA

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13 See NCB, Ethical Review, supra note 3 at 27-28.
14 FDA, Briefing Document, supra note 6 at 12.
15 Ibid.
affected genes will still be able to maintain a genetic link with their child without bearing the risks of transmission.

So what are some of the arguments that have been raised against the techniques’ introduction, and do they carry any real weight?

III. OBJECTIONS

(a) That the Safety and Effectiveness of the Procedures have yet to be Proven

Perhaps the most pressing of the objections raised thus far relate to the safety and effectiveness of the techniques.

The main risks of the procedure appear to be those faced by the child and, to some extent (as is explained later), the mother—although, since the techniques involve genetic manipulation, there exists potential risks to future generations as well.

There is a potential for inadvertent damage to be inflicted upon the manipulated oocyte or embryo during transfer, since the mitochondria’s distribution within each cell is thought to have some impact upon the process of early embryogenesis that the transfer techniques are subsequently liable to disturb.16 Also, since the developing fetus receives its nutritional, energy-based needs from its mother, a long-term impact may arise from manipulating the child’s mitochondria, which cannot be accurately detected before birth. Other concerns include the possibility of mutant mitochondrial DNA being carried over to the donor oocyte/embryo during transfer, and the risk of nuclear-mitochondrial incompatibility from the donor oocyte/embryo.17 The potential toxicity of the reagents used in conducting the transfer’s micromanipulation techniques poses a further known risk to the child; however, some evidence suggests that as long as care is taken, and given that the Medicines and Healthcare Products Regulatory Agency would need to be satisfied about the provenance and clinical safety of any such reagents first,18 it is thought their eventual usage would not be problematic.19

16 Ibid at 16. Further, see Lyndsey Craven et al, “Mitochondrial DNA Disease: New Options for Prevention” (2011) 20:R2 Human Molecular Genetics R168 at R170 who somewhat concernedly points out that “[w]hile the wealth of evidence from mouse studies indicates that pronuclear transfer is compatible with normal development, evidence from human studies indicates a 50% reduction in the proportion of embryos developing to the blastocyst stage,” although she also acknowledges that these were abnormal zygotes to begin with. The evidence she is referring to is presented in Lyndsey Craven et al, “Pronuclear Transfer in Human Embryos to Prevent Transmission of Mitochondrial DNA Disease” (2010) 465:7294 Nature 82.

17 FDA, Briefing Document, supra note 6 at 18. This issue arises from the fact that “the [mitochondrial DNA] of the recipient oocyte or embryo may be derived from a mitochondrial haplotype different from the nuclear donor. Therefore, the potential for nuclear-mitochondrial incompatibility . . . exists.”
The safety of the mother and oocyte/embryo donor must also be considered. Both will have to undergo ovarian stimulation to enable the transfer techniques to take place. The US Food and Drug Administration’s Cellular, Tissue and Gene Therapies Advisory Committee—a Committee which has decided not to allow the clinical application of the techniques at present—has suggested risks to the woman might include failure to become pregnant and/or deliver a child as well as risks associated with the mitochondrial manipulation technology procedure and risks pertaining to the toxicities of the reagents used in the technologies. However, little research appears to have been conducted that specifically looks at these issues from the perspective of the woman.

The Human Fertilisation and Embryology Authority (HFEA), the UK body charged with undertaking the government’s scientific review into the safety and efficacy of the proposed methods, while recognizing that “research can never answer every question before a new treatment is offered, nor can it be expected to guarantee safety or efficacy when applied for the first time in the clinic,” confirms that “the evidence available [in 2011 and 2013] did not suggest that [MST and PNT] are unsafe.”

The HFEA reviews—specifically commissioned by and to assist the government—canvass the available evidence to provide an informative overview of existing findings, and make suggestions on the areas that appear to require further research.

The HFEA reviews suggest that many of the above-mentioned concerns can be allayed. For example, they state that there is no evidence to suggest that epigenetic alterations through MST or PNT, if they exist, “have any significant or far reaching effect on development or health” and that once assessed as safe to use in clinical practice, children born as a result of the techniques could be followed up for an extensive period in order to assess any long term impact—arguably the best way to obtain the most accurate results on the matter. In relation to the potential for mitochondrial DNA carryover, the HFEA’s 2014 review states “evidence presented to the panel in 2013 continues to be reassuring that carryover after mitochondrial replacement is very low” and that:

[I]f any uncertainty about the degree of heteroplasmy in oocytes remains when women born as a result of MST or PNT wish to have

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19 See HFEA, 2011 Report, supra note 2 at 18-19.
20 See FDA Briefing Document, supra note 2 at 20.
21 HFEA, 2014 Report, supra note 18 at 5.
22 Ibid at 34.
23 Ibid at 24.
children, then either this should be examined directly in unfertilised oocytes collected from the women obtained after stimulation, and/or PGD should be carried out on fertilised embryos prior to selecting those with, no or very low, levels of abnormal mtDNA for transfer.24

Finally, in relation to the potential risk of nuclear-mitochondrial incompatibility arising from the donor oocyte/embryo, the HFEA, while suggesting the risk is very low, recommends that as a precautionary step, consideration should be given to mitochondrial DNA haplogroup matching, drawing a parallel to the similar processes that are undertaken in organ donation.25

In any event, and of key significance in this fast evolving field, the overarching regulatory mandate of the HFEA, which governs all assisted reproduction procedures that involve human gametes or embryos in the UK, would ensure the necessary clinical safety of the techniques has been demonstrated before applying the techniques to individual cases. The introduction of the regulations, therefore, will not necessarily lead to the techniques’ immediate roll out in clinical practice. Rather, it will give the HFEA the power to allow the clinical application of these potentially life-saving techniques, if and when it deems that such procedures are sufficiently safe.

(b) That the Procedures will have an Adverse Socio-Ethical Impact

The UK Parliament’s decision to pass the legislation, however, has rested on more than science alone.26 The mitochondrial donation techniques raise a number of socio-ethical issues that have also merited due consideration.

(i) Genetic Identity

One of the key sticking points of the techniques’ legalization debate thus far has been over its potential creation of “three parent babies”—the term in itself being a controversial coinage.

Since children born from the techniques would have a genetic connection to three people—namely the mother, the father, and the mitochondrial DNA donor—some may question whether the child’s sense of identity, in not truly knowing this third genetic contributor, could be harmed and whether our current conceptualizations of legal parenthood would, in turn, need to be revised. For some, the argument is simply non sequitur: “it would be misleading to describe children born following [M]ST or PNT as having biologically or legally, ‘three parents’ or ‘two mothers’. Indeed the genetic contribution from the mtDNA donor is small, constituting only 0.1% of the total DNA.”27

24 Ibid at 27.
25 Ibid at 5.
26 Ibid.
In spite of the seeming statistical irrelevance of mitochondrial DNA, in relation to one’s overall DNA makeup, some are understandably uncomfortable with the various attempts that have been made to downplay its underlying role. The fact that experimentation upon reproductive materials, as materials that contain the very essence of our genetic destiny are even meriting of their own set of regulations, suggests that these materials are in fact significant, perhaps precisely because of their genetic content and capabilities.

The fact that a child could therefore have a materially relevant genetic connection to three persons (or parents, perhaps by definition), is not, however, a sufficient reason to prevent the clinical application of the proposed techniques. Conceptions of the family and of parenthood are extremely fluid and have been recognized in law as such.28 It is assumed that most donors will not request the recognition of their parentage, and that, by and large, it would not be in the child’s best interests to recognize this third person’s status as that of a legal parent. Indeed, the regulations expressly prohibit donors from applying for a parental order on the basis of their mitochondrial DNA donation alone.29

One could imagine certain cases, however, where it could be appropriate to recognize a genetic donor’s legal parentage; for example, where two women intending to raise the child contribute to the child’s genetic makeup30 with the help of a known sperm donor who wishes to remain involved in the child’s life.31 Similar circumstances arose in the Ontario Court of Appeal’s decision in A. (A.) v. B. (B.),32 where the Court ruled that “allowing a child to have three registered legal parents”33 “could bridge a ‘legislative gap’ in the Children’s Law Reform Act 1990.”34 The UK House of Lords (now the UK Supreme Court) has also emphasized the significance of recognizing different kinds of legal parentage,35

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28 See, e.g., the case of G., Re, [2006] UKHL 43 (U.K. H.L.) Baroness Hale states, “There are at least three ways in which a person may be or become a natural parent of a child, each of which may be a very significant factor in the child’s welfare, depending upon the circumstances of the particular case. The first is genetic parenthood...The second is gestational parenthood. ..The third is social and psychological parenthood.”

29 Mitochondrial Donation Regulations, supra note 1, s. 18.

30 In relation to this fact scenario, however, Françoise Baylis questions whether it could arise as a result of less therapeutically aimed goals. She says, “it could be used to pursue non-therapeutic reproductive goals—imagine, a lesbian couple where both partners wanted a genetic link to the children they intend to parent”: Françoise Baylis, “The Ethics of Creating Children with Three Genetic Parents” (2013) 26:6 Reproductive BioMedicine Online 531 at 533.

31 In line with provisions of the current Human Fertilisation and Embryology Act, however, either the genetic father or female partner would have to forfeit their legal parenthood. See Human Fertilisation and Embryology Act 2008.


34 Ibid.
and of the need for such recognition to be available, in order to serve children’s various welfare needs.

The fact that a child could—in appropriate circumstances—come to have three parents, is arguably not at odds with the way that many families ultimately choose to raise their children—with multiple adults playing significant parent-like roles in their lives.

(ii) The Ethics of Human Enhancement

In altering the DNA content of an individual at the early embryonic stage of life, and in artificially fashioning the elements of their future being, some would argue that the proposed techniques will tamper with the very essence of what it is to be human—itself the subject of core beliefs, disagreement, and faith.

The natural state of affairs is held to be morally significant within a number of different arenas.\textsuperscript{36} From a theological perspective, respect for each individual human life and for the natural state that its maker has intended for it to be is intimately bound with the idea of the sanctity of human life. On this view, all human lives are inviolable and any interference with their natural sacrosanctity is immoral. In the democratic realm, however, religious dogmas are often dismissed as pious and irrelevant, particularly where science and its objective truths often appear able to provide a more reasonable and enlightened response.

However, inherent reverence for human nature resonates with a genre of more secular philosophies as well. Harvard’s Michael Sandel writes:

\begin{quote}
If bioengineering made the myth of the “self-made man” come true, it would be difficult to view our talents as gifts for which we are indebted, rather than as achievements for which we are responsible. This would transform three key features of our moral landscape: humility, responsibility, and solidarity.\textsuperscript{37}
\end{quote}

On this view, our natural desires for human perfection through enhancement must be mediated by a measure of respect for the natural gift of life with which we have been endowed, if we are to avoid a “one-sided triumph of willfulness over giftedness, of dominion over reverence, of molding over beholding.”\textsuperscript{38} Erik Parens characterizes the nature of the debate as fitting within two different but related frameworks of gratitude and creativity—the former emphasizing “our obligation to remember that life is a gift and that we need to learn to let things be,” and the latter “emphasiz[ing] our obligation to transform that gift and to exhibit our creativity.”\textsuperscript{39} Both frameworks, he says, aspire towards achieving

\begin{thebibliography}{9}
\bibitem{gerial}
G., Re, supra note 28.
\bibitem{kaebnick}
Gregory E Kaebnick, \textit{Humans in Nature: The World as We Find It and the World as We Create It} (Oxford: Oxford University Press, 2014) at ix.
\bibitem{sandel2}
\bibitem{sandel1}
\end{thebibliography}
authenticity—towards helping us to truly “become who we are.” Thus, while the adaptations the proposed techniques will likely inflict upon one’s human nature give rise to ostensibly conflicting ethical considerations, these considerations may be reconciled by justifying the techniques as means of realizing the dignity of the concerned individuals’ authentic selves.

(iii) The “Slippery Slope”

Ethical objections to the techniques also coincide with more pragmatic considerations. While the reasons currently underpinning the proposed techniques appear wholesome, some argue that given that “[t]here simply is no defensible way to draw a hard, bright line between medicine and eugenics . . . [which] provides a spectrum, from preventing disease to maximizing health to genetic enhancement,” we need to draw lines in ways that are most able to protect the values and principles that we, as a society, wish to safeguard. That is, if we do not believe that it is possible to “defend a ‘new’ morally defensible—or perhaps even praiseworthy—eugenics that is distinct from and will not lead to the ‘old’, bad, Nazi, and Fabian eugenics,” we need to make legal distinctions that, although they may inevitably harm some through the denial of particular treatments, will better serve the individual rights and dignity of peoples in the long run.

Given the unknown and evolving technologies that future societies will likely have at their disposal, however, it arguably does not make sense to limit the current potential of this new biotechnological discovery that—with a clear legal framework (as has been propounded) and regulatory oversight (that the HFEA is both able and mandated to provide)—could be used responsibly in order to prevent some of the suffering that is experienced today.

40 Ibid.
42 In drawing any lines, it is important to pay attention to the particular circumstances of the issue at hand. Thomas Murray, for instance, articulates the often misguided quest for the ethics of enhancement that is a “problem. . .with the definite article ‘the,’ denoting a singular all-purpose ethics for every form of human enhancement. . .the ethics of enhancement is deeply dependent on context. . .[that is,] what is important about a particular context is [to] elucidate[e] the values that are sought in or served by that sphere of human endeavor.” The boundaries of enhancement should therefore be determined by the values inherent to the sphere. See Thomas Murray, “The Misguided Quest for the Ethics of Enhancement” in Akira Akabayashi, ed, The Future of Bioethics: International Dialogues (Oxford: Oxford University Press, 2014) 193 at 193.
43 Robert Sparrow, “Ethics, Eugenics, and Politics” in Akabayashi, supra note 42, 139 at 139.
(c) That the Techniques are Prohibited in International Law

In October 2013, a group of 34 MPs of the Council of Europe, an organization representing EU and non-EU signatories to the European Convention on Human Rights, described the effects of the proposed techniques as "incompatible with human dignity and international law." At first glance, their statement is persuasive. Article 2(b) of the Universal Declaration on the Human Genome and Human Rights, for example, states that "dignity makes it imperative not to reduce individuals to their genetic characteristics and to respect their uniqueness and diversity"—ostensibly things the techniques could serve to threaten. Furthermore, article 13 of the Council of Europe’s Oviedo Convention states that any "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"—which is again, seemingly at odds with the effects the new techniques are likely to produce.

Taking a broad view, however, while article 13 of the Oviedo Convention prohibits interventions aiming to introduce modifications to the human genome of future descendants, by applying the bioethical principle of the "doctrine of double effect," one could argue that since the primary purpose of the proposed techniques is to introduce some measure of therapeutic benefit to an individual, it would not fall afoul of current international standards, since its likely effect of changing the genomic gene line (the potential "harm" in question) is not the primary purpose of the technique. More persuasively, however, article 1 of the Additional Protocol to the Oviedo Convention qualifies its provision that "[a]ny intervention seeking to create a human being genetically identical to another human being, whether living or dead, is prohibited," to confirm that "the term

48 The doctrine of double effect principle is one that would enable doctors, for example, to administer large doses of pain relieving drugs to a patient, if their primary purpose for so doing is to relieve the individual’s pain—irrespective of any inevitable side-effect of a more hastened death. For a more detailed explanation, see Alison McIntyre, “Doctrine of Double Effect” in Stanford Encyclopedia of Philosophy (Stanford, CA: Stanford University, 2014), online: <http://plato.stanford.edu/entries/double-effect>.
human being ‘genetically identical’ to another human being means a human being sharing with another the same nuclear gene set.”\(^{50}\) The Convention (uncharacteristically of many human rights instruments, which tend to be vague and principled), in specifically delimiting the prohibition to interventions upon the nuclear component of the cell, leaves open the possibility for interventions to be made using the mitochondrial component of a cell—which is confirmed in a Council of Europe explanatory report to the additional protocol.\(^{51}\)

Mitochondrial DNA transfer techniques are, in other words, not prohibited by international law. Conversely, and as David Lawrence argues, the use and application of human enhancement technologies appears “thoroughly defended in the canon of international human rights law, particularly under the fundamental rights to health, scientific progress and the enablement of the self.”\(^{52}\)

**IV. CONCLUSION**

In 2015, the UK Parliament voted to legalize regulations that will permit the clinical application of the mitochondrial DNA transfer techniques this article has discussed. While a number of objections have been made against the techniques’ introduction, this article has sought to show that the objections relating to the safety and efficacy of the techniques, to their socio-ethical impact, and to their conformity with international legal standards are perhaps not as strong as they may at first appear. The benefit that the proposed techniques appear to offer—the potential for children of individuals with serious inheritable mitochondrial DNA disorders wishing to have genetically related children to be spared often intolerable (but now seemingly preventable) suffering—should be welcomed. It is an extraordinary scientific feat that Parliament was correct to welcome.

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\(^{50}\) *Ibid*, art 1(2).


\(^{52}\) David R Lawrence, “To What Extent Is the Use of Human Enhancements Defended in International Human Rights Legislation?” (2013) 13:4 Medical L Intl 254 at 278.