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COMMENTARY

The ethics of creating children with three genetic parents

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Abstract This article on mitochondrial replacement technology briefly explains and defends the legitimacy of such terms as 'three-parent embryos', 'three-parent babies' and 'three-person IVF'. Next, it reviews select ethical objections to mitochondrial replacement technology that fall into four, sometimes overlapping, categories: (i) harms to egg providers; (ii) harms to potential offspring and future generations; (iii) harms to specific interest groups; and (iv) harms to society. Taken together, these ethical objections are cause for serious concern and yet the development and future use of mitochondrial replacement technology is likely inevitable.

KEYWORDS: ethics, mitochondrial disease, mitochondrial replacement technology, assisted human reproduction, egg donation, genetics

Introduction

Children born since the mid-1990s after ooplasm transfer (estimated to be few in number), and future children that may be born following mitochondrial replacement, have been dubbed 'children with three genetic parents': a man who contributes nuclear DNA, a woman who contributes nuclear DNA, and a woman who contributes healthy mtDNA (Anonymous, 2008; Hayden, 2008; Nuffield Council, 2012; Whitehouse, 2001). For some, this description is both misleading and a misplaced attempt at sensationalism; for others, the intentional genetic engineering of future children using genetic material from three persons is ethically objectionable and, for this reason, the underlying research should not proceed.

Mitochondrial replacement

When the mitochondria inside cells do not function properly, the consequences can be devastating. Mitochondrial diseases can result in serious health problems including neurodegenerative disease, stroke-like episodes, blindness, muscular dystrophy, diabetes and deafness and can lead to death in newborns, children and young adults. Mitochondrial diseases can be caused by mutations in nuclear DNA that affect the functioning of the mitochondria or by mutations in mitochondrial DNA (mtDNA) (Taylor and Turnbull, 2005).

Strategies to avoid the vertical transmission of mutations in mtDNA include adoption, embryo donation and egg donation. However, the absence of a genetic link between the children and the social parents (as with adoption and embryo donation) or the social mothers (as with egg donation) has been identified as problematic (Nuffield Council, 2012). Research suggests that it may be possible to overcome this problem using IVF and, either before or after fertilization, replacing the disease-linked mtDNA with healthy mtDNA. In this way, the transmission of mtDNA mutations could be avoided and the social parents could also be the genetic parents.

Research in this domain dates back to the mid-1990s, when Jacques Cohen and colleagues began injecting small amounts of healthy ooplasm (with normal mitochondria) into eggs with defective ooplasm (potentially including, but not restricted to, disease-linked mitochondria) as a

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'treatment' for recurrent implantation failure (Barritt et al., 2001; Baylis, 2009; Cohen et al., 1997, 1998). Since then, two experimental techniques that specifically aim to prevent the vertical transmission of diseases caused by mutations in mtDNA have been developed, both of which involve the transfer of nuclear DNA. Pronuclear transfer involves the transfer of the two pronuclei from a zygote with disease-linked mitochondria into an enucleated zygote with healthy mitochondria. Maternal spindle transfer involves the transfer of the spindle of chromosomes from an unfertilized egg with disease-linked mitochondria into an enucleated egg with healthy mitochondria (Craven et al., 2010; Nuffield Council, 2012).

Children with three genetic parents

Among those who endorse the use of mitochondrial replacement technology are some who object to the use of such terms as 'three-parent embryos', 'three-parent babies' and 'three-person IVF'. Typically, these commentators are keen to downplay the relevance of 'third-party' mitochondria in an individual's genetic make-up. They insist that the genetic and intending social parents provide more than 99.9% of the total genetic material (Nuffield Council, 2012, pp. 18–19) and that the physical traits and personal characteristics constitutive of identity are coded for in the nuclear DNA, not the mtDNA (Nuffield Council, 2012, p. 53).

However, personal identity is about so much more than appearance and character traits. As I have argued elsewhere, in defending a narrative account of identity, 'identity is not in the genes but in the world in which we live and the stories we construct and are able to maintain' (Baylis, 2003, p. 142) — [A] person's identity (including her traits, desires, beliefs, values, emotions, intentions, memories, actions and experiences) is informed by her personal relationships — relationships characterized by varying degrees and kinds of intimacy and interdependence' (Baylis, 2011, p. 109). Viewed from this perspective, health and illness are states of being that very much inform personal identity and it makes no sense to say that a safe and effective technology that eliminates mitochondrial disease in the newborn will have no impact on how that person's identity evolves.

A child of sperm A and egg B, born with a mitochondrial disease, will have a very different life narrative than a child of the same sperm A and egg B, born healthy as a result of mitochondrial replacement from egg C. To quote Annelien Bredenoord '... a person without a mtDNA disease will have a different life experience, a different biography and perhaps also a different character' (Bredenoord et al., 2011, p. 99). And, to quote the Nuffield Council, 'if the technique [mitochondrial replacement technology] were successful, the inclusion of a donor's mitochondrial genes and minimisation of the proportion of maternal mitochondrial genes could make such a very significant difference to the resulting person's life that they could be said to make them ''a different person''' (Nuffield Council, 2012, p. 55). It follows that a third-party genetic contribution of healthy mtDNA is important in shaping a person's narrative, viz. determining who a person will be.

Moreover, while it is undeniably true that the egg provider who contributes the healthy mtDNA provides less than 0.1% of the total genetic make-up of the newborn, this fact is irrelevant to the accuracy of the claim that there are three genetic parents. All that is relevant to this issue is the presence or absence of identifiable genetic material from someone other than the two individuals identified as genetic parents. In all instances involving mitochondrial replacement, where the egg provider is not a close maternal relative of the female genetic parent, there will be identifiable genetic material from a second female genetic parent. Only when the egg provider is a close maternal relative of the female who provided the nuclear DNA would the 'third-party' mitochondria be (nearly) identical to any healthy mitochondria of the female genetic parent. mtDNA passes through the female line — a woman is likely to have mtDNA closely similar to her siblings (female and male), her mother, her maternal grandmother, her maternal aunts and uncles, and so on. If the egg provider is one of these female relatives, then the children born following pronuclear transfer or maternal spindle transfer might have only two identifiable genetic parents. Otherwise, it would be both accurate and legitimate to speak of 'three-parent embryos', 'three-parent babies' and 'three-person IVF'.

As the goal of mitochondrial replacement is to prevent the vertical transmission of diseases caused by mutations in mtDNA, it is unlikely that the egg provider would be a close maternal relative (as she would be at risk of transmitting the same mutations). If the egg provider is not a close maternal relative, then there would be identifiable genetic material from a second female genetic parent, in which case any child born following the mitochondrial replacement would have three genetic parents.

Ethical objections to mitochondrial replacement technology

Why should we care if children are born with nuclear DNA from one woman and mtDNA from another? Moreover, why should we care if the female children born with non-familial mtDNA, in turn, pass this mtDNA on to their children? Some of the ethical objections to mitochondrial replacement technology are briefly described below. These objections fall into four, sometimes overlapping, categories: (i) harms to egg providers; (ii) harms to potential offspring and future generations; (iii) harms to specific interest groups; and (iv) harms to society.

Harms to egg providers

Drug-induced egg production and retrieval involves considerable time and inconvenience. On average, 56 h are required for interviews, counselling, screening, hormonal stimulation and egg retrieval (Ethics Committee ASRM, 2004). As well, there are physical and psychological risks associated with the requisite medical procedures (Maxwell et al., 2008). The daily hormone injections can be uncomfortable and painful. Moreover, they can result in cramping, abdominal pain, nausea, vomiting, bloating, mood changes and irritability. More serious potential physical harms include rapid weight gain and respiratory difficulty, damage

to the other organs such as the bladder, bowel and uterus, decreased fertility, infertility and life-threatening haemorrhage, thromboembolism and ovarian, breast or colon cancer. Potential psychological harms include significant stress and sequelae.

As a colleague and I have argued elsewhere (Downie and Baylis, 2013), it is one thing to incur the physical and psychological risks of hormonal stimulation and egg retrieval 'in pursuit of a personal reproductive project; it is quite another to do so for someone else's reproductive project'. In the first instance, there is likely to be a favourable harm—benefit ratio. The potential benefit of having a child weighs favourably against the potential harms of the requisite medical procedures. In the second instance, the harm—benefit ratio is not obviously favourable, in part because the benefits and harms devolve on to different people. The IVF patient has the potential benefit of having a child. The egg provider bears the potential harms of hormonal stimulation and egg retrieval; her only potential benefits are emotional (a good feeling from an act of altruism) and possibly financial (if payment is involved). Whether these potential benefits compensate for the potential harms is a contested matter.

Moreover, the discrepancy in the benefits and harms to egg providers explains the concern about the risk of coercion and exploitation to egg providers (Baylis, 2009). This concern is particularly acute when economically disadvantaged women are targeted as egg providers.

Harms to potential offspring and future generations

Mitochondrial replacement technology is experimental and there is very limited information about safety and efficacy. As with any germline intervention, there are significant and legitimate concerns about the health and wellbeing of future children and the potential short- and long-term harms to them and their progeny.

The mitochondrial replacement may not be successful and, worse, new harms may be introduced (some of which may not manifest for many years) (Nuffield Council, 2012). Simply put, 'we do not know ... whether a mixture of mtDNA from two different origins is safe' (Bredenoord and Braude, 2011). In response to this sort of concern, one could argue that risk and uncertainty accompany all clinical trials and that, for obvious reasons, these will be at their highest with first-in-human trials. Researchers can reduce risk and uncertainty through appropriate preclinical research, but they can't eliminate these: we can't and won't know until we try.

Therefore, the critical question is whether the risk to future children (subsequent generations) is worth taking. From one perspective, this approach to family making cannot be justified given the availability of less risky alternatives, which include not only adoption, embryo donation and egg donation, but also prenatal diagnosis followed by abortion and preimplantation genetic diagnosis followed by selective embryo transfer. The only reason not to pursue one of these alternatives (which have a known safety profile) is a desire on the part of prospective parents for a genetic link to the child(ren) they intend to care for. While much ink has been spilled on the importance (or not) of genetic links within families, we know this to be a 'wish' not a 'need' (there are happy well-functioning families with adopted children and with foster children; there are happy well-functioning blended families following divorce). It is unclear why a 'wish' for a genetic link on the part of prospective parents should be taken to justify the imposition of health risks on future children and subsequent generations. Family making should be about establishing loving, caring, nurturing relationships and these may or may not include genetic ties.

Harms to specific interest groups

Most recently, and especially in the USA, a sustained interest in ancestry tracing using mitochondrial and Y-chromosome DNA testing has emerged. For some, genealogical information of the type available through ancestry tracing is important for identity. Mitochondrial replacement technology represents a potential threat to genealogical research using mtDNA analysis, as it would obscure the lines of individual descent, thereby providing a false or confusing picture (Baylis and Robert, 2006). Now, admittedly, preserving the ability of DNA genealogists to do their research may not be a high social priority, it is nonetheless deserving of consideration recognizing that little is known at this time about personal and cultural attitudes towards mtDNA (Nuffield Council, 2012, p. 77—79).

Historical and anthropological research on human population migration patterns and demographic history uses mtDNA analysis and provides useful evidence of the geographical origins of humans, likely population sizes, and migration patterns. This research presumes 'the genetic continuity of humans from a single ancestral group and facilitated by the remarkable conservation of gene sequences through evolutionary history' (Baylis and Robert, 2006). This presumption is disrupted with intentional genetic modification of which mitochondrial replacement technology is but one instance. As with the previous objection to mitochondrial replacement, preserving the ability to research migration patterns and demographic history may not be a high social priority, but why foreclose this research to allow for family making using mitochondrial replacement when family making can occur by other means?

Harms to society

While the initial goal of mitochondrial replacement technology is 'therapeutic' insofar as it aims to avoid the birth of a child with mitochondrial disease, this technology could be used without therapeutic intent. For example, 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. An additional worry is the future use of this and other germline interventions to alter the human species in pursuit of enhancement objectives. For some, human enhancement is both our destiny and our responsibility. For others, this is not responsible stewardship, but 'playing God.'

While many doubt that the introduction of third-party mtDNA will have a serious impact on the gene pool, others worry about 'the ethics of tampering with our genetic

inheritance, thereby possibly violating what some claim as the ''right'' of subsequent generations to inherit an ''un-manipulated genome''' (Baylis and Robert, 2006). This concern with 'genetic patrimony' or 'common heritage' applies to genetic modification aimed at avoiding disease, as well as genetic modification directed towards improvement.

From a global health perspective, there is little justification for the investment of resources (time, talent and money) into research on avoiding the vertical transmission of mtDNA disease when there are much greater reproductive health needs experienced by women in both developed and developing countries (Baylis, 2009). While it is the norm to review and fund research on the basis of scientific excellence, we also need to consider social significance. Research resources should be directed to science that is not only excellent, but also socially valuable. At issue here is the ethical acceptability of allocating limited resources to research (and possibly future therapeutic interventions) to meet the needs of a very small minority for whom there are other reproductive options. In brief, the opportunity costs associated with research on mitochondrial replacement technology are considerable.

Conclusions

Taken together, these ethical objections are cause for serious concern. Yet, despite their cumulative weight, the development and future use of mitochondrial replacement technology is likely inevitable (Baylis and Robert, 2004). Why is this so? Because in our world — a world of heedless liberalism, reproductive rights understood narrowly in terms of freedom from interference, rampant consumerism, global bio-exploitation, technophilia and hubris undaunted by failure — no genetic or reproductive technology seems to be too dangerous or too transgressive.

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