Gendering the seed: Mitochondrial replacement techniques and the erasure of the maternal

Robert Sparrow, School of Philosophical, Historical and International Studies, Monash University.

Catherine Mills, Monash Bioethics Centre, Monash University.

John Carroll, Monash Biomedicine Discovery Institute, Monash Universit.

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Abstract

In order to avoid the implication that "mitochondrial replacement techniques" (MRT) would produce "three parent babies", discourses around these techniques typically dismiss the contribution of the mitochondria to genetic parenthood and personal identity. According to many participants in debates about MRT, "real parenthood" is a matter of contributing nuclear DNA, which in turn implies that men and women make the same contribution to the embryo. Even when the importance of the mitochondria is acknowledged, an emphasis on mitochondrial DNA still has the effect of valorising the role of DNA (and thus the paternal contribution to conception) at the expense of the role played by the cytoplasm of the oocyte in the development of the embryo and placenta, and that of the mother's body in gestation. In this way, discourses around MRT falsely imply that what men and women contribute to reproduction and parenthood is the same — nuclear DNA — and thus erase the distinctive contribution that women make to conception. The potential of MRT to reconfigure relationships between the sexes in the service of patriarchal norms is perhaps one of the most significant things about it and should, we argue, be counted in the discussion of the ethical and policy implications of legitimating these procedures.

Keywords: Mitochondrial replacement techniques; ethics; genetic parenthood; gender; reproduction.

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New reproductive technologies reconfigure perhaps as much as they are shaped by ideas about reproduction and the meaning of parenthood. In an essay entitled “Daddy plants a seed” Barbara Katz Rothman pointed out that the emphasis on genetic parenthood that resulted from the development of IVF involved a dramatic reconfiguration of our understanding of the role of the two sexes in reproduction (Rothman 1996). An emphasis on genetic parenthood makes the paternal contribution to reproduction equal to the maternal contribution and elides the role of pregnancy and the maternal body in the constitution of the embryo.

In this paper we will demonstrate that the development of, and discourses surrounding, what are loosely known as, “mitochondrial replacement techniques” (MRT) represent a further development and intensification of this dynamic. The dismissal of the contribution of the mitochondria to genetic parenthood and personal identity necessary to avoid the conclusion that these techniques would produce “three parent babies” implies that real parenthood is a matter of contributing nuclear DNA and thus that men and women make the same contribution to the embryo. Even when the importance of the mitochondria is acknowledged, an emphasis on mitochondrial DNA still has the effect of valorising the role of DNA (and thus the paternal contribution to conception) at the expense of the role played by the cytoplasm of the oocyte in the development of the embryo and placenta, and that of the mother’s body in gestation.

In short, discourses around MRT falsely imply that what men and women contribute to reproduction and parenthood is the same — DNA — and thus erase the distinctive contribution that women make to conception. The potential of MRT to further reconfigure relationships between the sexes in the service of patriarchal norms is perhaps one of the most significant things about it and should, we will argue, be counted in the discussion of the ethical and policy implications of legitimating these procedures.

The structure of our discussion is as follows. In the first section, “Mitochondrial manipulations,” we provide a brief account of the role played by mitochondria in the metabolism of eukaryotes and of the nature of the new reproductive technologies that have recently been developed in the attempt to help those who are at risk of having a child affected by mitochondrial disease caused by mutations in the mother’s mitochondria to have a healthy child who would be genetically related to both parents. In the second section, “Daddy plants a seed,” we introduce Barbara Katz Rothman’s argument in order that we may draw on it in subsequent discussion. Section 3, “Lionising the nucleus,” we discuss the way in which some of the discourses around MRT adhere to the patriarchal logic identified by Katz Rothman by discounting the contribution made by the maternal mitochondria to the development of the future child and emphasising the importance of the nuclear DNA transmitted in the gametes. Section 5, “Eliding the cytoplasm,” argues that even those discourses around MRT that emphasise the importance of the mitochondria subtly contribute to the dialectic identified by Katz Rothman by focusing on the role played by DNA, both nuclear and mitochondrial, while neglecting non-genetic contributions made by both parents to the constitution of the zygote and the future child. In the final section, “The futures of reproduction”, we suggest that these ideological effects of discourses around MRT should be taken into account in the broader ethical and policy debate about the wisdom of developing, and regulating, these technologies.

Mitochondrial manipulations

Mitochondria are organelles that reside in the cytoplasm of the cells of most complex organisms. They play a crucial role in a number of metabolic processes within eukaryotic cells, especially those regarding the production of energy and the removal of waste metabolites (Tachibana et al. 2009). Importantly, mitochondria contain DNA, which is separate from, although it interacts with, cells’ nuclear DNA. Because they are located in the oocyte cytoplasm, mitochondria and mitochondrial DNA are inherited via the maternal line.

Some variations in the functioning of the mitochondria, which may be prompted either by genes located in the mitochondrial DNA, or by genes in the nuclear DNA, are associated with debilitating genetic diseases. Where these are associated with mutations in the mtDNA, these diseases are transmitted maternally, which means that it may be difficult, or

sometimes impossible, for a woman to become the parent of a healthy child conceived using her own eggs.[1]

A number of different techniques have recently been pioneered in the attempts to provide couples who are at risk of having a child affected by mitochondrial disease caused by mutations in mtDNA with the opportunity to have a healthy child that would be genetically related to both parents. For reasons that will become clear in a moment, there is some dispute in the bioethics literature about the most appropriate name for these techniques. However, because they are motivated by the desire to replace the mother's "faulty" mitochondria, some authors have chosen to describe them as mitochondrial replacement techniques (Palacios-González 2016), which is the term we will also adopt for the sake of consistency with the existing literature.

The appropriateness of this name is contested because both techniques actually involve the transfer and replacement of *nuclear* material in either oocytes or the zygote (Baylis 2017; Newman 2014; Newson and Wrigley 2017; Nisker 2015). Maternal spindle transfer (MST) involves replacing the nuclear material in a donor oocyte with nuclear DNA obtained from the oocyte of a woman with the defective mitochondria, who wishes to become a mother, and then fertilising the reconstructed oocyte with the sperm of the partner of the commissioning mother (or, perhaps, donor sperm) (Tachibana et al. 2009). Pro-nuclear transfer (PNT) involves a similar procedure conducted after fertilisation. In this case, two zygotes are created, one using the commissioning mother's oocyte and her partner's sperm (or, perhaps, donor sperm) and the other using a donor oocyte and the partner's sperm (or, perhaps, donor sperm). A day after fertilisation, the two pro-nuclei in the zygote originating from the donor oocyte are removed (and destroyed) and replaced with the two pro-nuclei that develop in the zygote created from the commissioning mother's oocyte (Craven et al. 2010).

[1] In many cases where a woman is at risk of giving birth to a child who is likely to be affected by mitochondrial disease it may be possible for her and her partner to use prenatal testing to prevent the birth of a child likely to suffer mitochondrial disease or preimplantation genetic diagnosis to select an embryo that will not be affected (Poulton, Kennedy, Oakeshott, and Wells 2009). The use of a donor egg will also allow women at risk of conceiving a child who is likely to be affected by mitochondrial disease to conceive and gestate a child with healthy mitochondria. The justification for MRT must therefore rely on the putative moral weight of the commissioning mother's desire to have a child that will be genetically related to her by virtue of being conceived from her gametes. For a detailed critical examination of the "use case" for MRT, see Herbrand (2017).

The end result of both techniques is an embryo wherein the nuclear DNA of the cells therein is derived from the commissioning mother and her partner but where the mitochondria of the cells therein are derived from the cytoplasm of the egg donor. Thus provided with "healthy" mitochondria, the embryo now has the chance of developing into a child that will not be affected by mitochondrial disease.

The role played by mitochondria in cell metabolism means that researchers have also been interested in manipulating the mitochondria in order to increase success rates in particular patient cohorts in the context of IVF. Cytoplasmic supplementation is still experimental and unproven but is being tried in cases of advanced maternal age (AMA) and repeated IVF failure. It involves injecting mitochondria obtained from patient-derived (autologous) ovarian stem cell-like cells that are grown in culture (Kristensen, Pors and Andersen 2017). The premise is that cell-derived mitochondria enhance metabolic functions in the oocyte and increase viability. Whether this is true or not remains to be established.

Daddy plants a seed

In sociological research carried out in the 1980s and 1990s Barbara Katz Rothman demonstrated how the (then) new technology of *in vitro* fertilisation was operating to reinforce and promote patriarchal ideas about reproduction and the structure of the family (Rothman 1989 & 1996). The essential ideas of patriarchal kinship are that children are "born to men, out of women" and that the core aspect of reproduction is that of the "seed", that is, the "part of man that grows into the child of his likeness within the body of woman" (Rothman 1989, 1245). In contemporary patriarchy, according to Katz Rothman, we have come to accept that children are 'half his and half hers', but the centrality of the 'seed' is maintained (Katz Rothman 1989, 1245). The development of IVF and other reproductive technologies affirmed the importance of "the seed" by valorising the pursuit of genetic, as opposed to other forms of, parenthood and by focusing on manipulations of the gametes in order to achieve this. Thus, today, this seed is nuclear DNA, transmitted by the gametes, and genetic parenthood has come to be the paradigm of parenthood.

Katz Rothman argues that the emphasis on genetic parenthood encouraged by new reproductive technologies reconfigures our understanding of reproduction — and of the role of the two sexes in reproduction — along patriarchal lines in two ways.

First, the focus on the role played by the nuclear DNA contained in the gametes has the effect of eliding the specifically maternal contributions to conception, gestation and birth – that is, to the material development of a person. As Katz Rothman (1996, 1245) argues, "under patriarchy, the place in which the seed grows does not really matter. It can be a wife, a 'surrogate,' or an 'artificial womb'".

Second, and relatedly, information is privileged over matter. As Katz Rothman points out, DNA is often characterised through the metaphor – though we have largely forgotten it is a metaphor – of the program. This program is taken to provide the basic information that determines the form of the organism that develops from the seed (Oyama 2000). As Katz Rothman notes elsewhere, this privileging of genetic information has a class content (Rothman 1989 & 1998). Capitalism exalts the genius of those who control wealth and disparages the contribution of those who labour. Thus, the workers who lay the bricks and pour the concrete to construct a modern skyscraper are not thought of as those who really "build" it: this status is reserved for the architect who drew up the plans or the business "genius" who financed it. Intellectual "labour" is privileged over physical labour. The idea that the gametes contain the "genetic code" that provides the "instructions" or the "program" to "make" a baby both draws upon and reinforces these capitalist narratives. Of course, this class narrative is itself gendered. The architect or "builder" is implicitly — as well as actually, historically — male, while the workers who follow instructions, by virtue of being subordinated and implicated with the messy world of material things, are feminised in relation to their employer.

Lionising the nucleus

Newspaper headlines about MRT abound with references to "three parent babies" (a representative sample is provided in Jones and Holme 2013). Noting that the procedures would, if successful, produce a child from a combination of two eggs and a sperm, some authors have, not unreasonably, chosen to describe it as involving three genetic parents

(Baylis 2013; Bredenoord, Pennings, and de Wert 2008; Appleby and Karnein 2014). Perhaps because describing the results of MRT in this way constructs them both as unnatural and as a threat to the traditional patriarchal nuclear family, (some) scientists, bioethicists, and (some) regulators have wanted to insist that this is a misnomer (Bosely 2011; Harris 2016; Nuffield Council on Bioethics 2012; Winston 2015).[2] While the individual produced by these techniques would contain genetic material from three different individuals it would only contain the *nuclear* DNA from two individuals. Only the contribution of nuclear DNA, it is then asserted makes an individual a "genetic parent". For instance, Prof Robin Lovell-Badge, is quoted in Bosely (2001, para 7), as follows:

> This is not … "three-parent IVF", said Professor Robin Lovell-Badge, one of the authors of the review which has now gone to the government. "It is not a term we have used once in this report and it is not a term that should be used," he said. "This is a tiny, tiny bit of DNA. It is not carrying any characteristics except that you have normally functioning mitochondria."

Similarly, the Working Group on mitochondrial donation (Nuffield Council of Bioethics 2012, p 77) suggests that:

> ...where people do regard genetic links as signifying particular social relationships, it is possible that nuclear and mitochondrial genetic links may be viewed quite differently. … it does seem apparent to the Working Group that mitochondrial donation could be difficult to fit into some of the aspects often thought of as denoting characteristics of (nuclear) genetic 'parenthood'.

Because folk intuitions about genetic parenthood (if there are any such) seem to associate genetic parenthood only with the passing on of "genes", and because it's not obvious why the genes contained in the mitochondria should not count, the claim that the contributor of mitochondria is not a genetic parent is sometimes buttressed by the argument that individual identity is a product of nuclear DNA and not mtDNA. The nuclei of the two gametes involved in conception transmit (approximately) 24,000 genes to the developing embryo compared to the 37 genes contained in the mitochondria (Bredenoord, Dondorp,

[2] Dimond and Stephens (2018) and Jones and Holme (2013) each provide useful accounts of the scientific and political contestation concerning the number of parents generated by MRT.

Pennings, & De Wert 2011). It is sometimes suggested that this means that what makes us individuals is the genes in the nuclear DNA (Jones and Holme 2013; Winston 2015). One way this claim might be expressed colloquially is by saying that the large number of genes in the nucleus "outweighs" or "drowns out" the influence of the genes in the mitochondria. Another ground for discounting the contribution of mtDNA to identity points to the fact that, while the nuclear DNA of each parent is unique to them, because mitochondria are transmitted maternally with very low rates of mutation, the mitochondrial DNA of the donor is merely one of approximately 30 haplotypes (Van Oven and Kayser 2009). Whatever genetic relation is shared with the mtDNA donor is also shared with all other members of her mitochondrial haplotype. Thus, our mtDNA does not distinguish us from other individuals as much as our nuclear DNA does (Nuffield Council on Bioethics 2013, 1.9 & 4.24).

The implicit message of these attempts to exclude the mitochondrial donor from parenthood is that "real" DNA is *nuclear* DNA (Mills 2020). The distinctive genetic contribution of the mother, via the mitochondria, is dismissed, despite being vital to the development of the embryo (Newman 2014). The insistence that nuclear DNA is the real source of identity and genetic relatedness therefore validates and reinforces the patriarchal myths about parenthood and reproduction identified by Katz Rothman. The genetic contribution to reproduction made by men is taken as the norm and it is allowed only that women make the same genetic contribution that men do. While, formally, this account of the genetics of "the seed" is gender neutral, by adopting a male standard it discounts the distinctive role played by women in reproduction and therefore grants more social and political power to men.

Eliding the cytoplasm

These attempts to play down the significance of mitochondria have (rightly) come in for criticism. Scientists and parents would not be pursuing MRT but for the fact that mitochondria play an important role in the development and functioning of the human organism and that the difference between being born with the mitochondria transmitted by the commissioning and (nuclear) genetic mother and with the mitochondria transmitted by the donor is the difference between being born with a severe genetic disease and being

born healthy (Poulton, Kennedy, Oakeshott, and Wells 2009). The mitochondrial diseases that MRT is intended to prevent have implications for every cell in an individual's body and, consequently, often have a large phenotypic effect (Newman 2014). This means that they also have a large effect on the identity of the child (Bredenoord, Dondorp, Pennings, & De Wert 2011).[3]

The idea that the 24,000 genes derived from the nuclear DNA "outweigh" the 37 contributed by the mitochondria is based on the fundamental misunderstanding of the relation between genes and phenotype. It simply isn't the case that every gene has the same amount of impact on phenotype: how much effect any particular gene has on an organism's phenotype depends on its role in the development and metabolism of the organism, which varies dramatically. Moreover, the effects of genes do not simply "sum" but rather interact with each other in a complex network of dynamic relationships. Because of these interactions, strictly speaking it is a mistake even to talk of the "effects" of any particular gene. Rather, all phenotypic effects are the product of the interaction of multiple genes — including genes in the mitochondria — plus the environment (Kampourakis 2017).

Similarly, the fact that individuals share mitochondrial DNA with all their ancestors in their maternal line, as well as with other people outside of that line who share the same mtDNA haplotype, does not fundamentally distinguish the contribution made by mtDNA to identity from the contribution made by nuclear DNA. All human beings share the vast majority of their DNA with all other human beings yet this does not detract from the extent to which children are genetically related to their (nuclear) genetic parents.[4]

Finally, it's worth observing that our sense of the relative importance of nuclear and mitochondrial DNA may be transformed if we focus on the number of DNA molecules or total mtDNA encoded genes present in a cell, rather than the information that mtDNA and nuclear DNA contain. Because each cell contains around 1000-2000 copies of mtDNA, there

[3] Note that we are here limiting our concern to the "qualitative" identity of the child rather than the more philosophically complex question of their "numerical" identity. Because the key claims in the debate about whether the mitochondria "matter" — and therefore should be taken into account when determining the parents of a child — are whether they make a difference to the child's character and whether they render they child similar to the mitochondrial donor, it seems most plausible to interpret these as questions about qualitative identity. For some discussion of the vexed issue of the extent to which MRT matters for the numerical identity of the child, see: Rulli (2017); Scott and Wilkinson (2017); and, Wrigley, Wilkinson, and Appleby (2015).

[4] For a discussion of the complexities of the notion of genetic parenthood, see Sparrow (2006).

are 30,000-60,000 copies of the 37 mtDNA-encoded genes in each cell – this number blows out considerably in an oocyte, which contain 200,000-500,000 copies of mtDNA! Thus, the total amount of mtDNA in human cells is more than is suggested by the simple comparison of 37 mitochondrial genes to 24,000 nuclear genes. Acknowledging this fact makes it much less plausible to argue that mtDNA is unimportant.

Rather than dismissing the role of mtDNA, then, some discussions of MRT highlight it. The therapeutic case for performing MRT itself highlights the importance of the mitochondria for the development of the embryo and the life of the person it becomes (Haimes and Taylor 2017; Scully 2017). Some authors have also suggested that MRT might be employed precisely because it does generate a "genetic relatedness" relation between the oocyte donor and the child who is born (Dimond and Stephens 2018). For instance, lesbian couples who wanted to have a child that was genetically related to both of them might choose to use MRT in order that both women could think of themselves as being "genetic parents" of the child (Cavaliere and Palacios-González 2018, p. 835). The child would, of course, also have a genetic father. In this scenario, then, the fact that MRT would produce "three parent babies" is actually advertised as a virtue and the mitochondria play a central role in bringing it about.

While acknowledging the importance of mitochondrial DNA to the development of the embryo grants that the mother contributes something that the father does not, it elides the facts that the mitochondria are only *part* of the contribution made by the donor. The techniques also involve the transfer of cytoplasm, which also plays a vital role in the development of the embryo independently of the role played by the mitochondria. Cytoplasmic factors control the first few days of embryonic development from fertilisation to the 4-8-cell stage when the embryonic genome is first expressed (Braude, Bolton, & Moore 1988). As well – and apart from – the mitochondria, the cytoplasm of the oocyte represents an enormous reserve of organelles, proteins, mRNA and other regulatory molecules all of which contribute, to varying degrees, to the developing embryo. Furthermore, the fact that the cytoplasmic 'quality' is influenced by maternal age, diet, and maternal obesity, provides a reassuring complexity to the maternal contribution to the individual that extends well beyond the genetic code of the DNA.

Emphasising the role of mtDNA risks denying that these non-genetic factors also play a role in reproduction and subtly reinforces the idea that DNA is the "instructions for making a human body". It's worth noting that, as well as eliding the importance of the maternal cytoplasm, an emphasis on DNA also neglects the contribution made by the seminal fluid to conception. There is now some evidence that soluble factors and extracellular vesicles in seminal plasma influence the female reproductive system and the immune response to enhance implantation and placental development (Robertson and Sharkey 2016). That is to say, in traditional coitus the man also makes a non-genetic contribution to the constitution of the embryo, which is elided when we focus on the role of DNA, either nuclear or mitochondrial. However, dismissal of this contribution does not contradict — indeed, may even lend weight to — our larger argument given that this dismissal is itself arguably gendered in such a way as to sustain traditional narratives about masculinity.

As is well known, accounts of human sexuality and reproductive biology are often, regrettably, structured and informed by "folk" stereotypes about masculinity and femininity (The Biology and Gender Study Group 1988; Keller 1985). Men are the active participants who "compete for", and "penetrate", women, who are portrayed as choosing which mate to accept. Male bodies — and sexual organs — are "hard", "rigid" and have clearly defined boundaries — while women's bodies — including their sexual organs — are "soft" and "mysterious", leaking fluids. These gendered metaphors and interpretations extend to public and scientific understandings of the cellular mechanisms of reproduction (Campo-Engelstein and Johnson 2014). As Emily Martin (1991) analysed in a classic essay, sperm are portrayed as active, vigorous, and competitive, struggling to be the first to discover the egg and penetrate it, while the egg waits passively to be penetrated: in reality, such intentional language should play no role in cellular biology. In this context, the idea that men emit messy fluids that play an important role in "fathering" a child is a rhetorical and political embarrassment. Downplaying the importance of the seminal fluid therefore works to shore up traditional narratives about the power of the male seed.

Thus, while at one level MRT concedes that the maternal seed is more powerful than the male seed in determining the future of the embryo, by emphasising DNA at the expense of other cellular and molecular contributions by both partners to conception, at another level, the technology continues and reinforces the dialectic identified by Katz Rothman.

Reproduction is all about "the seed": the body of the mother is rendered invisible at the expense of real women who must undergo pregnancy, labour, and, increasingly, be subjected to experimental medical technologies, in order to realise what is represented as the "highest" reproductive goal of securing a genetically related child (Griffiths 2016).

The futures of reproduction

Katz Rothman was neither the first nor the last feminist to suggest that new reproductive technologies will have harmful social impacts by virtue of transforming social expectations around, and understandings of, reproduction (Corea 1985; De Melo-Martín 2016; Rowland 1992). Similar concerns are often shared by conservatives (Sandel 2007; Kass 2002; Annas 2005) and even, occasionally, those who would ordinarily self-identify as liberals (Lauritzen 1993). With the benefit of hindsight, we believe that past expressions of such concerns have typically been more valid than critics at the time allowed. Unsurprisingly, however, the moral weight of such concerns – and especially whether it is sufficient to justify restricting access to a technology – is contested. We have no ambition to try to settle the matter here. Whether the impact of one group of citizens' actions on the social meanings on which the members of another group rely is sufficient to justify restrictions of liberty is, after all, a classic dilemma in political philosophy more generally.

Nevertheless, we believe that it is worth highlighting the way that, for the most part, scientific and legislative discourses around MRT function to transform ideas about reproduction and parenthood in ways that reinforce patriarchal norms.[5] Social expectations and understandings shape our behaviour and so changes in them, especially regarding such a central human life experience as reproduction, have real social and political impacts. Shifts in social understandings of the role of men and women in reproduction are especially significant given that reproductive technologies always make greater demands on the lives and bodies of women. The insistence that men make as much as a contribution as women to the creation of new life provides rhetorical support for laws and policies — for instance those regulating access to abortion — that restrict the freedom of women in the interests of

[5] It is worth noting that Appleby and Karnein (2014) suggest, albeit only in passing, that MRT may work to *undermine* patriarchal ideas about nuclear families.

men.[6] These ideological impacts of MRT should be granted *some* weight in considering the wisdom of developing — and legalising — these technologies. Moreover, there is reason to believe that the *relative* weight of concerns about social impacts might be higher in the case of MRT than in the case of other reproductive technologies given the small number of couples who require access to MRT to satisfy their reproductive goals and the existence of alternative means (most obviously, the use of donor gametes) to facilitate the birth of healthy — if not genetically related — children even in these cases. Where the ultimate balance of these considerations lies, however, remains to be determined.

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[6] Conversely, attempts to restrict the reproductive freedom of women sometimes downplay the procreative contribution of men. For discussion of an example, see Mills' treatment of mandatory ultrasound laws (Mills 2018, p.26)

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