Ethical Implications of Permitting Mitochondrial Replacement

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Abstract. Mitochondrial replacement techniques (MRTs) have made headlines as some countries have passed legislation permitting the creation of "three-parent embryos" and because of the recent revelation that a child has already been born following the use of these techniques. MRTs assist women with severe mitochondrial disease to have children who are free from mitochondrial disease. Essentially, the mitochondrial DNA of an ovum or embryo is removed and replaced with the mtDNA of a donor. The purpose of this paper is to argue that MRTs are ethically impermissible but greater regulation is needed. There are five parts to this paper: (1) a brief history of mitochondrial manipulation, (2) a description of the MRT process, (3) ethical arguments in opposition to MRTs, (4) relevant counterarguments, and (5) a proposal for increased regulation. *National Catholic Bioethics Quarterly* 16.4 (Winter 2016): 619–631.

Mitochondrial replacement techniques made headlines in February 2015 when the United Kingdom became the first country "to approve laws to allow the creation of babies from three people."[1] MRTs are meant to create what is colloquially known as three-parent embryos. The purpose of this technology is to assist women with severe mitochondrial disease to have children without the disease.[2] Essentially,

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1. James Gallagher, "UK Approves Three-Person Babies," *BBC News*, February 24, 2015, http://www.bbc.com/.

2. Ian Sample, "'Three-Parent' Babies Explained: What Are the Concerns and Are They Justified?," *Guardian*, February 2, 2015, https://www.theguardian.com/.

the mtDNA (mitochondrial DNA) of an ovum or embryo is removed and replaced with the mtDNA of a donor.[3] The first report of a baby born by this technique was made public in September 2016.[4] While the United Kingdom has a tendency to pass legislation regarding assisted reproductive technologies before other nations, in February 2016, American ethicists also argued that in limited circumstances MRTs would be ethically permissible.[5] The purpose of this paper is to argue that MRTs are ethically impermissible and that, if the research continues, greater regulation is needed. This paper has five parts: (1) a brief history of mitochondrial manipulation, (2) a description of the MRT process, (3) ethical arguments in opposition to MRTs, (4) relevant counterarguments, and (5) a proposal for increased regulation.

Brief History of Mitochondrial Manipulation

Mitochondrial manipulation is not a new technology. In the late 1990s and early 2000s, fifty-eight children were born through a technique that injected "mitochondria from a younger woman's eggs into the eggs of older women, effectively creating babies born with genetic material from three people."[6] A small amount of cytoplasm (containing mitochondria) from a younger woman's ovum was injected into the intended mother's ovum.[7] The purpose of these injections was to increase the success rate of IVF. Subsequently, in 2001, the FDA "informed IVF clinics that using a third person's cytoplasm—and the mtDNA therein—would require an Investigational New Drug application." The FDA asserted jurisdiction, claiming that the technology was a drug, and the subsequent application was never approved.[8] One of the considerations for denying approval was the presence of "genetic abnormalities such as a missing X chromosome in a fetus created with the technique."[9] Moreover, many children who were born using this technique remain undocumented and have not been tracked. Of

3. Margaret Marsh, "'Three Parent Embryos' Back in the News," February 18, 2016, http://mmarsh.camden.rutgers.edu/.

4. American Society for Reproductive Medicine (ASRM), "Report of First Baby Born Using Spindle Nuclear Transfer to Prevent Mitochondrial Disease," news release, September 27, 2016, https://www.asrm.org/.

5. Anne B. Claiborne, Rebecca A. English, and Jeffrey P. Kahn, "Finding an Ethical Path Forward for Mitochondrial Replacement," *Science* 351.6274 (February 12, 2016), doi: 10.1126/science.aaf3091.

6. Sharon Kirkey, "Toronto Fertility Clinic Offers Controversial Egg Treatment for Women That Can Extend Child-Bearing Years," *National Post*, January 30, 2015, http://www.news.nationalpost.com/.

7. Kim Tingley, "The Brave New World of Three-Parent IVF," *New York Times Magazine*, June 27, 2014, https://www.nytimes.com/. This technique was developed by embryologist Jacques Cohen. See also "Aging Eggs: Exciting Research Is on the Horizon," Fertility Authority, accessed January 5, 2017, https://www.fertilityauthority.com/.

8. Tingley, "Brave New World."

9. Erika Check Hayden, "Regulators Weigh Benefits of 'Three-Parent' Fertilization," *Nature* 502.7471 (October 17, 2013): 284.

those children who have been tracked, at least one does not have genetic material from the cytoplasm donor, and two have genetic ties to three parents.[10]

In 2013, the FDA also asserted jurisdiction over OvaScience's Augment procedure, in which mitochondria from a woman are inserted into her own ova to "revitalize" them. The FDA deemed this a form of genetic therapy that required an investigational new drug application. As a result, OvaScience halted development of Augment in the United States and began using the technique abroad. At least one birth has been reported following its use.[11]

The FDA took a more proactive approach to three-parent embryos. In February 2016, the Institute of Medicine published a report titled *Mitochondrial Replacement Techniques: Ethical, Social and Policy Considerations*.[12] The report, sponsored by the FDA, resulted from a study conducted by prominent bioethicists, physicians, lawyers, and scientists regarding the ethical feasibility of MRTs. The committee concluded that investigative studies of these therapies are permissible as long as specific conditions are met. The report highlights many of the ethical issues and federal concerns with MRTs, but fails to comprehensively address the effect of MRTs on parentage laws.[13]

While an extended discussion is outside the scope of this paper, several legal parentage questions would have to be adequately addressed prior to permitting MRTs. Legal parentage in the United States is granted through genetic or gestational ties to children as well as through intention.[14] Historically, children had two legal parents: a legal mother and a legal father. Legal parentage was granted either through state law or through the Uniform Parentage Act. With the advent of nontraditional family structures and the legalization of same-sex marriage, individual states have had to amend their traditional notions of a legal father and legal mother to allow for two legal mothers or two legal fathers.[15] Generally, states are still reluctant to recognize

10. Tingley, "Brave New World." See also Steve Connor, "Three-Parent Babies: 'As Long as She's Healthy, I Don't Care,' Says Mother of IVF Child," *Independent* [UK], August 25, 2014, http://www.independent.co.uk/.

11. Alice Park, "Exclusive: Meet the World's First Baby Born with an Assist from Stem Cells," *Time*, May 7, 2015, http://time.com/; Taryn Hillin, "Why an Incredible New Method to Extend Fertility Is Off Limits in the U.S.," *Fusion*, August 4, 2015, http://fusion.net/; and Alison Motluk, "IVF Booster Offered in Canada but Not US," *Canadian Medical Association Journal* 187.3 (February 17, 2015): E89–E90, doi: 10.1503/cmaj.109-4975.

12. National Academies of Science, Engineering and Medicine, *Mitochondrial Replacement Techniques: Ethical, Social, and Policy Considerations* (Washington, DC: National Academies Press, 2016).

13. Ibid., 79–112; see also the briefing slides (February 2, 2016) at http://www.nationalacademies.org/.

14. Katarina Lee, "Shifting Surrogacy Laws and Legal Parenthood," *Voices in Bioethics*, August 26, 2015, https://voicesinbioethics.net/.

15. See Douglas NeJaime, "With Ruling on Marriage Equality, Fight for Gay Families Is Next," *Los Angeles Times*, June 26, 2015, http://www.latimes.com/.

three legal parents, although a small but growing number of courts and legislative bodies have done so.[16]

Lastly, while the bioethics committee suggested that MRTs may be ethically permissible, Congress's 2016 budget bill prohibits the government from funding "research in which a human embryo is intentionally created or modified to include a heritable genetic modification"—that is, any experiment that genetically alters a human embryo.[17] Additionally, the Dickey–Wicker amendment "prohibits *federal funds* being used for any research in which a human embryo is either created for research purposes or destroyed as part of the research."[18]

Mitochondrial Disease and the MRT Process

Before describing MRTs, it is important to understand what mitochondrial diseases are. Essentially they "occur when mitochondria fail to produce enough energy for the body to function properly."[19] This results from a mutation of either nuclear DNA or mitochondrial DNA.[20] Mitochondrial diseases vary in severity and can affect a variety of cells, including those of the eyes, ears, brain, nerves, muscles, heart, and other organs. Additionally, if mitochondria do not behave normally, they may cause secondary mitochondrial dysfunction leading to other diseases, including Parkinson's, Alzheimer's, Lou Gehrig's, autism, cancer, and diabetes.

As stated earlier, mutations are responsible for some mitochondrial diseases, but the remainder are due to genetic inheritance. Mitochondrial disease can be inherited in three ways, by autosomal recessive, autosomal dominant, or mitochondrial inheritance. For a child to inherit an autosomal recessive condition, both parents must be carriers, and the child must receive a copy of the mutated gene from each. Because each parent may pass on a normal or a mutated gene, every child born to these parents has a 25 percent chance of inheriting the condition. For a child to inherit an autosomal dominant condition, only one parent needs to be a carrier, and the child receives the

16. Ian Lovett, "Measure Opens Door to Three Parents, or Four," *New York Times*, July 13, 2012, http://www.nytimes.com/; Gabrielle Emanuel, "Three (Parents) Can Be a Crowd, but for Some It's a Family," NPR, March 30, 2014, http://www.npr.org/; and Patrick McGreevy and Melanie Mason, "Brown Signs Bill to Allow Children More Than Two Legal Parents," *Los Angeles Times*, October 4, 2013, http://articles.latimes.com/.

17. Consolidated Appropriations Act of 2016, Pub. L. 114-113, sec. 749. See also Joel Achenbach, "Ethicists Approve '3 Parent' Embryos to Stop Diseases, but Congressional Ban Remains," *Washington Post*, February 3, 2016, https://www.washingtonpost.com/; and Ike Swetlitz, "FDA Urged to Approve 'Three-Parent Embryos,' a New Frontier in Reproduction," *STAT*, February 3, 2016, https://www.statnews.com/.

18. Marsh, "'Three Parent Embryos' Back in the News," original emphasis; and Megan Kearl, "Dickey-Wicker Amendment, 1996," *Embryo Project Encyclopedia*, August 27, 2010, https://embryo.asu.edu/.

19. "What Are Mitochondrial Diseases?," Cleveland Clinic, reviewed October 9, 2014, http://my.clevelandclinic.org/.

20. Patrick F. Chinnery, "Mitochondrial Disorders Overview," National Center for Biotechnology Information, August 14, 2014, https://www.ncbi.nlm.nih.gov/.

mutated gene from that parent. Each child of a parent with an autosomal dominant condition, then, has a 50 percent chance of inheriting it. Mitochondrial inheritance is different: here, a mother has a gene mutation in her mitochondrial DNA, which is passed directly to all her children.[21]

As scientist Maureen Condic explains in a white paper on MRTs, the inheritance of mitochondrial disease may be prevented in three ways: by maternal spindle transfer, pronuclear transfer, or embryo cell nuclear transfer. *Maternal spindle transfer* replaces the nucleus of a donor's egg with the nucleus of the intended mother's egg. This results in an ovum that has the nDNA (nuclear DNA) from the intended mother (the women with mitochondrial disease) and the mtDNA from the donor. The ovum is then fertilized with sperm from the intended father or from a donor. *Pronuclear transfer* involves the creation of an embryo from two other embryos. The first is created from the ovum and sperm of the intended parents or the intended mother and a sperm donor, and the second is created from a donor ovum and donor sperm. Pronuclei (early-stage nuclei containing the nDNA of the embryo) are removed from both embryos, and a third embryo is produced by transferring the pronuclei from the intended parents' embryo into healthy cytoplasm from the donor embryo. Lastly, *embryo cell transfer* uses sperm from either the intended father or a donor to fertilize an ovum from the intended mother (the individual with mitochondrial disease), and the embryo is allowed to develop for a couple of days. A nucleus from one of the embryo's cells is then used to replace the nucleus of a donor egg cell, creating a cloned embryo with healthy mitochondria.[22]

Notably, the American ethics committee approved both maternal spindle transfer and pronuclear transfer as potentially viable options for the creation of three-parent embryos.[23] All three techniques use mtDNA from a donor, nDNA from the intended mother, and sperm from either the intended father or a donor.

Ethical Arguments in Opposition to MRTs

While MRTs may give women the opportunity to have genetically related children who will not inherit their mitochondrial diseases, there are several ethical arguments against these practices. In this portion of the paper, I will discuss (1) medical risks associated with the procedures, (2) informed consent concerns, (3) resource allocation issues, and (4) the effect MRTs will have on the assisted reproductive technology market. I have excluded a discussion of the ethical and moral permissibility of destroying embryos, as this debate, while important, is applicable to many reproductive technologies that do not use MRTs. It is important to note, however, that the potential destruction of embryos raises significant ethical questions

21. "What Are Mitochondrial Diseases?," Cleveland Clinic, original emphasis.

22. Maureen L. Condic, *Mitochondrial Donation: Serious Concerns for Science, Safety and Ethics*, Bioethics Defense Fund, February 19, 2015, 2–5, http://bdfund.org/.

23. Rebecca Taylor, "U.S. Panel Allows Scientists to Create Three-Parent Embryos with Sex Selection," *LifeNews*, February 5, 2016, http://www.lifenews.com/.

about duties to future persons as well as the rights of embryos.[24] Additionally, I will not argue that one form of MRT is more ethically permissible than another, but will note that the manipulation of ova rather than embryos poses fewer ethical quandaries.

Medical Risks Are Too Dangerous

Potentially the most persuasive argument against MRTs is based on the medical risks associated with the procedure. Medical risks exist for the intended mother, the ova donor, a gestational surrogate (if used), the embryo, and the children he or she may have after reaching adulthood. The medical concerns are mostly speculative at this time, because the limited available data, which come mostly from nonhuman studies, are inconclusive about the safety of these procedures.[25] Importantly, studies conducted with mice have shown an increase in exhaustion as well as a change in learning capabilities and behavior in mice with mismatched nuclear and mitochondrial DNA.[26] Moreover, the data on human zygotes and embryos are unclear because the subjects were abnormally fertilized, as they were unipronuclear and tripronuclear.[27]

While these embryos may be gestated by the intended mothers, it is also possible that surrogates will be employed. As a result, it is important to acknowledge potential health risks to both groups of gestating women as well as both groups of ova donors. As with other IVF procedures, the intended mother and the ova donor will have to undergo ova retrieval so that the intended mother's nDNA can be removed from her ovum and placed into the ovum with healthy mtDNA. Ova retrieval involves two main steps: In the first, the woman ingests a number of drugs to stimulate her ovaries and mature the ova; then clinicians retrieve the ova. Retrieval is typically done by transvaginal ultrasound aspiration, in which a needle inserted through the vagina punctures the ovary to retrieve matured ova.[28] Potential side effects of this process include bruising, nausea, allergic reactions, injury to adjacent organs, infection, and ovarian hyperstimulation syndrome, which in rare cases can lead to blood clots and kidney failure."[29]

24. Notably in the Roman Catholic tradition, the instruction *Dignitas personae*, by the Congregation for the Doctrine of the Faith (September 8, 2008), provides clear ethical and moral arguments supporting respect for the embryo from the beginning of its existence.

25. Rebecca Taylor, "UK Scientists Close to Creating Three-Parent Babies: Creating Children with Three Genetic Parents," *LifeNews*, November 2, 2015, http://www.lifenews.com/.

26. Swetlitz, "FDA Urged to Approve 'Three-Parent Embryos.'"

27. Lyndsey Craven et al., "Pronuclear Transfer in Human Embryos to Prevent Transmission of Mitochondrial DNA Disease," *Nature* 465.7294 (May 6, 2010): 82, doi: 10.1038/nature08958; and Neva Haites and Robin Lovell-Badge, "Scientific Review of the Safety and Efficacy of Methods to Avoid Mitochondrial Disease through Assisted Conception," Human Fertilisation and Embryology Authority, April 2011, 17, http://www.hfea.gov.uk/.

28. "In Vitro Fertilization (IVF): What You Can Expect," Mayo Clinic, June 16, 2016, http://www.mayoclinic.org/.

29. "Risks of In Vitro Fertilization," ASRM fact sheet, revised 2014, https://www.asrm.org/.

If the intended mother also wishes to gestate the embryo, she must undergo an additional drug regimen to prepare her uterus for embryo transfer.[30] Notably, this process increases the risk of ectopic pregnancy.[31] If a surrogate gestates the embryo instead, she will face this risk as well.

An additional concern for gestational surrogates is possible health effects from maternal–fetal cell exchange—the movement of fetal cells across the placental barrier and into various tissues (such as the brain and muscle) of her body. This means that DNA from the growing fetus will be present in the gestational mother. Similarly, cells crossing from the gestational mother to the fetus may cause tumors.[32] The sharing of cells between a fetus and its genetic mother, however, does not pose the same risks, because they share DNA. With MRT, though, even if the intended mother gestates the fetus, mtDNA from the donor may cross the placental border into the mother's body.

In additional to the risks of maternal–fetal cell transfer, there are generally four categories of concern regarding the embryo: (1) epigenetic harm caused by nuclear transfer, (2) mitonuclear mismatch, (3) other effects that mitochondria may have on the developing embryo, and (4) carryover mutated mtDNA.[33] The main worry over epigenetic harm is that "the nuclei of oocytes from mothers carrying mitochondrial mutations will have been exposed to such mitochondria during the period of egg maturation, which is a period of intense epigenetic activity." As a result, it is foreseeable that "imprinted genes … may later contribute to pathology."[34] Mitonuclear mismatch means that the mtDNA and the nDNA might not appropriately communicate with one another, resulting in health consequences. If the donor and the intended mother are related, it is predicted that there would be lower instances of mismatch.[35] Another concern is that the role of mitochondria may have been underestimated—that, in fact, they provide more than energy to the cell and "influence some of the most important aspects of human life—from memory and ageing to combating stress

30. "In Vitro Fertilization," Mayo Clinic; and "Drugs Commonly Used for Women in Gestational Surrogacy Pregnancies," Center for Bioethics and Culture Network, accessed February 8, 2017, http://www.breeders.cbc-network.org/.

31. "Risks of In Vitro Fertilization," ASRM.

32. Ibid. For other risks to gestational carriers, see ASRM Ethics Committee, "Consideration of the Gestational Carrier: A Committee Opinion," *Fertility and Sterility* 99.7 (June 2013): 1838–1841, doi: 10.1016/j.fertnstert.2013.02.042.

33. "Three-Person IVF: A Resource Page," Center for Genetics and Society, last modified December 21, 2016, http://www.geneticsandsociety.org/. See also letter from David L. Keefe to Anna Rajakumar, *Biopolitical Times* (blog), March 24, 2014, http://www.biopoliticaltimes.org/downloads/DKeefeMRconsiderations.pdf.

34. David King, "Report on the Safety of 'Mitochondrial Replacement' Techniques: Epigenetic Issues," *Human Genetics Alert*, March 2013, 4.

35. Klaus Reinhardt, Damian K. Dowling, and Edward H. Morrow, "Mitochondrial Replacement, Evolution, and the Clinic," *Science* 341.6152 (September 20, 2013): 1345–1346, doi: 10.1126/science.1237146. The author of this article suggests that mismatches between nDNA and mtDNA would be greater among human beings than among primates from the same "troop" because the genetic diversity between human intended mothers and ova donors would be greater.

and disease. Mitochondria even have influence over the DNA in your cell nuclei, and they change and evolve during your lifetime."[36] Lastly, carryover mutated mtDNA means that MRTs could "cause the very mitochondrial diseases the techniques are designed to prevent."[37]

Lastly, the offspring of individuals created through MRTs may experience adverse health effects. While the Institute of Medicine's report insists that initially only male embryos may be gestated, to avoid adversely affecting the germ line, using MRTs for both female and male embryos may have implications for future generations.[38] Other American scientists have argued that MRTs will "irreversibly alter the human germline."[39] The long-term medical effects are unknown. Foreseeably, the modified DNA of any child born through MRTs could affect subsequent generations.

While there are potential medical consequences for the women who participate in MRTs, arguably the greatest health risks will be faced by the embryos and by future generations. As will be addressed, the most persuasive arguments in support of MRTs are that individuals have the right to choose autonomously to procreate in this way and that the assumption of potential risks is an extension of their autonomous decision-making capacity. There are some procedures, however, to which individuals should not be able to consent, because they are simply too risky.

Informed Consent Concerns

Mitochondrial replacement techniques raise several informed consent concerns, including each participant's ability to understand and consent to the procedures. These participants are (1) the intended mother, (2) the gestational surrogate, (3) the intended father, (4) the sperm donor, (5) the ova donor, and (6) the embryos. While informed consent is the ideal in medical practice, it is not always achieved because of the criteria that must be satisfied. Studies consistently show that individuals do not fully comprehend what they are consenting to and that they have unrealistic expectations regarding a procedure's outcomes.[40] In the context of three-parent embryos, additional concerns about emotional ties arise because of the nature of the procedure.

36. Garry Hamilton, "Possessed! The Powerful Aliens That Lurk within You," *New Scientist*, September 17, 2014, https://www.newscientist.com/. See also "Three-Parent Babies: It's More Messy Than We Thought," *New Scientist*, September 17, 2014, https://www.newscientist.com/.

37. "Scientists from around the World Raise Warnings," Center for Genetics and Society, accessed January 9, 2017, http://geneticsandsociety.org/. See also Joerg Patrick Burgstaller et al., "mtDNA Segregation in Heteroplasmic Tissues Is Common In Vivo and Modulated by Haplotype Differences and Developmental Stage," *Cell Reports* 7.6 (June 26, 2014): 2031, doi: 10.1016/j.celrep.2014.05.020.

38. Achenbach, "Ethicists Approve '3 Parent' Embryos."

39. "Three-Person IVF," Center for Genetics and Society.

40. Crisol Escobedo et al., "Ethical Issues with Informed Consent," Center for Science, Technology, Ethics, and Policy, University of Texas at El Paso, http://www.cstep.cs.utep.edu/; and Jacquelyn Ann K. Kegley, "Challenges to Informed Consent," *EMBO Reports* 5.9 (September 2004): 832, doi: 10.1038/sj.embor.7400246; and Lokesh P. Nijhawan et al.,

While both intended fathers and intended mothers may have to consent to the creation of three-parent embryos, the woman will arguably be responsible for consenting to the procedure, considering that (1) she will most likely gestate the embryo, and (2) current MRTs focus on replacing her mtDNA. When informed consent is obtained from the intended mother, three issues need to be addressed: (1) her ability to consent to risky medical procedures, (2) her emotional desire to have a child, and (3) her understanding of potential long-term consequences.

Compared to the sperm provider and the ova donor, the intended mother bears significantly greater risk and responsibility. First, while both she and the ova donor must consent to undergoing the ova retrieval process, the intended mother is in most cases the one accepting the risks associated with gestation and consenting to the creation of the three-parent embryo. Given the limited data, it may be difficult for her to accurately consent to these procedures. Another concern, especially with the intended mother, is that her emotional desire to have a disease-free child may unduly motivate her to consent to the creation of the embryos. This is not to suggest that women cannot consent to procedures in which they are emotionally invested, but the desire to have a disease-free child to whom she is genetically tied arguably makes obtaining truly informed consent difficult, if not impossible. Intended mothers cannot consent objectively. Moreover, the intended mother bears the burden of consenting to a procedure that may, in fact, have negative health consequences for her future child. While several of these concerns are relevant in other assisted reproductive technologies, the limited data as well as disease prevention make obtaining informed consent from intended mothers more difficult.

Some controversies over the use of gestational surrogates are outside the scope of this paper, including risks of exploitation and the unequal bargaining power between gestational surrogates and intended parents. I focus here on informed consent concerns.[41] Studies report many instances in which gestational surrogates have not understood their contracts, have not understood the language their contracts were written in, and have not had access to adequate legal counsel.[42] These concerns are only amplified in the use of three-parent embryos. If gestational surrogates already have difficulty understanding risks associated with typical surrogacy arrangements, they are likely to have greater difficulty consenting to the gestation of embryos with three genetic parents.

If the intended mother enters into a three-parent arrangement with the intended father, he should be a part of the consent process. Notably, he may be the sperm generator or the legal father of the future child. In every case, he should be required to consent to the procedure. Like the intended mother, the intended father may have

"Informed Consent: Issues and Challenges," *Journal of Advanced Pharmaceutical Technology and Research* 4.3 (July–September 2013): 134, doi: 10.4103/2231-4040.116779.

41. Arthur Caplan, "Paid Surrogacy Is Exploitative," *New York Times*, September 23, 2014, http://www.nytimes.com/.

42. Malene Tanderup et al., "Informed Consent in Medical Decision-Making in Commercial Gestational Surrogacy: A Mixed Methods Study in New Delhi, India," *Acta Obstetricia et Gynecologica Scandinavica* 94.5 (May 2015): 465, doi: 10.1111/aogs.12576.

difficulty understanding the medical risks and may oppose a procedure that could harm the child created by MRT.

Both the ova donor and a potential sperm donor also need to be considered in these arrangements. The ova donor should undergo a consent process similar to that of the intended mother during the ova retrieval process. She should understand the risks associated with the hormones needed to induce ovulation as well as the risks posed by transvaginal aspiration. As with gestational surrogates, difficulties with obtaining consent may arise with ova donors, as they may be influenced by the payments they will receive and may have significantly less bargaining power than either the individuals or clinics purchasing their ova.[43] Sperm donation, while less medically risky, raises some of the same concerns about unduly inducing men to donate their sperm in exchange for financial compensation. Aside from the typical consent concerns, anonymous donors do not know what happens to their gametes after donation. Arguably, they may not want their gametic material to be used for the creation of three-parent embryos. As a result, fertility clinics would need to explicitly inform donors that their gametes could be used in these experimental procedures. In known-donor situations, this may be of less concern; however, it is still necessary that the donor comprehends the risks.

Lastly, it should be acknowledged that while embryos cannot consent to their creation, questions about whether intended parents should be able to consent to the creation of embryos using risky procedures are open to ethical debate. Most of this debate centers on duties to future persons, often referenced as the non-identity problem.[44] While it is extremely difficult to argue that an embryo is better off not existing than existing, some would argue that intended parents have a duty to not subject their future children to the undue risks posed by MRTs. Opponents of this concern would argue that individual autonomy permits intended parents to create children by the use of MRTs: given that the animal data are highly inconclusive and that individuals can create families by a variety of means, intended parents who use MRTs are not exposing their children to extraordinary risk. In light of the sheer number of parties involved in the creation of three-parent embryos as well as the medical risks and emotional ties associated with consenting to this practice, gaining truly informed consent is extremely difficult if not impossible.

Resource Allocation

Some general concerns with experimental procedures are (1) whether resources should be spent on a given protocol and (2) who should fund it. Since Congress has prohibited governmental funding, MRT procedures, if permitted by the FDA, would have to be privately funded. One of the largest concerns is that from a utilitarian perspective, investing in MRTs benefits a very small portion of the population. As Jeffrey Kahn highlights, only a few hundred individuals in the United States would

43. "Egg 'Donation' and Exploitation of Women," Center for Bioethics and Culture Network, accessed January 10, 2017, http://www.cbc-network.org/.

44. David Boonin, "How to Solve the Non-identity Problem," *Public Affairs Quarterly* 22.2 (April 2008): 129–159.

even be eligible to use these technologies, as the condition and the odds of severe mitochondrial defects are rare.[45] Conceivably, the procedure's resource cost is greater than its benefit to a few hundred individuals. Additionally, MRTs circumvent and, in theory, could eventually eradicate mitochondrial disease. They are not in fact treating mitochondrial disease. Arguably, resources should be spent on curing, not bypassing, disease. If MRT research is privately funded, additional concerns arise about insurance coverage as well as adverse-event protections. The United States offers very weak protections for individuals who experience an adverse event after engaging in experimental research.[46] If the research is government funded, there is likely to be significant discord, since many taxpayers believe that experiments on embryos are morally impermissible. Given the common practice of assisted reproduction in the United States, which is generally paid for out of pocket or through an employee compensation package, it is reasonable to expect that individuals who wish to undergo MRT treatments would pay for it in the same ways.[47]

Relevant Slippery Slope Concerns

While slippery slope arguments are fallible, because the permissibility of any given procedure will not necessitate a "jump" to another procedure, it is important to address the effect MRTs could have on assisted reproductive technologies. MRTs raise the question about the permissibility of other forms of genetic manipulation, especially in the context of eradicating disease. However, defining the difference between disease and enhancement further complicates the ethical debate surrounding genetic engineering. Moreover, if only the gestation of male embryos is supported, as recommended by the authors of the National Academies report, additional concerns about sex selection arise. Lastly, like all assisted reproductive technologies, MRTs could create an additional divide between the wealthy and the poor, since only the wealthy are likely to have access to such techniques and the ability to pay for them. While some of these concerns are secondary to the ethical permissibility of MRTs, they should be fully analyzed before the techniques are permitted in the United States.

Relevant Counterarguments

While unknown and known medical risks, obstacles to informed consent, concerns about resource allocation, and slippery slope concerns preclude the use of MRTs, three counterarguments should also be considered, namely, (1) autonomy, (2) beneficence, and (3) the advancement of science.

45. William Brangham, "Three-Parent DNA Treatment for Rare Defect Raises Debate," *PBS NewsHour*, February 3, 2016, http://www.pbs.org/.

46. See "Protection of Human Subjects" in the *Code of Federal Regulations*, specifically, 22 CFR §225.101.

47. Katarina Lee, "A Comparison of Canadian and American ART Law," *Voices in Bioethics,* October 14, 2015, http://voicesinbioethics.net/.

Autonomy

The strongest argument in favor of MRTs maintains that individual autonomy should be protected. The four traditional bioethical principles promulgated by Tom Beauchamp and James Childress are autonomy, beneficence, non-maleficence, and justice. If a given medical or research practice accords with these principles, it generally is considered ethically permissible. Autonomy, or "the obligation to respect the decision making capacities of autonomous persons," has become the most highly regarded of these principles.[48] Thus, the argument goes, if consenting adults decide to create embryos using MRTs, then scientists, medical researchers, and ethicists should support their decision. Proponents argue that this is especially true in this situation, since for a woman with mitochondrial disease, MRTs provide the only opportunity for her to have a healthy child who is genetically related to her.

However, autonomy has limits. Generally, autonomous choices are permissible if the individual can consent and the decision does not harm the individual or others.[49] As argued above, gaining truly informed consent from all parties involved in MRT procedures is difficult if not impossible, and considering the medical risks to both the gestating mother and the child, the autonomy argument is not persuasive. Moreover, as mentioned above, the creation of embryos in a laboratory setting is rejected on moral grounds by many ethicists, including those in the Roman Catholic tradition.

Beneficence

Beneficence, or the "obligations to provide benefits and to balance benefits against risks," is the second most compelling argument for permitting MRTs.[50] Mitochondrial diseases are terrible life-altering diseases that may result in death. Using MRTs will conceivably eradicate these diseases from the population, and eradicating disease provides a benefit to future children as well as to society. Moreover, proponents argue that society has an obligation to assist individuals in having children, as procreation is a natural human function.

While eradicating disease is clearly a benefit, the beneficence argument is not compelling because (1) the benefit of eradicating disease does not clearly outweigh the potential risks of MRTs; (2) practically, for inheritable mitochondrial defects to be eradicated, everyone with the condition would have to undergo MRTs or refrain from having children; (3) the MRT process is arguably eugenic, because it does not treat a disease but simply breeds it out; and (4) individuals have other opportunities to become parents.

48. T.L. Beauchamp, "Methods and Principles in Biomedical Ethics," *Journal of Medical Ethics* 29.5 (October 2003): 269, doi: 10.1136/jme.29.5.269.

49. See Andrew G. Shuman and Andrew R. Barnosky, "Exploring the Limits of Autonomy," *Journal of Emergency Medicine* 40.2 (February 2011): 229–232, doi: 10.1016/j.jemermed.2009.02.029; and Rebecca L. Volpe et al., "Exploring the Limits of Autonomy," *Hastings Center Report* 42.3 (May–June 2012): 16–18, doi: 10.1002/hast.46.

50. Beauchamp, "Methods and Principles in Biomedical Ethics," 269.

Advancement of Science

A less compelling argument in favor of MRTs is that the development of this technology is a positive scientific advancement. Not only will the technology help eradicate disease, but it also may aid further scientific advancement. Its development could provide insight into how genetic manipulation can be used to eradicate other diseases. Additionally, it will provide valuable information about the interactions between nDNA and mtDNA. Lastly, MRTs, if deemed safe and efficacious, may enable individuals to create children with genetic ties to three parents without a medical need. For example, female homosexual couples may wish to create a child that has genetic material from both partners. While scientific advancement is generally a positive goal, it is not a sufficient condition for permitting a practice that has significant medical risk.

Potential Policy

While I have argued that MRTs are ethically impermissible because of concerns about medical risk, informed consent, and resource allocation, as well as secondary ethical concerns, I acknowledge that if experiments in the United States begin, there will need to be significant regulation in order to protect those that wish to partake in this practice. Factors that should be adopted in a policy include (1) stringent selection criteria, (2) vigorous informed consent, (3) private payment for the procedure, (4) rigorous follow-up, and (5) strict government oversight.

To mitigate some of the ethical problems with MRTs, stringent selection criteria must be adopted, which means that participants must have a severe enough mitochondrial defect to warrant the use of this technology. Moreover, other factors, including the health and age of the intended mother, should be considered as well. Gestational surrogates should not be used. Finally, psychologists should appropriately screen participants. All parties should have to undergo a vigorous informed consent process, including educational testing to confirm that participants understand the medical risks they are assuming. Explicit consent would have to be gained from the intended mother, intended father, ova donor, and sperm donor. To avoid concerns about the use of public funds to pay for these procedures, only private funds should be used. There should be significant follow-up throughout the process as well as screening and data collection as the children grow. This information should be documented and published. Lastly, the FDA or another government body should oversee the clinics that provide MRTs to ensure that the clinics and the researchers abide by best practices.

While MRTs provide an opportunity for women who have severe mitochondrial diseases to have healthy genetically related children, the risks and ethical concerns outweigh the potential benefits. While I am sympathetic to women who are fearful of passing on a genetic defect, there are other mechanisms for them to become parents, as through ova donation or adoption. Nevertheless, given the ongoing efforts to make these procedures legitimate, they need to be regulated. The U.S. government has to assert jurisdiction over the practice and provide very clear regulations for its use. While MRT issues are likely to be a problem in the United States in the future, ethicists and regulators need to create policies now, prior to the beginning of human trials.