Creating a Three-Parent Child: An Educational Paradigm for the Responsible Conduct of Research

Ruth L. Fischbach*, Shawna Benston, and John D. Loike
Center for Bioethics, Columbia University College of Physicians and Surgeons, New York, NY 10032

The field of assisted reproduction is renowned for its remarkable advances and constant pushing forward of research boundaries in an effort to offer innovative and effective methods for enhancing fertility. Accompanying these advances, however, are physiological, psychological, and bioethical consequences that must be considered. These concomitant advances and consequences make assisted reproduction an excellent educational paradigm for inculcating responsible conduct in both research and clinical practice. Ultimately, responsible conduct rests on the ethical researcher and clinician. Here, we present the as-yet unapproved, contentious assisted reproductive technology of mitochondrial replacement transfer (MRT) as an ideal educational platform to foster the responsible conduct of research by advancing dialogue among multidisciplinary scholars, researchers, and students. Using a likely future case, we present the basic science, legal, and ethical considerations, and the pedagogical principles and strategies for using MRT as an effective educational paradigm. Society will benefit when the ethical issues inherent in creating children with three genetic parents as well as germline interference are discussed across multiple academic levels that include researchers, legal experts, bioethicists, and government-appointed commissions. Furthermore, undergraduate and graduate students should be included because they will likely determine the ethical fates of these biotechnologies. While emerging assisted reproduction technologies such as MRT are highly complex and will take years to be readily available for patients in need, now is the time to consider their scientific, legal, ethical, and cultural/religious implications for ensuring the responsible conduct of research.

INTRODUCTION

Assisted reproductive technologies (ART) have been developed to present safe and effective methods for enhancing fertility. Nonetheless, there are physiological, psychological, and bioethical consequences that push the boundaries of innovative ART (7, 9). Of great concern, for example, are the under-regulation and over-medication of women’s bodies when attempting to assist fertility.

These concerns make ART an excellent educational paradigm for inculcating responsible conduct in both research and clinical practice. It is imperative that research not race ahead of the ethics. Understanding the special ethical issues associated with human and animal research is a vital feature of research integrity. Ultimately, responsible conduct rests on the ethical researcher and clinician. In this article we discuss for the learner relevant ethical and legal principles underlying conduct essential for promoting safe, effective, and ethical research and clinical care.

Our case for promoting our educational paradigm is a highly controversial and to-date unapproved procedure awaiting testing: mitochondrial replacement therapy (MRT).

Case: Maria was born with a mitochondrial genetic disease leading to pronounced neuromuscular manifestations. Mitochondria are found in almost every cell of the human body and are the organelles that provide metabolic energy. Since mitochondrial DNA (mtDNA) is maternally inherited, every child Maria will have will inherit her mitochondrial genetic disease. Maria and her husband, Josh, have heard about an experimental procedure offered in the medical center that could be used to create a child without her mitochondrial defects. They are anxious to prevent problems in any future child and quickly volunteer to be part of this as-yet FDA-unapproved, cutting-edge clinical trial known as mitochondrial replacement therapy. The trial involves obtaining presumably healthy mitochondria from a donor, Anne, who has volunteered to donate her healthy eggs. The child born will have genetic information from not two, but three, parents: Maria, Josh, and Anne.
The science behind MRT

To put this case into perspective, it is essential for the learner to understand the basic science of MRT (23, 26, 28).

In almost every cell in the body there are two sources of genetic information: the nucleus and the mitochondria. Human beings have approximately 20,000 genes in their nuclear chromosomes and only about 35 genes in their mitochondria (24). While mtDNA represents less than 0.2% of the total human genome, these mitochondrial genes are nonetheless very important since their mutations can cause severe neurological conditions. As many as 1 in 5,000 children express mutations in their mitochondria, but their clinical manifestations vary considerably. Many have a few minor symptoms; however, a small cohort with mitochondrial disease experience progressive muscular weakness, blindness, heart failure, liver failure, learning disability, and/or diabetes. In rare instances, mitochondrial disease can lead to infant or childhood death. Whether these mutations occur spontaneously or are inherited, all future children from affected women will express mitochondrial mutations because mtDNA, unlike nuclear DNA, is maternally inherited.

MRT involves transferring the nucleus of an egg, obtained from the woman with the defective mtDNA, into the egg donated by a woman with healthy mtDNA. The donor egg will have all nuclear DNA removed so that the donor contributes only the healthy mtDNA. This reconstituted egg is then fertilized with sperm from the husband and implanted back into the gestational woman. The baby created will be free of genetic mitochondrial disease (21).

It is important to consider that a child produced this way would have DNA obtained from two women and one man, or three genetic parents. If the child is female, all of her future offspring will have sufficient healthy mitochondria and will not experience disabilities associated with mitochondrial mutations.

The FDA is currently considering whether to allow MRT research to proceed, and is specifically concerned with the medical risks and benefits of mitochondrial manipulation technologies prior to first in-human clinical trials. One of the FDA’s primary objectives during drug development is to assure the safety of the study subjects (6). Currently, there is an urgent need to identify risks associated with transferring a nucleus from one egg into another (somatic cell nuclear transfer).

The learner should know that there are particular concerns involving potential risks to the child, including: 1) mitochondrial disease (particularly in women with mitochondrial disease), as a result of carryover of abnormal mitochondria and heteroplasmy; 2) disorders due to nuclear-mitochondrial incompatibility; 3) disorders related to aberrant epigenetic modifications; 4) birth defects and other disorders associated with the specific mitochondrial manipulation technology of the procedure; and 5) toxicities of reagents used in mitochondrial manipulation technologies. There may be additional risks that are difficult to predict because of limitations in current knowledge (10). We do know there are societal concerns associated with germline therapy, such as fears of eugenics and tampering with the genome.

Legal considerations

The prospect of MRT raises legal questions, most notably because the process remains, at the time of writing (November 2014), in legal limbo. In the United Kingdom1 and the United States, Parliament and the FDA, respectively, have yet to rule on the permissibility of MRT (18, 27). The ambivalence of these organizations is fueled by public opinion and considerable misunderstanding of the procedure, and constrained by existing legal policies. Here, for the learner, we focus on two contentious issues: legal parenthood and child identity.

Legal parenthood. A double-sided issue of identity emerges with the prospect of three-parent babies: who are the legal parents, and who will the child consider its genetic ancestors when beginning to decipher the self? The former issue intrinsically involves questions of legal rights and duties, while the latter is perhaps less clearly defined because of the as-yet unknown ethical repercussions of crossing the germline.

The issue of legal parenthood in MRT is reminiscent of the legalities of sperm donation. Can a genetic donor—here, of mitochondria—be held responsible for financial child support, and can/should the resulting child be permitted to know of, and even form a relationship with, the donor? In the sperm-donation context, we have come to recognize the right of children born via in vitro fertilization (IVF) to learn the identities of their genetic parents, including anonymous sperm donors. In the MRT context, such questions must be considered before the MRT procedure is conducted, because the prospective child’s legal interests are ethically complex. Indeed, the very identity of a future generation (5) is put into stark relief by the MRT quandary. Not only is the female child’s genetic health altered through MRT, but so, too, is the genetic health of that child’s female descendants.

A seminal question for the learner to consider is, what duties—if any—do potential parents owe their prospective children? Legally, we might be unable to answer that question even after a baby is born via the MRT/IVF process. Do we extrapolate from the increasing number of cases of sperm donation in which the donors—even when anonymous—have been court-ordered to pay child support (17)? “Legal

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1 On September 1, 2014, The House of Commons debated and then resolved, That this House takes note of the Human Fertilisation and Embryology Authority’s most recent scientific review into the safety and efficacy of mitochondrial replacement techniques which highlights concerns for subsequent generations of children born through maternal spindle transfer and pronuclear transfer; welcomes the recent comments of scientists including Professor Lord Winston that, prior to the introduction of such techniques, more research ought to be undertaken and a full assessment conducted of the potential risk to children born as a result; and calls upon the Government, in light of these public safety concerns, to delay bringing forward regulations on mitochondrial replacement (http://www.publications.parliament.uk/pa/cm201415/cmhansrd/cm140901.debtext/140901-0003.htm#H40901250000001).
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experts agree that cases like this are becoming more common, and the courts are trending in this direction. And, in extreme cases where the mother becomes too sick to look after the child, she may want to seek out the anonymous donor for financial support” (13).

Furthermore, if MRT becomes an accepted procedure, other issues will likely emerge concerning MRT contracts, analogous to those in contractual surrogacy agreements (22). It has been proffered that only the intended parents should be recognized as the legal parents, so as to clearly delineate responsibilities (15, 16). Whose names should be placed on the birth certificate to accurately reflect birth parents is another unresolved issue. Two states, Florida and California, have presented approaches for three-parent birth certificates, but the debate in the MRT context will likely prove complicated (11, 20).

Does a child have a right to know, from an ethical and legal perspective, who all of its genetic parents are, even if one is contributing a small percentage of DNA (i.e., mtDNA)? One opinion is that because mtDNA is less than 0.2% of the genome, it represents a small enough fraction of the genome that it could be considered legally irrelevant. But others say that if the donor is found to have other genetic mitochondrial mutations, or if, in the future, we learn that there is biological interference between donor and recipient mitochondria, it could be critical for the child to know the donor’s identity. Ultimately, the question raised is whether the mtDNA donor should have the right to remain anonymous or be treated like a sperm donor whose identity can be learned.

The child’s identity. Debates for the learner swirl around the reconciliation of MRT’s sensationalism and its tangible benefits for the resulting child. “[It] is undoubtedly true that the egg provider [Anne] who contributes the healthy mtDNA, provides less than 0.2% of the total genetic make-up of the newborn”; yet the child’s personal narrative will have been radically altered by MRT (3). A child born with mitochondrial disease will lead a life imbued with disability, while one whose unhealthy mtDNA has been replaced with healthy mtDNA will lead a life devoid of mitochondrial illness. This major distinction in life experience—the difference between illness narrative and health narrative—must inevitably inform one’s very identity (3). In this way, regardless of percentage of genetic parenthood, the donor of healthy mitochondria confers a quite different identity on the resultant child.

The legal landscape of MRT has yet to be determined. Certainly the implications of legal ethics in MRT are many and varied, requiring extensive discussion by researchers, physicians, ethicists, and lawyers in order to attach responsibility to the process.

Informed consent

Informed consent is defined by the American Medical Association as “a process of communication between a patient and physician that results in the patient’s authorization or agreement to undergo a specific medical intervention.” It requires full disclosure by the physician about risks and benefits of, and alternatives to, the proposed treatment in order to protect the patient’s right to self-determination, bodily integrity, and his or her voluntariness in the healthcare decision-making process (1).

But the decision regarding what information is material and should be presented to the potential participant presents a challenge to the researcher in the informed consent process. Too much information can scare off a potential participant, while too little defies the Nuremberg Code (19) and Declaration of Helsinki Doctrine (8), that require fully informed consent.

The learner should keep in mind that the vulnerable, dependent, or demanding potential research participant needs added protections. In our case, because of their sense of urgency, Maria and Josh may forego rational considerations of risks, benefits, and long-term consequences. They are likely to fall victim of the therapeutic misconception in which they “deny the possibility that there may be major disadvantages to participating in clinical research that stem from the nature of the research process itself” (2). Furthermore, given their enthusiasm to participate in the experimental trial, they are likely to fall victim to therapeutic misestimation, which occurs when subjects overestimate the benefits, or underestimate the potential risks, associated with a particular study (12).

Ethical considerations

The Belmont Principles (4) can be applied by the learner to this paradigm. Autonomy is certainly the bedrock of responsible conduct of research. But are there limits to autonomy? Because an experimental procedure is available, does that mean that every patient who wants the experimental procedure has a right to that procedure (25)? Likewise, when autonomy is applied to the researcher, does that mean the researcher is obligated to offer the procedure to every patient in need or every patient who demands it as a right of access?

The technological imperative affirms, ‘if the technology exists, use it.’ But the bioethics mantra states that ‘it is not what you can do; rather, it is what you should do.’ The need to be beneficent while avoiding non-maleficence presents ethical challenges to the researcher. Keeping one’s zeal in check to avoid pushing the boundaries beyond what is tested and acceptable is also vital for the responsible researcher.

The principle of Justice implies that the procedure should be available to all in need, but will the cost limit the accessibility to only those who can afford it? How to make distributive justice a reality is another challenge.

Religious and cultural perspectives raise different issues regarding MRT. In Judaism, for example, the religion of the child is determined by the religion of the mother (14). In our case, in which there are two genetic mothers, perhaps
one Jewish and one not, what would be the religious status of the child?

Currently, no consensus exists as to how to resolve the bioethical challenges presented by our case. There are at least two lessons we should learn from an historical perspective extrapolated from the ethical challenges of stem-cell technology: First, discussing the future is better than having it appear unannounced; second, these ethical challenges will take years of debate before logical and effective recommendations can be implemented.

Pedagogical principles and strategies

We offer recommendations for using MRT as an effective paradigm for educating for the responsible conduct of research. General recommendations include:

• integrating the science of emerging biotechnologies (in this case, MRT), their ethical ramifications, and contemporary bioethical theories into interactive class sessions,
• structuring Socratic-based discussions to stimulate students to consider the impact of their moral intuitions when grappling with bioethical issues, and
• using specific actual and futuristic case studies to highlight bioethical issues and to help develop creative problem-solving skills.

Incorporating pedagogical strategies like these spark learners’ interests in both the science and the ethics. The plethora of political, public, and academic bioethical debates on emerging biotechnologies such as MRT underscore the need for learners to be prepared for future bioethical challenges emerging from these ever-evolving biotechnologies. The overall objective of educating for the responsible conduct of research should be to introduce future researchers and healthcare professionals to the bioethical questions they are sure to confront in their professional lives. This education should enable future professionals to develop personal strategies for grappling with bioethical dilemmas; it should empower them to present their views on how to manage and resolve contentious bioethical issues.

Experimental procedures like MRT offer an ideal educational platform to promote dialog among multidisciplinary scholars and students that fosters the responsible conduct of research. Case discussion, and especially role play, provide innovative opportunities for learners to express provocative views they might otherwise be reluctant to offer during typical class sessions.

CONCLUSION

Society benefits when the ethical issues of a new biotechnology are discussed across multiple academic levels that include researchers, legal experts, bioethicists, and government-appointed commissions. Additionally, our undergraduate and graduate students provide another rich source of fresh ideas as they will most likely determine the ethical fates of these biotechnologies. While emerging biotechnological procedures are highly complex and will take years to be readily available for patients in need, the time to begin considering the scientific, legal, ethical, and cultural/religious implications is now.

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