"Hello Father…Hello Mother…Hello…*Mother*?" 3-Person Cytoplasmic Transfer: Mitochondrial Genomes Redefine *In Vitro* Fertilization (IVF) for a Healthier Family in the Twenty-First Century

Joyce O. Hislop*

1063 Mosser Rd., B194 Breinigsville, PA 18031, United States

Abstract

In 1978, the idea of making a baby on a petri dish generated worldwide media attention as scientific and social controversy. On July 25th of that year, the world's first human *in vitro* fertilization (IVF) was accomplished in England, and Louise Brown was the first 'test-tube' baby. Once Louise was shown to be a healthy infant the protests subsided, and since then the IVF technique has gradually become accepted as an alternative to the 'natural' way for infertile couples to have a child. However, IVF is not without risks and possible disappointment, and for 37 years there has been no significant change in technique. However, in 2006 two colleagues in England developed a novel method for IVF that will eliminate inherited disease by using a woman's donated, healthy mitochondrial (mt) organelles (oxygen-energy cells), euginizing the mother's unhealthy mt cells that carry inherited chronic and/or serious disease. The transfer of these powerful, healthy cells into the mother's egg cell represents a 3-person IVF process by which many chronic and serious diseases are eliminated that would otherwise have been passed on by the mother to her child. In cytoplasmic (mt) implantation, the mother's cell nucleus is not affected and any characteristics of the child, for example hair and eye color, are from the mother and father. This technique has been successfully researched in mice, but to date not in humans. This year, the United Kingdom petitioned Parliament and was granted approval to research on humans. In the United States, the Food and Drug Association (FDA) has been reluctant to give human research approval to our own scientists, citing the factors of unknown physical risk, ethics and legalities. These issues will again be discussed in a 2016 symposium.

Designer babies? Or healthier generations to come? This article explains 3-person IVF process to our current and future nurses as the FDA will raise both sides of this argument within the next year for consideration to resume research with human subjects. In this day, clinicians, government employees, the public, and our media (including social media) contribute to the weighing of the value of eliminating any given inherited disease and increasing long-term family health versus the risks of physical, ethical and legal complications.

Keywords: *In vitro* Fertilization (IVF).

Abbreviations: IVF, *in vitro* fertilization; mt, mitochondrial; FDA, Food and Drug Association; DNA, deoxyribonucleic acid; OXPHOS, oxidative phosphorylation; ATP, adenosine triphosphate.

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***Coppresondence to:** Joyce O. Hislop, 1063 Mosser Rd., B194 Breinigsville, PA 18031, United States. Tel: 610-351-4967, E-mail: joycehisloprnocn@gmail.com

"*Three people to make a baby*?" My companion's tone expressed a shocked response to my comment that the British Parliament had announced in March 2015 that current research into healthy donor replacement of the mother's unhealthy mitochondrial (mt) DNA organelles warranted consideration to approve 3-person fertilization, a means to eliminate many inherited diseases that the mother would pass on and with consequential life-long caregiving by the family.[1–7] My colleague's off-handed reply was not meant to be sarcastic or to suggest an inappropriate tryst, but the idea of three IVF parents does at first sound bizarre. Yet, this is far from the case.

In vitro means 'outside the body'. *Fertilization* means sperm has attached to and entered the egg. Fertilization of an egg outside the body first began by experimenting with rabbits in 1932. By 1944, human ova were successfully fertilized in a petri dish but not implanted in a woman. The birth of the first 'test tube' IVF baby, Louise Brown, occurred on July 25, 1978 in England, accomplished after 4 years of unsuccessful challenges for her parents, scientist Robert Edwards, and Patrick Steptoe, a gynecologist and surgeon.[1,2,5,8] At the time, ethical questions flourished, cautioning against "laboratory breeding, unknown long-term health risks, socially ostracizing a child, and destruction of the nuclear family", to name only a few of many concerns vehemently voiced.[1,2,5,8–10] Indeed, to this day, the Catholic Church remains opposed to IVF.[2]

In 1977, England transformed IVF and possibilities for future couples to have a child. Media and the public were uncomfortable and skeptical with the idea of creating a child not by sexual procreation, but instead by technical science, raising valid concerns then and currently. Some that persist include: Would this process lead to conceiving children as "quality controlled products"? What if the child was handicapped mentally or physically? What about long-term health?[3,7–9]

'Mighty-mouse' mitochondrial organelles: what are they?

Advances in early 21st century research led to the discovery of the powerful ability of mitochondrial enzymes to block maternal transference of many inherited illnesses and diseases. Mitochondria are tiny organelles within each cell of the body, regulating 79% of a

cell's oxygen in order to sustain growth.[3,7] By about 2006, scientific research had discovered the significant influence of these tiny organelles, thousands within each cell, and their ability to block many inherited diseases and chronic illnesses. The research also determined that not all mitochondria are healthy and, when not, they can cause inherited chronic illness or disease in children and later, even in adulthood.

What is inherited mitochondrial disease?

The Foundation of Mitochondrial Medicine states on their website (http://mitochondrialdiseases.org/related-diseases/): "Mitochondrial disease can look like any number of better known diseases, including: autism, Parkinson's disease, Alzheimer's disease, Lou Gehrig's disease (ALS), muscular dystrophy and chronic fatigue syndrome, among others. Adults and children with it can have features similar to other disorders like: epilepsy, myopathy, developmental delay, learning disabilities and fibromyalgia."

In pediatrics and adult medicine, unhealthy, low-oxygenated mitochondria and mtDNA can cause cardiac, respiratory, gastroenterological (GI), endocrinal and parathyroid diseases, as well as poor growth, decreased muscle coordination, seizures, and cognitive and physical development delays, to name only a few of the potential pathological manifestations.[3,6,11] Teratology related to unhealthy mitochondria organelle low-oxygen levels affect an evolving cell and can make a difference between a healthy child or their inheriting chronic illness or a serious disease, having lifelong consequences for the child and the family caregivers.

Mitochondrial disease cannot be cured, and mutated mtDNA results in 25%–30% of mitochondrial disease.[7,12] It is estimated that 1 in 2,000 children in the United States will be born with or eventually develop an inherited disease that is caused by unhealthy mitochondria passed on by the mother. Cytoplasmic replacement, or replacing unhealthy mitochondria in the mother's egg with the healthy mitochondria of a female donor, effectively 'eugenizes' the unhealthy mitochondria and eliminates whatever inherited illness *only* the mother would pass on.[1,2] It is important to note that the 3rd person's donated mtDNA is not responsible for the characteristics of the child; for example, the child's hair and eye color and bodily appearance are their biological parent's characteristics because the mother's nucleus is not touched by the transfer of unhealthy mitochondria with the donor's healthy organelles.[1,4]

What is the chance that other siblings will be affected if the mitochondria are not replaced?

Autosomal inheritance involves the 22 pairs of chromosomes not concerned with determining the sex of a child. If a gene trait is *recessive* (one gene from each parent), often no other family members will appear to be affected; although, there is a 25% chance of the trait occurring in other siblings. If a gene trait is *dominant* (one gene from either parent), often the disease will occur in other family members; there is a 50% chance of the trait occurring in other siblings, the symptoms being either more or less severe, or the disease not developing until later in life, such as with type 2 diabetes or Parkinson's disease. Moreover, some siblings are more afflicted than others. The possibility of mitochondrial toxins can also cause acquired warning signs, and overall the prognosis of mitochondrial diseases is unpredictable and, as stated above, there is no cure.[3,6,11,12]

How are mitochondrial chronic illnesses and/or diseases diagnosed?

Diagnostic assessment is done by a system that is represented by one (or more) of the following three categories:[6,12]

1. *Metabolic testing*: Urine profiles, blood protein oxidative phosphorylation (OXPHOS), and adenosine triphosphate (ATP) processing. Through these molecules and processes, mitochondria turn the food we eat into energy to be utilized by major organs. OXPHOS, however, is not currently considered as adequate for diagnosis on its own.
2. *Muscle and liver tissue pathology*.
3. *Genetic testing*: mtDNA, nuclear DNA.

Criteria categorization of diagnosis

Possible

For the three tests described above, one is abnormal and the other two are normal or equivocal.

Highly probable

Greater than two tests are abnormal.[6,12]

It is important that the patient be evaluated by a physician who is experienced in mitochondrial diseases or syndromes, particularly if there is a recognizable clinical syndrome. *See web list of mitochondrial medicine specialists across the country.*[12]

What are the treatments for mitochondrial disease?

A ketogenic diet is suggested for patients with lower severity disease. Arginine, a supplement which increases nitric oxide production and results in vasodilation during resistance exercise therapy, has not been as effective as was hoped. Symptom management is appropriate for problems as they arise, such as seizures, diabetes mellitus and cardiac conditions, but the mitochondrial disease itself is unchanged.[6,12] The newly developed EPI-743 is a medication that could benefit children with a variety of mitochondrial diseases, and the manufacturer Edison Pharmaceuticals has entered into a partnership with Dainippon Sumitomo Pharma Co., Ltd of Japan to join in research for pediatric mitochondrial diseases, beginning with EPI-743.

How is donor replacement accomplished in 3-person IVF?

Mitochondrial donor replacement goes by several names: nuclear genome transfer, cytoplasmic transfer, and genetic modification of mitochondria organelles.[10] Replacing the unhealthy mitochondria with healthy mitochondria of a donor is effective to exclude the possibility of a mother passing on inherited disease or chronic illness related to the organelle's genome. The tiny mtDNA organelles, thousands in each cell, are the 'powerhouse', or the batteries, that send proteins and energy to the nucleus of each cell; by replacing the mother's unhealthy mitochondrial enzyme with a 3rd person female's healthy mitochondrial enzyme, the inherited disease genes are eliminated from the process.[1,3,6,11,13]

There are five stages of 3-person IVF. If at stage 4, multiple

embryos have developed, a single cell is removed from each and screened for genetic disorders, allowing the parents to implant only those embryos free of genetically-carried disease.[1,3,6,8,10,14,15]

Probable risks: physically, emotionally and ethically

Research in embryonic extension anticipates preventing birth defects and advancing prenatal care. One question of concern is: are there higher rates of disease in IVF children? Although, in 2016, IVF has matured to a point that it is now considered an accepted and common alternative to a couple's inability to conceive 'naturally', emotional and physical preparation is paramount for the parents and for a mitochondria donor in a case where the IVF would be a 3-person procedure. IVF may not be successful in either a 2-person or potential 3-person technique.[1,3,8,9,12]

In the United States, the FDA has not yet approved mitochondria cytoplasmic transfer, and the regulatory agency is holding off until more is known about the safety. A non-profit enterprise called *Mothers for a Human Future* cautions "awareness, advocacy, and activism about human biotechnologies that could alter the human species". Founder and Director, Enola G. Airds, in a letter dated 10/17/2013, urged the FDA to reject the request to allow clinical trials on germline mitochondrial techniques. Among the objections she lists are questions of ethical, social and legal concerns. Additionally, there is a concern that 'designer babies' could be the goal of some potential parents.[10,16,17] James Watson, co-discoverer of the DNA structure, had expressed to pioneer colleague Robert Edwards that he is not completely against IVF but "infanticide could occur"; coordinately, he asked, "…and what are we going to do with the mistakes?".[2]

Paramount to the parents investigating IVF is informed consent and verbal understanding of the drawbacks. Physical health side-effects, emotional disappointment and ethical considerations are major counseling issues, including their legal implications.[1,9,10,16–21] With 3-person IVF on the forefront, these issues become more complicated.[9,17,21] For some, the desire to have a family is so overwhelming that the risks of IVF to health and partnership are often met with selective hearing or even discounting that the embryos could ever be a source of division between the couple themselves or the donor. Several states have policies in place to protect the IVF child and parents, but these are based on the 2-person IVF and a clinic's policies. All states do not share common legal policies, and such is the case in foreign countries.

Common health risks of IVF include bleeding, infection, damage to bowel or bladder, possible multiple pregnancies, premature delivery, low birth weight and unsuccessful development of viable, even in cases of successful IVF. An additional significant concern is the great expense of IVF, currently at $12,000–$17,000 per one cycle in the United States. Success also depends on a diverse array of factors, including reproductive history, maternal age, cause of infertility and lifestyle factors. And, ultimately, pregnancy rates from IVF are not the same as live birth rates.[18,19]

Parentage and embryo outlook: legal issues

In the case of multiple embryos, a key question is: what do we do with the unused embryos?[2,18] There is the option of embryo banks using cryopreservation (freezing) until a carrier is found through charitable organizations. A childless couple can legally adopt the embryos for their own IVF procedure (this is another means of 3rd party reproduction). The couple or, in today's society, the single person who chooses to give up the additional, unused embryos releases all rights to them or any child issuing from the IVF and will have no knowledge of the new parents.[18,19] There have already been several legal battles between partners to have or refuse to give custody of unused embryos, and 3-person IVF will further engage legal parameters.

Summary

The adage of "no risk, no gain" may apply to IVF. Indeed, science itself would not have advanced if risks had not been taken. Medical "miracles" like penicillin and vaccines, such as those to prevent polio, bacterial meningitis, measles, pertussis, chickenpox, shingles, pneumonia, tetanus and hepatitis, would not have been developed without the pioneering scientists and research efforts that included challenge in monitored trials on humans. IVF was once a medical and societal storm, until Louise Brown's creation in a 'test tube' led to a healthy birth and, so far, a healthy life. It is estimated that in the United States 2,000 births a year are the result of IVF, making a family unit possible for childless partners.

As we look at fertility options since Louise Brown's birth, it has taken 37 years for any significant advancement. Healthy mitochondrial cells transferred during IVF can be the future of healthy generations, eliminating many inherited chronic conditions and diseases.[1,2] In the United States, the controversy surrounding the pros and cons of this, however, continues to be debated in scientific and societal conversations.

Question

If, in the next few decades, research scientists could ensure the purging of many inherited chronic and serious diseases through healthy donor mtDNA transfer, can we afford to *not* proceed?

Conflict of interest

The author has no conflict of interests related to this publication.

Author contributions

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