Mitochondrial therapy—More than “three parent” babies—Stalls in ethical battle

The idea of replacing disease-causing DNA with healthy genetic material—gene therapy—has been a popular one over the years. However, a version of this therapy involving mitochondria—the energy-producing “furnaces” of our cells—has run into stumbling blocks.

One problem facing the therapy is that media organizations and others have picked up on “three parent IVF,” in which, rather incorrectly, proposes that three whole people would contribute their genes to a single offspring. According to a BBC article in 2015:

> The UK has now become the first country to approve laws to allow the creation of babies from three people.
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> The modified version of IVF has passed its final legislative obstacle after being approved by the House of Lords. The fertility regulator will now decide how to license the procedure to prevent babies inheriting deadly genetic diseases. The first baby could be born as early as 2016.A large majority of MPs in the House of Commons approved “three-person babies” earlier this month.

But the “third person” really isn’t a person. And the therapy could be used without justifying fears of eugenics and creation of a genetically different human being.

Your cellular furnace

First, what are mitochondria? They are small components of cells known as organelles (there are other organelles, like the endoplasmic reticulum and the cell nucleus). Mitochondria are rod-shaped and have a double membrane, and act as the energy-producing and respiration center of a cell. Biochemical processes that convert oxygen and nutrients into energy-containing ATP (adenosine triphosphate) make their home in mitochondria.

Until the 1980s, scientists assumed that they understood how mitochondria functioned. Then, in 1988, Douglas Wallace at Emory University (now at the Children’s Hospital of Philadelphia) found that mitochondria didn’t just have its own DNA but that mutations in this DNA contributed to human disease.

About one in 5,000 people (others estimate between 30,000 and 60,000 Americans) have a mitochondrial disease. These are largely inherited disorders, and symptoms can include strokes, seizures, muscle weakness and fatigue, problems with movement, heart problems, vision and hearing loss and developmental issues. In addition, Wallace and others have started to find connections between mitochondrial functions and more common diseases like diabetes, Parkinson’s, Alzheimer’s and Huntington diseases, hearing loss, liver and kidney disease, and some cancers. Therefore, there’s a growing field of study focusing on the role of mitochondria in rare as well as common disorders that goes way beyond the “three-parent child.”

The unique world of mitochondrial genetics

For mitochondrial replacement therapies, an unfertilized (oocyte) or fertilized egg (zygote) has its intended mother's mitochondria replaced. The new mitochondria, from a separate female donor, would have mitochondrial DNA that doesn't have the pathogenic mutation in the original mitochondria. The children born from this would still only have nuclear DNA of his/her mother and father, but, as the BBC article we mentioned stated, there would be mitochondrial DNA from the "other" mother, amounting to about 0.1 percent of the newborn's total DNA. Not quite the same thing as "three parents." In addition, mitochondrial DNA is not distributed evenly like nuclear DNA. So, a mother may have some cells with mutated mitochondrial DNA, and other cells with none of the mutations.

Ethical implications pitted against life-saving uncertainty

The UK was the first nation to allow clinical testing of mitochondrial replacement therapy. But it is not certain if the therapy even works, so scientists, church leaders, and governments are approaching the technique cautiously. Researchers from the Children's Hospital of Philadelphia and other sites estimate that the technique probably won't be 100 percent effective at ridding the newborn of mutated mitochondrial DNA, but hypothesize that the remaining 1 to 2 percent mutated DNA remaining won't present a disease threat.

Some worry that the technique will open the door to eugenics, and enable a deliberate design of humans with "superior" traits based on changes in mitochondrial function. Others, including the Church of England and the Roman Catholic Church, have concerns that extend beyond efficacy and safety. The Right Reverend John Sherrington, a Roman Catholic bishop in Britain, told the BBC:

> No other country has allowed this procedure and the international scientific community is not convinced that the procedure is safe and effective. There are also serious ethical objections to this procedure, which involves the destruction of human embryos as part of the process.

Since the Right Reverend's comments, another country has moved in the direction of testing on mitochondrial DNA transfer: the United States. Earlier this year, the Institute of Medicine issued a report also advising caution, but advising the Food and Drug Administration (FDA), which is responsible for approving this and other clinical trials, to allow clinical testing in the field. But the IOM had a few caveats comprising its "slow cautious approach": only studying mitochondrial transfers to male embryos (since males do not transmit mitochondrial DNA to children, it gets passed solely through a maternal line). In addition, IOM urged researchers to share all research data with volunteer and patient participants in the trial, and make the novelty (and attendant risks) clear to them.

However, while the IOM was making what appeared to be a narrow gateway to continued research, the White House took a more contradictory step. Around the same time, President Obama signed an appropriations bill into law that prohibited the FDA from considering trials involving mitochondrial transfer therapy. In a June letter to the *Journal of the American Medical Association*, Eli Adashi, former dean of medicine at Brown University, and Harvard Law professor Glenn Cohen warned that "One big step

forward was taken by the IOM report. However, two steps back were taken with the enactment of a policy rider which precludes the FDA from further consideration of MRT." As of now, this means such research is at a standstill in the United States.

For now, the greatest benefit of this therapy is for mothers who may have mutated mitochondrial DNA which can be passed on to create serious, often fatal diseases to their children. Still more research may show a wider influence of mitochondrial DNA mutations. It remains to be seen if this technique will be sequestered in caution, or, as an article in the New England Journal of Medicine phrased it: "may be the poster child for highly targeted, personalized medicine."

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