CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor***Mitochondrial Replacement in the Clinic**

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Legislation passed by the House of Lords in 2015 enabled the performance of mitochondrial replacement in the United Kingdom for the prevention of severe mitochondrial diseases. The regulation of this procedure was delegated to the Human Fertilisation and Embryology Authority, which granted its first license to Newcastle upon Tyne Hospitals NHS Foundation Trust in 2017. Mitochondrial transfer (or “babies with three parents,” as it was known in the lay press) is now a nationally commissioned NHS service in England and Wales. In 2016, it was reported that a woman gave birth to a healthy boy in Mexico after oocyte spindle transfer to prevent the inheritance of a mitochondrial DNA (mtDNA) disorder.¹ Of particular concern, however, is that the technique has become available for the treatment of infertility at many fertility centers worldwide.²

Mitochondrial transfer refers to a number of techniques designed to move mitochondria from one cell to another. These techniques involve moving cytoplasm (including mitochondria) from a donor to a recipient oocyte or embryo. The transfer is typically made by adding or exchanging a small proportion of the total cytoplasmic volume, a procedure that has been proposed as a treatment for age-related infertility. A more extreme form of mitochondrial transfer involves exchanging as much of the cytoplasm as is possible. Such a procedure has been developed as a treatment to prevent the transmission of maternally inherited mtDNA diseases. In practice, this process is achieved by removing either pronuclei or nuclear spindles and placing them into a donor embryo or oocyte (Fig. 1).

Transferring donor cytoplasm to the ovum of a would-be mother to treat female infertility is not new, but the evidence linking age-related mitochondrial dysfunction with infertility is largely circumstantial. It is not clear that mitochondrial defects that are seen in the oocytes obtained from older women contribute to a risk of infertility or whether they are simply incidental col-

lateral damage of the aging process. Moreover, it is not known whether the transfer of mitochondria alone improves fertility. The reported benefits, if real, could be due to the transfer of other cytoplasmic contents that inevitably accompany any form of mitochondrial replacement. These concerns underpin the recent moratorium proposed by the European Society of Human Reproduction and Embryology (ESHRE) on the basis of the recommendation of an expert panel, which concluded that “the application of spindle transfer as a remedy for fertility treatment remains vague and unproven.”

The panel also made a statement about safety: “At the present stage, and until this technology has been proven to be effective and safe, ESHRE strongly discourages the use of mitochondrial donation to alleviate an infertility condition.” The position statement drew attention to the emerging evidence of an interplay between mitochondria and the cell nucleus² and highlighted the possibility of sequelae. Should concern about sequelae inform our position on mitochondrial transfer overall, including its application to prevent rare inherited mtDNA diseases? After all, a prospective mother harboring a disease-causing mtDNA mutation is just as likely to want a healthy child as a mother with infertility.

Before 2015, the limited evidence that mitochondrial transfer might have adverse effects was based on experimental work studying inbred laboratory flies and mice, in which the lack of genetic admixture creates a strikingly different scenario from that in the outbred human population. In humans, mtDNA and nuclear DNA appear to exchange and mix freely without detriment. However, three laboratories have seen unanticipated reversion back to the original mtDNA genotype in approximately 15% of embryonic stem-cell clones derived from human embryos after mitochondrial transfer. These reversions have included a severe pathogenic mtDNA mutation that causes the Leigh syndrome, a neuro-

A Pronuclear Transfer for the Prevention of Mitochondrial Disease

B Maternal Spindle Transfer for the Prevention of Mitochondrial Disease

C "Treatment" for Infertility

Figure 1 (facing page). Principles of Mitochondrial Transfer.

A prospective mother carrying a pathogenic mitochondrial DNA (mtDNA) mutation can be offered mitochondrial transfer to reduce the risks of having a child affected by mtDNA disease. Two approaches have been used: pronuclear transfer (Panel A) and spindle transfer (Panel B), which allow the nuclear genome to be transferred to a donor zygote or oocyte containing mitochondria without the mtDNA mutation. A similar approach has been offered to women with infertility in the hope of improving their chance of having a child through mitochondrial transfer to unfertilized oocytes. Early work in this field involved the transfer of cytoplasm from a healthy young donor to oocytes that had been obtained from a prospective mother with age-related infertility. More recently, spindle transfer has been used to transfer the nuclear DNA from an older mother's oocyte to an enucleated donor oocyte before in vitro fertilization (Panel C).

logic disorder that is usually diagnosed in the first years of life.³⁻⁵ The risk of reversion can be mitigated with the use of conventional diagnostic techniques both before and after implantation, but the reasons for the reversion are not known. There is now evidence that mitochondria are not simply cellular “power packs” that can be exchanged when they are exhausted. In mice, swapping the mtDNA between healthy, albeit inbred, laboratory strains has resulted in mismatching between the nuclear and mitochondrial genomes, which do not naturally coexist in the same strain. Such mismatching can lead to cardiometabolic phenotypes that emerge in the mice only in old age.⁵ That said, the apparent health of several monkeys born with the use of the technique provides some reassurance.

For the treatment of infertility, there is no objective evidence that mitochondrial transfer is effective, so it should not be used in routine clinical practice. And if there are uncertainties about side effects, would a clinical trial ever be ethically acceptable? As is often the case in medicine, new treatments are tested first in more severe diseases. Could the test case be mitochondrial disorders? Unlike mitochondrial transfer for infertility treatment, the use of the technique for the prevention of mitochondrial disorders has a clear scientific rationale underpinning its likely benefits, but what about the risks? The argument that is usually presented is that the risk of causing a severe, incurable mtDNA disease counterbalances the theoretical risks of the experimental treatment. However, preventing mitochondrial disease is not the same as treating mitochondrial disease. Before the initiation of mitochondrial transfer, there is no child. The risks to the child are generated by initiating the treatment itself, and the primary benefit is to give prospective parents the choice of having a child who shares their nuclear genome and does not carry a pathogenic mtDNA mutation.

In the United Kingdom, the Human Fertilisation and Embryology Authority has wisely stipulated the need for the long-term monitoring of health outcomes for any child born as a result of mitochondrial transfer. Because the hypothetical side effects could take years if not decades to emerge,⁶ complete reassurance will take some time. The reason why it is currently acceptable to offer mitochondrial transfer in one context and not in the other hinges solely on the scientific rationale for the procedure and not on the risk of side effects. In the event that mechanism-based benefits of mitochondrial transfer for the treatment of infertility can be established, it would be reasonable to consider a clinical trial of mitochondrial transfer for infertility when all other options have failed. Until such a trial has been carried out, treatment centers offering this procedure today as a routine clinical service should cease to do so, and physicians should warn patients about the lack of proven benefit.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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