Mitochondria Transplantation: Why?

To the Editors:

Mitochondria transplantation, i.e., mitochondria donation, is one of the most current topics in reproductive biology. For many years scientists have focused on the acquisition of genetic material from an organism's own parents—i.e., "vertical transfer"—and have made progress in treatment of familial genetic diseases and associated genes. However, horizontal transfer recently has been recognized as a significant concept. Horizontal gene transfer (HGT), also known as lateral gene transfer, is defined as any process that results in the acquisition of a genetic material of a second organism without being reproduced from the organism. The transfer of the second genetic data implies the presence of 3 different genetic structures in the bearing cell, which in turn corresponds to offspring with 3 parents.

One of the major causes underlying the popularity of HGT is the desire to increase the high fertility rate in the field of reproductive biology. Another reason is to prevent the natural transfer of mitochondrial-inherited diseases in order to be able to give birth to healthier individuals. How to achieve high pregnancy rates is the main challenge that we are facing today in assisted reproductive technology (ART). Gross embryo morphology is one of the most reliable markers of embryo viability.[1] The correlation between blastomere uniformity and a positive outcome of intracytoplasmic sperm injection (ICSI) procedures is well established. Zonal thickness, presence of multinuclear blastomeres, formation of polar bodies, and, most important, cytoplasmic factors (such as mitochondria) that are known as intrinsic factors play significant roles during oocyte maturation and the early development of fertilization.[2]

The mitochondria are major subcellular organs in the cytoplasm, and mitochondria account for 23% of the cytoplasm in the preimplantation human embryo. Mitochondria are maternally inherited organelles that use oxidative phosphorylation to supply adenosine triphosphate (ATP) to the cell. Unlike other organelles, which are produced via transcription and translation of nuclear chromosomal DNA, the genetic information for mitochondria is contained within the organelle itself. Mitochondrial DNA (mtDNA) is a double-stranded, circular DNA molecule of approximately 16.5 kb in all mammals in which it has been sequenced.[3] The mitochondrial genome is transferred between generations according to the principles of vertical transfer and only through the oocyte cytoplasm. It does not show Mendelian inheritance. The mtDNA in the ovum is transferred to offspring of both genders. The minute amount of mtDNA in the sperm cannot be transferred to the next generation. Thus, each individual's mtDNA is completely inherited from the mother.[4]

Mitochondria divide with binary fission, and within a cell all mitochondrial chromosomes generally bear identical copies of the mtDNA (homoplasmy). mtDNA is vulnerable to the harmful effects of reactive oxygen species due to its localization in the mitochondrial matrix and the lack of histone proteins and intronic sequences.[5] The mutation rate in mtDNA is approximately 20-fold higher as compared to nuclear DNA.[4] When exposed to oxidative stress, point mutations and deletions occur in mtDNA over time. Both single-cell and hybrid cell studies indicate that mutant mtDNA needs to exceed a critical threshold level (threshold effect) in order to result in a biochemical anomaly in the cellular mitochondrial respiration chain.[6] Depending on the number of mtDNA mutations, deletions increase with age. With respect to fertility there is a correlation between maternal age and the rate of mtDNA deletion in human oocytes and granulosa cells.[7] The sensitive nature of mitochondrial DNA to reactive oxygen radicals decreases the success of ART in advanced ages. The presence of healthy and mutant mtDNAs in the same oocyte—i.e., heteroplasmy—is a challenging situation to eliminate. Therefore, mitochondria transplantation (even if the mitochondrial genetic sequence in the oocyte is healthy) becomes questionable. The reflection of this situation in social life is the induction of a sensational reaction that a "youth vaccine" is discovered. The trend towards marriage and childbearing at older ages results in mitochondria being exposed to more oxidative stress and decreased ovarian reserves, thus leading to a natural decrease in the live birth rate with ART.

Following oocyte mitochondria transplantation via HGT+ICSI, the individual starts to carry the genetic information and characteristics of a third individual, before the transfer of the embryo to

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the uterus. Currently, a serious debate exists in the United Kingdom (U.K.) about how children conceived by this method would feel, when to tell those children the facts about their conception, potential effects on parents, and the status of women who would donate their mitochondria. The current concerns about the safety of the technique have not yet been overcome. Additionally, serious objections have been directed towards this method, as it could lead to genetically modified "designer babies."

Another consideration is the potential need for treatment for a great number of diseases that may develop as a result of vertical transfer of mitochondrial genome because inherited mutations in mtDNA are important causes of genetic diseases for which there is no effective treatment. Mitochondrial hereditary diseases include chronic progressive external ophthalmoplegia; Kearns-Sayre syndrome; mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS syndrome); myoclonic epilepsy with ragged red fibers (MERRF); neuropathy, ataxia, and retinitis pigmentosa syndrome (NARP); and Leber's hereditary optic neuropathy (LHON). The main functions of mitochondria include oxidative phosphorylation and ATP production (cellular energy source). Thus, systems with a high energy requirement, such as the skeletal system and central nervous system, are more affected.[8]

Familial inheritance of mitochondrial mutagenic genes is a major health problem; yet, the main concern of scientists is to predict how many women who use ART would benefit from mitochondria transplantation, and to develop strategies in this field. It is natural that this calculation depends on the prevalence of clinically relevant pathogenic mtDNA mutations in the population and the fertility of women with pathogenic mtDNA mutations. The Medical Research Council (MRC) of the U.K. has evaluated the data obtained from the Mitochondrial Disease Cohort. By using the fertility data on live births (1,000 individuals/year) of women >15 years old, they have investigated whether or not the fertility rate of carriers of pathogenic mtDNA mutations is affected as compared to the general population. The MRC has identified 154 women with inherited mutations in the U.K. and reported that pathological mtDNA mutations do not have a significant effect on female fertility.[9] According to the national fertility rates of the U.S. and the U.K., the mean number of births per women at risk of transferring mtDNA diseases is 152 in the U.K. and 778 in the U.S.[9] These findings are considered to have a significant effect on all countries that are planning to use IVF/ICSI techniques to prevent serious mtDNA diseases. While depending on multiple variables, each country could predict potential mtDNA diseases by considering its fertility rate as a reference. A need for improvement of the technique, potential risks, and unknown aspects of its potential outcomes still represent major problems.

It should be particularly emphasized that the first individuals who would receive mitochondria transplantations are early experimental subjects. In addition, the existence of a high expectation towards the success of mitochondria transplantation should be also considered. In conclusion, scientific, ethical, and legal exit points opposing the potential unfavorable conditions in mitochondria transplantations should be known. In particular, the rights to be incurred after potential legal problems, health problems following mitochondria transplantation, and fatal anomalies are indefinite. Therefore, if there is no "exit strategy" in case something goes wrong, it is best to be cautious towards mitochondrial transplantations. In addition to success and safety, a great number of severe problems exist in the future of mitochondria transplantation, including scientific, ethical, and legal problems.

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