

Mitochondrial Replacement Therapy and Jewish Law

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Mitochondria, energy-producing organelles in cells of the human body, float in the cytoplasm, a liquid substance located externally to the nucleus. The main function of mitochondria is to metabolize sugar and fats and transform them in the process of oxidative phosphorylation into a usable form of cellular energy. The energy produced by this process is stored in the form of the molecule adenosine triphosphate, or ATP. The cellular energy released from hydrolysis of bonds of ATP molecules is subsequently used to power metabolic processes. Since most metabolic processes require an energy input, mitochondria are crucial for sustaining life. There are hundreds to thousands of mitochondria in every cell of the human body [1]. Within each mitochondrion is a circular double stranded DNA, known as mitochondrial DNA (mtDNA), containing 37 genes. These genes are in addition to the 25,000 more commonly discussed genes, which are located on nuclear DNA (nDNA), found on the 23 pairs of chromosomes in the nucleus of a cell. Nuclear DNA determines the traits of a person, such as eye and hair color. Mitochondrial genes, on the other hand, are responsible for the production of enzymes that are crucial for carrying out oxidative phosphorylation, in addition to producing rRNA and tRNA, needed for protein production [2]. Although both eggs and sperm contain nDNA and mtDNA, when a sperm penetrates an egg during fertilization, only the sperm's nDNA enters the egg cell while its mtDNA does not. Therefore, the child produced from the fertilized egg inherits nDNA genes from both of parents but mtDNA only from the mother [3].

Mutations, alterations in DNA that occur spontaneously or that are induced by environmental agents, may be passed on from parent to child. Mutations in nDNA as well as mtDNA can be the cause of many mitochondrial diseases. Mutations in nDNA can affect the maintenance of mtDNA and thereby cause mitochondrial diseases [3]. Mutations in mtDNA can cause diseases as well. The rate of mutation of mtDNA is much higher than the rate of mutation of nDNA. The proportion of damaged mtDNA to undamaged mtDNA is what is significant in determining whether a person will suffer from a mitochondrial disease. Therefore, if a woman carries a small proportion of mutated mtDNA, she is asymptomatic and may therefore be unaware that she is carrying a potential disease. Her offspring, on the other hand, may possibly inherit her mtDNA in different proportions from her and even from each other. They therefore may have various degrees of a mitochondrial disease, that can range from mild to severe, as it is the balance between mutant mitochondria and normal mitochondria that determines the disease outcome [4]. Furthermore, the percentage of mutated mtDNA also determines when symptoms of mtDNA mitochondrial disease will first appear. If a person has a high proportion of mutated mtDNA, symptoms of disease will present themselves early in life. A person with a smaller percentage of abnormal mtDNA may not have the disease or may exhibit a milder form or develop symptoms later in life [5].

Mitochondrial diseases involve a chronic loss of cellular energy. Problems caused by mitochondrial diseases include neurological damage, heart disease, and blindness [6]. Severe forms of mitochondrial disease are very debilitating and some are even lethal. Since mitochondrial diseases are caused by mutations present in every somatic cell, they have no cure. Diseases such as diabetes or external environmental factors can also induce the occurrence and severity of mitochondrial diseases. For example, medications used in chemotherapy can induce mutations in mtDNA. Pollutants, such as tobacco smoke, have also been implicated in causing these mtDNA mutations [5]. In the United States it was estimated that 4,000 children a year are born with mtDNA diseases and few live into adulthood [6]. These diseases affect Jews as well as non-Jews. Some rare mitochondrial diseases have been found to be more prevalent in Ashkenazi Hungarian Jews and in Persian Jews [7].

Researchers are investigating ways to eliminate mtDNA-based diseases. Work is being done on a groundbreaking technique called mitochondrial replacement therapy. This new procedure, which aims to eliminate mutated mtDNA in a fertilized egg cell, involves a woman with mutant mitochondrial genes (woman A), a donor woman with normal mtDNA (woman B), and a father. Woman A is the individual seeking to conceive a child free of mtDNA-based disease. An egg is extracted from the donor woman (woman B) and its nucleus is removed, leaving only an enucleated egg with normal mitochondria. An egg is taken from the woman with the mutated mtDNA (woman A). The nucleus of this egg is then removed and inserted into the enucleated egg of woman B. The resultant egg contains the nDNA of woman A and mtDNA of woman B. This egg, fertilized by the father's sperm, forms a zygote which undergoes a few mitotic divisions and then is implanted into the uterus of woman A. In the United States this procedure was successfully performed on rhesus monkeys in 2009. The monkeys that were born after this procedure appeared normal. In 2012 a human embryo was created with this technology, but was not implanted because the Federal Drug Administration (FDA), the agency which has authority over all reproductive issues, had not, as yet, approved this procedure. The FDA is currently conducting studies on this technology but has not ruled on whether to approve this procedure for the humans [8]. In February 2015 the British House of Commons, as well as the House of Lords, approved this procedure by a wide majority. However, a licensing process must first be drafted which will determine who will be approved for this revolutionary treatment. Each application will then be analyzed and evaluated on its own merits. By 2016, the world may see the first human baby born through mitochondrial replacement therapy [9, 10]. Technically, such a child has three parents: the father, the woman who donated her mtDNA and her cytoplasm, and the woman who donated her nDNA and carried the fetus to term.

Mitochondrial replacement therapy has raised many ethical as well as halachic issues. Some have argued that mixing the DNA of three people is creating a new type of life and therefore should not be done. There is also concern that since all the intricacies of the interactions between nDNA and mtDNA are not fully understood, there could be dire consequences to mixing the genes of two women and the health of the child may be seriously affected. Critics worry whether the child could be altered by using the genetic material from two different women and are concerned about social and legal consequences for the child and society. Additionally, others argue that this type of genetic engineering is a slippery slope that can lead to creating children with specific “designer” character traits. Critics argue that there are other options for women who carry mtDNA mutations. These women can use a donor egg in its entirety and have children free of mitochondrial disease (albeit, in this choice, the mother has no genetic connection to the child) or can use prenatal genetic diagnosis to identify those preembryos with few mtDNA mutations [6, 8, 9].

The halachic problems posed by the implantation of an embryo formed through mitochondrial replacement therapy are similar to those raised with surrogate motherhood and egg donation. Egg donation involves two mothers, the genetic mother and the birth mother. The most important halachic question about egg donation concerns the halachic lineage of a child born using an egg donor. This issue is of the utmost concern because Jewish law defines a Jew as someone who was born to a Jewish mother. The question concerning whether the child is Jewish arises when the birth mother is Jewish and the egg donor is not, or vice versa. A related question concerns future marriage. Jewish law, like secular law, forbids incest, including marriage between brothers and sisters. When the father is not the same, the identity of the mother may determine whether a marriage is allowed or forbidden. There is no explicit Talmudic discussion of whether a birth mother or a genetic mother is considered the halachic mother when the two are different people. If the rabbis of the Talmud ever contemplated such a possibility, their discussions and conclusions were not recorded and are lost to posterity. Not surprisingly, there is no current consensus.

It appears that when this question first arose concerning egg donors, the majority rabbinic opinion was that the birth mother, not the egg donor, determined halachic maternity. Among major halachic authorities who held this view were Rabbi Z.N. Goldberg (Techumin, 5:248-259); Rabbi J.D. Bleich (Chalav Treifah and the definition of maternity, Bnetivot Ba’Halacha, 3:47-48); Rabbi Moshe Sternbuch and Rabbi Moses Soloveitchik [11]; and Rabbi Moshe Tendler [12]. These authorities cited various Midrashic and Talmudic sources as precedent or proof by analogy. A discussion of these sources is outside of the scope of this article. However, none of these sources addressed the issue directly, and some of the sources are used as proof by both sides of the issue. (For an excellent and succinct review see Loike and M. Tendler [14]).

The pendulum has apparently shifted and the current majority view appears to be that the genetic egg donor is the halachic mother. Major halachic authorities holding this revised view include Rabbis Avraham Sherman, Meir Brandsdorfer, Mordechai Halperin, and Yosef Shalom Elyashiv [12]. An early authority favoring this view was Israel’s Chief Rabbi Shlomo Goren [13].

There are other opinions as well. Rabbi Shlomo Zalman Auerbach held that there is no definitive answer and that a stringent view must be taken to erase all doubt (Nishmat Avraham 4:186,2004) and Rabbi Eliezer Waldenberg held that a child born through in vitro fertilization has no legal birth mother (Responsa Tzitz Eleizer 45:15). To my knowledge, nobody holds that both the egg donor and the birth mother as dual mothers (as opposed to just a doubt). However, the case of a half-slave half-free person, i.e. a Canaanite slave freed by one half-owner but not the other, is precedent for a mixed halachic status. Recently, Rabbi Moshe Tendler argued that current research showed that both the genetic and birth mother contribute to the development of the child and that therefore, as a stringency, both must be considered mothers. He proposed that in a case of surrogacy, when a Jewish mother’s egg is used, a non-Jewish surrogate should be used and the child should be converted [14].

The view most favorable to mitochondrial replacement therapy is that the birth mother is the halachic mother. Under this opinion, the Jewish gestational mother is the mother and the use of mitochondria from a donor is irrelevant. However, one cannot ignore the authorities who hold the opposing view concerning egg donors. If we accept, by analogy, that use of another’s mtDNA is equivalent to that of the egg donor, then this leads to uncertainty whether the halachic mother is the woman who donates the mtDNA or the woman who supplies the nDNA. A possible halachic solution, following Rabbi Moshe Tendler’s suggestion, would be to use a non-Jewish mtDNA donor and to convert the child, at least a measure of stringency.

There is one other possible solution. There is a broad halachic principle that mixtures follow the attributes of the majority material in the mixture. Concerning matters of whether an item is permitted or allowed under Jewish law, we go after rov, that is, the majority. The mitochondria donor donates only a very small amount of DNA; of the total cellular DNA, 99.9% of the genetic material comes from the nDNA and only 0.01% from the mtDNA. In addition, the majority influence of the makeup of the child is nDNA [15]. Under the principle that in mixtures we go after rov, the identity of the mother should follow the birth mother, even according to those who hold that in surrogacy the egg donor is the halachic mother. This is, of course, only a suggestion. Ultimately, the major halachic decisors of our time will determine the halacha applied to mitochondrial replacement therapy.

Others have argued that the essence of a person comes from the traits created by the 25,000 genes of the nDNA while only energy production comes from the 37 mitochondrial genes, and therefore the procedure should be allowed since it can eliminate horrendous diseases. Since the 37 mtDNA genes are the energy producers, the “batteries” of the cells, they do not determine the characteristics of a person. Therefore 99.99% of genetic material would still come from the mother and the father and only 0.01% from the mtDNA donor. Mitochondrial replacement therapy would only correct potentially debilitating and fatal diseases. In the case of an egg from a donor, the neither the nDNA nor the mtDNA of the birth mother is transmitted to her offspring. Thus, she has no genetic connection to her child. Proponents of mitochondrial disease therapy argue that the procedure is analogous to a recipient of a

kidney transplant or of a blood transfusion. This therapy allows a woman with many mutant mtDNA to have healthy children and terminates the inheritance of her defective mtDNA from transmission to future generations [15]. Another argument is that prenatal genetic diagnosis would not guarantee healthy offspring, whether now or in future generations, because the proportion of mutant mtDNA in one cell of an embryo can be different from the mutations in other cells. The proportion of mutant mtDNA in a cell will also change with development of a fetus, as well as that of an adult [6].

Although mitochondrial replacement therapy has not been tested in humans, it holds potential for alleviating concerns for those who carry mitochondrial mutations of having children with mtDNA-based diseases. To date, there has been no discussion among poskim as to who would be considered the halachic mother if this procedure is performed. However, with the recent decision of the House of Commons and the House of Lords in Great Britain, the ethical questions surrounding mitochondrial replacement therapy have become more pressing. While mitochondrial replacement therapy theoretically has the potential to help many people, its impact on halachic discourse remains to be seen.

Acknowledgements:

First and foremost I would like to thank my parents for supporting me in my education, as well as in all other areas of my life. I would also like to express my deepest appreciation to Dr. Babich for all the advice and encouragement he has given me throughout my years at Stern.

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