Mitochondrial Replacement Therapy

By **Amanda Rubin**

The first recorded commandment in the Torah appears towards the end of the creation narrative. G-d instructs Adam to "be fruitful and multiply, fill the earth and subdue it" (Genesis 1:28). Jewish tradition considers this as the first of many commandments, or *mitzvot*, that G-d gave the Jewish people. The *gemarah* in *Nida* 31a teaches that there are three individuals involved in the creation of a child: G-d, the father, and the mother. This principle has held true for thousands of years, but the emergence of modern biotechnology challenges this doctrine. As medical innovations continue to arise and combat the challenges of infertility, a new parental model has manifested to include several other figures. Instead of consisting of only three figures, the team necessary to create a child has become much larger, and can now include the doctor, the scientist, and even several donors in addition to the model described by the *gemarah*. While these revolutionary procedures have opened new doors for infertile couples, it has also restructured the prototypical parental model.

In vitro fertilization (IVF) is a revolutionary technique that has changed the lives of those who have had difficulties conceiving. This technique has provided couples who have spent years struggling with infertility with a miraculous solution, allowing them to finally realize their dream of parenthood. Despite its major beneficial contribution to society, IVF has also opened new doors of discussion and conflict within ethical, social, and religious realms.

The process of IVF begins by procuring eggs from the mother and sperm from the father and combining them in a Petri dish, allowing for the egg to be fertilized by the sperm. The fertilized egg, or zygote, is allowed to undergo a few mitotic divisions and is then implanted into uterus of the perspective mother, and after a nine month gestation period, the baby is born [3]. While this appears to be a simple process, numerous complications, both scientific and ethical in nature, arise in light of this new technique and other therapies that have stemmed from IVF.

One such example of a therapy derived from IVF is Mitochondrial Replacement Therapy (MRT), an innovation that combines reproductive medicine with genetic bioengineering. Mitochondria are cellular organelles vital for survival of an organism. Each cell has numerous mitochondria, which serve as the power source of the cell by converting glucose into energy through the process of aerobic cellular respiration. Oxygen is mandatory for this process and a lack of oxygen would prevent the cell from properly converting nutrients to energy and a lack of energy would ultimately result in death [1].

The mitochondria are significant in questions of inheritance because they have their own DNA. The origin of mitochondrial DNA has been linked to an early endosymbiotic relationship between prokaryotes. Over millions of years, a smaller prokaryote, while still retaining its DNA, became completely incorporated into a larger prokaryote, with the smaller prokaryote evolving into a mitochondrion. The mitochondrial genome has important implications in issues of inheritance. When a sperm fertilizes an egg, only its head, which contains its DNA, penetrates into the egg. The middle piece containing paternal mitochondria and the flagella tail do not penetrate the egg [1]. Similar to nuclear chromosomal DNA, mitochondrial DNA is subject to mutation. In the United States alone, about 12,000 women have genetic mutations of their mitochondrial DNA. These mutations have been linked to numerous mitochondrial diseases including heart disease, liver disease, muscular dystrophy, respiratory problems, and sometimes death [2]. Mitochondrial mutations tend to affect tissues that have the highest metabolic demands. There are no curative treatments currently available to treat mitochondrial diseases and without medical intervention, all children born to a woman with a mutated mitochondrial genome may inherit this genetic aberration [5].

Mitochondrial Replacement Therapy was designed to prevent children from inheriting these devastating diseases arising from defective mitochondrial DNA. The accepted protocol, known as spindle nuclear transfer, allows for the replacement of all defected mitochondria in the zygote. The mother's egg is first fertilized with the father's sperm. Before the zygote has a chance to divide, the fertilized egg is enucleated. This isolated nucleus is implanted into a donor cytoplasm from an enucleated egg of a healthy woman. The modified zygote is then implanted into the mother who carries it full term. These genetically modified embryos are born of three parents: the original couple who contributed to the child's nuclear DNA and the cytoplasmic donor who contributed her mitochondria and consequentially her mitochondrial DNA [1].

It is important to note that this procedure is no longer within the sphere of possibility, but rather has reached the realm of actuality. In April 2016, the first child was successfully conceived using the spindle-transfer technique by researchers at the New Hope Fertility Center in New York City. The baby boy was born to Jordanian parents who sought medical help after previously losing two children. The mother was a carrier for a rare mitochondrial disease called Leigh syndrome, which is a neurological disorder [4]. This birth provided the validity of MRT as a legitimate treatment to infertility resulting from mitochondrial diseases and opens the floodgates to numerous questions concerning its implications.

Issues arising from Jewish Law, or *halakha*, have emerged as a result of MRT and the resulting three parent model of inheritance. *Halakhic* authorities originally questioned whether the mitochondrial DNA donor had any significant parental status. Much debate emerged concerning the importance of the donor mitochondria within the genetic development of the child, for as discussed above, mitochondria contain their own unique DNA. However, many questioned the true weight of the donor's contribution because the mitochondrial DNA only contributes 37 genes of the approximately 20,000 present in the human genome. Despite this, authorities concluded that it is a question of quality and not quantity. Without these mitochondrial genes the embryo cannot develop, and so the third donor does maintain a position of consequence [2].

The authoritative conclusion to give the mitochondrial donor the status of motherhood brings in several important questions regarding the child's standing in *halakha*. Firstly, Judaism is transmitted through the mother, and so if the donor of mitochondrial DNA is not Jewish how does that affect the child's status? Is it enough for just one DNA donor to be Jewish? Furthermore, *halakha* has specific prohibitions against marrying family members. Is this child allowed to marry a direct family member of his or her mitochondrial DNA donor? [2].

Additionally, these issues of maternity can be applied to ethical and legal questions as well. What is the parental status of the mitochondrial donor if she one day decides to claim custody? In the event of a sudden and tragic death of the child's parents, is his or her mitochondrial DNA donor considered the next of kin? Many ethicists are also concerned that this MRT may be used for non-therapeutic purposes such as genetic enhancement of an offspring. Many worry that this pursuit of genetic superiority will allow humanity to "play God" [6]. This issue of inherited status plays a critical role in understanding a new onslaught of both ethical and *halakhic* questions that have arisen in response to IVF and its related therapies.

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