Mitochondria are present in all human cells and vary in number from a few tens to many thousands. As they generate the majority of a cell’s energy supply which power every part of our body, and hence, their number varies in different cells as per the energy requirement of the cell. Mitochondria have their own separate DNA, which carries total 13 genes. All of these 13 genes are involved in energy production. For normal functioning of cells, the mitochondria need to be healthy. Unhealthy mitochondria can cause severe medical disorders known as mitochondrial disease. In case of mitochondrial disease, the most commonly affected organs are the heart, kidney, skeletal muscle, and brain. The diseases related to defects in these organs are quite prevalent in the society. Majority of these mitochondrial diseases are caused by genetic defects (mutations) in the mitochondrial DNA. Unlike nuclear genes, mitochondrial DNA is inherited only from our mother. Mothers can carry abnormal mitochondria and be at risk of passing on the serious disease to their children, even if they themselves show only mild or no symptoms. Due to the complex nature of these diseases, their diagnosis and therapy are very difficult. Hence, till now, only the different methods for management of these diseases are known. However, after understanding the complexity related to the cure of these diseases, alternative methods have been developed to minimize/stop the transfer of mitochondrial diseases from mother to offspring. This latest technique is called mitochondrial replacement or “donation.”

In the present review, we are discussing the methodological details and issues related to the technique of mitochondrial donation. Our study is also a step toward raising awareness about mitochondrial diseases and advocating for the legalization of mitochondrial donation, a revolutionary in vitro fertilization technique.

**Keywords:** Diseases, donation, issues, mitochondria

**Introduction**

Mitochondria are double-membraned cell organelles present in nucleated mammalian cells in large numbers. These are involved in the adenosine triphosphate (ATP) generation of the cell through the oxidative phosphorylation (OXPHOS). Mitochondrial production of ATP by OXPHOS occurs in virtually every cell of the body and the number of mitochondria per cell varies. Every cell has 100–1000 mitochondria, and this variation in copy number, depends on the energy requirement of the type of organ. The organs, which require high energy for their proper function, such as heart, kidney, brain, and skeletal muscles, commonly have a higher number of mitochondria to cope with the increased energy requirement. Therefore, deficits in mitochondrial function are likely to be experienced differently throughout the body, with the potential for multi-tissue/organ involvement. Further, each mitochondrion contains its own specific DNA, and its number is 2–10 copies of DNA per mitochondria. Mitochondrial DNA (mtDNA) has 37 genes and code for
13 polypeptides which are an integral part of OXPHOS system.[2] Unlike nuclear DNA, mtDNA is a naked DNA and pretty close to the site of production of reactive oxygen species, hence suffers through high mutation rate. Since the mtDNA copy number is quite variable and higher in number, hence mtDNA may exist in heteroplasmic conditions, that is, wild-type and mutated copy of mtDNA may coexist in a cell, at the same time cell can compensate for reduced wild-type mtDNA.[3] The effect of these mutations is not phenotypically visible until a certain threshold is met.[4] The threshold depends on nature of mutation and cell types as well. For example, neurons have a lower threshold for the disease state. In terms of its genetics, all the mitochondrial content is strictly inherited from the maternal oocyte, hence mutations in the mtDNA of oocyte may be inherited to the offspring.

Mitochondrial Diseases and Their Cure

Mutations in mtDNA, either alone or in conjunction with certain nuclear DNA mutations, can result in serious disorders. Diseases caused by mutations in mtDNA were first described in 1988. Since then over 700 mutations, both germline and somatic, have been identified, some of which have been associated with human disorders including myopathies, neurodegenerative diseases, diabetes, cancer, and infertility.[5-7]

Most of these mitochondria diseases are quite severe and life-threatening. Some common mitochondrial diseases are mitochondrial myopathy, encephalomyopathy, lactic acidosis, stroke-like symptoms (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), myoneuropenetic gastrointestinal encephalopathy (MNGIE), neuropathy, ataxia, retinitis pigmentosa, and ptosis, Leigh syndrome, Leber’s hereditary optic neuropathy, and diabetes mellitus and deafness.[7,8] Due to the involvement of different organs, mitochondrial diseases exhibit phenotypic heterogeneity. These diseases have also shown very common overlapping clinical features with other nonmitochondrial diseases. This is the reason, mitochondrial diseases are often difficult to diagnose. Further, multiple copy numbers of mtDNA, its heteroplasmic condition in patients and variable threshold effects, create a challenge for the development of strategies for the cure of these diseases.[4] In the absence of efficient treatment methods, the clinical phenotypes of mitochondrial diseases are just managed by different approaches. Even the management was possible due to two main therapies, involving exercise therapy and gene therapy. Exercise therapy aims at improving the overall fitness and quality of life in patients who have high levels of heteroplasmy in the muscle’s mtDNA by improving OXPHOS functioning. As per studies, exercise can be used to improve the quality of life of the patients suffering from mitochondrial disease only but cannot treat the disease completely.[1,6,9,10]

Gene therapy, on the other hand, aims at creating a shift from mutant to wild-type mtDNA through different approaches such as antigenomic therapy and finally manipulating the expression of these biochemical defects.[61] Expression of wild or mutant genes is critical in determining the extent or presence of the disease. Hence, by inhibiting the expression of mutant varieties, some reduction in diseases can be observed. In some cases, gene therapy also targets the regulatory genes present in the nuclear genome which codes for polypeptides, utilized by the mitochondria.[12,13]

However, in certain conditions (such as MELAS, MERRF, and MNGIE), even the management of such patients is also very expensive as it needs a lot of medical attention.[14-16] Thus, the management of mitochondrial diseases is not possible to be afforded by everyone in need. Due to the lack of any foolproof technique that can cure or eradicate mitochondrial diseases altogether, a need for a permanent solution still remains a necessity. Hence, with these limitations, in the present condition to develop a method which controls the transfer of “faulty” mitochondrial from mother to child will be a smart approach. Reproductive technologies designed to uncouple the inheritance of mtDNA from nuclear DNA may enable affected women to have a genetically related child with a greatly reduced risk of mtDNA disease.

In an attempt to reduce the load of mutant mitochondria in growing fetus, previously, a technique called preimplantation of genetic diagnosis (PGD) has been employed for patients with high levels of mutant mitochondrial DNA.[17-19] This technique analyzes embryos produced by in vitro fertilization (IVF) techniques and only transfers those embryos to the mother, who has low risk of mutant mtDNA. PGD is performed at a very early stage in development and (from an embryo containing 6–10 cells) considered representatives of the whole embryo. PGD is generally followed by chorionic villus sampling (before 15 weeks) for a more confident result.[4] PGD is possible for mitochondrial diseases resulting from mutations occurring in the nuclear DNA (responsible for 80% of mitochondrial diseases).[20] However, due to the number of genes responsible for the mitochondrial function being large, the accuracy of PGD is only for known causative mutations. For diseases caused due to mutations in mitochondrial DNA, the risk of embryos being affected is very high due to the maternal inheritance of mitochondria.[21] In 2014, panels concluded that girls produced after PGD with a reduced
mitDNA load may still be at risk of carrying affected oocytes (with mutant mitochondria). Furthermore, due to limitations in assessing the extent of heteroplasmy in mtDNA and predicting the risks accurately, the genetic counseling of patients is challenging. The patients have to deal with the grief of losing a child and terminating pregnancy, if the results are positive for diseases. To avoid these conditions, there is a need to generate a better alternative approach to prevent the transmission of mitochondrial diseases. Recently, a new technique named mitochondrial donation has been developed as an alternative of PGD in the United Kingdom (2015).

**Mitochondrial Donation**

In contrast to the previous approach (PGD), instead of trying to reduce the risk of occurrence of mitochondrial disease, this technique of mitochondrial donation focuses at eliminating the risk of mitochondrial diseases altogether from the oocyte or the fertilized egg. It is possible due to replacement of all the mitochondrial content of diseases mother’s oocyte with a healthy female’s oocyte, that is, if the mitochondria could be donated by a healthy oocyte to the diseased oocyte. This method is called mitochondrial donation technique (sometimes called mitochondrial manipulation technology or MMT). This is a special form of IVF, in which the mitochondrial DNA of the future baby comes from a third party. This technique is used in cases when mothers carry genetic mitochondrial diseases, and conventional IVF techniques do not work. What this implies is that a baby is being produced with the DNA of both parents, as well as some DNA (only mitochondrial) from a healthy donor of mitochondrial contents. Due to the uncharted nature of producing a child with three sources of DNA, this subject is currently quite contentious in the field of bioethics, as is the case with many other gene therapies. Currently, mitochondrial donation techniques are legal in the United Kingdom. In February 2016, a report was issued by the US Food and Drug Administration declaring that further research into mitochondrial donation is ethically permissible. The two most common techniques in the mitochondrial donation are pronuclear transfer and maternal spindle transfer.

**Maternal spindle transfer technique**

Maternal spindle transfer (MST) technique has been proposed as a means of removing defective mitochondria and the associated diseases from recurring in the future generations. It is carried out using the genetic material from three different sources to form a disease-free embryo: the father and mother’s nuclear DNA and a healthy donor’s mitochondrial DNA. The embryo will have its entire cytoplasm exchanged with the donor’s, removing the risk of mitochondrial diseases entirely.

Technically, MST involves the transfer of biological mother’s nuclear genetic material (nucleus) from her oocyte into an enucleated healthy donor female’s oocyte followed by fertilization of the reconstructed oocyte with the father’s sperm and embryo development (Figure 1). The transfer is conducted between mature eggs or metaphase II oocytes. The resulting child inherits its nuclear genetic material from its biological parents and mitochondria from the healthy donor. Due to the substitution of the mutant mitochondrial load with healthy mitochondria (with little or no transfer of mutant mtDNA), the child born along with its subsequent generations is free from any risk of mitochondrial diseases.

In the year 2009, researchers at Oregon Health and Science University effectively removed mitochondrial diseases through MST. They successfully executed the MST technique in nonhuman primate offsprings and showed its efficiency by conducting a deep genetic analysis of the offsprings. Their research explained that how the reconstructed oocytes formed after MST was capable of undergoing normal fertilization and embryo development. The study also elaborated the process through which the infants formed inherited their nuclear DNA from the spindle donors and their mitochondrial DNA from the cytoplasm donor.

The MST technique has come forth as a means of avoiding passing on the faulty disease-causing mitochondria from the mother to her child through substitution of cytoplasm from a healthy donor. However, this is a tricky procedure because of major two reasons; first, it is dependent on the successful extraction of the nucleus from the healthy as well as unhealthy oocyte of donor and mother, respectively. This step is immediately followed by another crucial step of substitution of donor’s nucleus with mother’s nucleus in donor’s oocyte and fertilization to form the healthy embryo. Hence, this technique requires a very high level of precision during
handling the biological samples ensuring that the nucleus of the biological mother is removed without any faulty mitochondria being dragged along with it.

**Pronuclear transfer**

Pronuclear transfer technique is a substitute to MST which uses a slightly different approach. Like MST, the source of genetic material is from three individuals: the father and mother’s nuclear DNA and the donor’s mitochondrial DNA. Here, the gametes are allowed to fuse twice, once between the biological parents and once between the father and the donor. These zygotes, now form a pronuclei, a membrane-bound state of the zygote before fusion of the two nuclei (from oocyte and the sperm) which is always followed immediately by mitosis and resultant two-cell stage. The pronuclei formed from the parents can now replace the donor pronuclei, resulting in a healthy embryo.[25] Pronuclear transfer (PNT) technique is another alternative developed to replace the mutant mtDNA containing cytoplast of the pronuclei (formed from the parent’s oocyte and sperm) with the cytoplast of a healthy donor pronuclei (formed from the healthy donor oocyte and father’s sperm) [Figure 2]. This methodology again results in the formation of a child with the nuclear genetic material inherited from its parents and the healthy mtDNA inherited from the donor cytoplast.[26]

In the year 2010, scientists at the Newcastle University showed in human zygotes the successful transfer of pronuclei conducted in abnormally fertilized zygotes (parent’s) into the cytoplast of healthy donor’s zygote, with minimal carryover. Their studies also concluded that PNT was compatible with onward embryo development (17% as compared to normally fertilized embryo’s 32%) and carryover of mutant mtDNA in the PNT performed embryos was <2% to none.[27] Later in the year 2016, Hyslop et al.[28] reported the preclinical studies on pronuclear transplantation. Surprisingly, techniques used in proof-of-concept studies involving abnormally fertilized human zygotes were not well tolerated by normally fertilized zygotes. They developed an alternative approach based on transplanting pronuclei shortly after completion of meiosis rather than shortly before the first mitotic division. It promoted the efficient development to the blastocyst stage with no detectable effect on aneuploidy or gene expression. After optimization, mtDNA carryover was reduced to <2% in the majority (79%) of PNT blastocysts. The importance of reducing carryover to the lowest possible levels is highlighted by a progressive increase in heteroplasmy in a stem cell line derived from a PNT blastocyst with 4% mtDNA carryover.

PNT technique is simpler in the sense; it involves extraction of embryos and substitution of the cytoplasm replacing the unhealthy mitochondria to form a healthy embryo. However, there are certain technical difficulties and concerns too. The primary concerns are that some faulty mitochondria could have slipped through the net. It is virtually impossible to leave behind all the mitochondria from the mother’s egg when removing the nucleus, even with the steadiest hand. Moreover, the level of mutated mitochondria that can cause symptoms varies by disease. One concern is that “bad” mitochondria, even in tiny amounts, could be better at replicating than “good” mitochondria – eventually tipping the balance and causing disease further down the line. A second concern is that having mitochondria from two sources could disturb the normal relationship between the nucleus and mitochondria, although it is unclear if this is the case. It is a good sign that the boy is healthy, but he will need to be

![Figure 2: The steps involved in mitochondrial donation by pronuclear transfer method (adopted from https://static.independent.co.uk)](image-url)
carefully monitored over the coming years. Thus, it can be concluded that PNT has the potential to reduce the risk of mtDNA disease, but it may not guarantee prevention.

**Issues with Mitochondrial Donation**

Mitochondrial donation is a technique that benefits many and claims to be a boon for the families having a history of carrying mitochondrial diseases from generations to generation. As beneficial as this technique may be, it comes with a fair share of concerns that may be perceived as a burden or a curse on the society by some scientists. According to them, some technical practicalities of these techniques cannot be overseen. First, the technique itself does not guarantee the complete removal of “Faulty Mitochondria” as the complete extraction of nucleus without some mitochondria remaining attached to it is tricky even for experts. Second, the extent of mutation and frequency of division of faulty mitochondria depends on the kind of disease. If these faulty mitochondria find their way into the embryo, it will tip-off the balance between healthy and faulty mitochondria and the disease may still continue in the subsequent generations. Third, there may also be a risk of mismatch between the mtDNA haplotype of the surrogate and the donor mother.

Apart from these, the ethical, legal, and social issues that are raised with respect to these reproductive techniques are debatable and are mainly the reason why these techniques have not been legalized globally.

**Ethical issues**

Although the adverse effect of this genetic modification has not been seen in the future generations, the safety of the technique is yet to be established. As it involves the modification of the original germ line, hence this technique is capable enough to pass on the changes to the subsequent generations if the child is female.[26,29,30]

In maternal spindle transfer, the paternal DNA is intact, but the maternal DNA is in pieces. Both the mothers involved have parts of their DNA in the embryo. Apart from these issues, the biggest concern is the use of early embryos in PNT. The transfer of the pronuclei results in the destruction of the extra embryo (that came from the fusion of sperm and ovum of the parents) which had the potential to develop into a healthy individual. This can be avoided with the use of MST technique that only involves the use of eggs. A debate is also raised as the child formed has the DNA from three parents.[31] Furthermore, donation of eggs is a complex process that can be risky for the donor due to development of ovarian hyperstimulation syndrome.

Many religious groups also believe that this is yet another example of human’s meddling with the natural processes. However, at the same time, if these processes are used then many children who are born with such genetic disorders would not have to undergo the painful ordeal of growing up or dying because of them at an early age. These procedures can reduce infant mortality.

**Legal issues**

The legal issues are much more complicated, as the child formed has the genetic content from three different parents. Furthermore, in the UK, Human Fertilization and Embryology Authority (HFEA) Act 1990 stated that an egg or sperm used or an embryo formed through scientific reproductive techniques should be such that its genetic content has not been altered or modified.[32] However, these techniques of mitochondrial donation do involve the definite alteration of the mitochondrial genome, and hence, initially, the research on mitochondrial donations faced a lot of legal allegations and obligations. However, later on, after analyzing the results obtained from the conducted research and thorough debates on the concerns involved by the established committees, the HFEA amended their original Act in 2008, to grant a power that would allow the use of techniques to avoid serious mitochondrial diseases.[33,34]

**Social issues**

These techniques being expensive have been argued to benefit certain economically forward social groups only. Social issues also arise due to the tripaternal aspect, as children formed from these techniques might be subjected to mental agony due to discrimination or it may cause legal complications. Besides, if the donor is a female from the father’s family, the germ line will remain within the family, but it will complicate the relationships of the parents with the child. Furthermore, these mutations may reoccur later during the lifetime of the individual and may also appear in the future generations. However, the frequency of these disorders is very high, if they can be removed, then there will be less economic pressure on the society, and it will be more productive.[31,33]

Apart from these major issues, there are some additional arguments and concerns also exist in a relation of this technique of mitochondrial donation. For example, some people have argued that the technique is unnecessary. After all, it will not help those who have already been born with mitochondrial diseases. Parents often do not find out they are carriers of these diseases until they give birth to sick children. Moreover, those who do know they could pass on a disease have other options, such as using a donor egg. The technique is specifically for people who carry genes for the disease but want to have a child genetically related to them.

Another concern is that, by creating a new mix of genetic material, embryologists are creating lasting genetic changes that will be passed down through generations,
before we have a chance to find out if they are dangerous. Some argue that this starts us on a slippery slope of germ line editing one that could eventually lead to “designer babies.”

**CONCLUSION**

Even though the research in this field still remains in infancy, mitochondrial donation comes out as a boon to a huge fraction of the population that is affected with mitochondrial diseases, for which no cure is available. This approach may eliminate these diseases from the subsequent generations as well making this a remarkable solution. Approximately 2500 women of child-bearing age in the United Kingdom in the year 2015 were found to be at the risk of passing on mitochondrial diseases to their children. Globally, these numbers are bound to increase along with the chances of removal of these mitochondrial diseases from the whole population. As far as the ethical issues regarding the “Three-Parent Baby” are concerned, the mitochondrial DNA plays no role in determining the physical appearance of the baby; only its overall metabolic fitness. On the same note, even discarding an embryo or a potential child in the PNT technique is as inevitable as in case of any other reproductive technique. Further research in analyzing the long-term effects of this technique, however, is still due and subjected to considerations. Moreover, these techniques surely benefit those families that have a slim chance of quality life for their future children that will suffer greatly and may not live beyond early childhood due to mitochondrial diseases.

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There are no conflicts of interest.

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