

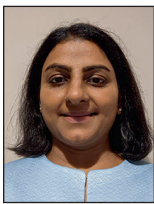


Narrative Review Article

Reproductive Choices for Women with Mitochondrial Mutations

Rekha N. Pillai¹

¹Newcastle Fertility Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, International Centre for Life, Newcastle upon Tyne, United Kingdom.



***Corresponding author:**

Rekha N. Pillai,
Newcastle Fertility Centre,
International Centre for
Life (ICFL), Central Pkwy.,
Newcastle, United Kingdom.

rekha.pillai@nhs.net

Received: 03 August 2025
Accepted: 06 August 2025
Published: 26 September 2025

DOI
10.25259/FSR_45_2025

Quick Response Code:



ABSTRACT

Mitochondrial mutations cause debilitating health conditions, and assisted reproduction broadens novel treatment options in women with mitochondrial mutations to reduce the risk of the mutations in their offspring. This editorial elaborates on the Mitochondrial Donation Programme licensed in the United Kingdom as a risk-reduction fertility treatment option for women suffering from mitochondrial mutation. This is the first licensed fertility treatment programme for women with mitochondrial mutation in the world, followed by the Australian parliament licensing it, and it is currently in the process of setting up the programme.

Keywords: Mitochondria, Mitochondrial donation, Mutation, PGT, Pronuclear transfer

INTRODUCTION

Mitochondria are a double-membraned organelle in eukaryotic cells responsible for oxidative phosphorylation (OXPHOS). Mitochondrial disorders are a group of neurometabolic disorders affecting organs of the body heavily dependent on aerobic metabolism, leading to defective OXPHOS.^[1] These mutations cause a spectrum of diseases associated with severe disease burden, morbidity and mortality.^[2] Though there are many recent advances in the field, treatment options are limited, and there are no known cures for these conditions.^[3] This editorial focuses on assisted reproductive treatment options for these women to reduce the risk of offspring inheriting these severely debilitating conditions from their mothers.

MITOCHONDRIAL MUTATIONS AND ITS INHERITANCE PATTERN

The mitochondria are under the genetic control of both nuclear and mitochondrial DNA (mtDNA). The mtDNA has 37 genes which code for polypeptide subunits, transfer RNA and ribosomal RNA.^[4] Mitochondrial mutations can be large-scale rearrangements such as deletions or point mutations.^[4,5] In patients with mtDNA disease, if all the mitochondria are mutated, it is called homoplasmy, and if there is a mixture of wild-type and mutated mtDNA, then it is called heteroplasmy.^[4] The mutations to the mtDNA show some specific characteristics. The mutations in the mtDNA are purely maternally inherited due to a programmed degeneration of mitochondria in the sperm cell after fertilisation.^[4] The risk of transmitting the mutation to

the offspring is unpredictable due to a genetic bottleneck. During oocyte development, a reduction in the number of mtDNA molecules occurs, leading to a 'bottleneck' where only a subset of the original mtDNA population is passed on to the next generation.^[5] This can make genetic counselling quite challenging, as different members of the same family can have different mutation loads. This is further challenged by the variability of the disease penetrance and variation in the critical threshold level beyond which the disease can manifest. The threshold effect is the level of mutation above which the disease manifests, and this level can vary with the type of mutation.^[4] It is the proportion of mutated to wild-type mitochondria that determines the phenotypic manifestation of disease, and often, women with high levels of mutations are more likely to manifest the disease. Also, mtDNA replication is independent of the cell cycle, and this can result in different cells in the body having different mutation levels. This replication of mtDNA in the postmitotic cells can lead to clonal expansion of somatic mitochondrial mutations generated through oxidative stress.^[4]

CLINICAL PRESENTATIONS

The mitochondrial mutation causes multiorgan involvement with an extensive list of both neurological and non-neurological manifestations, and some of the presentations are blindness, deafness, seizures, peripheral neuropathy, cardiomyopathy, liver failure, respiratory failure and diabetes. Common syndromes related to the mitochondrial disease include Kearns-Sayre syndrome, Leigh syndrome, Leber's hereditary optic neuropathy, myoclonic epilepsy, lactic acidosis, stroke-like episodes, myoclonic epilepsy with ragged red fibres and neurogenic weakness with ataxia and retinitis pigmentosa (NARP).^[6-11] The prevalence of all mitochondrial mutations is estimated to be 5–15 per 100,000 in childhood to 12.5 per 100,000 in clinically affected adults.^[2]

FERTILITY OPTIONS

The fertility options to prevent transmission of mitochondrial disease to the offspring include prenatal testing with the option to terminate the pregnancy if the mutation load in the foetus is clinically significant, egg donation, preimplantation testing for mitochondrial mutation (PGT-Mito) and mitochondrial replacement.^[5] Prenatal testing with the option of termination is both an emotionally and ethically difficult option for the couple, whereas egg donation doesn't offer the option of having genetically related children. PGT-Mito and mitochondrial replacement enable the couple to have genetically related children. PGT-Mito is only possible in women who have low or moderate heteroplasmy levels. Mitochondrial replacement is offered to homoplasmic women and women who have high heteroplasmic mutations. Alternatively, it is also offered when PGT-Mito is not producing

low clinically insignificant mutation load embryos. The couples are always offered alternate family-building options of adoption and fostering, too.

PGT-MITO

Preimplantation genetic testing of the embryos was developed 20 years ago, and the same technique is used to reduce the risk of mitochondrial mutation.^[12] PGT-Mito involves removing one or two cells from a day 3 old embryo, testing it for the mutation and subsequently transferring an embryo with an undetectable mutation or low mutation load.^[5] Cell-to-cell segregation of the mutation is a concern with mtDNA mutation, which can lead to different mutation loads in the child than the load of the biopsied cells. Though studies in non-human primates have shown significant variations in the mutation load between blastomeres, limited data from studies in human embryos have revealed minimal variation between cells of the cleavage-stage embryo.^[13,14] The first case of PGT-Mito was reported by Steffann *et al*; 2006.^[15] in a NARP patient, and the baby was born successfully, and since then, multiple babies have been born using this technique.^[15] It is difficult to determine the threshold of mutation for transfer, and it is often determined based on the type of mutation, previously published data, family history of the women and the couple's/women's wishes.^[5] PGT-Mito is not a suitable option for women who are homoplasmic for the mutation or for those who produce eggs with only a high mutation load. Overall, the PGT-Mito results so far show that it is a suitable risk reduction strategy, particularly in those who are not homoplasmic or in those without high heteroplasmic levels for the mutation.^[5]

MITOCHONDRIAL DONATION

Mitochondrial donation, or mitochondrial replacement, is an in vitro fertilisation (IVF)-based technique where the nuclear material from an oocyte or a zygote containing mutated mitochondria from affected women is replaced into a donor oocyte or a zygote with wild-type, unaffected mitochondria.^[16] This can be done before fertilisation using techniques such as mitochondrial spindle transfer (MST), polar body transfer or germinal vesicle transfer or after fertilisation using techniques such as pronuclear transfer (PNT). The resultant embryo will have the nuclear materials from the parents and mitochondria from the donor. The most used techniques are MST and PNT.

Pronuclear Transfer (PNT)

A pronucleus containing two haploid sets of chromosomes with a definite membrane becomes visible in a zygote after fertilisation, and PNT involves removing this pronucleus from the parental zygote to an enucleated donor zygote [Figure 1].^[5] The removal of a karyoplast bound in a membrane with only a little cytoplasm around it can be achieved by

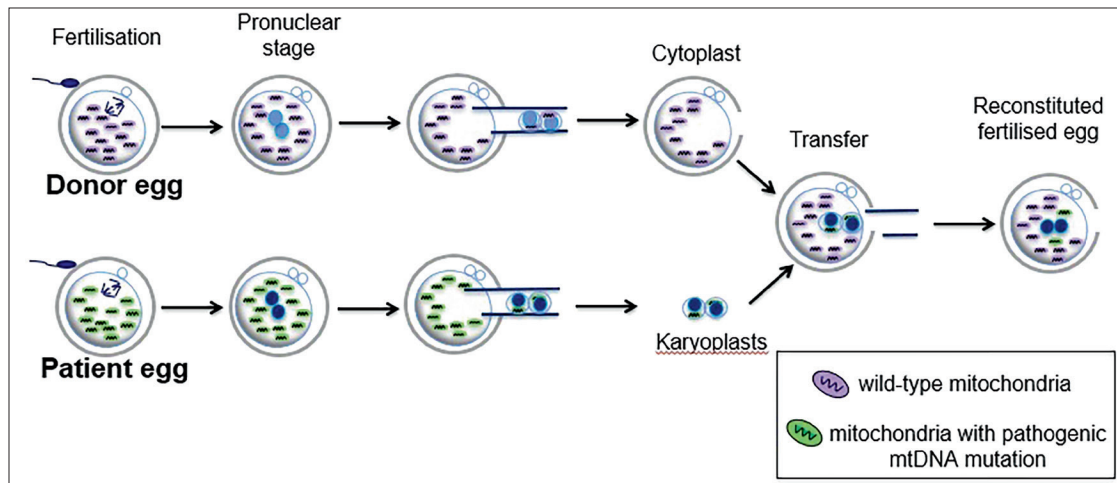


Figure 1: Pronuclear transfer schematic diagram.

using cytoskeletal inhibitors such as cytochalasin B and colcemid, or nocodazole. This karyoplast is then transferred into an enucleated zygote using an inactivated viral envelope protein called Human agglutinating virus of Japan (HVJ-E).^[17]

Mitochondrial Spindle Transfer (MST)

MST involves removing the spindle complex from the oocyte of the mother and replacing it with an enucleated donor oocyte with healthy mitochondria. The spindle complex forms in the oocyte during the second meiotic division. The remodelled oocyte is then fertilised using the partner's sperm to create the embryo. The spindle complex, due to its birefringent properties, can be easily visualised using polarised microscopy rather than invasive fluorescent staining.^[5] The spindle complex is removed as a karyoplast and transferred to an enucleated MII oocyte using HVJ-E. Studies have shown a high incidence of abnormal fertilisation in human zygotes following MST, possibly due to premature oocyte activation or damage to the spindle during transfer.^[18]

Both techniques have shown mtDNA carryover, where some of the affected maternal mitochondria can get transferred along with the karyoplast into the new reconstituted oocyte or zygote.^[19] Another phenomenon that has been noticed is mitochondrial reversion, where the mutated mitochondria come back after successfully replacing them with unaffected mitochondria and the reasoning behind this process is still unknown. A study on MST conducted to improve fertility outcomes in women who had repeated IVF noticed that one in six children born following MST showed mitochondrial reversion.^[20]

MITOCHONDRIAL ASSISTED REPRODUCTION PROGRAMME

The United Kingdom (UK) parliament approved the regulation to license the mitochondrial donation programme

in December 2014, and the programme was established in the Newcastle Fertility Centre, UK. The patients will be initially assessed, and their mutation confirmed, in the mitochondrial reproductive assisted choices clinic. The clinic is composed of mitochondrial disease experts, and the patients will be assessed for mitochondrial disease, and their health will be optimised for fertility treatment and pregnancy. Once they are ready to consider pregnancy, they will be referred to the Mitochondrial assisted reproduction technology (MART) clinic. This is a multidisciplinary clinic run by both fertility experts and mitochondrial disease experts. In this clinic, patients will have a fertility assessment and an assessment of the safety of carrying the pregnancy. If required, advice will be sought from obstetricians, anaesthetists and other healthcare professionals to plan their pregnancy care. Once a plan for fertility treatment and pregnancy is in place, they will be referred for Mitochondrial Assisted Reproduction treatment (PGT-Mito or PNT) depending on the mutation load. All patients having PNT need individual application and approval from the human fertilisation and embryology authority, the regulatory body for fertility clinics in the UK. All individual applications will be evaluated by an advisory expert committee to assess the appropriateness of PNT for treatment. Those who are not suitable for treatment due to low ovarian reserve or patient choice will be referred back to their local clinician.

RESULTS FROM MITOCHONDRIAL ASSISTED REPRODUCTION PROGRAMME

Eight healthy babies are born from 22 completed PNT cycles (36%). There were four boys and four girls, including one set of identical twins. The babies exhibited no or low levels of mutation below the clinical threshold levels and have shown normal development since birth. Sixteen out of 39 PGT-Mito treatment cycles resulted in clinical pregnancies,

leading to the birth of 18 babies (including two sets of twins). The heteroplasmy levels of the tested babies were low, below clinically significant levels.^[21,22]

CONCLUSIONS

In conclusion, assisted reproduction is evolving beyond treating subfertility to a treatment approach to reduce the burden of genetic conditions in the population. The mitochondrial donation programme is a risk-reduction fertility programme for women with mitochondrial mutations, which uses novel techniques such as PNT and MST. The programme has been rolled out with regulations and procedures in place to monitor for any complications or risks, with strict follow-up and reporting criteria for the babies born through this programme. The programme, using a combination of PGT-Mito and mitochondrial donation treatment based on clinical indications, is effective in reducing the mitochondrial mutation to a clinically insignificant level.

Acknowledgement: Thank you to Dr Hyslop L, Newcastle Fertility Centre, United Kingdom for providing the schematic figure for PNT.

Author contributions: RNP: Conceived the idea, wrote and edited the manuscript and approved the final draft of the manuscript.

Ethical approval: Institutional Review Board approval is not required.

Declaration of patient consent: Patient's consent is not required as the patient's identity is not disclosed or compromised.

Financial support and sponsorship: The Mitochondrial Donation Programme is funded by NHS England in the UK.

Conflicts of interest: Dr Rekha N. Pillai is the current Clinical Lead for the Mitochondrial Donation Programme, Newcastle Fertility Centre, United Kingdom.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

REFERENCES

- McFarland R, Taylor RW, Turnbull DM. Neurological Perspective on Mitochon. *Lancet Neurol* 2010;9:829–40.
- Gorman GS, Chinnery PF, DiMauro S, Hirano M, Koga Y, McFarland R, *et al.* Mitochondrial Diseases. *Nat Rev Dis Primers* 2016;2:16080.
- Nightingale H, Pfeffer G, Bargiela D, Horvath R, Chinnery PF. Emerging Therapies for Mitochondrial Disorders. *Brain* 2016;139:1633–48.
- Lax NZ, Turnbull DM, Reeve AK. Mitochondrial Mutations: Newly Discovered Players in Neuronal Degeneration. *Neuroscientist* 2011;17:645–58.
- Craven L, Tang MX, Gorman GS, De Sutter P, Heindryckx B. Novel Reproductive Technologies to Prevent Mitochondrial Disease. *Hum Reprod Update* 2017;23:501–19.
- Kearns TP, Sayre GP. Retinitis Pigmentosa, External Ophthalmoplegia, and Complete Heart Block: Unusual Syndrome with Histologic Study in One of Two Cases. *AMA Arch Ophthalmol* 1958;60:280–9.
- Ciafaloni E, Santorelli FM, Shanske S, Deonna T, Roulet E, Janzer C, *et al.* Maternally Inherited Leigh Syndrome. *J Pediatr* 1993;122:419–22.
- Wallace DC, Singh G, Lott MT, Hodge JA, Schurr TG, Lezza AM, *et al.* Mitochondrial DNA Mutation Associated with Leber's Hereditary Optic Neuropathy. *Science* 1988;242:1427–30.
- Pavakis SG, Phillips PC, DiMauro S, De Vivo DC, Rowland LP. Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like Episodes: A Distinctive Clinical Syndrome. *Ann Neurol* 1984;16:481–8.
- Fukuhara N, Tokiguchi S, Shirakawa K, Tsubaki T. Myoclonus Epilepsy Associated with Ragged-Red Fibers (Mitochondrial Abnormalities): Disease Entity or a Syndrome? Light-and Electron-Microscopic Studies of Two Cases and Review of Literature. *J Neurol Sci* 1988;47:117–33.
- Holt IJ, Harding AE, Morgan-Hughes JA. Deletions of Muscle Mitochondrial DNA in Patients with Mitochondrial Myopathies. *Nature* 1988;331:717–9.
- Handyside AH, Kontogianni EH, Hardy K, Winston RM. Pregnancies from Biopsied Human Preimplantation Embryos Sexed by Y-Specific DNA Amplification. *Nature* 1990;344:768–70.
- Lee HS, Ma H, Juanes RC, Tachibana M, Sparman M, Woodward J, Ramsey C, *et al.* Rapid Mitochondrial DNA Segregation in Primate Preimplantation Embryos Precedes Somatic and Germline Bottleneck. *Cell Rep* 2012;1:506–15.
- Monnot S, Gigarel N, Samuels DC, Burlet P, Hesters L, Frydman N, *et al.* Segregation of mtDNA Throughout Human Embryofetal Development m.3243A>G as a Model System. *Hum Mutat* 2011;32:116–25.
- Steffann J, Frydman N, Gigarel N, Burlet P, Ray PF, Fanchin R, *et al.* Analysis of mtDNA Variant Segregation During Early Human Embryonic Development: A Tool for Successful NARP Preimplantation Diagnosis. *J Med Genet* 2006;43:244–7.
- Richardson J, Irving L, Hyslop LA, Choudhary M, Murdoch A, Turnbull DM, *et al.* Oncise Reviews: Assisted Reproductive Technologies to Prevent Transmission of Mitochondrial DNA Disease. *Stem Cells* 2015;33:639–45.
- McGrath J, Solter D. Nuclear Transplantation in the Mouse Embryo by Microsurgery and Cell Fusion. *Science* 1983;220:1300–2.
- Tachibana M, Amato P, Sparman M, Woodward J, Sanchis DM, Ma H, *et al.* Towards Germline Gene Therapy of Inherited Mitochondrial Diseases. *Nature* 2013;493:627–31.
- Hyslop LA, Blakeley P, Craven L, Richardson J, Fogarty NM, Fragouli E, *et al.* Towards Clinical Application of Pronuclear Transfer to Prevent Mitochondrial DNA Disease. *Nature* 2016;534:383–6.
- Costa-Borges N, Nikitos E, Späth K, Miguel-Escalada I, Ma H, Rink K, *et al.* First Pilot Study of Maternal Spindle Transfer for the Treatment of Repeated In Vitro Fertilization Failures in Couples with Idiopathic Infertility. *Fertil Steril* 2023;119:964–73.
- McFarland R, Hyslop LA, Feeney C, Pillai RN, Blakely EL, Moody E, *et al.* Mitochondrial Donation in a Reproductive Care Pathway for mtDNA Disease. *N Engl J Med* 2025;393:461–8.
- Hyslop LA, Blakely EL, Aushev M, Marley J, Takeda Y, Pyle A, *et al.* Mitochondrial Donation and Preimplantation Genetic Testing for mtDNA Disease. *N Engl J Med* 2025;393:438–49.

How to cite this article: Pillai RN. Reproductive Choices for Women with Mitochondrial Mutations. *Fertil Sci Res.* 2025;12:29. doi: 10.25259/FSR_45_2025