# PREVENTING MITOCHONDRIAL DISEASE: REPRODUCTIVE CHOICES FOR FAMILIES

## KEY POINTS

- Mitochondrial disease (mito) can be caused by variations in nuclear DNA (nDNA) and mitochondrial DNA (mtDNA), as well as sporadic mutations when there is no family history.
- Preconception genetic counselling is recommended for all couples where there is a diagnosis or family history of mito.
- Depending on the genetic mutation, and the couple's individual preferences, the following options may be available:
    - Prenatal diagnostic testing following a natural conception
    - Prenatal genetic diagnosis (PGD) following in vitro fertilization (IVF)
    - Egg or embryo donation through IVF
- Mitochondrial donation, an IVF technique which may prevent transmission of mtDNA mutations is available in the United Kingdom. AMDF is advocating for legislative change to allow couples in Australia to access this technique.

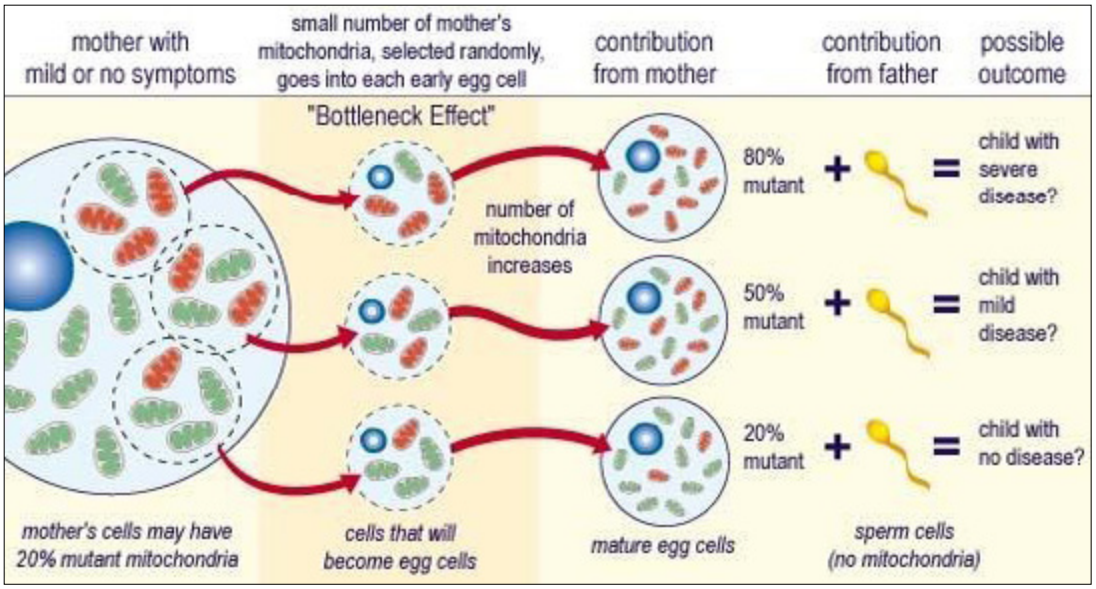
## INHERITANCE OF MITO

Mito can be caused by variations in nuclear DNA (nDNA) or mitochondrial DNA (mtDNA), or by sporadic mutations when there is no family history.

Mutations in nDNA are most commonly inherited in an autosomal recessive manner, where both the mother and father are carriers of the genetic variant. In some rare instances, the disorder can be inherited in an autosomal dominant manner (only one copy of the variant nDNA is needed and it will usually be inherited from either the mother or father) or have X-linked inheritance (the mutation is passed down from the mother's X chromosome).

Mutations in mtDNA are generally inherited from the mother. These disorders can appear in every generation of a family when the mutation is inherited down the female line, and can affect both males and females. Fathers who are affected by a disorder from a mtDNA variant do not pass the mutation on to their children.

Each cell has a large number of mitochondria. In people with mtDNA mutations, there will be a mix of healthy and unhealthy mitochondria in each cell. Having a ratio of unhealthy to normal mtDNA is called heteroplasmy, and influences the severity of mito. Levels of heteroplasmy may change over time, leading to disease onset later in life. The percentage of unhealthy mitochondria may vary between individuals in the same family and also among organs and tissues within the same individual.




*Muscular Dystrophy Association. 2017. 'Mitochondrial Myopathies (MM)' What are mitochondrial myopathies. Viewed 9th February 2018, < https://www.mda.org/disease/mitochondrial-myopathies>*

## PREGNANCY OPTIONS

There are a number of reproductive options that may be available to you when considering pregnancy, specifically for people who carry a genetic mutation in their nDNA or mtDNA. Individuals will need to assess their options, considering factors such as cost, amount of physical and emotional burden they are willing to undergo, and how they would respond to different outcomes of testing. The appropriate option for each individual will, in part, depend on the underlying genetic variant. Premature ovarian failure can occur in several mitochondrial disorders which will also influence whether a couple can conceive naturally. It is recommended that couples receive pre-conception counselling by an experienced genetic counsellor to assist them to consider their options and make an informed decision. Information on genetic counselling can be found **here**.

In cases associated with nDNA variants, autosomal recessively inherited variants have a 25% risk of recurrence in offspring, while autosomal dominant variants have a 50% risk. For X-linked inheritance, nearly everyone affected is male, although females can carry the gene. In cases with nDNA variants, where the variant has been identified, prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD) can be offered.

For mtDNA variants, the inheritance risk is much more difficult to determine which is partly caused by variations in heteroplasmy.

### 1) NATURAL CONCEPTION AND PRENATAL DIAGNOSIS

Following a natural conception, should the parents wish to undertake genetic testing there are two types of invasive diagnostic prenatal testing that can be done to identify potential genetic variations in a pregnancy. Prior to testing, it is important for couples to receive appropriate counselling so that the outcomes of the testing, can be considered.

Chorionic Villus Sampling (CVS) is undertaken at 11-13 weeks gestation and involves the collection of a small sample of cells from the developing placenta by inserting a needle through the abdomen (performed under local anaesthetic) or by inserting a catheter through the cervix. Both procedures are performed with ultrasound guidance and have a miscarriage risk of less than 1%.

Amniocentesis is conducted at 15-17 weeks gestation and involves using a transabdominal needle to collect a sample of amniotic fluid which contains different cell types from the growing fetus. This procedure is guided by ultrasound and has a miscarriage risk of around 0.5%.

Due to potential differences in the amount of variant mtDNA between different tissue types and organs, prenatal diagnosis can have significant limitations for mtDNA mutations. These tests may not provide a definitive diagnosis as to the clinical severity of the disease, or predict the likelihood of a couple having a severely affected child.

### 2) PRE-IMPLANTATION GENETIC DIAGNOSIS

Pre-implantation genetic diagnosis (PGD) can be used for both mtDNA mutations and nDNA mutations. PGD is considered as an ‘add on’ to in vitro fertilization (IVF). Briefly, a small number of cells from an embryo are obtained after IVF and are analysed. For nDNA mutations, embryos will be determined as affected, carriers or free from mito. For mtDNA mutations, only those embryos with very low-level mutant levels are transferred to the uterus. However, these techniques are of little help to women who have intermediate-level heteroplasmic mtDNA mutations, where uncertainty regarding the mutation threshold for developing disease remains.

**Click here** to read about the Taprell family’s experience of PGD.

## 3) EGG CELL OR EMBRYO DONATION

Egg donation involves the donor undergoing treatment through an IVF cycle. Multiple eggs are collected which are then fertilized with the recipient's partner's sperm to create embryos. The resulting embryos are then transferred to the recipient's uterus. In Australia, egg donations are altruistic. Most often, donors are known to the recipients and may be a sister, cousin or friend. For mtDNA mutations, it would be important to receive a donation from an individual who is not on the maternal line to prevent the potential transmission of the mtDNA mutation.

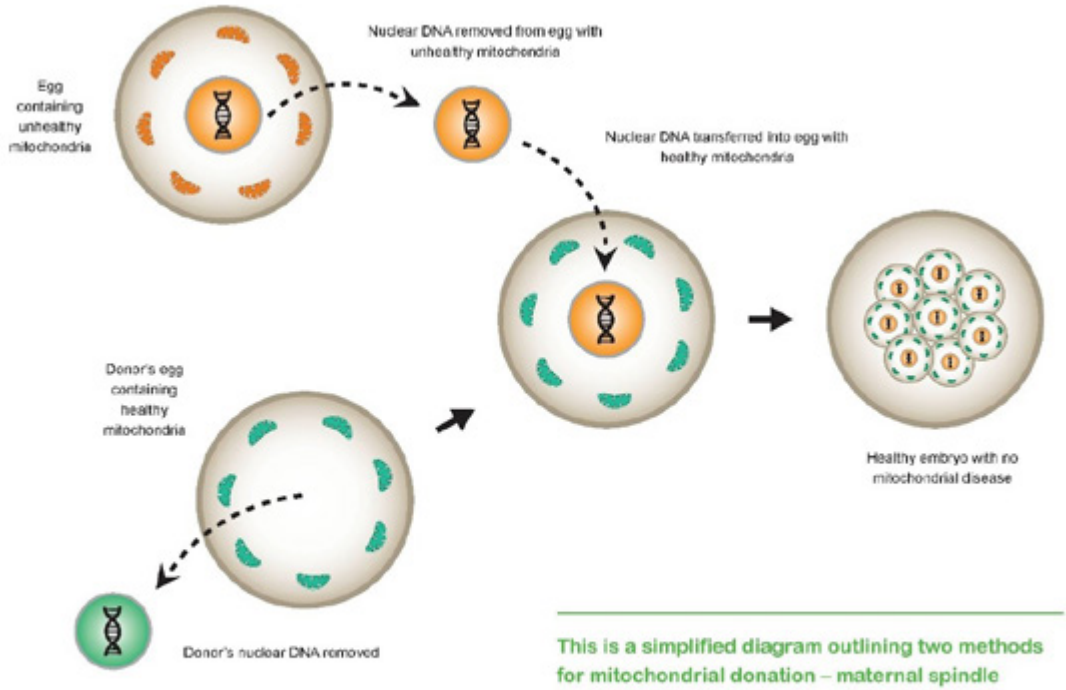
Embryo donation may also be an option. Individuals who have had success using IVF may consider donating their additional embryos to other couples.

For both egg donation and embryo donation, counselling is required for the donors and recipients regarding the emotional and legal considerations of donations.

### Mitochondrial donation

Mitochondrial donation is an IVF technique (also known as mitochondrial replacement IVF technique, mitochondrial transplant or mitochondrial replacement) that could prevent transmission of mtDNA mutations from mother to child.

The two mitochondrial donation techniques being developed are maternal spindle transfer and pronuclear transfer. They involve transferring nuclear genetic material from the affected mother's egg into a donor egg that has had its nuclear DNA removed and retains only its healthy mitochondrial DNA. Therefore, the transmission of mito to the resulting child may be prevented.




This is a simplified diagram outlining two methods for mitochondrial donation – maternal spindle transfer (prior to fertilisation) and pronuclear transfer (after fertilisation).

Mitochondrial donation is not yet available in Australia. In March 2017, the first clinical mitochondrial donation license was granted in the United Kingdom, following many years of consultation and expert reviews.

AMDF is advocating for legislative change in Australia to allow couples access to mitochondrial donation.

Further information about mitochondrial donation is available from the Mito Foundation website.

Contact the Mito Foundation Helpline on 1300 977 180.

*Information contained in this document is intended for use as a guide of a general nature only. The Mito Foundation recommends individuals with suspected or confirmed mitochondrial disease, and individuals with a family history of mitochondrial disease, discuss their reproductive options with their specialist. Preconception counselling with an experiences genetic counsellor is recommended to ensure couples understand their options and can make an informed decision.*

mito FOUNDATION
Hope for mitochondrial disease