Mitochondrial Donation/Mitochondrial Replacement Therapy/3-parent babies.

Mitochondria are the energy-producing organelles of a cell, with number of mitochondria per cell depending on the cell type and how much energy it needs. Mitochondria contain about 0.1% of a person’s DNA (mtDNA), but it is different to the rest of the human DNA found in the cell nucleus - the DNA sequences are concentrated with no spare pieces of DNA (introns) between the 37 genes that code for proteins mostly acting in the respiratory chain complexes of the mitochondria. However, not all the proteins coded for by mtDNA are known yet. DNA from each mitochondrion from one cell does not all contain the same sequencing, and is prone to rapid changes/mutations. Mitochondria are inherited only through the maternal line, through the oocyte/egg.

Mitochondrial DNA disease affects at least 1 in 200 children in the UK, with the first mtDNA mutations identified in 1988. While many people will be asymptomatic or have mild, late-onset or undiagnosed problems, around 1 in 6500 children are thought to develop more serious mitochondrial disorders, commonly affecting multiple different organs causing loss of movement control, muscle weakness, diabetes, heart problems, epilepsy and stroke-like episodes, and in serious cases death. Children born with severe mitochondrial DNA disease are unlikely to survive childhood, and currently there is no cure.

UK history of Mitochondrial Donation research - the Wellcome Trust Centre for Mitochondrial Research at the Newcastle University, UK, has developed and clinically tested two mitochondrial donation techniques to help prevent mitochondrial DNA disease being passed on from mother to child: [http://www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/Mitochondrial-diseases/](http://www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/Mitochondrial-diseases/)

1) pronuclear transfer (PNT) where the intending parents’ egg and sperm are combined to produce embryo 1, and father’s sperm and donor egg are combined to produce embryo 2. The nuclear DNA from embryo 1 (with rest of embryo 1 discarded) is transferred to embryo 2 (with its nucleus discarded). Embryo 2 has intending parents’ nuclear DNA and donor’s healthy mitochondrial DNA.

2) maternal spindle transfer (MST) where the mother’s and a donor’s egg nuclear chromosomal spindles are removed, the mothers spindle is transferred to the donor egg with donor spindle discarded. The egg with donor mitochondria and mother’s nuclear DNA then undergoes IVF.

In February 2015, mitochondrial donation was legalised by the UK House of Commons voting to allow changes to current legislation (Human Fertilisation and Embryology Act 2008), and the House of Lords voting to allow fertility clinics to be licenced to offer mitochondrial donation. Only women with mitochondrial mutations undergoing IVF (in vitro fertilisation) will be considered, and specialists will offer this amongst other options on a case by case basis. Other options include IVF with Preimplantation Genetic Diagnosis to transfer only embryos free of the mutation. The UK is the only country to have allowed mitochondrial donation – up until now an international consensus to not allow this procedure has been upheld. Marcy Darnovski, Center for Genetics and Society in Berkeley California, said that this UK decision crosses the international ethical line. Two main reasons for this ethical opposition have been that mitochondrial donation alters the DNA sequencing of the inheritable germline, and the creation of an embryo from DNA of 3 parents and two other embryos.

Is it Genetic Modification? Opinions vary – some say no, others say yes. No? Those who don’t believe mitochondrial donation is genetic modification say this technique only allows for unaltered nuclear DNA to be transferred to an egg or embryo that has unaltered healthy mitochondria. These techniques only replace, rather than alter, a small number of unhealthy mitochondrial genes with healthy ones. Mitochondrial donation is not known to alter nuclear DNA, which is thought to carry the personal characteristics and traits of a person; it will simply allow future generations to be born
without mitochondrial DNA disease. It is not, and cannot, be used for 'eugenics' (deliberate alteration of physical traits). Genetic modification of nuclear DNA will remain illegal.

Yes? Others believe this technique does have a risk of altering someone’s characteristic genome. We do not yet know for sure that mtDNA has no effect on nuclear DNA (through epigenetics, protein interactions etc), or on a person’s physical characteristics (phenotype). Guido de Wert, Professor of Biomedical Ethics at Maastricht University, The Netherlands said in The Guardian 2012: "We should be honest and acknowledge that we are talking about genetic modification, that this changes the genome, and it may be transmitted to future generations. We should also be careful in arguing that this is only about energy in cells. **Scientists do not fully understand at this moment the importance of the mitochondrial genome for all sorts of human characteristics.**"

http://www.theguardian.com/science/2012/jun/05/mitochondrial-genetic-disease-ethical-doubts

While gene therapy (inserting healthy genes) has been used to treat patients in the past, this marks a new level of human genetic modification, and sets a precedent by introducing genetic changes in the germline that pass down to future generations. Additionally any biological faults introduced by the technique could be handed down from one generation to the next.

Is it ethical? The Wellcome Institute in the UK have reported back to the UK Parliament before the law change that the UK public has been **extensively consulted** on the ethical acceptability of mitochondrial donation and there is broad support. The Nuffield Council on Bioethics, UK, found that ‘given the benefit to individuals, if shown to be sufficiently safe, the techniques are ethical for families to use. However, mitochondrial donors should not have the same rights in regulation as embryo or egg donors with no requirement to be identified by adult offspring’. The UK Human Fertilisation and Embryology Authority’s public dialogue exercise prior to legislation changes found the UK public to be broadly supportive of mitochondrial donation. However, a long list of clinicians, scientists and ethicists from the UK and internationally have opposed the new legislation. The National Catholic Centre, USA concluded that mitochondrial donation ripples the mother-father link and dilutes parenthood. And the Catholic and Anglican Churches in England said the idea was not safe or ethical, not least because it **involves the destruction of embryos**.

Guido de Wert, Netherlands, also said ‘One of the major objections to genetically modifying an embryo is that it might infringe the child's right to what bioethicists call an "open future". The concern is reasonable if a modification gives the child a certain hair or eye colour, for example, because the child may feel that they have been tailored to suit their parents’ expectations. But preventing a child from inheriting a nasty disease gives them a more open future, not less.’ Margaret Somerville, McGill University, Canada, said that ‘the benefits and risks have been weighed, but there is not yet any surety in the risks. MtDNA is not known to have no effect on a person’s character, and the risk is higher because mitochondrial genes do affect development and metabolism. Our basic research on the epigenetics and other interactions between mitochondrial and nuclear genes is lacking. Mitochondrial donation is not the same as somatic cell gene therapy or organ transplants. Our inherited DNA is an intrinsic part of who we are, and requires special respect’.

http://www.geneticsandsociety.org/article.php?id=7026. Marcy Darnovsky, Center for Genetics and Society in Berkeley, California, said 'The question raised by these proposals is whether a risky technique, which would at best benefit a small number of women, justifies shredding a global agreement with profound significance for the human future. We need a moratorium on procedures based on human germline modification while that question is widely and fairly considered'.