

Three to one – an ethicolegal outline of mitochondrial donation in the South African context

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Mitochondrial donation or mitochondrial transfer enables a woman with mitochondrial disease to have a genetically related child without transmitting the disease to the child. The techniques used for mitochondrial donation or transfer which are maternal spindle transfer or pro-nuclei transfer, require three gametes to ultimately produce a healthy embryo. Both these techniques result in the child inheriting nuclear DNA from the intending parents and mitochondrial DNA from the female donor. Following the legalisation of mitochondrial donation in the UK, after a rigorous process of scientific and ethical review, and the birth of another baby using the technique, coupled with the fact that there is no cure for mitochondrial disease, suggests that it is prudent for us to consider this reproductive intervention and its application in the South African setting. In addition, the 2019 UNESCO Report of the International Bioethics Committee (IBC) on assisted reproductive technologies (ART) and parenthood, encourages debate on changes in models of parenthood influenced by ART including the emergence of new models of families and forms of parenthood that extend beyond the classical rule of *mater semper certa est* (the mother is always known). ART, in particular mitochondrial donation, challenges this rule. The aim of this paper is to provide an outline of the legal and ethical positions of mitochondrial donation and resume the discussion with specific focus on the South African context.

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In 2015, the UK Parliament approved the clinical application of novel in vitro fertilisation (IVF) procedures, namely, 'maternal spindle transfer' and 'pro-nuclear transfer', otherwise known as mitochondrial donation or mitochondrial transfer.^[1] These techniques require three gametes to produce a healthy embryo: two gametes from the intending parents and one gamete from a female donor. In May 2023, it was reported that the first UK baby had been born using mitochondrial donation treatment (MDT). However, the UK is not the only country to use this technique.^[2] In 2016, a team of doctors from the New Hope Fertility Center in New York announced the world's first successful MDT birth after treating a Jordanian woman who, prior to receiving the treatment, suffered four miscarriages and the death of two children. The technique was also used in Ukraine in 2017 to assist a woman with 'unexplained infertility', and in Greece in 2019 to assist a woman who had endured four unsuccessful cycles of IVF treatment.^[3]

Mitochondrial donation or mitochondrial transfer enables a woman with mitochondrial disease to have a genetically related child without transmitting the disease to the child.^[4] The technique, which uses tissue from the eggs of healthy female donors to create embryos that do not contain mutations carried by the biological mother that are likely to be detrimental or even fatal to her prospective children, is currently legal in the UK, where approval is provided on a case-by-case basis by the UK's Human Fertilisation and Embryology Authority (HFEA). Women with mitochondrial disease had limited options prior to this technique, and no option to have a genetically related child. They could either use an egg donor or adopt a child – however, neither option provides genetic affinity, which is the case with mitochondrial donation.^[5]

Following the legalisation of mitochondrial donation in the UK, after a rigorous process of scientific and ethical review, and the birth of another baby using the technique, coupled with the fact that there is no cure for mitochondrial disease, it is prudent to consider this reproductive intervention and its application in the South African (SA) setting. In addition, the 2019 UNESCO Report of the International Bioethics Committee (IBC) on assisted reproductive technologies (ART) and parenthood encourages debate on changes in models of parenthood influenced by ART, including the emergence of new models of families and forms of parenthood that extend beyond the classical rule of *mater semper certa est* (the mother is always known). ART, particularly mitochondrial donation, challenges this rule. The aim of this article is to provide an outline of the legal and ethical positions of mitochondrial donation and to resume the discussion with a specific focus on the SA context.

Mitochondrial donation or transfer and its legal position in South Africa

Following an expert meeting held by the World Health Organization (WHO) in 2001 titled 'Medical, ethical and social aspects of assisted Reproduction', certain recommendations were put forward that have implications for infertility issues and the use of ARTs in low- to middle-income countries (LMICs). These recommendations included recognising infertility issues in LMICs as a public health issue and the idea that ARTs should complement other ethically acceptable sociocultural solutions to infertility.^[6] IVF is a type of ART that assist people with infertility issues. Dubbed a novel IVF procedure, the SA legal framework regarding mitochondrial donation or transfer will now be considered.

Currently, the 2012 regulations relating to the artificial fertilisation of persons (GN35099) under chapter 8 of the National Health Act No. 61 of 2003 (NHA) govern the circumstances under which artificial fertilisation takes place. The definition of artificial fertilisation under these 2012 regulations includes in vitro fertilisation, which is in turn defined as: 'the process of spontaneous fertilisation of an ovum with a male sperm outside the body in an authorised institution.'

Thus, IVF involves retrieving eggs from a woman's ovaries and fertilising them with sperm outside the human body. The resulting embryo can then be transferred to the woman's uterus in the hope of having a healthy baby. Regulation 10(2)(a) of the same regulations, which govern the control over artificial fertilisation and embryo transfer among others, indicates that:

'...A competent person shall not effect in vitro fertilisation except for embryo transfer, to a specific recipient and then only by the union of gametes removed or withdrawn from the bodies of – (i) such recipient and an individual male gamete donor; or (ii) an individual male and an individual female gamete donor.'

Mitochondrial donation prevents the transmission of the mother's damaged mitochondria to the child by replacing the latter with the mitochondria of a healthy donor egg. However, when regulation 10(2)(a) is considered, the reference to 'such recipient' and 'individual male' and 'individual female' gamete donor points to a union of gametes removed or withdrawn from *one* male and *one* female (emphasis), thus implying that a third gamete donor (second female) is not permissible within the context of in vitro fertilisation. This then casts doubt as to whether mitochondrial donation or transfer is permissible as a novel form of IVF in SA.

Propelling the argument against mitochondrial donation being legally valid in SA is section 294 of the Children's Act No. 38 of 2005, which provides for the genetic origin of the child. This section indicates that no surrogate motherhood agreement is valid unless the conception of the child is to be effected by the use of the gametes of both commissioning parents, or if that is not possible due to biological, medical or other valid reasons, the gamete of at least one of the commissioning parents, or where the commissioning parent is a single person, the gamete of that person. This section also does not appear to cater for a third gamete donor. In addition, it has been put forward that the properties characteristic of mitochondrial inheritance mean that most mitochondrial donation techniques belong to a sub-class of genetic modification.^[7]

Equating mitochondrial donation with cloning

SA does not have specific genetic modification legislation. It does, however, under section 57(1) of the NHA, prevent the reproductive cloning of human beings. Section 57(1) of the NHA states that:

'A person may not: (a) manipulate any genetic material, including genetic material of human gametes, zygotes or embryos; or (b) engage in any activity, including nuclear transfer or embryo splitting, for the purpose of the reproductive cloning of a human being.'

Reproductive cloning is further defined under section 57(6)(a) as: 'the manipulation of genetic material in order to achieve the reproduction of a human being and includes nuclear transfer or embryo splitting for such purpose'. Therefore, on a plain reading of

this definition, where the intention is to achieve the reproduction of a human being, the manipulation of genetic material in that instance would be considered illegal. The wording of this definition is clearly problematic and raises the question of whether any manipulation of genetic material that results in the reproduction of a human being could be classified as reproductive cloning and therefore be considered illegal. Section 57(2) of the NHA allows for therapeutic cloning, as permitted by the Minister of Health, utilising adult or umbilical cord stem cells. Therapeutic cloning is defined in section 57(6)(b) as: 'the manipulation of genetic material from either adult, zygotic or embryonic cells in order to alter, for therapeutic purposes, the function of cells or tissues.' This broad definition of therapeutic cloning includes genome editing therapies. In the case of mitochondrial donation, it could be argued that the manipulation of genetic material is aimed at ultimately achieving the reproduction of a human being, and could also fall within the objectives of 'therapeutic purpose' (i.e., healing mitochondrial disease) as per the definition of therapeutic cloning. While the science indicates that maternal spindle transfer and pronuclear transfer (the two most promising types of nuclear transfer to prevent mitochondrial disorders) do not amount to reproductive cloning,^[8,9] the current ambiguous definition of reproductive cloning in the NHA does little to provide solid clarity regarding what is and what is not legally permitted. It is further prudent to distinguish reproductive adult cloning from reproductive embryo cloning. According to Reznichenko *et al.*^[9] 'Adult cloning involves the transfer of adult (diploid) nuclear material into an enucleated oocyte. In contrast, the cell to be transferred in embryo cloning originates from an embryo. The latter implies that the resulting child will be the first of its kind and not a clone of an already existing human.' The definition of reproductive cloning under the NHA does not provide for this distinction. For argument's sake, if it has been scientifically established that mitochondrial donation is not tantamount to reproductive cloning, could this procedure then fall under the ambit of therapeutic cloning? Even if the argument is provided that MDT is more concerned with the treatment of mitochondrial disease, with the result of achieving a healthy baby free from genetic mutations, the implication that a third gamete donor (second female) is not permissible within the context of in vitro fertilisation under regulation 10 of the regulations relating to the artificial fertilisation of persons, and the conditions of the validity of surrogate motherhood per section 294 of the Children's Act No. 38 of 2005, suggests that mitochondrial donation is not currently covered under the SA legal framework.

Historically, mitochondrial donation or transfer has not been without controversy, because the techniques used introduce a third genetic contributor within the reproductive process, with the genetic change being capable of being passed down to subsequent generations.^[1] An analysis of some of the ethical issues, as related to the SA context, will now be discussed.

The ethics of mitochondrial donation specific to the South African context

Several ethical questions have been raised and flagged as concerns in the past regarding mitochondrial donation^[1,4,9,10] The following discussion includes a few key points that require further analysis, specific to the SA context.

Infertility issues in Africa

Although mitochondrial donation is not a treatment for infertility *per se*, it requires the use of ART procedures. It is a way to avoid transmission of mitochondrial disorders, which often cause severely debilitating and disabling health problems and can result in the death of babies, children and young people.^[11] The family structure in developing countries usually depends on children for economic survival, therefore being unable to have a healthy child, or being infertile, is not only regarded as an individual medical problem but also as a social and public health issue.^[6] With the success of marriage in many African countries resting on the ability of women to bear children, the consequences of infertility or being unable to bear children, especially in African societies, can be devastating.^[12] The effects of infertility or involuntary childlessness create much broader issues for women in Africa as compared with Western societies. African women who cannot have children are often stigmatised, isolated, subjected to physical and psychological abuse and may even find themselves disinherited by their own families and cut off from their communities.^[6] According to the 2022 global infertility prevalence estimates published by the WHO, approximately one in six people have experienced infertility at some stage in their lives globally.^[13] Lifetime infertility prevalence (defined as the proportion of a population which has experienced infertility in their life) was recorded as 17.8% in high-income countries (HICs) and 16.5% in LMICs. Of the lifetime infertility prevalence statistics, 13.1% was recorded as the lifetime infertility prevalence of the WHO African region. Therefore, any belief that infertility is not an issue in poor countries, specifically on the African continent where population rates are high, should be quashed. According to 2019 statistics, out of 151 registered IVF units in Africa, 37 were found in SA.^[6] In addition, the African countries with the highest number of IVF centres included SA, Egypt, Ghana, Kenya and Nigeria. This emphasises the demand for treating various forms of infertility issues in SA. While the treatment of infertility issues as a broad concept is not in question, mitochondrial donation has its own specific set of ethical concerns that merit discussion before the issue of whether this type of ART should be covered under our current ethicolegal framework is considered.

The 'three-terminology' debate

The techniques used for mitochondrial donation or transfer, which are essentially maternal spindle transfer or pro-nuclei transfer, require three gametes to ultimately produce a healthy embryo. Both these techniques result in the child inheriting nuclear DNA from the intending parents and mitochondrial DNA from the female donor.^[14] As a result, these techniques introduced the 'three-parent embryos', 'three-parent babies' and 'three-person IVF' debate, with the implication that the children born from the use of these techniques may suffer from psychosocial problems as a result of having more than two parents.^[10] However, if the child only inherits mitochondrial DNA from the donor (<30 genes) and all its nuclear DNA (>20 000 genes) from the intending parents,^[9] it could be argued that the 'three' terminology is merely used to garner public interest and excitement and spur controversy, at the expense of accuracy. Similarly, debates around mitochondrial donation in the UK, prior to its legalisation, regularly drew upon figurative and emotive language.^[1] Lord Robert Winston, renowned fertility expert

and IVF pioneer, warned against the use of the 'three parent child' terminology, indicating that it was used to cause controversy over the issue. In addition, a report by the Department of Health (2014a), a central institution of UK biomedical regulation, concluded that a mitochondrial donor could not be considered a second mother and regarded the term 'three parent families' as unacceptable. The report further stated that:

'...genetically, the child will, indeed, have DNA from three individuals but all available scientific evidence indicates that the genes contributing to personal characteristics and traits come solely from the nuclear DNA, which will only come from the proposed child's mother and father. The donated mitochondrial DNA will not affect those characteristics.'^[1]

The use of the 'three-parent' terminology also brings into question other forms of infertility treatment that are widely accepted in current society, for example, egg and sperm donation, adoption and surrogacy. Mitochondrial donation appears to be an extension of the development of scientific technology aimed at tackling mitochondrial disease and should be treated as such, with the same psychosocial risks considered as in other types of infertility treatment. However, even if mitochondrial donation could be considered as another type of ART, is there a case for its application in SA?

A case for mitochondrial donation in South Africa

According to Meldau *et al.*,^[14] the number of undiagnosed cases of mitochondrial disease, which is prevalent in all SA populations, is astonishingly high. Furthermore, even though they are individually rare, mitochondrial genetic disorders, as a group, are thought to be responsible for a significant proportion of inherited metabolic diseases.^[14] In addition, there is no cure for mitochondrial disease, exclusively inherited from the mother, with treatment being mainly supportive. A woman with mutant mitochondrial DNA can pass the disease on directly through female offspring, resulting in heritable genetic afflictions transmitted for multiple generations down the maternal line.^[15] The effects of the disease on the child can be devastating and even fatal. However, even if the resulting child does not inherit mitochondrial disease because of mitochondrial donation, the long-term effects on the child and future generations remain unknown, as the technology is relatively new. The 2019 UNESCO Report of the International Bioethics Committee on assisted reproductive technologies (ART) and parenthood recognises mitochondrial donation under its section on 'technological and scientific developments', but however cautions that 'more investigation on the possible effects of introducing mitochondrial DNA from a different individual is necessary to evaluate the safety and feasibility of this treatment'.

The question then becomes whether the risk outweighs the benefits regarding a new technique that may introduce new harms which may only manifest years later. Seeing as there is little insight as to how mitochondrial donation will impact the child in the long term and affect future generations, more research is required on its long-term effects. However, more research on these effects can only be undertaken if the technique is applied in SA under regulatory controls. Allowing the application of mitochondrial donation in a regulated manner could also dispel any fears about eugenics and the definition of normality.

Relevant entities to input on mitochondrial donation

The South African Society of Obstetricians and Gynaecologists (SASOG) was formed in 1946. It aims to achieve its vision – excellence and equity in women’s health – by (including but not limited to): improving women’s health in SA; promoting excellence in clinical practice, training and research in obstetrics and gynaecology; and representing the discipline of obstetrics and gynaecology nationally, regionally and internationally.^[16] The Infertility Awareness Association of South Africa (IFAASA) is a non-profit organisation established in 2013 to support southern Africans living with reproductive health issues. IFAASA’s vision is to be the leading southern African infertility awareness association while driving public and industry awareness and understanding of infertility.^[17] Perhaps as a first step, a multidisciplinary team consisting of scientists, ethicists and legal experts could be convened by SASOG and IFAASA to consider whether mitochondrial donation should be taken forward in SA.

Conclusion

Currently, it appears that mitochondrial donation is not covered under the SA legal framework, as a third gamete donor (second female) does not appear permissible in the context of in vitro fertilisation. However, the law always tends to lag behind scientific developments, and it is possible that this novel form of IVF was not envisaged at the time the regulations were written. However, if mitochondrial donation is included within our legal framework, guided checks and balances need to be put in place to ensure that the technology is not abused. Any guidance must also consider the fact that modifications to heritable genetic afflictions may widen inequity gaps, specifically where there are concerns about accessing a procedure or treatment. In addition, amending the ambiguities in the NHA regarding the definition of reproductive cloning should also be taken forward as a parallel process. The current definition is ambiguous, and the failure to distinguish between reproductive adult cloning and reproductive embryo cloning adds to the already ambiguous interpretation of the definition.

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