Original article

Mitochondrial donation – birth of a policy

Andrea Büchler[a], Karène Parizer[a]

a University of Zurich, Collegium Helveticum ETH/UZH

Abstract

Mitochondrial donation (or mitochondrial replacement techniques, MRT) is a special form of in vitro fertilisation involving the mitochondrial DNA (mtDNA) of a third (donor) party. This technique eliminates the risk of severe mitochondrial pathologies, genetically inherited from the mother, by replacing part of her mtDNA with healthy mtDNA from another woman, the donor.

This paper explores the ethical dimensions of this technique and their impact upon policy decisions. In particular, it is argued that despite the spectacular fact that a child might have three genetic sources, the biparental paradigm is not truly challenged. The most important issue surrounding mitochondrial donation is the fact that it involves germline modification. To this extent, approval of such a technique sets a precedent. There is a wide and traditional international consensus on prohibiting human germ-line modification, and this paper examines whether the specific procedure of mitochondrial donation falls within this logic.

Key words: mitochondrial donation, mitochondrial replacement techniques (MRT), medical assisted procreation, germ-line modification.

A. Introduction

Mitochondrial donation (or mitochondrial replacement techniques, MRT) is a special form of in vitro fertilisation involving the mitochondrial DNA (mtDNA) of a third (donor) party. This technique eliminates the risk of severe mitochondrial pathologies, genetically inherited from the mother, by replacing part of her mtDNA with healthy mtDNA from another woman, the donor. This implies that the future child will have DNA from both parents, as well as some DNA from a healthy female donor of mitochondrial contents.

Mitochondria are small structures contained in the cytoplasm of human cells, including eggs. They generate the majority of a cell's energy supply which powers every part of our body. The genetic contribution of mitochondria is small, both qualitatively and quantitatively. Qualitatively, because they do not transmit any of the traits that confer the usual family resemblances and distinctive personal features. Quantitatively, mitochondria constitute approximately 0.1% of the human genotype. Nevertheless, for any cell to function, the mitochondrial genes need to work properly, so the impact when they fail to function is considerable. Mitochondria with gene abnormalities can cause severe medical disorders known as mitochondrial diseases. Mitochondrial diseases affect parts of organs that use a lot of energy, causing problems such as loss of muscle coordination, heart disease, liver disease, neurological problems, diabetes mellitus, deafness and dementia, leading to morbidity and in some cases to premature death. In fact, patients can be mildly, severely or fatally affected, depending on which organs are dysfunctional and to what extent. According to the Human Fertilisation and Embryology Authority (the UK regulator of the use of gametes and embryos in assisted reproduction and research), in the UK, one in 200 children is born with mitochondrial disease each year, with symptoms ranging from light to severe,[1] whereas in the scientific literature it is estimated that one in 400 persons carries a disease-causing mitochondrial mutation [1]. However, the probability of a child being born with mitochondrial disease is difficult to evaluate [2]. It is estimated that the number of women likely to be eligible for the procedure under consideration will be around 150 per year in Britain [3] and about 800 per year in the United States [4].

Both sexes can inherit a mitochondrial disease, but it is only women who are at risk of transmitting the disease to their children. The two most common techniques used for mitochondrial transfer are maternal spindle transfer (MST) and pronuclear transfer (PNT). In the first method, MST, a patient's nuclear genetic material is removed from her eggs and transferred into donated eggs once their nuclear genetic material has been removed. The eggs containing the patient's nuclear genetic material and the donor's healthy mitochondria are fertilised with the intended father's (or a donor's) sperm to create embryos. In the second method, PNT, the patient's eggs are fertilised with the intended father's (or a donor's) sperm in a laboratory to create embryos. The nuclear genetic material within each embryo is then transferred into embryos created using donated eggs and sperm from the sperm provider, once the nuclear genetic material has been removed. In both MST and PNT, the resulting embryos containing the female patient's and her partner's (or sperm donor's) genetic material as well as the mitochondria donor's healthy mitochondria are transferred to the patient's womb and hopefully implant and develop into a foetus. There is a wide and traditional international consensus on prohibiting human germ-line modification,[2] and in

1 Confer www.hfea.gov.uk/7517.html (accessed 30/1/2017).

2 The Universal Declaration on the Human Genome and Human Rights (UNESCO) indicates in Art. 24 that "Germ-line interventions" could be "contrary to human dignity".

this paper we will examine whether the specific procedure of mitochondrial donation falls within this logic. Initial projects involving gene editing with the CRISPR/Cas9 method have prompted extensive discussion of its various dimensions. Consensus has been reached among many scientists that a moratorium on germ-line interventions is needed to reflect on their medical and ethical implications [5, 6]. This is not the place for extensive discussion of the various issues; instead, we would like to highlight the special features of mitochondrial donation *versus* germ-line editing with CRISPR/Cas9, for example.

To date, the United Kingdom is the first and only country to have set a regulatory framework,[3] enabling women who are at significant risk of passing a mitochondrial disease onto their children to receive treatment at a clinic which has been granted a specific licence to carry out this new technique.[4] The UK is known for its forefront approach in reproductive technologies (including the birth of the first IVF baby, Louise Brown, 1978) and genetics (Dolly, the cloned sheep, 1996), as well as its liberal policy: it is one of the few countries where the creation of embryos for research,[5] including mixed human-animal embryos[6] is allowed.

As for other countries, this prohibition is often subject to debate with no policy change in sight, including in the US where a cautious approach has been adopted. Before analysing the various attitudes, we would like to draw attention to a semantic difference: whereas in the UK, this technique is usually named 'mitochondrial donation', highlighting the altruistic dimension of such a procedure, US scholars and policy makers tend to use a more general term, namely 'mitochondrial replacement technique' (MRT).

The technique of mitochondrial donation has attracted intense media interest, even before the first babies were born through this procedure.[7] On the one hand, this breakthrough technique has gained the support of a number of scientific reviews [7, 4], as well as some academics [8–11]. On the other hand, there has been much reluctance, mostly due to the third party's contribution and a lack of long-term experiments [25]. In this paper we will discuss the ethical aspects of this technique and their impact on policy decisions. In particular, we argue that despite the spectacular fact that a child might have three genetic sources, the biparental paradigm is not truly challenged. The most important issue surrounding mitochondrial donation is the fact that it involves germ-line modification. To this extent, approval of such a technique sets a precedent.

B. Ethical considerations and public interest

An important general ethical consideration underlying any decision in the field of reproductive technologies is reproductive autonomy. The other ethical considerations and aspects of public interest are more specific to the mitochondrial donation procedure.

1. Reproductive autonomy

Whereas infertility is recognised as pathology by the World Health Organisation (WHO), procreation is considered to be an element of the physical and mental well-being of a person. The wish to have a child has long been considered by the Swiss Federal Court as a basic expression of personality development, and the Court placed it under the protection of the fundamental right to personal liberty enshrined in Art. 10(2) of the Swiss Constitution.[8] The reason given by the Court was that the decision to have and raise children belongs, for many people, to the essential elements that give meaning to their lives. The inability to procreate is seen as a burden by people who cannot have children for biological reasons, or who, because of a genetic predisposition or risk to the health of the unborn child, do not consider natural childbearing as responsible.[9] According to this jurisprudence, State regulations that limit access to medically assisted procreation and thus hinder the achievement of the desire for children, infringe on a fundamental right [12, 13]. Whereas this position was not widely shared initially [14, 15], the desire to have a child or to become a parent is gaining broad recognition as a fundamental aspect of the development of personality and personal autonomy [12, 13, 16–19]. Thus, in accordance with this jurisprudence, any restrictions on medically assisted procreation methods constitute a violation of the fundamental right to personal liberty.[10] Any restriction on personal liberty – like any other restrictions on fundamental rights – are defensible only if they rely on a sufficient legal basis,

3 Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015.

4 Confer www.hfea.gov.uk/9942.html (accessed 30/1/2017).

5 Contrary to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, according to which: "The creation of human embryos for research purposes is prohibited" (Art. 18-2). This is one of the reasons that the UK has never signed this so-called Oviedo Convention.

6 According to the Human Fertilisation and Embryology Act 2008, in pursuance of a licence, mixed embryos can be created for a period of 14 days, but it is prohibited to place them in a woman.

7 The first baby, whose mother carries genes associated with Leigh syndrome (a fatal disorder that affects the developing nervous system) was born in September 2016 after treatment of his parents, Jordanian citizens, by a US-based team in Mexico (Exclusive: World's first baby born with new '3 parent' technique. New Scientist. September 27, 2016. Available at: www.newscientist.com/article/2107219-exclusive-worlds-first-baby-born-with-new-3-parent-technique [accessed 30/1/2017]). Another baby was born in the Ukraine in January 2017 after using mitochondrial donation as infertility treatment of his mother (First baby born using 3-parent technique to treat infertility. New Scientist. January 18, 2017. Available at: www.newscientist.com/article/2118334-first-baby-born-using-3-parent-technique-to-treat-infertility [accessed 30/1/2017]).

8 ATF 115 Ia 234; ATF 119 Ia 460.

9 ATF 115 Ia 247 (5a); similarly ATF 119 Ia 475 (5a).

10 ATF 115 Ia 247.

are justified in the public interest or for the protection of the fundamental rights of others and must be proportionate to the specific goal.[11]

This brings us to the question of whether any of the following considerations of public interest justifies restricting access to mitochondrial donation.

2. Safety

The safety of the mitochondrial replacement procedure has not been completely established. It has been shown to be successful in mice [20] and monkeys [21], but these experiences are recent and one could argue that it is necessary to wait until these primates have reproduced and their offspring have been examined. The move from animal and other preclinical studies to the first human application is always uncertain [22] and ethically contentious [23, 24]. Risks and uncertainties of a first-in-human application still exist.

The main disagreements are about the function of the mitochondria, its interactions with nuclear DNA (nDNA) and the health implications of mitochondrial donation. Complex interactions between nDNA and mtDNA [25] and organelles contained in the cytoplasm might introduce epigenetic alterations in nDNA [26]. Some remaining concerns include epigenetic harm caused by nuclear transfer, mito-nuclear mismatch, impact of mitochondria on traits, i.e. not just metabolic function, and preferential replication of even tiny amounts of carryover-mutated mtDNA.[12] Very recently, scientists using human cells have shown that even small amounts of mtDNA carried over during nuclear transfer for mitochondrial replacement can lead to mtDNA genotype reversion [27]; in other words, it can potentially cause the disease the therapy was designed to avoid. Nevertheless, according to Dieter Egli, the stem-cell scientist at the New York Stem Cell Foundation Research Institute who led this work, the problem identified can be surmounted, for instance, by improving techniques to reduce the level of carried-over mitochondria or matching donors such that their mitochondria are unlikely to compete, but until this is shown for certain, caution is highly recommended [28].

3. Using human embryos and eggs

Pro-Nuclear Transfer (PNT) and Maternal Spindle Transfer (MTS) both concern mitochondrial donation, but whereas only the first technique involves creating and destroying embryos in the process, both require egg donation.

Using human embryos in research is controversial; in PNT procedures embryos are created specifically for this kind of treatment. On the other hand, this technique may avoid aborting affected foetuses. To this extent, it is similar to pre-implantation genetic diagnosis (PGD).

As for human egg donation, egg extraction is a very common but complex process [29], with potential risks for the healthy donor. These risks include memory loss, bone pain, seizures and Ovarian Hyperstimulation Syndrome. The medical risks are often downplayed and follow-up care tends to be minimal. In the specific context of mitochondrial donation, recruiting egg donors can be even more difficult, as maternal relatives are at risk of transmitting the same mutation. However, this specific risk could be avoided by the participation of female paternal relatives, sharing the father's mitochondrial DNA. Research in this field has already required hundreds of eggs from women, and in this context, there is a concern that the great need for human eggs would lead to further exploitation. It is thus not surprising that several critics have pointed out that a market in women's eggs is ethically problematic in terms of the doctor's duty to do no harm and the limitations of 'informed' consent [30].[13] On the other hand, one could argue that eggs could be donated by women who are conscious of the medical risk and who are truly willing to give without any financial pressure, *a fortiori* when the eggs have already been extracted and are leftovers that will not be used by the donors.

4. Germ-line intervention and genetic modification

The ethically and politically most contentious aspect of mitochondrial donation is that it is a technique that introduces germ-line intervention. The new mtDNA can be transmitted to the child's offspring. Approval of the technique could set a precedent for genetic alteration and it is feared this could be used for enhancement purposes. The mitochondrial replacement procedure, however, concerns a specific pathology that the parents-to-be would like to avoid. It does not involve multicriteria seeking of common pathologies, nor social or esthetic enhancement. In practice, it seems that physicians are more worried about passive attitudes, i.e. abstention of diagnosis, resulting in a birth of a child with substantial pathological risk, than about unfounded applications, which are more theoretical than real [31].

However, the key issue in understanding mitochondrial donation technologies is the fact that it involves the transfer of genetic but not nuclear material. There is a significant difference between modification of mitochondrial DNA (mtDNA) and modification of nuclear DNA (nDNA):[14] first, MRT is different from any technology that could be applied to the nuclear genome in that it would entail replacement of pathogenic mtDNA with unaffected mtDNA, as opposed to targeted genomic editing of either mtDNA or nDNA. The replacement of

11 Art. 36, Federal Constitution of the Swiss Confederation of 18 April 1999 (Status as of 1 January 2016).

12 3-Person IVF, information provided by the Center for Genetics and Society. Available at: www.geneticsandsociety.org/internal-content/3-person-ivf-resource-page#3 (accessed 30/1/2017).

13 The author qualifies the phenomenon of ignorance of potential female exploitation: 'the lady vanishes', referring to Alfred Hitchcock's spy movie of 1938.

14 The following explanations were provided in the FDA commissioned report [34].

whole, intact, and naturally occurring mitochondrial genomes represents a qualitatively different form of potentially heritable genetic change from that resulting from any approach for modifying nDNA, which would likely involve gene editing rather than wholesale replacement. Second, although mtDNA plays a central role in genetic ancestry, traits that are carried in nDNA are those that in the public understanding constitute the core of genetic relatedness in terms of physical and behavioural characteristics, as well as most forms of disease. Third, though some forms of energetic 'enhancement' (such as selecting for mtDNA to increase aerobic capacity or cognitive skills) might hypothetically be possible through MRT, they appear to be far less likely relative to what might be possible in modifications of nDNA.

In the UK, the fact that these techniques, despite being a germ-line modification, do not involve a genetic modification as the nuclear substance remains intact, was the main consideration of the policy maker: "There is no universally agreed definition of 'genetic modification' in humans – people who have organ transplants, blood donations or even gene therapy are not generally regarded as being 'genetically modified'. While there is no universally agreed definition, the Government has decided to adopt a working definition for the purpose of taking forward these regulations. The working definition that we have adopted is that genetic modification involves the germ-line modification of nuclear DNA (in the chromosomes) that can be passed on to future generations. This will be kept under review" [32].

In anticipation of these concerns, the government and leading supporters have attempted to clearly demarcate the boundaries between mitochondrial donation and nuclear modification, although leading scientists have questioned this position, accusing the government of dishonesty, misleading the public and acting by stealth.[15] It seems that making clear that this is not genetic modification was politically prudent as it would have been unlikely that the public would accept attempts to approve the modification of the nuclear genome at this stage [33].

In the US, the position of the authors of the FDA-commissioned report was similar. While insisting on the significant and important distinctions between modification of mtDNA to prevent transmission of mtDNA disease through MRT and modification of nDNA, it was concluded that "[c]oncerns raised by potential heritable genetic modification warrant exercising significant caution and imposing restrictions rather than completely prohibiting the use of MRT to prevent transmission of serious mtDNA disease" [34]. Nevertheless, as we shall see, some limitations on the use of these techniques have been set in this report.

15 Connor S. Exclusive: Scientists accuse government of dishonesty over GM babies in its regulation of new IVF technique. The Independent. July 28, 2014.

5. Tri-genetic contribution

The tri-genetic contribution at stake was the main focus of the media (often under the spectacular heading of 'three-parent babies')[16] during and after the UK parliamentary discussions in 2015.

Due to the fact that three sources of DNA are involved, mitochondrial donation is currently quite contentious, adding more complexity to the issue of genetic therapies. As mitochondria play an important role in many bodily processes, the genetic contribution of the donor might be viewed as considerable. However, as we saw, mitochondrial donation involves the transfer of genetic but not nuclear material. Moreover, the third party's implication should not be overestimated: this contribution concerns less than one per cent of the future child's genome. These qualitative and quantitative aspects explain why mitochondrial donation should be associated with tissue donation rather than egg donation. In other words, the bi-parental legal paradigm is not challenged.

As for the psychological aspects of this technique: the question can be raised whether the genetic make-up of children born as a result of mitochondrial replacement will affect their emotional well-being when they become aware that they are different from other children, that their conception was experimental, and also by the fact that they will be encouraged to participate in follow-up studies throughout their life. We think that this argument should be tempered by the long-term experience with (entire) gamete donation. According to most of the studies [35–39], children conceived through gamete donation are doing well, they consider the people who raise them as parents, and not the donor (the question of donors' anonymity is another issue). Thus, the social dimension of parenthood overrides the genetic one. In any case, the probability of people condemned unnecessarily to a life of pain and illness complaining about an identity crisis would be extremely low considering the benefit at stake.

6. The slippery slope argument

Mitochondrial donation has raised anxiety over a possible slippery slope in two directions:

Firstly, towards full-scale germ-line manipulation seeking to address a broader range of conditions: it might be used not only to cure mitochondrial diseases, but also to enhance female idiopathic or age-related infertility,[17] for example. In fact, women's fertility declines considerably after the age of 35, because of ageing of the egg cytoplasm, the non-nuclear part of the egg that is replaced during mitochondrial transfer.

16 Achenbach J. Ethicists approve "3 parent" embryos to stop diseases, but congressional ban remains. The Washington Post. February 3, 2015; Sample I. "Three-parent" babies explained: what are the concerns and are they justified? The Guardian. February 2, 2015; Gallagher J. UK approves three-person babies. BBC News. February 24, 2015.

17 Smyth C. Allow three-parents IVF to help older women too, says pioneer. The Times. February 9, 2015.

Indeed, one of the American scientists who pioneered research in this domain, Dr Shoukhrat Mitalipov, a senior scientist at the Oregon Health and Science University in Portland, has requested permission from the US Food and Drug Administration (FDA) to conduct trials of mitochondrial transfer as a treatment for age-related infertility.[18] According to Marcy Darnovsky, executive director of the Center for Genetics and Society (a nonprofit information and public affairs organisation based in Berkeley, California), "it's important to realise that if the FDA were to approve these techniques, it would have few mechanisms for preventing what would essentially be 'off-label uses'."[19] This reasoning presumes that the risk is about extending the initial pathological framework to other circumstances, sometimes social. This 'slippery slope' argument is rejected by others, like John Harris, who claims that this kind of argument "is applied to the extension of the technique, not to the use of the same technique for another therapeutic purpose – and treating infertility is recognised as a therapeutic purpose".[20] This brings us to the question of the definition of age-related infertility: is it social, because women often prefer to wait before getting pregnant, or therapeutic, as John Harris considers it? Following his reasoning, it would be hard to argue that it can be used for one group of patients, but not for another, assuming that the procedure is effective and safe.

Secondly, the technique of mitochondrial donation can be put towards progressively eliminating the clear line between nuclear and mitochondrial interventions. It has been argued that if mitochondrial donation is permitted, there will almost inevitably be a case in which potential parents with a condition that might be prevented by intervention in the nuclear DNA will argue that there really is no significant difference between that and (permitted) intervention in the mitochondrial DNA. For them, and many others, the legislative bar and the reasoning behind it will be meaningless [40].

7. Other alternatives

Given the uncertainty, unpredictability and irreversibility of germ-line modification, other alternatives must be examined. The two current primary alternatives to mitochondrial donation for women with mitochondrial disease who wish to have a genetically related child (at least to the woman's partner) are egg donation and pre-implantation genetic diagnosis (PGD). The option of prenatal genetic diagnosis also exists but it implies abortion if the embryo carries the disease. Egg donation excludes a genetic link between the mother and the child and relies on a supply of donor eggs. As for PGD, where embryos created in vitro are tested and low-risk embryos are selected to start a pregnancy, it seems that the complexity of mitochondrial disorders means that this kind of testing reduces the risk of transmission but is never able to completely eliminate it. Since the relationship between the proportion of mutations in the embryo and the severity of disease in the resulting offspring is not yet understood clearly for all mutations, it may be unclear what limits should be set to exclude an embryo from transfer [41–43]. In many cases, the best one can achieve is the selection of the 'least' affected embryo for transfer. In fact, PGD is not reliable enough to ensure a healthy child, and can only aim to reduce reproductive risk; this raises challenging questions about parental and medical responsibilities from an ethical point of view [43–46]. So although several studies have shown that PGD would be promising for the prevention of mitochondrial diseases [47–50], it would have limited success for those with homoplasmic mitochondrial disease (women with close to 100% of their mtDNA mutated). However, in such rare cases, pregnancy would also be considered as endangering the woman's health. Of course, when penetrance of the disease is significantly lower in one sex, PGD involving sex selection might be efficient [51].

C. Current policies

Mitochondrial donation is a new phenomenon and policy is starting to be established. We will examine the current situation in three countries with fundamentally different approaches.

In the United Kingdom, under the licensing regime defined in February 2015 by the *Human Fertilisation and Embryology (Mitochondrial Donation) Regulations* (in force since 29 October, 2015), clinics are allowed to perform these techniques if they provide clear evidence to the HFEA that they have both experienced staff and the necessary equipment. Each application is considered on a case-by-case basis and the potential patient's specific circumstances are taken into account.[21] These regulations do not permit the use of mitochondrial donation for fertility treatment, but only for the purpose of avoiding the inheritance of serious mitochondrial disorders. More precisely, access is permitted under the following circumstances: 1. There is a particular risk that any egg extracted from the ovaries of a woman or an embryo created by the fertilisation of such an egg may have mitochondrial abnormalities caused by mitochondrial DNA; 2. There is a significant risk that a person with those abnormalities will have or develop serious mitochondrial disease.[22] Only women who meet these two conditions are eligible to use the

18 Connor S. Scientist who pioneered "three-parent" IVF embryo technique now wants to offer it to older women trying for a baby. The Independent. February 8, 2015.

19 Available at: www.geneticsandsociety.org/press-statement/strangely-mixed-signal-report-germline-mitochondrial-manipulations (accessed 30/1/2017).

20 Ibid.

21 HFEA, Press release, 29 October, 2016, World first as mitochondrial donation regulations come into force.

22 Section 5(a) and section 8(a), Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015.

techniques. Neither lesbian couples who wish to use these techniques to conceive a child who would be genetically related to both women, nor persons who seek to enhance fertility are eligible.

Moreover, these regulations follow a 'tissue-donation-oriented attitude' towards these techniques. They limit the application of the *Human Fertilisation and Embryology Authority (Disclosure of Donor Information) Regulations 2004*: they do not apply to information requests about mitochondrial donations. In other words, children born following mitochondrial donation will only be able to access limited and non-identifying information about their mitochondrial donor, such as screening tests, family health and personal information provided by her. Provision is also made for the mitochondrial donors to access limited and non-identifying information about children born from their donations, although they will not be notified about requests for information.[23]

A fortiori, a person who donated mitochondria is not eligible to apply for a Parental Order on the basis of this donation alone.[24] In fact, the idea of triple legal parenthood was rejected by the UK Ministry of Health during the preparation of the *Human Fertilisation and Embryology Act 2008* [52], section 26 of which had already set the HFEA competence to regulate such a technique in the future.

The 2015 Regulations formed the end of a long enquiry process:[25] three scientific reviews by an expert panel,[26] a dialogue exercise to assess public attitudes delivered by Sciencewise,[27] a call for evidence on the ethical issues organised by the Nuffield Council on Bioethics [53], public consultation and government guidance on draft regulations led by the UK Department of Health [32] and several debates within the Houses of Parliament.[28] The technique was eventually approved for clinical use by the HFEA in December 2016,[29] and the first licence was awarded in March 2017 to the Newcastle Fertility Centre.[30]

In fine, the general assumption of the British policy maker was that the ultimate test to prove whether any novel IVF techniques work is through human application, and this involves accepting that there will be risks [33].

In the United States, mitochondrial replacement is currently not approved as safe and effective. The US does not have an equivalent to the HFEA,[31] but applications for permission to use any form of gene therapy must be submitted to the Food and Drug Administration (FDA), which has started a process to assess the scientific and ethical questions surrounding these techniques. On 3 February, 2016, a report commissioned by the FDA was issued by the Institute of Medicine of the National Academies of Sciences, Engineering and Medicine [34] confirming that it is ethically permissible for clinical research into mitochondrial replacement techniques to continue under certain conditions. The most important restriction that this report includes is the following: as MRT results in genetic modification of germ cells, and because mtDNA is solely inherited from the mother, these techniques producing female offspring would constitute heritable genetic modification (germ-line modification), as the children could pass on these genetic changes. Such modification is not heritable in males, however, since sperm do not contribute mtDNA to the next generation. Thus, MRT producing male offspring would not constitute heritable genetic modification (germ-line modification). Following this reasoning, the authors of the report recommend proceeding in two stages. In the first stage, initial MRT clinical investigations should be considered by the FDA only if and when certain conditions are met;[32] in particular, intrauterine transfer for gestation is limited to male embryos. In the second stage, following successful initial investigations

23 Explanatory Note, Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015.

24 Section 18, Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015.

25 For a reaction to the criticism according to which the new regulations were rushed through, see [54].

26 HFEA, Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: update 2014. Available at: www.hfea.gov.uk/8807.html (accessed 30/1/2017).

27 HFEA, Mitochondria replacement consultation: Advice to Government, March 2013. Available at: www.hfea.gov.uk/docs/Mitochondria_replacement_consultation_-_advice_for_Government.pdf (accessed 30/1/2017).

28 House of Commons debate, February 3, 2015. Available at: www.parliament.uk/business/news/2015/february/commons-debate-statutory-instrument-on-mitochondrial-donation/ (accessed 30/1/2017); House of Lords debate, February 24, 2015. Available at: www.parliament.uk/business/news/2015/february/lords-mitochondrial-donation-si/ (accessed 30/1/2017).

29 HFEA, HFEA permits cautious use of mitochondrial donation treatment, following advice from scientific experts, December 15, 2016. Available at www.hfea.gov.uk/10563.html (accessed 30/1/2017).

30 Available at: www.hfea.gov.uk/10635.html (accessed 30/1/2017).

31 For other differences between the UK and the USA, see [55].

32 Initial safety is established, and risks to all parties directly involved in the proposed clinical investigations are minimised; likelihood of efficacy is established by preclinical research using in vitro modelling, animal testing, and testing on human embryos as necessary; clinical investigations are limited to women who otherwise are at risk of transmitting a serious mtDNA disease, where the mutation's pathogenicity is undisputed and the clinical presentation of the disease is predicted to be severe, as characterised by early mortality or substantial impairment of basic function; if the intended mother at risk of transmitting mtDNA disease is also the woman who will carry the pregnancy, professional opinion informed by the available evidence determines that she would be able to complete a pregnancy without significant risk of serious adverse consequences to her health or the health of the foetus; clinical investigations are limited to investigators and centres with demonstrated expertise in and skill with relevant techniques; FDA has reviewed haplogroup/haplotype matching and if compelling, considered it as a means of mitigating the possible risk of mtDNA–nDNA incompatibilities.
The report also sets more general principles for a cautious approach, such as the priority of the health and well-being of any future children born as a result in the balancing of benefits and risks in clinical investigations; setting standards of study designs and of techniques protocols; integration of data from research or clinical practices outside FDA jurisdiction; and collection of long-term information regarding psychological and social effects on children, including their perceptions about their identity, ancestry, and kinship.

in males, the FDA could consider extending research to include the transfer of female embryos, under further conditions.[33] The authors of the report consider that the mere fact of genetic contribution from two women of different maternal lineage, despite its complexities, should not form a basis for prohibiting initial investigations. As for the manipulation of human embryos, useful ethical frameworks that have already been developed regarding their responsible use could inform appropriate parameters for embryo manipulation in the conduct of preclinical and clinical investigations.

However, the probability that MRT will be used soon in the US seems low for political reasons [56, 57]. Two obstacles are in the way: first, the 2016 *Appropriations Act* (framing spending permissions to federal agencies for the fiscal year of 2016). This law prevents the FDA from using federal funds to accept 'investigational new drug applications' (INDs) that would allow them to approve research into heritable genetic modification of a human embryo. Second, the Dickey-Wicker amendment of 1995, which prohibits federal funds being used for any research in which a human embryo is either created for research purposes or destroyed as part of the research. Even though this amendment has no power to prevent private research, the situation is blocked under these two laws in combination: the FDA declared that MRT needs its approval, but the 2016 federal law prohibits the FDA from reviewing proposals for research. In other words, whether the private sector would be funding the research or not, the FDA gets the final say over whether research can proceed. But since the FDA is not allowed to use federal money to approve any INDs, its hands appear to be tied, unless Congress eliminates these provisions, which is a very unlikely perspective given the political climate.

In Continental Europe, the technique of mitochondrial donation is prohibited, or at least not explicitly authorized,[34] due to the very solid consensus on germline modification. Switzerland does not make any exception,[35] as any kind of germ-line intervention is strictly forbidden. According to the Federal Constitution, "All forms of cloning and interference with the genetic material of human reproductive cells and embryos are unlawful."[36] This constitutional disposition is laid down in the *Federal Act on Medically Assisted Reproduction*: "(1) Any person who genetically modifies a germ-line cell or an embryonic cell shall be liable to a term of imprisonment. (2) The same penalty shall apply to any person who uses a genetically modified reproductive cell for impregnation or uses a similarly modified impregnated ovum for further development into an embryo."[37] The reasoning behind both norms is to protect human dignity. Their scope covers the technique of mitochondrial donation which has consequences for future generations. However, in the Swiss context, unlike some other countries in Continental Europe, forbidding mitochondrial donation might also be considered as coherent with the prohibition of egg donation[38] (egg donation is also prohibited in Germany and Norway). Although mitochondrial donation cannot be viewed in the same way as egg donation for the reasons we saw, where an entire gamete is at stake, the donation of any portion of a female reproductive cell seems to be excluded as mitochondria form part of the egg, and egg donation is strictly forbidden. This aligns with the traditional argument concerning the fear of splitting motherhood, which could also be a reason to reject this technique [59]. This argument has served as a justification to prohibit not only egg donation, but also embryo donation and surrogacy. In fact, several reasons are regularly put forward to justify the prohibition of these procedures: egg donation goes far beyond natural procreation, in contrast to sperm donation which can occur without medical intervention, and thus is not viewed as a new human experiment; child welfare considerations require that the child be protected against any form of splitting of biological, genetic and social motherhood, which is important for the development of the child's identity; egg donation might impair the donor's health and expose her to the risk of exploitation [60]. Indeed, allowing for egg donation has just recently been put on the political agenda. Nevertheless, it is very unlikely that the technique of mitochondrial donation – which implies much more than egg donation – will be allowed in Switzerland in the short or medium term.

In the meanwhile, also in Switzerland preliminary discussions have taken place [16, 56] and a call for a moratorium has been voiced [61]. This transitional period of time, comparable to the one which was set by the *Federal Act on Non-Human Gene Technology*,[39] is considered necessary for the definition of a consolidated

33 Clear evidence of safety and efficacy from male cohorts, using identical mitochondrial replacement procedures, were available; preclinical research in animals had shown evidence of intergenerational safety and efficacy; the FDA's decisions were consistent with the outcomes of public and scientific deliberations to establish a shared framework concerning the acceptability of and moral limits on heritable genetic modification.

34 Article 13 of the 1997 *Convention on Human Rights and Biomedicine* states that "An intervention seeking to modify the human genome may only be undertaken for preventive, diagnostic or therapeutic purposes and only if its aim is not to introduce any modification in the genome of any descendants". However, according to Philipp Reuss, in the Netherlands, which indeed is not a signatory State to the Convention, mitochondrial donation is permitted to women with mitochondrial DNA alteration, as the procedure does not fall within the prohibition of Art. 24 of the 2002 Dutch Embryo [58].

35 For further legal analysis, see [61].

36 Art. 119 (2)(a) (Reproductive medicine and gene technology involving human beings), Federal Constitution of the Swiss Confederation of 18 April 1999 (Status as of 1 January 2016).

37 Art. 35 (Germ-line modification), Federal Act on Medically Assisted Reproduction of 18 December 1998 (Status as of 1 January 2013).

38 Art. 4, Federal Act on Medically Assisted Reproduction of 18 December 1998 (Status as of 1 January 2013).

39 See Art. 37a (Transitional period for putting genetically modified organisms into circulation), Federal Act on Non-Human Gene Technology, March 21, 2003 (n° 814.91).

policy, and would integrate further research in this field. Indeed, this position converges with certain scientific voices [62], according to which critical safety and efficacy questions need to be answered before regulatory approval or clinical use can occur.

D. Conclusion

Mitochondrial disease causes severe illness and distress to certain families and the potential to prevent it exists. An ethical assessment of the treatments that are available is essential, but the impact of the involvement of three genetic origins should not be overestimated. What is more important is how society defines genetic modification when germ-line modification is involved. To this extent, factors such as definitions, level of evidence, risks that are appropriate to assume, and communication of accurate and relevant information to the public need to be continually updated and are crucial challenges for policy makers. These challenges are not new, given the difficulties in legislating for cutting edge, yet unproven, reproductive technologies.

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Zusammenfassung

Die mitochondriale Ersatztherapie ist eine spezielle Form der In-vitro-Fertilisation unter Verwendung von mitochondrialer DNA einer Spenderin. Mit dieser Methode kann das Risiko, an einer schweren Erbkrankheit zu erkranken, die auf eine Genmutation im mitochondrialen Erbgut zurückgeht, beseitigt werden, indem Mitochondrien der potenziellen Mutter durch solche einer Spenderin ersetzt werden.

Der Beitrag geht den ethischen Implikationen dieser Technik nach. Wir argumentieren, dass, auch wenn das Kind genetisches Material von drei Personen hat, das «Zwei-Eltern-Paradigma» nicht angetastet wird. Der zentrale Punkt ist die Tatsache, dass die Mitochondrienspende eine Modifikation der Keimbahn darstellt. In diesem Sinne schafft die Zulassung derselben einen Präzedenzfall. Es besteht ein breiter internationaler Konsens darüber, dass Eingriffe in die menschliche Keimbahn untersagt sein sollen. Der Beitrag untersucht, inwiefern das spezielle Verfahren der Mitochondrienspende darunterfällt.

Résumé

Le don mitochondrial (ou les techniques de remplacement mitochondrial, TRM) est une forme spéciale de fécondation in vitro impliquant l'ADN mitochondrial (ADNmt) d'un tiers (donneuse). Cette technique élimine le risque de pathologies mitochondriales graves, génétiquement héritées de la mère, en remplaçant une partie de son ADNmt par un ADNmt sain d'une autre femme, la donneuse.

Cet article explore les dimensions éthiques de cette technique et leur impact sur les décisions politiques. En particulier, on fait valoir que, malgré le fait spectaculaire qu'un enfant ait trois sources génétiques, le paradigme biparental n'est pas véritablement mis à mal. Le problème le plus important concernant le don mitochondrial est le fait qu'il implique une modification de la lignée germinale. L'approbation d'une telle technique établit donc un précédent. Il existe un large consensus international traditionnel sur l'interdiction de la modification de la ligne germinale humaine et cet article examine si la procédure spécifique du don mitochondrial s'inscrit dans ce cadre.

Correspondence
Prof. Dr. Andrea Büchler

E-mail: andrea.buechler[at]rwi.uzh.ch

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