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UK's Legalization of Mitochondrial Donation in IVF Treatment: A Challenge to the International Community or a Promotion of Life-Saving Medical Innovation to Be Followed by Others?

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Abstract

Mitochondrial DNA diseases are rare genetic disorders, which can have a devastating effect on the patients' health and well-being. There is no cure for such diseases, although the recent experiments suggest that there may be a way to prevent them, by genetically altering the eggs or embryos through a procedure known as mitochondrial donation. However, such procedure not only raises serious safety and ethical concerns, but legal challenges as well, since it involves germline gene modification, which until recently was not legal in the UK or elsewhere. In February 2015 the UK Parliament amended the relevant legislation to allow such procedure, making UK the first state to openly challenge the global policy on germline gene modification. The article presents the scientific background to the procedure and discusses theregulatory challenges brought by the first case of its legalization.

Keywords

genetic mutations; mitochondrial donation; germline gene modification; genetic engineering; risk regulation; uncertainty; slippery slope; global policy

1 Introduction

In February 2015 the UK Parliament, both the House of Commons and the House of Lords, voted in favour of the highly controversial amendments to the 1990 Human Fertilization and Embryology Act (HFE Act),[1] which legalize the use of donated mitochondria in *in vitro* fertilization (IVF) treatment, making UK the first country in the world to officially allow this procedure. This step, however, was not an easy one and it thus took 7 years to implement the possibility of legalizing such treatment, initially introduced by 2008 amendments to the HFE Act.[2] These years witnessed much debate and polarized opinions over the safety issues as well as the legal and ethical implications of mitochondrial donation. Thus, advocates pointed out the devastating effect of mitochondria-related health disorders on the quality of life, and, sometimes, even death of persons affected by such

[1] Human Fertilization and Embryology Act 1990, http://www.legislation.gov.uk/ukpga/1990/37/contents, retrieved 23 April 2015.
[2] Human Fertilization and Embryology Act 2008, http://www.legislation.gov.uk/ukpga/2008/22/contents, retrieved 23 April 2015.

disorders in their early childhood or youth. Meanwhile, the opponents challenged the treatment as evidently unethical, due to the introduction of a third person's, hence parent's, DNA into the future child. Moreover, they claimed that the fully undiscovered nature of this procedure makes it unsafe, while the very intervention into the future child's genome constitutes germline gene modification, which puts the fragile balance of international consensus on the human rights in biomedicine at serious risk. So what exactly is mitochondrial donation in IVF treatment and what makes it so challenging? The article presents the scientific background to the procedure and discusses the regulatory challenges brought by the first case of its legalization.

2 Mitochondrial DNA Diseases

2.1 *Nature and Epidemiology*

Mitochondria are tiny organelles in the cytoplasm of all nucleated cells.[3] These organelles carry their own genome (mtDNA) which is extremely small compared with that of the nuclei (for example, human mtDNA encodes only 37 genes, while the nuclei 20 000 – 30 000)[4] and, unlike it, is transmitted from one generation to another solely through the mother's egg, making mtDNA strictly maternally inherited.[5] Although mitochondria function in many ways,[6] the contemporary science commonly considers these organelles to play a key role in the production of energy, needed for the normal functioning of the cells.[7] On some occasions, however, mutations in nuclear genes, mtDNA, or both, result in the mitochondria "malfunction", leading to serious health disorders that may be passed on to next generations.[8]

The nature of pathogenic mtDNA mutations is quite complex, involving environmental factors, nuclear DNA background, etc.; however, the clinical manifestation of the pathology usually depends on the percentage of mutant mtDNA within each cell.[9] A cell may contain only one type of mtDNA (homoplasmy), which is mutated; alternatively, two or more types of mtDNA may be present in a cell (heteroplasmy) as a mixture of normal and mutant mtDNA.[10] In most of the latter cases, the so called "threshold effect" is observed, implying that a certain minimum percentage of mutant mtDNA within cells is required for the disease to show symptoms.[11] With the increase in this percentage (which may often occur in patients over time), the chance of patient showing severe

[3] E. A. Schon et al., 'Human mitochondrial DNA: roles of inherited and somatic mutations', *Nature Reviews Genetics* 13(12) (2012) 878-890, at 878.
[4] R. W. Taylor and D. M. Turnbull, 'Mitochondrial DNA Mutations in Human Disease', *Nature Reviews Genetics* 6(5) (2005) 389-402, at 391.
[5] See: L. Craven et al., 'Mitochondrial DNA disease: new options for prevention', *Human Molecular Genetics* 20(2) (2011) 168-174, at 169; D. P. Wolf et al., 'Mitochondrial replacement therapy in reproductive medicine', *Trends in Molecular Medicine* 21(2) (2015) 68-76, at 68-69.
[6] *Supra* note 3, at 878.
[7] See: P. Amato et al., 'Three-parent in vitro fertilization: gene replacement for the prevention of inherited mitochondrial diseases', *Fertility and Sterility* 101(1) (2014) 31-35, at 31; Wolf et al., *supra* note 5; J. P. Burgstaller et al., 'Mitochondrial DNA disease and developmental implications for reproductive strategies', *Molecular Human Reproduction* 21(1) (2015) 11-22, at 11.
[8] H. J. M. Smeets, 'Preventing the transmission of mitochondrial DNA disorders: Selecting the good guys or kicking out the bad guys', *Reproductive BioMedicine Online* 27(6) (2013) 599-610, at 599.
[9] H. A. L. Tuppen et al., 'Mitochondrial DNA Mutations and Human Disease', *Biochimica et Biophysica Acta (BBA) – Bioenergetics* 1797(2) (2010) 113-128, at 115.
[10] M. Tachibana et al., 'Mitochondrial gene replacement in primate offspring and embryonic stem cells', *Nature* 461(7262) (2009) 367-372, at 367. Generally, heteroplasmy mutations are the cause of most frequent and severe mtDNA diseases. *Supra* note 7.
[11] This threshold may vary from 60% to 90%. See *supra* notes 7 and 9.

manifestation of mtDNA disease increases.[12] However, there is no "uniform" threshold to cause a clinical manifestation due to different tolerance of mutant mtDNA levels among cells, body tissues, individuals and even pedigrees.[13] Besides, the absence of clinical symptoms in some heteroplasmic women with low mutant mtDNA level does not mean that they do not pass the mutation to future generations (carryover); even worse, the phenomenon of hereditary heteroplasmic mutant mtDNA carryover is such that the offspring may inherit much higher mutation levels and suffer from most devastating health disorders.[14]

Although mtDNA is only a miniscule part of the total number of genes within a cell, mtDNA mutations may manifest in a wide spectre of health disorders, owing to the mutation-induced failure in energy supplying function of mitochondria.[15] The chronic loss of cellular energy affects many organs and tissues, though the ones with high energy demand (for example, brain, heart, eyes, ears and skeletal muscle) are typically affected most, which leads to stroke, cardiac failure, blindness, deafness, exercise intolerance, etc.[16] In recent years there have also been reports on the presence of mtDNA mutations in cancer cells and the correlation between mtDNA mutations and many common late-onset diseases, for example, Parkinson's disease.[17] Effectively, in most severe cases, early-onset multisystem disorders occur (for example, Leigh's syndrome), which usually lead to patient's death in infancy or early adulthood.[18]

Due to the heterogeneity of mtDNA diseases and their onset, the epidemiology of such diseases may be significantly downplayed.[19] The general consensus is that mtDNA diseases are among the most common genetic disorders, with the disease prevalence rate ranging from 1 in 5000 to 1 in 10 000 persons across different countries, regions, population groups and mutation expressions.[20] These numbers, however, represent only those affected with mtDNA diseases, while the number of those who inherit and carry mtDNA mutations has been reported at much higher frequency – approximately 1 in 200.[21]

2.2 *Treatment Options*

Despite the fact that scientists have been aware of mtDNA diseases for more than two decades, no effective cure has been developed for them, thus the only way of treating the persons affected is to alleviate the existing symptoms and prevent complications by means of exercise therapies, gene therapies, etc.[22] Furthermore, the existing genetic screening methods, which are used to identify potential mtDNA disorders in embryos, though promising, are not always reliable, besides, such

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[12] D. C. Samuels et al., 'Preventing the transmission of pathogenic mitochondrial DNA mutations: can we achieve long-term benefits from germ-line gene transfer?', *Human Reproduction* 28(3) (2013) 554-559, at 554.

[13] See: P. F. Chinnery et al., 'Epigenetics, epidemiology and mitochondrial DNA diseases', *International Journal of Epidemiology* 41(1) (2012) 177-187, at 178; Wolf et al., *supra* note 5.

[14] See: Amato et al., *supra* note 7; *supra* note 12, at 555.

[15] P. F. Chinnery and G. Hudson, 'Mitochondrial genetics', *British Medical Bulletin* 106(1) (2013) 135-159, at 141-142.

[16] *Ibid*.

[17] *Supra* note 3, at 884-887.

[18] *Ibid*.

[19] S. Bannwarth et al., 'Prevalence of rare mitochondrial DNA mutations in mitochondrial disorders', *Journal of Medical Genetics* 50(10) (2013) 704-714, at 704.

[20] See: A. Shaefer et al., 'Prevalence of Mitochondrial DNA Disease in Adults', *Annals of Neurology* 63(1) (2008) 35-39, at 35; H. R. Elliot et al., 'Pathogenic Mitochondrial DNA Mutations Are Common in the General Population', *American Journal of Human Genetics* 83(2) (2008) 254-260, at 254. With regard to demographics, it has been estimated that the average number of births per year among women at risk for transmitting mtDNA disease is about 150 in the UK and about 780 in the US. See G. S. Gorman et al., 'Mitochondrial Donation – How Many Women Could Benefit?', *New England Journal of Medicine* 372(9) (2015) 885-887, at 886.

[21] *Ibid*.

[22] *Supra* note 9, at 122-123.

methods are not suitable for high-level heteroplasmic and homoplasmic women.[23] Consequently, if such women wish to have children they must choose between adoption, egg donation or surrogacy egg donation (which would result in a birth of genetically non-related child), or risk of giving birth to an affected child. In the light of the above-mentioned factors, the attention inevitably shifts towards searching for treatment methods that could altogether prevent the transmission of mutant mtDNA from mother to the prospective offspring.[24]

In the late 1990s, a method called cytoplasmic transfer (CT) was developed in the US, which involved a transfer of a small amount of cytoplasm with healthy mitochondria from a donor's egg into the recipient's egg.[25] The procedure, which for the first time in history made it possible for a child to have genetic link to three different persons, resulted in about 30 births.[26] However, the very goal of this procedure, to "rejuvenate" the eggs of the recipient, is of little help in case of mtDNA diseases, since the amount of injected mitochondria is too small and the persisting recipient's mutated mitochondria are enough to affect the future child.[27] Moreover, the procedure itself raised serious safety concerns, which led to it being banned by the USA Food and Drug Administration (FDA) in 2001.[28] Hence, a more appropriate technique was needed to ensure the prevention of mutant mtDNA carryover.

One such technique, the "pronuclear transfer" (PNT), has actually been known for some time, and its use, though restricted to mice, in the early 1980s, showed the potential of reducing the carryover.[29] The technique involved *in vitro* manipulation with fertilized donor's and recipient's eggs, which had already reached the single-cell embryo stage (zygotes), with the objective of transferring both parents' pronuclei from a recipient's zygote to the enucleated donor's zygote.[30] The efficacy of this method in mice, though, was undermined, due to high carryover.[31] Nevertheless, the method was rendered feasible for use in humans in the 2010 report by the UK scientists, who used abnormal human zygotes and witnessed low carryover (<2%).[32] The in-depth assessment and research on the safety and efficacy of PNT in normal human zygotes, however, is yet to be achieved.[33]

Meanwhile, in 2009, a method called "maternal spindle transfer" (MST), which involves the *in vitro* transfer of the spindle of chromosomes (nuclear genetic material) from an unfertilized recipient's egg into the unfertilized enucleated donor's egg, which is then fertilized, was applied by the USA scientists in the treatment of rhesus macaques.[34] The resulted offspring were reported to be healthy with only insignificant carryover (<3%)[35] and the 3-year follow-up study on these monkeys revealed no deviation from age-matched controls.[36] Despite the inspiring outcome of the pioneer

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[23] *Supra* note 12, at 555.
[24] See: Burgstaller et al., at 12; Amato et al., supra note 7.
[25] *Ibid*.
[26] M. Araki and T. Ishii, 'International regulatory landscape and integration of corrective genome editing into in vitro fertilization', *Reproductive Biology and Endocrinology* 12(1) (2014) 108.
[27] *Supra* note 10, at 371.
[28] *Ibid*.
[29] Wolf et al., *supra* note 5.
[30] P. Amato et al., *supra* note 7.
[31] Wolf et al., *supra* note 5.
[32] L. Craven et al., 'Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease', *Nature* 465(7294) (2010) 82-85.
[33] *Ibid*., at 84; Wolf et al., *supra* note 5.
[34] *Supra* note 10.
[35] *Ibid*.
[36] M. Tachibana et al., 'Towards germline gene therapy of inherited mitochondrial diseases', *Nature* 493(7434) (2013) 627-631, at 630.

nonhuman primate trials, the initial application of MST procedure in human eggs by the same scientific team was not that successful, resulting in abnormalities in a number of zygotes.[37]

3 The Process of Legalization

Until recently, the HFE Act (as amended in 2008) explicitly prohibited the use of human reproductive cells and embryos with altered nuclear or mitochondrial DNA for reproductive purposes (Section 3ZA (2-4)), although their use for research was legal, but contingent on the grant of license by the regulating body, the Human Fertilization and Embryology Authority (HFEA).[38] In 2010, the UK Department of Health was asked by medical researchers to provide new regulations, permitting the use of new techniques for treating mtDNA diseases.[39] The request was based on Section 3ZA(5) of the amended HFE Act, which allowed to adopt such regulations. The Department, therefore, contacted the HFEA to convene an Expert Panel to review the existing scientific evidence of safety and efficacy of the novel treatment techniques.[40] The latter presented its findings in 2011, 2013 and 2014 reports,[41] which concluded that both PNT and MST "have the potential for all patients with mtDNA disorders" and the evidence at hand "does not suggest that these techniques are unsafe".[42] Still, the latest report reiterated the opinion expressed earlier, that until the techniques are tested in human treatment, uncertainty with regard to their use will persist, although this fact should not preclude carrying out further research studies.[43]

Furthermore, realizing the cutting edge of both science and ethics involved, the HFEA launched a public consultation in late 2012 in order to gather public views on the social and ethical impact of making PNT and MST available to patients.[44] Earlier that year, an almost 100-page report was also published by Nuffield Council of Bioethics (Nuffield Council), an independent body, which carried out an extensive 6-month study on the ethical aspects of such treatment.[45]

Finally, in 2013 the UK Government proceeded with preparing draft regulations, which were subsequently put to public consultation in 2014[46] and approved by the UK Parliament in February 2015.

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[37] *Ibid*.
[38] Section 11(1)(c) and Schedule 2. Thus, for example, the above-mentioned PNT procedure carried out by the UK scientists on the abnormal human zygotes was granted such license by the HFEA in 2005.
[39] Impact Assessment on The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, http://www.legislation.gov.uk/ukia/2015/138/pdfs/ukia_20150138_en.pdf, retrieved 23 April 2015, at 4-5.
[40] *Ibid.*
[41] All reports are available at the HFEA website, http://www.hfea.gov.uk/6372.html, retrieved 23 April 2015.
[42] Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2014 update, http://www.hfea.gov.uk/docs/Third_Mitochondrial_replacement_scientific_review.pdf, retrieved 23 April 2015, at 34, 37.
[43] *Ibid.*, at 37-40.
[44] Mitochondria public consultation 2012, http://www.hfea.gov.uk/9359.html, retrieved 23 April 2015.
[45] Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review, http://nuffieldbioethics.org/wp-content/uploads/2014/06/Novel_techniques_for_the_prevention_of_mitochondrial_DNA_disorders_compressed.pdf, retrieved 23 April 2015.
[46] Mitochondrial Donation: A consultation on draft regulations to permit the use of new treatment techniques to prevent the transmission of a serious mitochondrial disease from mother to child, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/285251/mitochondrial_donation_consultation_document_24_02_14_Accessible_V0.4.pdf, retrieved 23 April 2015.

4 Mitochondrial Donation Regulations 2015

4.1 Requirements for PNT and MST procedures

The adopted Mitochondrial Donation Regulations 2015[47] set a number of mandatory conditions which are to be met in carrying out such treatment.

First, for the time being, only PNT and MST procedures are allowed in eggs and embryos (regulations 4 and 7 respectively).[48] Furthermore, no other alterations in the nuclear or mitochondrial DNA of an egg or embryo are permitted (regulation 3(c) and 6(c)(i) respectively); the addition of other cells to the embryo, other than by the division of its own cells is also prohibited (regulation 6(c)(ii)).

Second, the application of PNT and MST is strictly limited to those cases, where there is a particular risk that an egg or embryo may have mitochondrial abnormalities caused by mtDNA mutations and a significant risk that a person with those abnormalities will have or develop a serious mitochondrial disease (regulations 5 and 8). Both these conditions are to be determined by the HFEA, although the initial estimate of persons eligible for such treatment each year is about 20.[49]

Last, clinics are not permitted to carry out PNT or MST unless they hold a license from the HFEA with an express permission to perform such procedures (regulation 9). The HFEA will consider applications for such specific approval on a case-by-case basis.

4.2 Legal Status of Donors, Parents and Children

The Mitochondrial Donation Regulations 2015 are based on the assumption that the actual genetic relationship is based entirely on the inheritance of nuclear DNA from both parents. Therefore, unlike the entire egg/embryo donation, only non-identifying information on the mtDNA donor may be disclosed to children conceived from the donation (regulation 11(c))[50] and no information is provided about other children who share the same donor (regulation 15). Nor is the mitochondrial donor-conceived person considered related to the donor or any other children conceived as a result of her donation; therefore, no information in connection with entering into a marriage, civil partnership or intimate physical relationship is provided to such a person (regulation 12).

On its part, only limited information on children conceived from the donation may be available to the donor herself.[51] Furthermore, a donor is not eligible for a parental order in relation to the resulting child on the basis of mtDNA donation alone, even in case of a surrogacy arrangement (regulation 18), since the control over the egg or embryo resulting from the procedure pertains to those persons who provide the nuclear material (regulation 17). Therefore, a consent from the donor to use her egg or embryo may be withdrawn only before the nuclear DNA is inserted into them (regulation 16).

5 Legal and Ethical Implications of Legalizing Mitochondrial Donation

Although the UK Parliament has consented to the use of PNT and MST in clinical practice and the Mitochondrial Donation Regulations 2015 are to come into force on October 29th 2015, many technical and social challenges remain unresolved. For instance, the complex and controversial

[47] The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015, http://www.legislation.gov.uk/uksi/2015/572/contents/made, retrieved 23 April 2015.
[48] The techniques refer to the terms 'polar body' (maternal-chromosomal spindle) and 'associated organelles' (nuclei) (regulation 2(2 and 3 respectively).
[49] *Supra* note 45, at 6.
[50] For example, the screening tests carried out on the donor and her personal or family medical history may be disclosed.
[51] For example, the number of persons in respect of whom the donor is a mitochondrial donor (regulation 14).

ethical issues related to the notion of identity of the child with donated mitochondria, the potential of such treatment to discriminate people already affected by mtDNA diseases, the challenge to the traditional notion of family, generic risks of egg donation, etc.[52] There is no denying that such questions are of crucial importance not only while deliberating whether to legalize such treatment, but whether it is acceptable for some families altogether. However, as the legalization of mitochondrial donation is no longer an intention, but rather a fact, those challenges that the regulators will, or may potentially face in the nearest and long-term perspective, inevitably come into larger focus. Such challenges mainly include concerns over safety and efficacy of mitochondrial donation and its potential to influence policy on human rights in biomedicine both in the UK and globally.

5.1 Safety and Efficacy Concerns

However promising the initial results obtained by both the UK and USA scientists may be, the novelty of the techniques as well as their experimental nature clearly demonstrate the need for further research.[53] As mentioned above, mitochondrial donation does not actually treat mtDNA diseases, rather, it is focused on preventing the transmission of mutant mtDNA, therefore the major beneficiaries are future children, free from the suffering and pain caused by it. Unfortunately, neither technique has currently the capacity of ensuring total elimination of carryover, although ideally, both should.[54] Yet this factor may play a decisive role in either elimination or recurrence of the disease in the pedigree.[55]

Still, at this point, the concerns over PNT and MST safety and efficacy are rather vague and reflect the general lack of scientific knowledge in this field. Thus, for example, scientists have questioned whether the breach in egg membrane and further inevitable exposure of eggs to foreign biological and/or chemical reagents needed for the treatment could have detrimental effect.[56] Furthermore, concern has been expressed about the potential incompatibility between nuclear and mtDNA genomes.[57] Accordingly, studies on mitochondrial-nuclear "mismatch" have been conducted on mice and revealed possible risks associated with subspecies crossing; meanwhile, studies on subspecies of macaques did not confirm such findings.[58] Nevertheless, the possibility of a "mismatch" between two humans is rendered highly unlikely, although it has been recommended to consider this factor when selecting donors.[59] Adding all these points of concern to the incapacity of ensuring total elimination of mutant mtDNA carryover in today's state of the art, it could be

[52] These issues have been specifically addressed not only by the Nuffield Council (*supra* note 45, at 52-86), but by scholars from around the world as well. See e.g.: A. Bredenoord et al., 'Ethics of modifying the mitochondrial genome', *Journal of Medical Ethics* 37(2)(2011) 97-100; C. Jones and I. Holme, 'Relatively (im) material: mtDNA and genetic relatedness in law and policy', *Life Sciences, Society and Policy* 9(4) (2013) 1-14; F. Baylis, 'The ethics of creating children with three genetic parents', *Reproductive BioMedicine Online* 26(6) (2013) 531-534; T. Ishii, 'Potential impact of human mitochondrial replacement on global policy regarding germline gene modification', *Reproductive BioMedicine Online* 29(2) (2014) 150-155.

[53] *Supra* note 42, at 37-40.

[54] Burgstaller et al., *supra* note 7, at 14.

[55] The importance of keeping the level of carryover as low as possible could best be illustrated by saying that it should be limited to at least <3%, while >5% is associated with a strong possibility of the mutation's recurrence in the future generations. *Supra* note 12, at 556-557.

[56] See: Amato et al., *supra* note 7, at 33-34; Wolf et al., *supra* note 5, at 74-75.

[57] *Ibid*.

[58] *Ibid*.

[59] *Supra* note 42, at 30-33. For example, some scientists suggested using mitochondria of a maternal relative who does not carry pathological mutation, since mtDNA is almost identical in maternally related persons.

concluded that the risks associated with safety and efficacy of the treatment in the long run should not be disavowed, particularly because such treatment involves germline gene modification.[60]

Overall, with no results on human subjects obtained through sound clinical trials and long-term follow-up, the risks and benefits of PNT and MST remain unknown. Therefore, the only way to find out the true impact of both techniques is to carry out pioneer treatment, which inevitably implies putting the future generations at certain risk. This ultimately leads to thinking that these future generations are very much "experimental"[61] and the view expressed by the Nuffield Council (as well as many others) that safety and efficacy of PNT and MST should constitute the major factor determining the ethical acceptability of applying these techniques in clinical practice,[62] somewhat disregarded. Unfortunately, as acknowledged by the HFEA Expert Panel, it is in the nature of any emerging technology to be surrounded by scientific uncertainty and mitochondrial donation is no exception; hence, the decision on how to handle it rests not on science alone.[63]

Whether the UK's step at this particular time should be hailed or condemned from a purely scientific point of view is, therefore, open to debate. The notion of most strict precaution, implying that no action takes place before a full assessment of risks is carried out,[64] would require many years of research not only on animals, but more importantly on human eggs and embryos.[65] Clear enough, such long-term research would be met with both technical and ethical objections. Moreover, foreseeing every potential outcome while tampering with human genome is, possibly, beyond the capabilities of any scientific team, thus even the most rigorous follow-up may still omit important details.[66] In other words, this option would most probably imply relinquishing the idea of such treatment and promoting other forms of parenthood, such as adoption, entire egg donation, etc.[67] On the other hand it could be argued that absolute precaution, if applied universally, would effectively paralyze any scientific progress altogether.[68] Such argument would put in favour carrying out the treatment as soon as it is deemed safe and spending the next few decades of medical follow-up of "experimental" progeny, some of whom may still be at risk.[69]

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[60] As discussed by the Nuffield Council, different views exist as to whether mitochondrial donation should be considered germline gene therapy. The Council, however, adopted the view that PNT and MST include germline gene modification because 'they introduce a change that is incorporated into the [mtDNA] of the resulting people, and so will be incorporated into the germline that they will go on to develop' (*supra* note 45, at 57-59).

[61] Indeed when the question of safety was addressed by the Nuffield Council, some opinions were even put forward to introduce sex selection to the treatment, allowing only male offspring, which would ensure no further mtDNA transmission until more information is gathered. Others, however, discarded such option as obviously discriminating, rendering boys 'experimental offspring' and emphasized that limiting the risk to one sex only would mean that too little is known about the treatment's safety (*supra* note 45, at 80). The HFEA Expert Panel did not support sex selection either, by emphasizing not only ethical, but also additional technical risks to embryos (*supra* note 42, at 27).

[62] *Supra* note 45, at 88.

[63] *Supra* note 42, at 5.

[64] See e.g. G. E. Marchant and R. A. Lindor, 'Prudent Precaution in Clinical Trials of Nanomedicines', *Journal of Law, Medicine and Ethics* 40(4) (2012) 831-840, at 832.

[65] As observed by the HFEA Expert Panel, due to differences in human and animal (including macaques) eggs and embryos, the animal trials may not always be helpful and at the worst, even misleading (*supra* note 42, at 22). See also *supra* notes 10 and 36.

[66] This concern was expressed by the International Bioethics Committee in its 2003 report. Report of the IBC on Pre-implantation Genetic Diagnosis and Germ-line Intervention, http://portal.unesco.org/shs/en/files/2397/10554294261ReportfinalPGD_en.pdf/ReportfinalPGD_en.pdf, retrieved 23 April 2015, at 11.

[67] Baylis, *supra* note 52, at 533.

[68] *Supra* note 64.

[69] This was the view of the HFEA Expert Panel expressed in the 2014 report: 'Once assessed as safe to use in clinical practice, the panel strongly recommends that permission is sought from the parents of the children born from MST or PNT to be followed up for an extensive period, and then seek permission from the children themselves, when old enough. In the case of females, this ideally should be extended to the next generation' (*supra* note 42, at 35-36). No need

The legalization of the procedure in the UK clearly indicates that the latter path was chosen, though again, the decision on whether the treatment could be deemed safe enough to proceed rested not on scientists, but on the legislators. Whatever the case, the first child may be born from mitochondrial donation as early as 2016, which brings about the question of what is going to happen next.

5.2 The "Slippery Slope" Dilemma and Global Policy

The next main question to be addressed is how the legalization could impact both the UK and global policy with regard to human rights in biomedicine, which arguably, may be at serious risk due to the possible subsequent descent down the "slippery slope".[70] The latter may be characterized by two future development trends with regard to clinical application of mitochondrial donation and other genome-editing techniques.

The first constitutes the aftermath of legalizing mitochondrial donation in the narrow sense, that is the potential misuse of the techniques themselves for purposes other than the prevention of mutant mtDNA transmission.[71] Thus, for example, such treatment could become an alternative to CT and some older women would seek it merely to "rejuvenate" the eggs. As already seen, in the case of the UK this would require subsequent amendments to the HFE Act, since the newly adopted Mitochondrial Donation Regulations 2015 allow only PNT and MST, thus CT remains illegal under the above-mentioned Section 3ZA(2) of the amended 1990 HFE Act. However, in those states where there is no explicit ban on CT or other forms of germline gene modification, such use of PNT and MST (or indeed any other technique of similar nature) would be perfectly possible.[72] It should also be kept in mind that due to the relative proximity in nature and objectives of CT and PNT and MST (i.e. the birth of healthy offspring), the application of the two latter techniques, should they prove safe and effective, could be legally extended to a more general assisted reproduction treatment in the future in both the UK and any other state that follows the same regulatory pattern.

Furthermore, the treatment may be used by some civil unions in order to have a child, genetically related to two women.[73] Again, this would not imply, in the case of the UK, the recognition of the donor as a "second mother", or a "third parent" at least as the current HFE Act provisions stand.[74] Nevertheless, in future perspective, it should not be deemed entirely impossible for the existing legal stance to evolve into recognizing the donor as a third legal parent, especially in the light of contemporary trends in the legal notion of family in some other jurisdictions.[75]

At the same time, the legalization of mitochondrial donation may have far greater consequences in the broad sense of scientific possibility and legality. Effectively, the UK's decision to legalize germline gene modification may be viewed as the opening of Pandora's box, leading to further intervention into human genome, not only mtDNA, but nuclear DNA as well. In other words,

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to say that a follow-up lasting for several decades, though dictated by both technical and ethical considerations, may prove difficult to fulfil on the part of both families and researchers, especially considering the previous experience with other newly-introduced assisted reproduction techniques, as acknowledged by the Nuffield Council. The Council, therefore, recommended the creation of a centrally-funded register, which would keep track of mitochondrial donation procedures performed in the UK, to be accessible to researchers over several decades (*supra* note 45, at 89).

[70] Ishii, *supra* note 52, at 154.

[71] Baylis, *supra* note 52, at 533.

[72] CT is actually offered for health tourists in a number of clinics across the world. *Supra* note 45, at 39.

[73] Baylis, *supra* note 52, at 533.

[74] According to section 27(1) of the 1990 HFE Act, only 'the woman who is carrying or has carried a child as a result of the placing in her of an embryo or of sperm and eggs […], is to be treated as the mother of the child'. Meanwhile, the 2008 amendments to the HFE Act introduced the notion of two women parenthood, stipulating that if no man is treated as the child's father, a second woman may be regarded as the child's other parent (not mother though) by virtue of civil partnership (section 42) or express consent (sections 43-45).

[75] See: *supra* note 45, at 47; Jones and Holme, *supra* note 52, at 6.

this precedent could be used for legalizing even more interventional, and consequently, selective genetic engineering of human beings, genetic enhancements, etc.,[76] which would shatter the existing consensus of non-meddling with human genome.

Such concerns are particularly worrisome, since the above-mentioned consensus is very fragile and is based on either soft law instruments or instruments with weak legal enforceability only. Thus, for example, the UNESCO 1997 Universal Declaration on the Human Genome and Human Rights,[77] which overall hails the research on prevention and treatment of genetic disorders (Article 17), if carried out on the basis of rigorous and prior assessment of risks and benefits (Article 5(a)), refers to germline interventions as "contrary to human dignity" (Article 24). Another example is the 1997 Convention on Human Rights and Biomedicine[78] by the Council of Europe, which explicitly prohibits germline gene modification (Article 13). The latter instrument is a good example of weak enforceability, seeing that it "does not itself give individuals a right to bring proceedings before the European Court of Human Rights" (ECHR), unless a state is liable for the same infringement under the European Convention of Human Rights.[79]

The reason behind this is, of course, the general reluctance of states to willingly expose their national policy with regard to sensitive ethical issues raised by human rights in biomedicine to an international debate due to the high polarity of opinions among different states. An example of such unwillingness to harmonize the policy, even in a regional international organization, the above-mentioned Council of Europe, is perfectly reflected in the decisions of the ECHR on issues related to reproductive rights,[80] medically assisted procreation[81] and euthanasia[82] within the framework of the European Convention of Human Rights. In all such cases, when the relevant policy of a member state was put into question, the ECHR stressed that there was, and remains, the lack of consensus on such sensitive moral or ethical issues in the international law; therefore states enjoy a wide discretion in setting the policy vector as they are best aware of the underlying legal, moral, or cultural motives.[83] In other words, speaking in purely legal terms, there seems to be no "right" or "wrong" decision in this matter, only the willingness of a state to either permit a sensitive issue or ban it, according to the prevailing social attitudes.

It is therefore of no wonder that states are even less willing to bind themselves with international treaties on such matter. Thus, the UK is not a party to the Convention on Human Rights and Biomedicine, nor indeed are many other members of the Council of Europe, including Belgium, Germany, etc., while some other states, for example the Netherlands, Sweden, etc. signed the Convention but did not ratify it.[84] It is true though that the above-mentioned states pertain to the

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[76] See: Baylis, *supra* note 52, at 533; T. Ishii, at 154.

[77] Universal Declaration on the Human Genome and Human Rights, http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html, retrieved 23 April 2015.

[78] 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, http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm, retrieved 23 April 2015.

[79] Explanatory Report, http://conventions.coe.int/Treaty/EN/Reports/Html/164.htm, retrieved 23 April 2015. The ECHR also pertains a right to 'give, without direct reference to any specific proceedings pending in a court, advisory opinions on legal questions concerning the interpretation of the present Convention' (Article 29).

[80] See: *Vo v. France* [GC], no. 53924/00, judgment of 8 July 2004; *A, B and C v. Ireland* [GC], no. 25579/05, judgment of 16 December 2010; *R.R. v. Poland*, no. 27617/04, judgment of 26 May 2011.

[81] See: *Evans v. the United Kingdom* [GC], no.6339/05, judgment of 10 April 2007; *S.H. and Others v. Austria* [GC], no. 57813/00, judgment of 3 November 2011.

[82] See: *Haas v. Switzerland*, no. 31322/07, judgment of 20 January 2011; *Koch v. Germany*, no. 497/09, judgment of 19 July 2012.

[83] See e.g. *S.H. and Others v. Austria*, *supra* note 81, paras. 94-97.

[84] As of April 2015, 29 member states of the Council of Europe were parties to the Convention, with 6 more member states signing, but not ratifying it. Meanwhile, the Convention is open for signature and accession not only to all 47 member states of the Council of Europe, but to Australia, Canada, Holy See, Japan, Mexico, the USA and the EU. A

EU legal system, which generally has a negative attitude towards germline gene modification by denying the financial support to this field of research.[85] Furthermore, germline gene modification is considered contrary to *ordre public* (public order) and morality in EU patent law, which renders such procedures unpatentable.[86] However, denying a patent does not mean that scientific research on germline gene modification or its application in clinical practice is illegal under EU law *per se*, as reflected in the case-law of the European Court of Justice (ECJ).[87]

What *does* make such practice illegal, at least partly, is Article 9(6) of the EU Clinical Trials Directive[88] which prohibits to carry out gene therapy trials resulting in "modifications to the subject's germ line genetic identity". Indeed, this provision was invoked by some opponents of the legalization of mitochondrial donation in the UK.[89] The UK Department of Health retorted that the legalization does not infringe the Directive, seeing that the latter regulates those cases, where the safety and/or efficacy of medicinal products are ascertained (Arts 1 and 2(a)); whereas PNT and MST procedures are not "medicinal products", nor does the licensing of PNT or MST on a case-by-case basis by the HFEA constitute a permission to carry out a clinical trial (i.e. safety/efficacy assessment), but rather a permission to carry out the treatment itself.[90] Although it is not in the scope of this article to describe the 20-year history of ECJ case-law on the definition of medicinal product, nor does it seem productive to delve into polemics of whether the clinical use of PNT and MST constitutes only treatment,[91] it would be fair to observe that the compliance of Mitochondrial Donation Regulations 2015 with the EU legislation on clinical trials could indeed be questioned by the ECJ, should a relevant case be brought before it.[92]

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more detailed information on the participation is available at http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=164&CM=&DF=&CL=ENG, retrieved 23 April 2015.

[85] Article 19(3)(b) of the Regulation (EU) No 1291/2013 of the European Parliament and of the Council of 11 December 2013 establishing Horizon 2020 – the Framework Programme for Research and Innovation (2014-2020) and repealing Decision No 1982/2006/EC [2013] OJ L 347/104.

[86] Article 6(2)(b) of Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions [1998] OJ L 213/13. The Directive, similar to UNESCO 1997 Declaration, refers to germline gene modification as offending human dignity (recital 38) and states that such position is a result of consensus between the EU Member States (recital 40).

[87] See: *Oliver Brüstle v. Greenpeace e.V.* (C-34/10) [2011] ECR I-9821, par. 40; *International Stem Cell Corporation v. Comptroller General of Patents, Designs and Trade Marks* (C-364/13) [2014] (ECJ, December 18, 2014), par. 22

[88] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [2001] OJ L 121/34. This Directive is to be replaced by Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC [2014] OJ L 158/1, but the provision on germline gene modification remains untouched (Article 90).

[89] For example, the Scottish Council on Human Bioethics, etc. Written evidence presented to the House of Lords, http://www.parliament.uk/documents/lords-committees/Secondary-Legislation-Scrutiny-Committee/Human_Fertilisation_Written_Evidence.pdf, retrieved 23 April 2015.

[90] http://www.publications.parliament.uk/pa/ld201415/ldselect/ldsecleg/99/9905.htm, retrieved 23 April 2015.

[91] Considering the most novel nature of both techniques, the strict eligibility criteria to undergo the treatment and the highly recommended exceptionally long-term follow-up.

[92] It should be observed that the EU legislation on medicinal products is not yet fully harmonized, which results in different interpretations of the definition of medicinal product by EU Member States. However, PNT and MST involve manipulations and procedures with eggs or single-cell embryos, which are, as a general rule, regulated by Tissues and Cells Directive 2004/23/EC (recital 7), thus it is not clear whether they could fall under the definition of a medicinal product, as defined in Article 1(2) of the Medicinal Products Directive 2001/83/EC. Still, the latter is construed broadly, therefore should such eggs/embryos be 'substantially manipulated', they could be considered advanced therapy medicinal products as defined in Part IV of Annex I to the Medicinal Products Directive and Article 2 of the amending Regulation (EC) No 1394/2007. Indeed the problem of 'borderline areas' was addressed by the European Medicines Agency, which issued a relevant reflection paper in 2012 and its update in 2014 (both available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000296.jsp, retrieved 23 April

Still, as may be perceived, even the Clinical Trials Directive, hence EU law, does not altogether ban germline gene modification, which signifies that for the time being the latter could be effectively banned only by national legislation. Yet, an insight in to the regulatory landscape suggests that states apply different approaches in regulating germline gene modification. For example, although the majority of West European states, Australia, Brazil, Canada, etc. place a legislative ban on it, China, India and Japan ban germline gene modification on the basis of non-legislative guidelines only; on its part, the USA upholds to restrictive policy with a moratorium on germline gene modification, while a considerable number of states, including Argentina, Chile, Russia, etc., remain ambiguous with regard to restrictions altogether.[93] Such ambiguity, however, is reflected not only in the policy of those states that keep germline gene modification unregulated, but in the policy of some states that actually restrict it, which means that there may be ways to circumvent the restrictions and even bans, as in the case of CT.[94] In other words, the existing regulatory landscape implies that germline gene modification is not totally prohibited across the world, which makes states more "vulnerable" to regulatory oscillations elsewhere.[95]

Indeed, the UK is not the only state which faced the medical, legal and ethical dilemmas of whether to legalize germline gene modification in the face of mitochondrial donation, as a very similar debate is ongoing in the USA,[96] another crucial contributor to the scientific development of such treatment. Thus, in February 2014 a hearing on the matter was organized by the FDA;[97] furthermore, the latter has asked the Institute of Medicine to conduct a study on mitochondrial donation in IVF treatment, which should address issues discussed earlier by the Nuffield Council, including the question of whether the treatment should be considered germline gene modification, the safety issues, the ethical and social issues with regard to informed consent and "three-parenthood", etc.[98] As the study will last for some time[99] and considering that any necessary subsequent legislative and technical procedures (should the decision be made to proceed forward with the question of legalization) will also be time demanding, there are no clear indications that mitochondrial donation will be approved in the USA any time soon. Still, opinions are expressed

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2015). At the moment, though, it is too early to predict whether mitochondrial donation would be affected by the legislation on the advanced therapy medicinal products, considering the novelty of both such treatment and the respective legislation, as well as the fact that the treatment focuses on the prevention of mtDNA disease in future offspring, not in the woman who actually undergoes the treatment. Should the EU legislation on medicinal products nevertheless aspire to regulate mitochondrial donation, the ECJ could witness litigation similar to that which took place in the USA between the federal authorities and companies offering treatment based on patient's own stem cells (see in this regard G. Pivarnik, 'Cells as Drugs? Regulating the Future of Medicine,' *American Journal of Law and Medicine* 40(2-3) (2014) 298-321).

[93] See: *supra* note 26, Ishii, *supra* note 52, at 154. For more information about national policies on germline gene modification, cloning, sex selection, etc. as it was in 2008, see the testimony of Richard Hayes in the USA House of Representatives. 'Is There an Emerging International Consensus On the Proper Uses Of the New Human Genetic Technologies?', http://democrats.foreignaffairs.house.gov/110/hay061908.pdf, retrieved 23 April 2015.

[94] *Supra* note 45, at 38-39. In fact, a large number of states mentioned by the Nuffield Council officially prohibit germline gene modification; however, due to differences in the respective legal systems as well as the nature of prohibition itself (e.g., legislative or non-legislative), CT may be, or actually is performed in some of these states.

[95] See: *supra* note 26, at 8; T. Ishii, (2014), at 153-154.

[96] N. Farahany, 'FDA considers controversial fertility procedure. What's at stake?'*The Washington Post*, February 25, 2014, http://www.washingtonpost.com/news/volokh-conspiracy/wp/2014/02/25/fda-considers-controversial-fertility-procedure-whats-at-stake/, retrieved 23 April 2015.

[97] FDA briefing document for Cellular, Tissue, and Gene Therapies Advisory Committee. 'Oocyte Modification in Assisted Reproduction for the Prevention of Transmission of Mitochondrial Disease or Treatment of Infertility', February 25-26, 2014, http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/cellulartissueandgenetherapiesadvisorycommittee/ucm385461.pdf, retrieved 23 April 2015.

[98] http://www8.nationalacademies.org/cp/projectview.aspx?key=IOM-HSP-14-25, retrieved 23 April 2015.

[99] The study began in September 2014 and is to last approximately 19 months, i.e. until Spring 2016.

that USA will be the next to legalize such treatment, followed by China, Japan and other states with more flexible policy on germline gene modification.[100]

In conclusion, though the advent of new technologies, hence mitochondrial donation, is likely inevitable,[101] the persisting polarized discrepancies in opinions will continue to loom over the regulatory bodies, which may hinder the process of legalizing such treatment in the majority of states in the near future, but not entirely prevent it. After all, even in case of the UK, the "battle of opinions" was a tough one, with patients, scientists, bioethicists and politicians expressing directly opposite views as to whether mitochondrial donation should be legalized.[102] Such polarization is, of course, a natural attribute of today's society, given the exceptionally high diversity in social perception. And as usual, no moral choice could aspire to be acceptable for every member of a society, including the legislators. Therefore, the fate of abortions, euthanasia and other similar bioethical dilemmas will most probably await the mitochondrial donation with the additional element of high scientific novelty, making it all the more difficult for policy-makers to handle. Nevertheless, when, or putting it less optimistic, if science reaches a stage of considerable control over human genome, it may not be a matter of moral choice whether to legalize such advanced and intervening treatment, but rather a necessity, dictated by state's political and economic interests[103] coupled with humanity's constant drive towards progress.

6 Conclusion

By consenting to the clinical use of PNT and MST, the UK has not only become the first state to explicitly allow mitochondrial donation, but the first to openly challenge the fragile global policy with regard to germline gene modification. A precedent thus has been created; however, it does not necessarily mean that other states will follow the UK's example in the near future, seeing that the procedure itself is quite experimental and its full impact is likely to be assessed only in several decades. Furthermore, the fragmented global policy on human rights in biomedicine makes it much more difficult to predict whether other states will approve germline gene modification in the short, or even long perspective, since the matter raises very sensitive ethical issues, which may not be overcome that easily due to prevailing legal, moral and cultural traditions. On the other hand, it could not be entirely denied that those who oppose the advent of such treatment, possibly, only delay the inevitable. While a question could be addressed as to whether the legalization of mitochondrial donation is timely, the desperate wish of families to have genetically related healthy children and the search for new ways of eradicating mtDNA diseases, have prevailed over the persisting uncertainty about the treatment's safety and efficacy as well as the ethical barriers. Such decision may not be without a price though, as in the unclear future of further scientific progress this

[100] See: *supra* note 26; Ishii, *supra* note 52, at 153-154.

[101] Baylis, *supra* note 52, at 534.

[102] The polarization in views may be easily perceived through written evidence presented to the House of Lords, *supra* note 89.

[103] It may be argued that the investment of resources into research on mitochondrial donation is not justified, seeing that greater reproductive health needs exist, while the problem at hand could be easily evaded by other reproductive options (Baylis, *supra* note 52, at 534). Indeed, in case of the UK the question of whether the policy is 'worth' taking was discussed in the Impact Assessment, which best estimated the net benefit of the policy at about £320 million in the run of 2015-2024, assuming 20 treated persons per year (*supra* note 39, at 23-24). On the other hand, competition on the global market of advanced technologies, including emerging medicinal technologies, should also be kept in mind; for example, opinions were put forward that funding and regulatory barriers for human embryo research in the USA (the Dickey-Wicker Amendment) pose the risk that the latter will 'lag behind' other states with more flexible policy, namely the UK, in this novel area of research and therapeutics (Amato et al., *supra* note 7, at 35).

first act of legalization could become a reminiscence of a small, yet decisive step towards further intervention into the very essence of human life.