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See table of contents

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Article abstract

Mitochondrial/nuclear transfer (M/NT) to avoid the transmission of serious mitochondrial disease raises complex and challenging ethical, legal and social issues (ELSI). In February 2015, the United Kingdom became the first country in the world to legalize M/NT, making the heated debate surrounding this technology even more relevant. This critical interpretive review identified 95 relevant papers discussing the ELSI of M/NT, including original research articles, government-commissioned reports, editorials, letters to editors and research news. The review presents and synthesizes the arguments present in the literature in relation to the most commonly raised themes: terminology; identity, relationships and parenthood; potential harm; reproductive autonomy; available alternatives; consent; impact on specific interest groups; resources; “slippery slope”; creation, use and destruction of human embryos; and beneficence. The review concludes by identifying those ELSI that are specific to M/NT and by calling for follow-up longitudinal clinical and psychosocial research in order to equip future ELSI debate with empirical evidence.

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ARTICLE (ÉVALUÉ PAR LES PAIRS / PEER-REVIEWED)

Mitochondrial/Nuclear Transfer: A Literature Review of the Ethical, Legal and Social Issues

Raphaëlle Dupras-Leduc[1], Stanislav Birko[2], Vardit Ravitsky[3]

Résumé

Le transfert mitochondrial / nucléaire (M/NT) visant à éviter la transmission de maladies mitochondriales graves soulève des enjeux éthiques, juridiques et sociaux (ELS) complexes. En février 2015, le Royaume-Uni est devenu le premier pays au monde à légaliser le M/NT, rendant le débat houleux sur cette technologie encore plus pertinent. Cette revue d'interprétation critique identifie 95 articles pertinents sur les enjeux ELS du M/NT, y compris des articles de recherche originaux, des rapports gouvernementaux ou commandés par le gouvernement, des éditoriaux, des lettres aux éditeurs et des nouvelles de recherche. La revue présente et synthétise les arguments présents dans la littérature quant aux thèmes les plus fréquemment soulevés: terminologie; identité, relations et parentalité; dommage potentiel; autonomie reproductive; alternatives disponibles; consentement; impact sur des groupes d'intérêt spécifiques; ressources; « pente glissante »; création, utilisation et destruction des embryons humains; et bienfaisance. La revue conclut en identifiant les enjeux ELS spécifiques au M/NT et en appelant à une recherche de suivi longitudinale clinique et psychosociale afin d'alimenter le futur débat sur les enjeux ELS de preuves empiriques.

Mots clés

transfert mitochondrial / nucléaire, FIV, ELS, Royaume-Uni, revue d'interprétation critique

Abstract

Mitochondrial/nuclear transfer (M/NT) to avoid the transmission of serious mitochondrial disease raises complex and challenging ethical, legal and social issues (ELSI). In February 2015, the United Kingdom became the first country in the world to legalize M/NT, making the heated debate surrounding this technology even more relevant. This critical interpretive review identified 95 relevant papers discussing the ELSI of M/NT, including original research articles, government-commissioned reports, editorials, letters to editors and research news. The review presents and synthesizes the arguments present in the literature in relation to the most commonly raised themes: terminology; identity, relationships and parenthood; potential harm; reproductive autonomy; available alternatives; consent; impact on specific interest groups; resources; "slippery slope"; creation, use and destruction of human embryos; and beneficence. The review concludes by identifying those ELSI that are specific to M/NT and by calling for follow-up longitudinal clinical and psychosocial research in order to equip future ELSI debate with empirical evidence.

Keywords

mitochondrial/nuclear transfer, IVF, ELSI, United Kingdom, critical interpretive review

Introduction

In February 2015, the United Kingdom became the first country in the world to legalize a new *in vitro* fertilization (IVF) technology called **mitochondrial/nuclear transfer** (M/NT) [1-4]. M/NT aims to avoid the transmission of serious mitochondrial diseases from an affected mother to her progeny by using one of two techniques: maternal spindle transfer (MST) and pronuclear transfer (PNT). Both techniques result in offspring with genetic material from three different persons: the nuclear DNA (nDNA) of the two prospective parents and the mitochondrial DNA (mtDNA) of the egg donor [5-9]. These modifications of the germ-line are inheritable and, therefore, transmitted to the offspring's progeny [5,8,10,11]. When mtDNA carries mutations, it can result in serious, potentially fatal, and currently untreatable diseases such as Leigh's syndrome, affecting mostly the organs whose operation requires the most energy: the central nervous system, heart, liver, kidneys, etc. [12].

The UK's decision to legalize M/NT has provoked a heated debate regarding the ethical, legal and social issues (ELSI) related to the technique. UK regulations came into force on October 29, 2015 [1]. However, the first live birth of a boy following M/NT (MST) occurred in Mexico in 2016 [89-92][1]. At the time of our review in 2015, no review of the literature concerning the ELSI of M/NT had been published. The current review addresses this need by identifying the ELSI associated with M/NT that have been put forward in the literature as of July 2015.

Methodology

Critical interpretive review

The ELSI debate on M/NT is taking place in research articles, commentaries, editorials, government-commissioned reports, letters to editors, and research news. We therefore chose to perform a critical interpretive review of all these relevant sources [18]. While considerable discussion also occurs in blog posts, we did not include them in the review due to great variability in their quality. Each step described below was performed independently by two researchers (RDL and SB).

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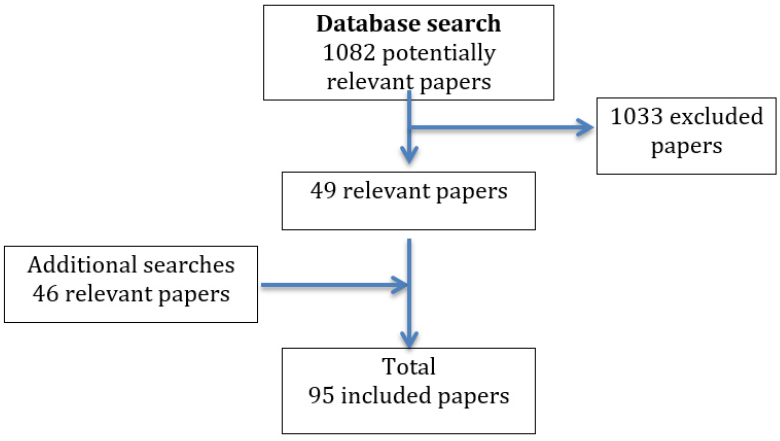
Search

The first step – performed in July 2015 – consisted of a systematic search, with the key words and phrases listed in Table 1, of the following databases which were considered by the authors to be the most relevant for this review: PubMed, CINAHL (EBSCOHost), Science Direct, Embase and PsycInfo. A total of 1 082 potentially relevant titles were found. From these, 1 033 papers were excluded as they did not meet either of the inclusion criteria, which were: a focus on M/NT, discussion of ELSI (i.e., not having exclusively scientific content), availability in French or English, availability online, not being duplicate titles or conference abstracts. The database search thus generated 49 papers that were selected for the review. Key websites (Google Scholar and the Georgetown Library) and journals (Nature, Science, BMJ, Fertility and Sterility, Human Reproduction, Reproductive Biomedicine Online and The Lancet) likely to offer essential papers were also searched. Researchers in the field were consulted to help identify additional papers. Finally, relevant references from bibliographies of included papers were also included (using the same inclusion criteria as above). This generated 46 additional papers, for a total of 95 (see Appendix A).

Table 1: Key words and phrases

Maternal spindle transfer
Mitochondrial donation
Mitochondrial DNA replacement
Mitochondrial DNA transfer
Mitochondrial gene transfer
Mitochondrial gene replacement
Mitochondrial replacement
Mitochondrial transfer
mtDNA replacement
mtDNA transfer
Nuclear genome transfer
Polar body genome transfer
Pronuclear transfer
Three parent baby*
Three parent embryo*
Three parent in vitro fertilization (or IVF)
Three person baby*
Three person embryo*
Three person in vitro fertilization (or IVF)

Figure 1. Paper Selection Process



Analysis

The analysis was performed by two independent researchers using NVivo10 [19] and adapting Burnard's [20] stage-by-stage process of content analysis. The coding of all papers was performed both inductively and deductively, separately by RDL and SB. The results were then compared one by one and discussed by RDL and SB. When necessary, the results were discussed by all three authors until consensus was achieved. The themes were generated by the researchers' codes and subsequently classified into the following categories: terminology; identity, relationships and parenthood; potential harm; reproductive autonomy; available alternatives; consent; impact on specific interest groups; resources; "slippery slope"; creation, use and destruction of human embryos; and beneficence.

Table 2. Ethical, Legal, Social Implications of M/NT addressed in the literature, by theme and type of article

ELSI theme	% of papers	% of scientific articles & reports [rank among themes]	% of editorials & news items [rank among themes]
Harm to future child	86	83 [1]	88 [1]
Beneficence	60	69 [2]	55 [2]
Slippery slope	55	60 [4]	52 [3]
Identity of Child	54	66 [3]	47 [4]
Available alternatives	45	60 [4]	37 [5]
Relationships formed as a result of M/NT, donor status, legal parenthood	42	60 [4]	32 [6]
Harm to future generations	36	49 [7]	28 [7]
Harm to egg donors	32	43 [8]	25 [9]
Resources	27	26 [14]	28 [7]
Long-term follow-up	24	34 [9]	18 [10]
Consent of prospective parents	21	34 [9]	13 [15]
Reproductive autonomy	21	31 [11]	15 [13]
Creation, use and destruction of human embryos	20	29 [13]	15 [13]
Impact of M/NT on scientists and researchers	20	26 [14]	17 [11]
Impact of M/NT on persons suffering from mtDNA diseases	17	31 [11]	8 [16]
Consent of the future child	14	26 [14]	7 [18]
Terminology	14	9 [18]	17 [11]
Harm to prospective parents	9	11 [17]	8 [16]

Supplementary file – Themes (See Annex 1)

Results

Terminology

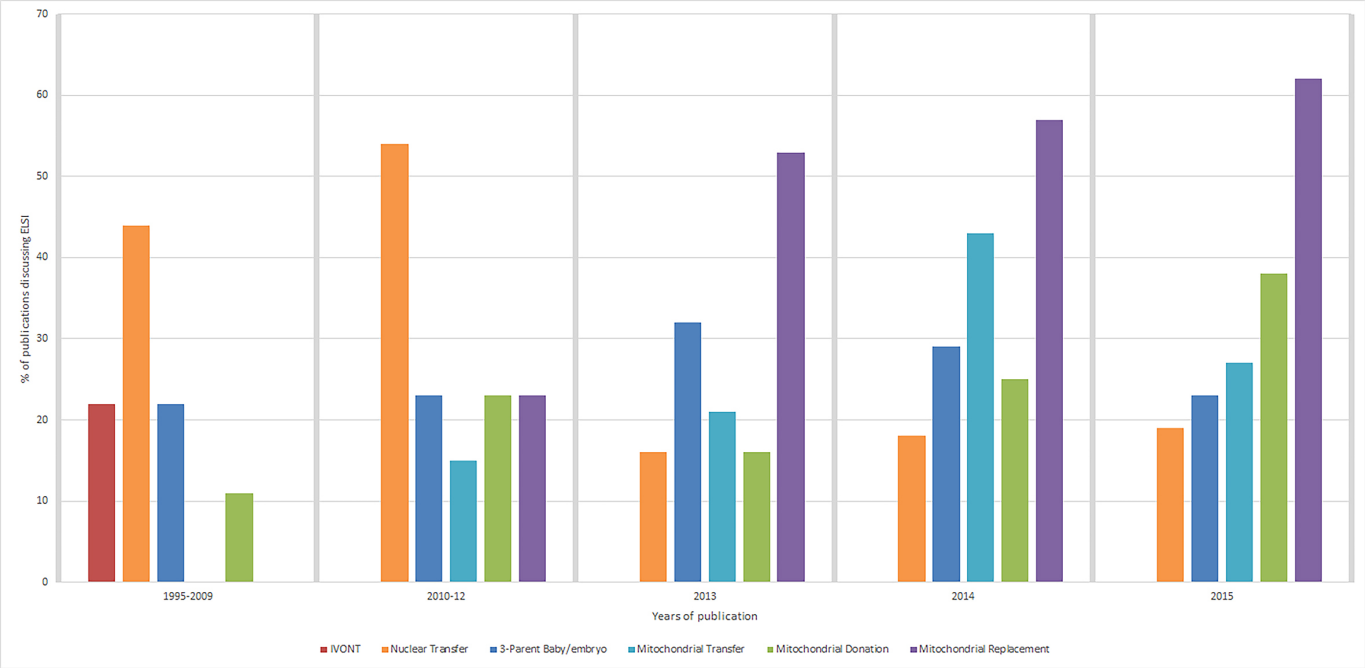
The technology – as well as resulting offspring – is referred to using numerous terms (Table 5). The expression "mitochondrial transfer" does not actually reflect what M/NT involves (i.e., the transfer of the spindle or the *pronuclei* – not of mitochondria – from the prospective mother's egg to the donor's) [7]. Bredenoord et al. use the term "mtDNA modification" citing important previous use in the literature, while stating that "mtDNA replacement" is a more accurate expression [13].

Table 3. Use of Terminology in the Scientific Literature When Referring to the Technology

Term used	% of papers (n=95)	% of scientific articles & reports (n=35) [rank among all terms used]	% of editorials & news items (n=60) [rank among all terms used]
"mitochondria(l) replacement / MRT"	47	37 [2]	53 [1]
"mitochondria(l) (DNA) transfer"	26	29 [4]	25 [3]
"3 / three(-)parent baby(ies) / embryo(s)"	26	17 [6]	32 [2]
"nuclear (genome) transfer / NT"	25	43 [1]	15 [5]
"mitochondria(l) donation"	25	34 [3]	20 [4]
"3 / three(-)parent in vitro fertilization / IVF"	12	20 [5]	7 [8]
"mtDNA replacement"	9	11 [7]	8 [7]
"mitochondria(l) manipulation"	6	9 [8]	5 [9]
"3/three(-)person in vitro fertilization / IVF"	5	6 [9]	5 [9]
"genetically modified baby(ies) / embryo(s) / child(ren)"	5	6 [9]	5 [9]
"oocyte modification"	3	6 [9]	2 [15]
"IVONT / In Vitro Ovum Nuclear Transplantation"	2	3 [12]	2 [15]
"mitochondria(l) (gene) therapy"	2	0	3 [12]
"DNA/genome transplant"	2	0	3 [12]
"3 / three(-)person embryo(s) / baby(ies)"	1	0	2 [14]
"DNA swap"	1	0	2 [15]
No term selected (technique is described but no term used)	6	0	10 [6]

Some terms arguably convey relative neutrality, such as "mitochondrial/nuclear *transfer*", while others are more value-laden, such as "mitochondrial *therapy*" [21]. In the present review, the phrase mitochondrial/nuclear transfer (M/NT) is used to designate both MST and PNT.

Figure 2. Evolution of Terminology Use in the Scientific Literature



Identity, relationships and parenthood

i) Identity of the child

51 papers address the issue of whether M/NT affects the identity of offspring.

> [A] general assumption is that mtDNA does not really constitute our genetic make-up; it does not influence our phenotype, as it only governs cellular energy production. Modification of essential or defining characteristics is considered to be ethically more problematic, because it determines one's identity or personality. Modifying the nuclear DNA is therefore often regarded [as] more problematic than modifying the mtDNA [22, p.674].

A response to the above argument is that one's identity is about more than physical appearance and character traits. Most nuclear genes do not contribute to the physical appearance and character traits of a person, but rather are involved in fundamental processes, just like mitochondrial genes [23]. Hence, it is argued that the reasons for considering energy production to be an "unimportant physical function" are not clear [24, p.6] and that such premises could lead to the conclusion that it is acceptable to "tinker" with most genes [23]. mtDNA's role may be considerably underestimated and it may, in fact, have an impact on traits such as athleticism, fertility, ageing and intelligence, behaviour and health, variables that play a role in defining one's identity [9,22,25,26].

The qualities of DNA may thus be more relevant to the debate than its quantity [27]. Genes carried by mtDNA can have a pervasive effect on metabolism and physical development [28], potentially causing debilitating illness [Murdoch, in 29]. A person born free of mtDNA disease can thus have a very different life story, experience and even personality, because medical conditions can have a determining impact on one's self-perception and identity. If successful, M/NT can thus have a considerable influence on the resulting child's identity [6,13,14,30,31-33]. While mtDNA may not directly impact character or physical traits, it may still be similar in some ways to nDNA modification, which is often perceived as more problematic than M/NT [22]. Study participants believed that because both mtDNA and nDNA can lead to serious disabilities, both kinds of DNA are identity-defining [16]. Like M/NT, "many other medical interventions, whether they involve genetic materials or not, are 'identity-altering' according to a variety of notions of identity" [31, p.55].

Some argue that M/NT is compatible with the child's "right to have one's future options kept open" [11, p.203] [see also 13,16,29], since it would eradicate the disease and therefore arguably broaden one's future options [11,13,16,29]. Others argue that M/NT would to a certain extent impede the child from making her/his own future choices [29].

The child's identity may be subject to confusion or ambiguity as s/he may be considered to have three genetic parents, leading to unknown social consequences [14,22,29,31,35-41]. Some argue that having three genetic parents is not a major ethical

concern [41], but others fear social stigmatization that may influence the child's conception of self [40]. Some suggest that the child should be informed, as in the case of other reproductive technologies involving a third-party contribution [37].

Ancestry tracing using mtDNA can provide genealogical information, which for some "suggests that the maternal input on the part of the donor is far from negligible" [42, p.19]. M/NT could make it impossible for the child to trace maternal genetic lineage [6], causing concerns regarding potential "ancestry confusion" [6,24,27,31,40,43]. However, it is argued that this confusion already exists due to egg, sperm and embryo donation [27].

ii) Relationships formed as a result of M/NT, donor's status and legal parenthood

M/NT may be considered controversial because, like other assisted reproductive technologies, it increases the number of parents a child may possibly have [44].

The third party genetic contribution may threaten some cultures' traditional concepts of family and parenthood [14,22,45]. However, three- (and more) parent families already exist: lesbian couples with a sperm donor, gay couples with a surrogate mother, reconstituted families, etc. [14,45]. M/NT is arguably closer to the "traditional nuclear family" than egg donation, since the prospective mother contributes her nDNA, carries, gives birth to and raises the child [30, p.14]. Nevertheless, M/NT challenges the definition of biological parenthood thus raising ethical and conceptual issues [13,46].

The availability of M/NT can be seen as a "double-edge sword" [47, p.3], making prospective parents responsible whether they choose to use or reject it. This may open the door to blame and possibly affect the parent-child relationship. Counselling of prospective families on how to manage the "three-parent family" may be needed, before and after conception, and at least until puberty – when children start asking questions about their origins [16]. Furthermore, the fact that the child was created to satisfy the parents' need of a genetically linked progeny may affect the relationship between the child and its parents by "commodifying" the child [24,30,42,48].

Some are concerned that the mtDNA donor may develop strong maternal feelings and may want to develop a relationship with the child. The prospective (nuclear) mother may feel that because of the donor's contribution, the offspring is not "fully hers" and confusion may result [49, p.1268]. However, current lack of data makes it challenging to anticipate the effect of M/NT on children's relationships with their parents and the donor, which will probably vary from one family to another, as it does in the case of reproductive egg donation [31].

When considering the third party's genetic contribution, questions about the privileges, rights, obligations and responsibilities of the donor are raised [16,40,43,49,50]. Some doubt whether children born following M/NT should know the donor's identity [16,43,51]. Paller-Rzepka presents some of the arguments put forward against the donor's recognition as a legal parent, highlighting the negative consequences of co-parentage on the child, as well as legislators' potential refusal to change existing legislation accordingly [50].

In the UK, when a child conceived with gamete donation after 2005 reaches adulthood, s/he can access the gamete donor's identity [52]. Moreover, the donor in these cases is not legally related to the resulting child and cannot obtain a parental order [29]. UK law allows the legal recognition of only one "mother" – the woman who carries and gives birth to the child [3,31]. Some argue that the same limitations should apply to M/NT [22,30,31]. According to the UK's M/NT regulations, mtDNA donors will be treated as tissue donors rather than as egg donors, with both children and the donor given access solely to limited non-identifying information about each other [4,29,30]. It is unclear how mtDNA donors would be viewed in other jurisdictions [53].

Currently, there is a dearth of data regarding how mtDNA donors view the social significance of their donation [31]. Nevertheless, a voluntary system of contact or information exchange between the donor and the resulting child, arranged with mutual consent, is suggested [27,31,54,55].

Potential harm

i) Harm to the future child

Issues regarding the limited available information about the safety and efficacy of M/NT as well as the potential physical or psychological harms to the resulting child, include: "mitochondrial disease, as a result of carryover of abnormal mitochondria and heteroplasmy"; "disorders due to nuclear-mitochondrial incompatibility"; "disorders related to aberrant epigenetic modifications"; "birth defects and other disorders associated with the specific mitochondrial manipulation technology procedure"; and "toxicities of reagents used in mitochondrial manipulation technologies" [56, p.20].

Because the goal of M/NT is a viable pregnancy, it "cannot be gradually phased into use" [31, p.65]. Furthermore, the germ-line effects of M/NT on the offspring will be irreversible [10,14,22,31,54]. The possible future discontinuation of M/NT as a treatment due to negative effects outweighing the benefits will be of little consolation to those children who are already negatively affected [31]. However, the risk of not offering M/NT to women who carry mutant mtDNA is that children may be born with diseases caused by mtDNA mutations [29,31].

The potential risks of M/NT raise the question of when it would be appropriate to offer it for the first time [10,16]. Introducing its use in humans through clinical trials is seen as essential, even if the design of such trials must accept some risks [5,6,16,39,55,58,59]. Many currently accepted reproductive technologies would not have been implemented without accepting some risk: e.g., IVF, prenatal genetic diagnosis (PGD) [5,22,14,27]. While the precautionary principle is suggested by some [10,22,29,50], others argue that prioritising precautions "stifles discovery or paralyzes scientific and technical progress…. To govern the introduction of new reproductive technology one could also adhere to a 'proof first' approach, placing the burdens on the regulator to demonstrate a high risk of serious harm" [22, p.673].

Finally, some raise concerns regarding the consequences that the prospective mother's health may have on the wellbeing of the child [31]. If the mother is affected by a serious mitochondrial disorder and consequently has a reduced life expectancy, she might have a limited ability to take care of her child.

ii) Harm to future generations

M/NT involves germ-line modifications that will be transmitted down the generations, thus complicating the risk/benefit analysis [61]. As with other reproductive technologies, the real impact of M/NT will not be known until numerous generations are born [31]. Thus, Baylis mentions the "right of subsequent generations to inherit an un-manipulated genome" [6, p.533-534].

As mitochondria are inherited maternally, male offspring do not transmit their potentially mutant mtDNA to progeny, which leads to a discussion of the ethical acceptability of selecting only male embryos for M/NT in order to avoid the transmission of health risks to subsequent generations [8,13,16,31,36,39,56,62-64]. The UK Human Fertilisation and Embryology Authority (HFEA) ultimately rejected this idea, but recommends that any female born following M/NT be informed of the potential risks of transmitting mtDNA disease to her own children [8].

iii) Long-term follow-up

Because M/NT's effects may not manifest for many years, long-term and even intergenerational follow-up on the safety and efficacy of the technique is suggested, including "social research into how children born from mitochondria replacement feel about their origins" [39, p.5]. Some suggest making parental consent to long-term follow-up of resulting children a condition for participation in trials [16,31,54], but the HFEA recommends that permission to follow-up be obtained from the resulting children when they come of age [8]. Appleby argues that the procedure should only be offered to parents who plan on telling their child that s/he was born following the M/NT, since it would allow her/him to knowingly seek appropriate health care [36].

For some, long-term follow-up raises concerns regarding the burden put on children since "[b]eing made the enforced subjects of research over an indefinite period could be detrimental to their mental and emotional health" [30, p.7-8], while others believe that it would not be ethically problematic [16].

It is anticipated that it will be difficult to ensure long-term follow-up, since this has been a problem in the past for other assisted reproductive technologies [31]. A central register facilitating long-term follow-up that would be accessible to researchers is recommended [31,54], requiring government commitment to its maintenance [31,32,54].

iv) Harm to egg donors

Aside from ELSI related to regular egg donation, M/NT research requires an increase in availability of donated eggs, even as current shortage of donated eggs is acknowledged [22,30,31,32,59,65,66]. Moreover, eggs used for M/NT should be fresh – as opposed to cryopreserved – placing "time pressures on mitochondrial donors in terms of aligning their donation with someone's convenience other than their own" [30, p.11].

v) Harm to prospective parents

Risks of harm to prospective parents include failure to become pregnant [58,60], failure to give birth to a child [56], and health risks during childbirth due to the mitochondrial disorder affecting the mother-to-be [7]. Additionally, risks arising from hormonal stimulation and egg retrieval associated with IVF must be taken into account [6].

Reproductive autonomy

Reproductive autonomy is defined as "a principle concerning the non-interference in reproductive decision making" [31, p.70]. M/NT arguably widens the reproductive options available to women at risk of transmitting serious mtDNA diseases [16,29,31,37,67-71]. However, "[b]ecause an experimental procedure is available, does that mean that every patient who wants the experimental procedure has a right to that procedure" [44, p.188] [see also: 48]? And "is the desire for a genetically related child a positive right and is there a corresponding social obligation to support its realization" [57]? Could M/NT "create needs people never knew they had" [Bonnicksen, in 57, p.19]? Conversely, potential pressure on women to undergo M/NT if it becomes available may result in diminished reproductive autonomy [30,39,56] and in the emergence of a parental duty to prevent the transmission of mtDNA diseases [30].

Available alternatives

Alternatives to M/NT include adoption, IVF with egg donation, pre-implantation genetic diagnosis (PGD) and pre-natal genetic diagnosis (PND). Given available alternatives for preventing the birth of an affected child and for parenting a healthy child, the question of the reasonableness of using the M/NT arises [31]. However, these alternatives are not without limitations. Adoption and IVF with egg donation do not address the parents' desire to have a genetically related child [8,14-16,22,29,32,37,59]. Finding an egg donor can be challenging, especially when considering that the prospective mother's relatives may also be carriers [22]. PGD and PND are not a suitable technique for women with homoplasmy or a very high level of heteroplasmy [8,66,72]. On the other hand, PND can detect mutation in the fetus [22], but this is not necessarily decisive [10].

The drawbacks of these alternatives may be outweighed by being considered less ethically challenging than M/NT [10,28,73]. However, "PGD and other forms of reproductive technology are more prone to promote some kind of eugenics (by their active selection) than M/NT. […] [PGD] involves embryos that have already been created, rather than dealing with the potential of embryos" [14, p.4].

Consent

i) Consent of the future child

The most commonly raised concern related to consent of the prospective child is similarly pertinent to already accepted reproductive technologies: while the prospective mother is the one undergoing the intervention, the one who bears most of the potential risks is the offspring, and who obviously could not consent at the time of the decision [5,9-11,22,31,39,60,74-76].

ii) Consent of prospective parents

While everyone can agree that participants in M/NT trials must be fully informed of the potential risks and benefits of M/NT, "[g]iven the uncertainty – particularly in the early days of human trials – as to the safety and/or efficacy of the new techniques, is it possible that a true, informed consent could actually be given" [29, p.84]? Indeed, while "new genetic technology widens reproductive options for couples, it makes them dependent on experts to make an informed decision, and concepts in mitochondrial inheritance are particularly difficult" [10, p.5].

Possible pressure to undergo M/NT can jeopardize free and informed consent [30]. Couples "may forgo rational considerations of risks, benefits, and long-term consequences" and "are likely to fall victim of the therapeutic misconception in which they 'deny the possibility that there may be major disadvantages to participating in clinical research that stem from the nature of the research process itself'" [Appelbaum et al., in 43, p.188]. The fact that researchers and clinicians will be working very closely might further obfuscate the frontiers between research and clinical practice [61]. There is a lot to learn about the way mitochondrial disease is "experienced, measured and communicated", including "how [the] mutation ratio combines with experience to provide estimations of risk and projections of the future, how normative decisions are made about acceptable levels of mitochondrial mutation and how the boundaries between normal and pathological are negotiated by both patients, families and health professionals" [47, p.9].

Informed consent will vary from one family to another and the acceptable level of risk will remain a personal matter [31]. The "difference across patients in the severity of expected offspring symptoms in the event that [M/NT] is not taken will shape the decision of choosing the treatment versus waiting for the outcomes of further research" [64, p.1346].

Impact on specific interest groups

i) Persons suffering from diseases caused by mtDNA mutations

Some raise concerns regarding stigmatization of persons currently afflicted by mitochondrial disease [29,30,31,37], including a possible "knock-off effect on attitudes towards disabled people more generally" [39, p.18]. However, these arguments apply equally to currently socially accepted reproductive technologies aiming to avoid the transmission of genetic diseases [37,39]. Additionally, there is concern about the stigmatization of children born following M/NT as well as of parents who choose not to undergo the procedure [39].

ii) Scientists and researchers

The implementation of M/NT, or lack thereof, affects the relationship science has with society [10,22]. A specific area of research affected by M/NT is "[h]istorical and anthropological research on human population migration patterns and demographic history us[ing] mtDNA analysis and provid[ing] useful evidence of the geographical origins of humans, likely population sizes, and migration patterns" [6, p.533]. However, this issue was already addressed when egg and embryo donation were debated [27,30].

Resources

An important debate is centred on whether the costs associated with developing and introducing M/NT technology are justified by their supposed benefits [6,31]. Some argue costs are not justified because potential beneficiaries are "a very small minority

for whom there are other reproductive options" [6, p.534]. However, others say that categorizing potential beneficiaries as a "very small minority" tends to diminish their pain [27]. The annual number of women who can benefit from M/NT in the UK had been estimated between 10 [37,74,77] and approximately 150 [69,71].

An argument for the costs of the technology not being justified is that it does nothing for those already affected by the targeted diseases, and that the money invested in M/NT research might be better spent on looking for treatment options [16,22,28]. However, "families may use their own resources to pursue M/NT…minimizing public expenditure while increasing scientific knowledge and experience" [37, p.345]. While it is true that the targeted conditions affect a relatively small portion of the population, the financial cost of mtDNA diseases on children and their families is significant [27,37]. The usual cost-benefit analysis calculations may not be directly applicable to the case of M/NT, since it prevents disease "at the very beginning of life", whereas many therapies used as examples in the debate take place "at the end of life", thus making the net gain of M/NT "considerable" [22, p.676], especially if everyone can access it regardless of their financial situation [16,23,31].

An aspect of the uncertainty involved in implementing a new technology is the way in which it can be applied for other purposes. Scientists expect unexpected "spin-off" applications of M/NT to be significant [10,16,22,77]. Some, such as age-related infertility [16,78], "ageing and cancer" [40, p.10] are already being discussed.

Slippery slope

A slippery slope is defined as "[i]ntroducing or accepting a technology or application A that in itself is not morally problematic, would be problematic if doing so makes it impossible to avoid the subsequent introduction or acceptance of another technology or application B that is morally unacceptable" [22, p.675].

Four different kinds of slippery slopes have been raised in the literature. First, a slippery slope towards eugenics, whereby "once germ-line modification is accepted for therapeutic uses, it will lead to the application for non-medical uses, i.e., enhancement" [22, p.675] [see also: 9,11,14,15,17,24,27,28,29,37,41-45,48,50,51,58,60,61,73,74,79-82]. While M/NT may be eugenic in its "aims", it does not follow that it is "any *more* eugenics than existing methods of selective reproduction (abstinence, adoption, egg donation, etc.)" [34, p.638].

Second, the slope towards reproductive cloning involves the argument that although neither MST nor PNT are equivalent to reproductive cloning [8,11,44], "once they are accepted, they may well lead to [blastomere transfer], which clearly is a type of reproductive embryo cloning" [22, p.675] [see also: 8,11,31,44,58,61,83].

The third slippery slope argument is as follows: "If PNT or MST were approved for treatment in a jurisdiction, and the techniques became accessible and acceptable to prospective parents, clinicians or patients might then ask to use the techniques for purposes other than the avoidance of the transmission of serious disease, or which have no therapeutic intention" [31, p.81]. Three examples of such "misuse" are given:

a) using M/NT as an assisted reproductive technique for older, perimenopausal women seeking to have children [17,22,31,66,70];
b) using M/NT to establish a genetic link between the prospective child and more than two prospective parents when the prospective mother does not carry mtDNA mutations [6,27,30,31,44,73,82]; and
c) using M/NT "to allow a woman with a major genetic problem in her nuclear genes to create a genetic link with her child through the use of her mitochondria, without passing on nuclear DNA" [31, p.82].

Fourth, there may be a legal slippery slope whereby "the lifting of the UK ban may facilitate lifting of the ban and initiation of mitochondrial replacement in other countries" [74, p.154]. This argument may be refuted by the ultimate independence of different jurisdictions' legal systems [81,84].

Some claim that the slippery slope effect is an important enough ethical concern to impede the adoption of M/NT: "once one kind of germ-line therapy is accepted, other kinds will almost certainly follow" [42, p.20] [see also: 72]. However, the slipperiness of the slopes may be doubted. A "clear legal distinction between modification to the different genomes [exists], thereby forming a practical barrier to the threat of 'slippery slope' arguments" [31, p.65] [see also: 27,37,39]. Moreover, "this slippery slope is purely philosophical – not methodological, and it is certainly one that is easy to prevent by regulations" [27, p.518]. While technological innovations often carry the potential of abuse with them, this does not necessarily mean that they should not be implemented when the use does not constitute abuse [27,51].

Some question the wrongness of all those things at the bottom of the slopes: eugenics, reproductive cloning, etc. [22,39]. They argue that these "horrors worthy of a dystopian fiction novel" [61, p.3] are perceived as such because of an argument of last resort, often used to vilify possible applications of genetics in assisted reproduction: "unnaturalness" [55, p.1965]. Moreover, it is pointed out that this kind of debate is not new and that similar fears arise when other new technologies first become available [31,51,55].

Creation, use and destruction of human embryos

The "development of [M/NT] may necessitate the creation of embryos especially for research" [22, p.672] [see also: 10]. While research on human embryos is unacceptable to some [22], others argue that it is ethically acceptable when it aims to alleviate human suffering, and more specifically, that of children at risk of inheriting mitochondrial diseases [37,82]. Adopting a similar perspective and starting from the premise that few alternatives are available to affected families, the Nuffield Council on Bioethics (NCB) Working Group "agreed that, with the appropriate oversight, research that may destroy or alter eggs or embryos (and which may develop treatments which require the same), is justifiable in seeking to prevent serious genetic illnesses being transmitted" [31, p.85].

Beneficence

Physicians have a "duty to act to benefit their patients – both prospective parents and children," and parents have a duty to ensure the children they bring into this world do not suffer needlessly [37, p.345]. Authors point out that M/NT "falls within the good medical practice of preventing serious illness" [29, p.88] and "could offer significant health and social benefits to individuals and families, who could potentially live their lives free from what can be very severe and debilitating disorders" [9, p.74].

While no one debates the validity of the beneficence argument, the question remains "whether the benefit of averting severe disease overrides societal objections to changing the human germ line" [70, p.827]. The lack of debate regarding what constitutes an "acceptable risk-benefit balance" is lamented. "[W]e may be facing a whole new set of ethical questions related to intergenerational risk/benefit analysis" [61, p.4], that may require novel approaches. Braude suggests that prospective parents are "best placed to balance the risks" and benefits of the technology [83, p.1].

How much weight do the benefits carry? Some authors argue that we are nothing less than morally obliged to reduce suffering in future people at risk of disease [30,82]. Others bring to our ethical attention "the potential to remove an entire class of adverse and truly devastating genetic mutations from affected families and possibly from the human population as a whole" [27, p.518] [see also: 26,37,63]. It may be our duty as parents and society to prevent future children from inheriting genetic disorders [30,60]. Yet, given the recognition that it is possible to prevent future suffering without recourse to M/NT, the risk/benefit question becomes: "Does fulfilling some prospective parents' desire to be genetically related to their child override societal objections to changing the human germ line?" [6,9,11,14,31,37,57,83] Indeed, the NCB's Working Group argues that "[i]n light of the health and social benefits to individuals and families living free from mitochondrial disorders, and where potential parents express a preference to have genetically-related children…if the PNT and MST techniques are proven to be acceptably safe and effective, on balance it would be ethical for families wishing to use them to do so" [31, p.88].

This view is based on the often-implicit recognition of prospective parents' desire to be genetically related to their child as "being natural or even instinctive, whilst also being influenced by contemporary cultural and social norms" [31, p.68]. Others, while acknowledging the importance of such a desire, question whether it constitutes a right [16,24,48], especially when juxtaposed with ethical concerns. Then again, such questioning puts in doubt the acceptability of other socially sanctioned reproductive technologies whose main benefit is ensuring genetic relatedness between parents and children [14,53].

While it may seem that the scientific and bioethics communities are largely undecided on the matter, the literature suggests that there is, in fact, almost a consensus, with 15 articles [26,29,31,34,37,39,41,51,53,61,63,83,85-87] explicitly stating that "ethical concerns are outweighed by the arguments in favour of permitting mitochondria replacement" [39, p.4], and only 1 explicitly stating the opposite [24]. The remaining reviewed articles do not make explicit their position on where the ethical balance lies.

Limitations

A potential limitation of the present review is that a significant portion of the debate took place in the blogosphere as well as other types of popular media. While some blogs have a higher degree of credibility than others, it was decided that such texts should be excluded from a review of the scientific literature on the topic of M/NT. Nonetheless, the large number of commentaries, editorials, and letters to the editor that were included in the present review compensates for the omission of blogs and popular media. Moreover, aside from the usual caveats of qualitative analysis – albeit mitigated by the fact that two researchers coded the sources independently – several of the identified ELSI overlapped with one another (for example, the issue of financial "resources" invested in research on N/MT is often discussed in connection with the impact of M/NT on "*persons suffering from diseases caused by mtDNA mutations*", since the resources invested in N/MT are not intended to cure these people).

Discussion

The present critical interpretive review of the ELSI of M/NT highlights the issues most prevalent in the literature. Most of them – namely, identity of the child, relationship with the donor, parenthood, unknown risks to the offspring, risks to egg donors, the existence of available alternatives, consent of the yet unborn child, the impact of the technology on persons suffering of the same disability, the slippery slope argument, and the use of human embryos – have already been raised in relation to other assisted reproduction technologies that have since been accepted by society, such as IVF, PGD and intracytoplasmic sperm injection (ICSI).

The ELSI particular to M/NT are those stemming from the fact that M/NT involves germ-line modification, especially potential harms to future generations. Additionally, M/NT crossing the line into germ-line modification shapes the issues of intergenerational follow-up and the slippery slopes to nuclear DNA modification and misuse of the technique. These novel issues specific to M/NT call for a new framework for risk-benefit analysis, new research ethics guidelines, a register for long-term follow-up, a new system of contact or information exchange between the child and the donor, and an assessment of how M/NT will affect egg donors.

Arguments in the debate on the identity of the child go beyond those in the context of gamete donation, since they address the child's genetic link to three persons. Some of the arguments both for and against the implementation of M/NT are based on how the child's identity is affected by M/NT, and this is influenced by views on the nature of the genetic contribution of mtDNA [16]. These views in turn affect both the terminology chosen to refer to M/NT (e.g. "three-parent babies") and views on the relationship between the donor and child [39].

Given the diversity of potential ethical arguments against implementing M/NT in humans, it is possible to lose sight of the ethical argument in favour: beneficence. Some of the articles reviewed ignore this argument, possibly because the duty to benefit seems so obvious that it goes without saying and does not require discussion.

As M/NT was applied clinically to humans for the first time in 2015, its risks have yet to be studied. This contributes to much of the debate taking place in the media rather than in scientific articles. Commentaries, editorials, letters to the editor, and research news items made up the majority of the papers included in this review, which may lead to an overrepresentation of certain issues. Furthermore, of the 30 research articles reviewed, only two were based on empirical qualitative studies [16,47], neither of which analyzes specifically the views of M/NT's potential users (although Dimond has interviewed people suffering of mitochondrial diseases, they were not necessarily potential M/NT users). Even in the HFEA's public consultation, the focus group meeting included only 7 patients – some patients did, however, attend the "Open consultation meetings" that took place in two different cities [39]. Potential users are the target audience of M/NT and arguably the main stakeholder; they must therefore take significant part in the debate.

It is important to heed the calls of researchers, especially for follow-up research [5,10,24,54]. This should include longitudinal clinical research on all parties involved, as well as psychosocial longitudinal research to equip the ELSI debate with reliable evidence regarding questions such as: are there psychosocial harms and identity issues for the child and for the future generations, and if so, what are they? And what is the impact on egg donors, persons currently suffering of mtDNA diseases, and scientists?

Finally, when the stakes are this high, it is crucial to learn from past mistakes, such as the absence of registries in the context of gamete donation [88]. Registries to record the identities of donors, parents and children conceived through M/NT should be mandatory. The unpredictability of the risks to future generations largely justifies this approach.

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References

1. United-Kingdom Parliament (House of Commons). The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015. 3 February 2015
2. United-Kingdom Parliament (House of Lords). The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015. 25 February 2015
3. United-Kingdom Government. The Human Fertilisation and Embryology Act 1990 (As Amended in 2008)
4. United-Kingdom Government. The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015
5. P. Amato et al. Three-parent in vitro fertilization: gene replacement for the prevention of inherited mitochondrial diseases. Fertil Steril 2014; 101(1): 31-35
6. F. Baylis. The ethics of creating children with three genetic parents. Reprod Biomed Online 2013; 26: 531-534
7. D. Dickenson & M. Darnovsky. Is the UK being too hasty over three-parent babies? New Sci 2014
8. Human Fertilisation and Embryology Authority (HFEA). Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2014 update. 2014
9. D.P. Wolf, N. Mitalipov & S. Mitalipov. Mitochondrial replacement therapy in reproductive medicine. Trends Mol Med 2015; 21(2): 68-76
10. A.L. Bredenoord & P. Braude. Ethics of mitochondrial gene replacement: from bench to bedside. BMJ 2010; 341: c6021
11. A.L. Bredenoord et al. Nuclear transfer to prevent mitochondrial DNA disorders: revisiting the debate on reproductive cloning. Reprod BioMed Online 2011; 22: 200-207
12. R.W. Taylor & D. Turnbull. Mitochondrial DNA mutations in human disease. Nat Rev Genet 2005; 6: 389-402;
13. A.L. Bredenoord et al. Ethics of modifying the mitochondrial genome. J Med Ethics 2011; 37: 97-100
14. M.D. Garasic & D. Sperling. Mitochondrial replacement therapy and parenthood. Glob Bioet 2015; 26(3-4): 198-205
15. S. Grossman. Mitochondrial replacement therapy and Jewish law. Derech Hateva 2015
16. Hens, W. Dondorp & G. De Wert. A leap of faith? An interview study with professionals on the use of mitochondrial replacement to avoid transfer of mitochondrial diseases. Hum Reprod 2015; 30(5): 1256-1262;
17. J.Y. Nau. Transfert mitochondrial : pari génétique britannique à haut risque. Rev Med Suisse 2015; 461: 426-427.
18. R. McDougall. Reviewing literature in bioethics research: increasing rigour in non-systematic reviews. Bioethics 2015; 29(7): 523-8
19. NVivo qualitative data analysis software; QSR International Pty Ltd. Version 10, 2012
20. P. Burnard. A method of analysing interview transcripts in qualitative research. Nurse Educ Today 1991; 11(6): 461-466
21. V. Ravitsky, S. Birko & R. Dupras-Leduc. The "three-parent baby": A case study of how language frames the ethical debate regarding an emerging technology. Am J Bioeth 2015 ; 15(12): 57-60
22. A.L. Bredenoord, G. Pennings & G. De Wert. Ooplasmic and nuclear transfer to prevent mitochondrial DNA disorders: conceptual and normative issues. Hum Reprod Update 2008; 14(6): 669-678
23. M. Le Page. Crossing the germ line – facing genetics' great taboo. New Sci 2015
24. Human Genetics Alert. Human genetic engineering on the doorstep: the threat of 'mitochondrial replacement' techniques. 2012; 1-7
25. N. Lane. One baby, two mums. New Sci 2008
26. Anonymous. Three-parent babies: It's more messy than we thought. New Sci 2014
27. M.N. Johnson. Tri-parenthood – a simply misleading term or an ethically misguided approach? Reprod Biomed Online 2013; 26: 516-519
28. N. Darnovksy. A slippery slope to human germline modification. Nature 2013; 499: 127
29. S.A.M. McLean. Mitochondrial DNA Transfer: Some Reflections From The United Kingdom. BiolawJournal 2015; 2: 81-88

30. R. Briscoe. Ethical Considerations, Safety Precautions and Parenthood in Legalising Mitochondrial Donation. New Bioeth 2013; 19(1): 2-17;
31. Nuffield Council on Bioethics (NCB). Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review. 2012
32. H.J.M. Smeets. Preventing the transmission of mitochondrial DNA disorders: Selecting the good guys or kicking out the bad guys. Reprod Biomed Online 2013; 27, 599-610
33. I. Szebik. Response to "Germ line therapy to cure mitochondrial disease: protocol and ethics of in vitro ovum nuclear transplantation" by Donald S. Rubenstein, David C. Thomasma, Eric A. Schon, and Michael J. Zinaman. Camb Q Healthc Ethics 1999; 8: 369–374
34. A. Wrigley, S. Wilkinson & J.B. Appleby. Mitochondrial replacement: ethics and identity. Bioethics 2015 ; 29(9): 631-638
35. G.N. Allahbadia. Is the world of ART ready for a ménage à trois? J Obstet Gynaecol India 2015; 65(2): 71-74
36. J.B. Appleby. The ethical challenges of the clinical introduction of mitochondrial replacement techniques. Med Health Care and Philos 2015; 18: 501-514
37. R. Klitzman, M. Toynbee & M.V. Sauer. Controversies concerning mitochondrial replacement therapy. Fert Steril 2015; 103(2): 344-346
38. S. Mitalipov & D.P. Wolf. Clinical and ethical implications of mitochondrial gene transfer. Trends Endocrinol Metab 2014; 25(1): 5-7
39. Human Fertilisation and Embryology Authority (HFEA). Mitochondria replacement consultation: Advice to Government. 2013
40. C. Jones & I. Holme. Relatively (im) material: mtDNA and genetic relatedness in law and policy. Life Sci Soc Policy 2013; 9(4)
41. Anonymous. Ethics of mitochondrial donation. The Lancet 2012; 379: 2314
42. A. Sutton. A case against germ-line gene therapy. Ethics Med 2013; 29(1): 17-22
43. R.L. Fischbach, S. Benston & J.D. Loike. Creating a three-parent child: an educational paradigm for the responsible conduct of research. J Microbiol Biol Educ 2014; 15(12): 186-190
44. A.S. Levine. Reproductive technologies and the new math: When it takes three parents to make an embryo. Contemp Ob Gyn 2015; 1-3
45. P. Ball. The art of medicine: unnatural reactions. The Lancet 2014; 383: 1964-1965
46. H.S. Liu & P.L. Chu. Three-parent embryo: The therapeutic future for inherited mitochondrial diseases. J Formos Med Assoc 2014; 114(11): 1027-1028
47. R. Dimond. Patient and family trajectories of mitochondrial disease: diversity, uncertainty and genetic risk. Life Sci Soc Policy 2013; 9(2)
48. J. Ravindra Fernando. Three's company: a constitutional analysis of prohibiting access to three-parent in vitro fertilization. Notre Dame J Law Ethics Public Policy 2015; 29: 523-548
49. G.P.A. Bongaerts. How to prevent 'half-bastard' progeny? or An alternative for three-parent babies: Two-parent babies through transplantation of sperm mitochondria. Med Hypothesis 2006; 67: 1266-1269
50. A.J. Paller-Rzepka. Are you my mother? Why mitochondrial DNAtransfers require states to rework traditional, two-person legal parentage frameworks. Biotechnol Law Rep 2014; 33(5): 193-206
51. Y. Margalit, M. Hirano & J.D. Loike. Three-way parenthood. The Scientist Magazine 2013.
52. United-Kingdom Government. The Human Fertilisation and Embryology Authority (Disclosure of Donor Information) Regulations 2004.
53. P. Cheruvu. Three-parent IVF and its effect on parental rights. Hastings Sci Tech Law J, 2014; 6(1): 73-81
54. N. Hawkes. Intervention to prevent transmission of mitochondrial disorders should be allowed, subject to safeguards, report says. BMJ 2012; 344:e4089
55. I. Torjesen. Government gives the go ahead for mitochondrial donation during IVF. BMJ 2014; 349: g4801
56. Cellular, Tissue, and Gene Therapies Advisory Committee. FDA Briefing Document: Oocyte Modification in Assisted Reproduction for the Prevention of Transmission of Mitochondrial Disease or Treatment of Infertility. 2014; 1-35
57. S. Grauman & H. Haker. Some conceptual and ethical comments on egg cell nuclear transfer. Politics Life Sci 1998; 1: 17-19
58. E. Callaway. Reproductive medicine: The power of three. Nature 2014; 509: 414-417
59. J. Poulton & P. Oakeschott. Nuclear transfer to prevent maternal transmission of mitochondrial DNA disease. BMJ 2012; 345: e6651
60. Donald S. Rubenstein, David C. Thomasma, Eric A. Schon, & Michael J. Zinaman. Germ-line therapy to cure mitochondrial disease: protocol and ethics of in vitro ovum nuclear transplantation. Camb Q Healthc Ethics 1995; 4: 316-339
61. M. List. Mighty mitochondria: a tiny organelle that can, and should, save lives. Michigan State Bioethics 2014.
62. A.L. Bredenoord et al. Avoiding transgenerational risks of mitochondrial DNA disorders: a morally acceptable reason for sex selection? Hum Reprod 2010 ; 25(6): 1354-1360
63. Anonymous. Don't fear babies made with genes from three parents. New Sci 2013

64. K. Reinhardt, D.K. Dowling & E.H. Morrow. Mitochondrial replacement, evolution, and the clinic. Science 2013; 341: 1345-1346
65. D.L. Dickenson. The commercialization of human eggs in mitochondrial replacement research. The New Bioethics 2013; 19(1): 18-29
66. J. Richardson et al. Concise reviews: assisted reproductive technologies to prevent transmission of mitochondrial dna disease. Stem Cells 2015; 33: 639-645
67. A.L. Bredenoord & I. Hyun. The road to mitochondrial gene transfer: follow the middle lane. Mol Ther 2015; 3(6): 975-976
68. S. Fischer. State of the art: emerging genetic technologies in reproductive medicine are rapidly making real what once was science fiction—are we ready for it?. IEEE Pulse 2015
69. Z. Kmietowicz. UK becomes first country to allow mitochondrial donation. BMJ 2015; 350: h1103
70. G. Vogel & E. Stokstad. U.K. Parliament approves controversial three-parent mitochondrial gene therapy. Science 2015
71. J. Wise. Mitochondrial donation could benefit 150 UK women a year, study says. BMJ 2015; 350: h536
72. M. Herbert & D. Turnbull. Mitochondrial replacement to prevent the transmission of mitochondrial DNA disease. Embo Reports 2015; 16(5): 539-540;
73. J.G. Armstrong. Three-parent babies: a debate of eugenics. Penn Bioeth J 2015; 10(2): 9
74. T. Ishii. Potential impact of human mitochondrial replacement on global policy regarding germline gene modification. Reprod Biomed Online 2014; 29: 150-155
75. M. Legge & R. Fitzgerald. Numerical identity: the creation of tri-parental embryos to correct inherited mitochondrial disease. N Z Med J 2013; 126(1385): 71-75
76. S. Norcross. How and why mitochondrial replacement gets our vote. Reprod Biomed Online 2014; 29(2): 267-268
77. S. Mayor. Chief medical officer advises government to allow mitochondrial replacement to prevent disease. BMJ 2013; 346: f4211
78. G. Vogel. FDA considers trials of 'three-parent embryos'. Science 2014; 343: 827-828
79. E.C. Hayden. Regulators weigh benefits of 'three-parent' fertilization. Nature 2013; 502: 284-285
80. G.R. Passi. The three parent embryo. Indian Pediatr 2015; 52: 261
81. G. Pennings. International harmonization and mitochondrial replacement. Reprod Biomed Online 2014; 29: 269
82. Randerson, J. Scientists seek to create 'three-parent' babies. New Scientist 2004
83. J. Wise. Draft UK regulations for mitochondrial donation are published. BMJ 2014; 348: g1846
84. F. Flinter. Concerning Tetsuya Ishii's article: Potential impact of human mitochondrial replacement on global policy regarding germline gene modification. Reprod Biomed Online 2014; 29: 270
85. D. Cyranovsky. DNA swap could avoid inherited diseases. Nature 2009.
86. Anonymous. Mitochondrial manipulations. Nature Medicine 2014; 20(5); 451-452
87. J. Wise. Mitochondrial donation is "not unsafe," review confirms. BMJ 2014; 348: g3723
88. V. Ravitsky. Conceived and deceived: the medical interests of donor-conceived individuals. Hastings Center Report 2012; 42(1): 17-22

2017 Updated references (not included in the literature review)

89. J. Zhang et al. Live birth derived from oocyte spindle transfer to prevent mitochondrial disease. Reprod Biomed Online 2017; 34(4): 361-368
90. M. Alikani et al. First birth following spindle transfer for mitochondrial replacement therapy: hope and trepidation. Reprod Biomed Online 2017; 34(4): 333-336
91. Anonymous. Baby's DNA mix revealed. Nature 2017; 544: 17-18
92. C. Palacios-Gonzalez. Mitochondrial replacement techniques, Mexico and the legal unknowns. Bionews 2017; 897

Appendix A. List of Articles and Reports Selected for the Review

Author	Year*	Title	Journal
Natural Science Original Research Articles (n=8)			
Amato, P. et al.	2014	Three-parent in vitro fertilization: gene replacement for the prevention of inherited mitochondrial diseases	Fertility and Sterility
Bongaerts, G.P.A.	2006	How to prevent 'half-bastard' progeny? or An alternative for three-parent babies: Two-parent babies through transplantation of sperm mitochondria	Medical Hypothesis
Mitalipov, S. & Wolf, D.P.	2014	Clinical and Ethical Implications of Mitochondrial Gene Transfer	Trends in Endocrinology & Metabolism
Richardson, J. et al.	2014	Concise Reviews: Assisted Reproductive Technologies to Prevent Transmission of Mitochondrial DNA Disease	Stem Cells
Rubenstein, D.S. et al.	1995	Germ-line therapy to cure mitochondrial disease: protocol and ethics of in vitro ovum nuclear transplantation	Cambridge Quarterly Healthcare Ethics
Smeets, J.M.H.	2013	Preventing the transmission of mitochondrial DNA disorders: Selecting the good guys or kicking out the bad guys	Reproductive Biomedicine Online
Spikings E.C. et al.	2006	Transmission of mitochondrial DNA following assisted reproduction and nuclear transfer	Human Reproduction Update
Wolf, D.P. et al.	2015	Mitochondrial replacement therapy in reproductive medicine	Trends in Molecular Medicine
Social Science Original Research Articles (n=21)			
Appleby, J.B.	2015	The ethical challenges of the clinical introduction of mitochondrial replacement techniques	Med Health Care and Philos
Bredenoord, A. & Braude, P.	2010	Ethics of mitochondrial gene replacement: from bench to bedside	BMJ
Bredenoord, A. et al.	2011[a]	Ethics of modifying the mitochondrial genome	Journal of medical ethics
Bredenoord, A. et al.	2011[b]	Nuclear transfer to prevent mitochondrialDNA disorders: revisiting the debate on reproductive cloning	Reproductive Biomedicine Online
Bredenoord, A. et al.	2010	Avoiding transgenerational risks of mitochondrial DNA disorders: a morally acceptable reason for sex selection?	Human Reproduction
Bredenoord, A. et al.	2008	Ooplasmic and nuclear transfer to prevent mitochondrial DNA disorders: conceptual and normative issues	Human Reproduction Update
Briscoe, R.	2013	Ethical Considerations, Safety Precautions and Parenthood in Legalising Mitochondrial Donation	The New Bioethics
Cheruvu, P.	2014	Three-Parent IVF and its Effects on Parental Rights	Hastings Science and Technology Law Journal
Dickenson, D.	2013	The Commercialization of Human Eggs in Mitochondrial Replacement Research	The New Bioethics
Dimond, R.	2013	Patient and family trajectories of mitochondrial disease: diversity, uncertainty and genetic risk	Life Sciences, Society and Policy
Fischbach, R.L. et al.	2014	Creating a Three-Parent Child: An Educational Paradigm for the Responsible Conduct of Research	Journal of Microbiology & Biology Education
Garasic, M.D. & Sperling, D.	2015	Mitochondrial replacement therapy and parenthood	Global Bioethics
Grossman, S.	2015	Mitochondrial Replacement Therapy and Jewish Law	Derech Hateva
Hens, K. et al.	2015	A leap of faith? An interview study with professionals on the use of mitochondrial replacement to avoid transfer of mitochondrial diseases	Human Reproduction

Jones, C. & Holme, I.	2013	Relatively (im) material: mtDNA and genetic relatedness in law and policy	Life Sciences, Society and Policy
McLean, S.A.	2015	Mitochondrial DNA transfer: some reflections for the United-Kingdom	BioLaw Journal
Moraes, C.T. et al.	2014	Manipulating mitochondrial genomes in the clinic: playing by different rules	Trends in Cell Biology
Paller-Rzepka, A.J.	2014	Are you my mother? Why mitochondrial DNA transfers require states to rework traditional, two-person legal parentage framework	Biotechnology Law Report
Ravindra Fernando, J.	2015	Three's company: A constitutionnal analysis of prohibiting acces to three parent in vitro fertilization	Notre-Dame Journal of Law, Ethics and Public Policy
Tendler, M.D. & Loike J.D.	2015	Mitochondrial Replacement Therapy: Halachic Considerations for Enrolling in an Experimental Clinical Trial	Rambam Maimonides Med J
Wrigley, A. et al.	In Press	Mitochondrial Replacement: Ethics and Identity	Bioethics

Reports & documents (n=6)

Department of Health	2014	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	
FDA Cellular, Tissue, and Gene Therapies Advisory Committee	2014	Briefing Document. 2014. Oocyte modification in assisted reproduction for the prevention of transmission of mitochondrial disease or treatment of infertility	
HFEA	2015	Regulating Mitochondrial Donation: Seeking Expert Views	
HFEA	2014	Third scientific review of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception: 2014 update	
HFEA	2012	Mitochondria replacement consultation: Advice to Government	
Nuffield Council on Bioethics	2012	Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review	

Editorials, Commentaries, Letters to the Editor (n=37)

Allahbadia, G.N.	2015	Is the World of ART Ready for a Ménage à Trois?	Official Journal of the Federation of Obstetrics and Gynaecological Societies of India
Anonymous	2014	Three-parent babies: It's more messy than we thought	New Scientist
Anonymous	2014	Mitochondrial manipulations	Nature Medicine
Anonymous	2013	Don't fear babies made with genes from three parents	New Scientist
Anonymous	2012	Ethics of mitochondrial donation	The Lancet
Ball, P.	2014	The art of medicine: Unnatural reactions	The Lancet
Baylis, F.	2013	The ethics of creating children with three genetic parents	Reproductive Biomedicine Online
Bredenoord, A. & Hyun, I.	2015	The Road to Mitochondrial Gene Transfer: Follow the Middle Lane	Molecular Therapy
Chinnery, P.F. et al.	2014	The Challenges of Mitochondrial Replacement	PlosGenetics
Cohen, I.G. et al.	2015	Transatlantic lessons in regulation of mitochondrial replacement therapy	Science
Darnovsky, M.	2013	A slippery slope to human germline modification	Nature
Dickenson, D. & Darnovsky, M.	2014	Is the UK being too hasty over three-parent babies?	New Scientist

Fischer, S.	2015	State of the ART : Emerging genetic technologies in reproductive medicine are rapidly making real what once was science fiction?	Pulse IEEE
Flinter, F.	2014	Concerning Tetsuya Ishii's article: Potential impact of human mitochondrial replacement on global policy regarding germline gene modification	Reproductive Biomedicine Online
Gemmell, N. & Wolff, J.N.	2015	Mitochondrial replacement therapy: Cautiously replace the master manipulator	Bioessays
Graumann, S. & Haker, H.	1998	Some conceptual and ethical comments on egg cell nuclear transfer	Politics Life Science
Herbert, M. & Turnbull, D.	2015	Mitochondrial replacement to prevent the transmission of mitochondrial DNA disease	Embo reports
Human Genetics Alert	2012	Human Genetic Engineering on the Doorstep : The threat of Mitochondrial Replacement Techniques	briefing by Human Genetics Alert
Ishii, T.	2014	Potential impact of human mitochondrial replacement on global policy regarding germline gene modification	Reproductive Biomedicine Online
Johnson, M.H.	2013	Tri-parenthood – a simply misleading term or an ethically misguided approach?	Reproductive Biomedicine Online
Klitzman, R. et al.	2015	Controversies concerning mitochondrial replacement therapy	Fertility and Sterility
Lane, N.	2008	One Baby, Two Mums	New Scientist
Le Page, M.	2015	Crossing the germ line	New Scientist
Legge, M. & Fitzgerald, R.	2013	Numerical identity: the creation of tri-parental embryos to correct inherited mitochondrial disease	The New Zealand Medical Journal
Levine, A.S.	2015	Reproductive technologies and the new math: When it takes three parents to make an embryo	Contemporary Ob/Gyn
Liu, H.S. & Chu, P.L.	2014	Three-parent embryo: The therapeutic future for inherited mitochondrial diseases	Journal of the Formosan Medical Association
Loike, J. D. et al.	2013	Threeway parenthood: dealing with the logistics of embryos created by three-parent IVF technologies that avoid the transmission of mitochondrial disease	The Scientist
Nau, J.-Y.	2015	Transfert mitochondrial: pari genetique britannique a haut risque	Revue Médicale Suisse
Norcross, S.	2014	How and why mitochondrial replacement gets our vote	Reproductive Biomedicine Online
Pennings, G.	2014	International harmonization and mitochondrial replacement	Reproductive Biomedicine Online
Poulton, J. & Oakeshott, P.	2012	Nuclear transfer to prevent maternal transmission of mitochondrial DNA disease	BMJ
Reinhardt, K. et al.	2013	Mitochondrial Replacement, Evolution and the Clinic	Science
Sutton, A.	2013	A case against germ-line gene therapy	Ethics and Medicine
Szebik, I.	1999	Response to "Germ Line Therapy to Cure Mitochondrial Disease: Protocol and Ethics of In Vitro Ovum Nuclear Transplantation" by Donald S. Rubenstein, David C. Thomasma, Eric A. Schon, Michael J. Zinaman.	Cambridge Quarterly Healthcare Ethics
Tanaka, A.J. et al.	2013	Harnessing the Stem Cell Potential: The path to prevent mitochondrial disease	Nature Medicine
Winter, G.F.	2015	Mitochondrial Donation	British Journal of Midwifery
Wong, C.C. & Johnson, M.H.	2014	Therapy for mitochondrial genetic disease: are we at the thin end of the wedge?	Reproductive BioMedicine Online

Published news pieces (n=23)

Armstrong, J.G.	2015	Three-Parent Babies: A Debate of Eugenics	Penn Bioethics Journal
Asprey, D.	2010	Researchers transfer genetic material between two eggs	BMJ
Callaway, E.	2014	Reproductive Medicine: The Power of Three	Nature News
Callaway, E.	2013	Wide support in UK for novel DNA 'transplants' in human egg cells	Nature

Cyranoski, D.	2009	DNA swap could avoid inherited diseases	Nature
Dyer, C.	2015	UK is set to allow mitochondrial donation after MPs vote in favour	BMJ
Hamzelou, J.	2011	Three-parent babies on their way	New Scientist
Hawkes, N.	2012	Intervention to prevent transmission of mitochondrial disorders should be allowed, subject to safeguards, report says	BMJ
Hayden, E.C.	2013	Regulators weigh benefits of 'three-parent' fertilization	Nature
Kmietowicz, Z.	2015	UK becomes first country to allow mitochondrial donation	BMJ
List, M.	2014	Mighty mitochondria: a tiny organelle that can, and should, save lives	MSU Bioethics
Mayor, S.	2013	Chief medical officer advises government to allow mitochondrial replacement to prevent disease	BMJ
O'Dowd, A.	2014	UK will be groundbreaker if proposed regulations for mitochondrial donation are adopted, MPs hear	BMJ
Passi, G.R.	2015	The Three Parent Embryo	India Pediatrics
Pitts-Tucker, T.	2012	UK fertilisation authority launches consultation on mitochondrial replacement techniques	BMJ
Randerson, J.	2004	Scientists seek to create 'three-parent babies'	New Scientist
Torjesen, I.	2014	Government gives the go ahead for mitochondrial donation during IVF	BMJ
Torjesen, I.	2013	UK moves a step closer to being first country in world to allow "three parent babies"	BMJ
Vogel, G.	2014	FDA Considers Trials of 'Three-Parent Embryos'	Science
Vogel, G. & Stokstad, E.	2015	UK parliament approves controversial three parent mitochondrial gene therapy	Science
Wise, J.	2015	Mitochondrial donation could benefit 150 UK women a year, study says	BMJ
Wise, J.	2014[a]	Mitochondrial donation is "not unsafe," review confirms	BMJ
Wise, J.	2014	Draft UK regulations for mitochondrial donation are published	BMJ

* In the case of 2 items having identical "author" and "year" entries, they are distinguished by an uppercase letter after the year