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A leap of faith? An interview study with professionals on the use of mitochondrial replacement to avoid transfer of mitochondrial diseases

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STUDY QUESTION: What are the opinions of professionals in the field of genetics, reproductive science and metabolic diseases on the development of mitochondrial replacement technologies to be used in the context of medically assisted reproduction?

SUMMARY ANSWER: Although concerns regarding safety remain, interviewees supported the development of nuclear transfer techniques to help women who are at risk of transferring a mitochondrial DNA disease to their offspring conceive a genetically related child.

WHAT IS KNOWN ALREADY: Technological developments in the field of nuclear transfer have sparked new interest in the debate on the acceptability of the use of donor oocytes to prevent the transmission of mitochondrial diseases. For example, in the UK, extensive public consultations have been done to investigate whether such techniques would allow the passing of a law that involves making changes to a human oocyte or embryo before transfer to a woman's body. Until now, continental European countries seem to await the outcome of the British debate before themselves considering the arguments for and against this technology.

STUDY DESIGN, SIZE, AND DURATION: We interviewed 12 professionals from Belgium and The Netherlands.

PARTICIPANTS/MATERIALS, SETTING, AND METHODS: We conducted 12 interviews with fertility specialists, scientists, clinical geneticists, a pediatrician specialized in metabolic diseases and a specialist in metabolic diseases. The profiles of the interviewees varied but all had experience with mitochondrial diseases, either in treating patients or in providing counseling to patients or to prospective parents. The interviews were conducted face-to-face and took 30–45 min. The language of the interviews was Dutch. We analyzed the transcript of these interviews using QSR NVIVO 10 software to extract themes and categories.

MAIN RESULTS AND THE ROLE OF CHANCE: This study has shown that, although amongst the professionals we interviewed there was support for the development and deployment of nuclear transfer, this support does not necessarily correspond to uniform opinions about the importance of having a genetically own child or the contribution of mitochondrial DNA to essential characteristics of an individual.

LIMITATIONS, REASONS FOR CAUTION: In translating the quotes from Dutch to English some of the linguistic nuances may have been lost. We only interviewed 12 individuals, in two countries, whose view may not be representative of existing values and opinions that may be held by professionals worldwide on this matter. To further explore the issue at hand, a subsequent investigation of the opinions of people affected by mitochondrial diseases and of the general public is necessary.

WIDER IMPLICATIONS OF THE FINDINGS: With this study we have demonstrated there is in principle support for the nuclear transfer technique from Dutch and Belgian professionals. Further research, both scientific and ethical, is needed to define the modalities of its possible introduction in the fertility clinic.

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Introduction

Mitochondrial DNA (mtDNA) has specific characteristics distinct from nuclear DNA, in that it is only transferred maternally and its transmission is unpredictable. Hence, mutations in mtDNA may be transferred in various degrees, and the severity of the phenotype is often dependent on the mutant load. At present no cure exists for diseases associated with mutations in the mtDNA (Smeets, 2013).

Current options for some of the women who carry a disease related to a mutation in the mtDNA and who desire to reproduce with their own genetic material without transmitting the disease are PGD and prenatal diagnosis. PGD has been demonstrated in a few cases (e.g. NARP, neuropathy, ataxia, and retinitis pigmentosa, a mitochondrial disease affecting chiefly the nervous system, Steffann *et al*., 2006) and MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, a mitochondrial disease affecting chiefly the brain, nervous system and muscles, Heindryckx *et al*., 2014), and, unlike PGD for mutations in the nuclear genes, consists of picking the embryo with a mutant load below a certain threshold. However, this is not a solution for homoplasmic women, or for those with a very high mutation load, as these women would always transfer a high mutant load to their offspring. Even in the case of heteroplasmic transmittance the technique has its drawbacks as it has been suggested that heteroplasmy may be variable between cells, and hence the biopsied blastomere may not be representative of the embryo (Sallevelt *et al*., 2013). Also prenatal diagnosis, such as amniocentesis, has its drawbacks as it implies an investigation of cells from a subset of tissues, and the mutant load may differ between tissues (Smeets, 2013). The only option at the moment for couples who want to avoid the transfer of a mitochondrial disease to their children is to opt for oocyte donation, but this implies that the mother is unable to pass on her own genetic material to her child. A potential future route which would avoid the pitfalls present in PGD or prenatal diagnosis for mitochondrial diseases and which would allow a carrier woman to use her own nuclear genetic material for procreation is mtDNA replacement through nuclear transfer. This would allow women who are homoplasmic or who have a high mutant load and those who want to avoid all residual risk to have their genetically own children. Currently, at least two techniques are under development (HFEA, 2014). One technique consists of the transfer of the spindle of chromosomes from an oocyte of the woman wishing to conceive to a donor oocyte, before fertilization (Tachibana *et al*., 2009; Paull *et al*., 2013). The other technique involves the transfer of the pronuclei of a fertilized oocyte (zygote) of the woman wishing to conceive to an enucleated donor oocyte (Craven *et al*., 2010). Other possible techniques include polar body transfer (Wang *et al*., 2014), which is suggested to imply less risk of mtDNA carryover than transfer of the pronuclei, or the transfer of the nucleus of a blastomere of an embryo, which may lead to reproductive cloning.

The possibility to use germ-line therapy to cure mitochondrial disease has been discussed already since the 1990s (Rubenstein *et al*., 1995; De Wert, 2000; Gezondheidsraad, 2001). More recently, technological developments have sparked new interest in the debate, especially in the UK. In documents from the Human Fertilisation and Embryology Authority (HFEA) and The Nuffield Council on Bioethics specific ethical issues that arise with this technology were discussed (Nuffield Council on Bioethics, 2012; HFEA, 2013). A major issue in this debate is the question at which point the technique was considered safe enough to be introduced in the clinic. A related issue concerns the necessity and extent of follow-up of children and perhaps also of further generations. Further, questions regarding the fact that this would imply germ-line modification were raised, as it would mean modifying the genome that a person can transmit to her child and the child's entire lineage. Another topic of debate was the status of the mtDNA donor and her relation to the future child. Does the donation of cytoplasm introduce a third parent? Do donors have the right to receive information about resulting children and do donor children have the right to receive information about the mtDNA donor? How does the fact that these children are created and conceived using the DNA of three parties, in experimental circumstances, affect their sense of identity, if at all? And, given that this technique would only apply to the context of a limited number of people, does this allow for the spending of research money and should the resulting treatment be part of public health coverage?

Until now, continental European countries seem to await the outcome of the British debate before themselves considering the arguments for and against this technology (on 3 and 24 February 2015, while this paper was in press, both houses of Parliament in the UK voted in favor of new rules allowing the HFEA to grant licenses for experimental use of mitochondrial replacement technologies in humans. Clinics can apply for such licenses as from the autumn of 2015 (Devlin, 2015)). However, there are several reasons for making this an international debate. Firstly, also in other countries prospective parents facing the risk of transmitting a mitochondrial disorder have an interest in the development of effective and safe technologies that may help them to have healthy children. Secondly, many of the concerns raised by the prospect of using mitochondrial replacement technologies to help those couples are of an ethical rather than merely technical nature. This means that whatever the outcome of the British debate, the weighing of relevant considerations may lead to different conclusions in other societal and cultural contexts. Thirdly, as the use of these technologies may be regarded as a 'crossing of the Rubicon' with regard to germ-line gene therapy, this is an issue of more than national interest that requires a proactive international debate.

As a contribution to this wider debate we present the outcomes of a study of the views and opinions of Belgian and Dutch scientists and professionals on the development of mitochondrial replacement technologies to be used in the context of medically assisted reproduction. Although close neighbors geographically, Belgium and the Netherlands are very different countries with regard to general attitudes to medically assisted reproduction and embryo research. Very much like the UK, Belgium has a strong tradition of innovation in this field, combined with a liberal legislation that does not impose many limits upon the use of reproductive technologies. Under certain conditions the Belgian Embryo Act allows the creation of embryos for research. It also allows manipulations of reproductive material that would amount to germ-line gene therapy, unless these procedures would fall under the interdiction of procedures with 'eugenic' intent. Hence, there is no legal barrier to taking the step to clinical experiments with this technology in Belgium. The Netherlands, by contrast, does not have a strong tradition of research in this field and the cultural and political climate with regard to assisted reproduction is generally more conservative. For example, the Dutch Embryo Act forbids the creation of embryos for research (HC 2001). Unlike both the UK and Belgium, the Netherlands is one of the cosignatories of the 1997 Oviedo Convention (Declaration on Human Rights and Biomedicine) of the Council of Europe, article 13 of which includes a general prohibition of

germ-line gene modification. However, the Netherlands has made a provision allowing her upon ratification to restrict this ban only to modification of the nuclear DNA. This was done in order to keep options open precisely with regard to mitochondrial replacement technologies (Gezondheidsraad, 2001; Dondorp and Bolhuis, 2002). But as pointed out by the Health Council of the Netherlands, the legal provision forbidding the creation of embryos for research still stands in the way of effectively developing technologies that would involve creating embryos to be used in preclinical safety studies.

By selecting interviewees from countries with a different legal context and tradition in embryo research we expected to find different ethical opinions on the desirability to create and use embryos for this research. We also expected to find a strong opposition toward the use of the term tri-parent baby. We found, however, that the use of embryos for this type of research was in general condoned, and that the attitude toward the mtDNA donor was related to how participants viewed the status of mtDNA.

Methodology

As this is the first study in Belgium and the Netherlands querying stakeholder views with regard to the acceptability of the use of nuclear transfer to allow carrier women to have unaffected offspring using their own oocytes, we chose a qualitative research method. We interviewed 12 professionals to perform an exploratory analysis and overview of important concepts and themes. We selected an initial list of respondents involved with genetics and reproduction in the context of mitochondrial diseases. This resulted in six interviews. Another six participants were contacted based on suggestions by the participants. Interview transcription and data analysis was started by K.H. at the same time as the data collection. After the 12th interview no new themes were discovered, meaning that saturation was obtained. The interviews took place between March and September 2014. The profiles of the interviewees varied but all had experience with mitochondrial diseases, either in treating patients or in providing counseling to patients or to prospective parents (Table I). The interviews were conducted face-to-face and took 30–45 min. The language of the interviews was Dutch.

The themes in the interview guide were inspired by the discussions and the consultations of the HFEA (HFEA, 2013), the Nuffield Council of Bioethics (Nuffield Council on Bioethics, 2012) and the report of the Dutch Health Council (Gezondheidsraad, 2001). The first part of the interview focused on the two major techniques (spindle transfer and pronuclei) and contained open-ended questions on acceptable risk (physical and psychosocial), necessity and acceptability of embryo research, a comparison with the alternatives (PGD/preimplantation genetic screening/oocyte donation), need for follow-up of the resulting children and the importance of genetically related children. The second part dealt with topical ethical issues, such as the status of the mtDNA donor, the acceptability of germ-line modification, the difference between mitochondrial and nuclear DNA and the question whether this research should be funded and any resulting treatment should be part of publicly funded health care. A semi-structured interview scheme was used, as this allows for the investigation of similar themes across the subjects while facilitating the exploration of individual values of the interviewees in depth and facilitating further exploration of additional themes that would come up during the interview (Sankar and Jones, 2008). K.H. was the interviewer in all cases.

Audiotapes of the sessions were transcribed verbatim. QSR Nvivo 10 (supplied by the Maastricht University) was used to code the transcripts. First, an open coding was performed to break down the data into different concepts. In a second pass, these concepts were rearranged according to different tree structures. Ultimately, codes were combined into core categories. G.d.W. and W.D. read through the transcripts and suggested additional themes. Quotes were selected to highlight the themes and were translated into English. We have not provided the profession or affiliation of the interviewee with specific quotes as we have guaranteed them complete anonymity. We also use the pronoun 'she' when referring to the interviewee regardless of gender for the same reason.

Table I Information about the interviewees in a study of professionals on the use of mitochondrial replacement to avoid transfer of mitochondrial diseases.

		#
Profession of interviewees	Scientist	1
	Clinical geneticist	4
	Fertility specialist	5
	Pediatrician	1
	Specialist in metabolic diseases	1
Location of interviewees	The Netherlands	6
	Belgium	6

Results

The importance of a genetically own child

All interviewees stated that the use of IVF with (entire) donor oocytes is a safe and tested solution to help couples at risk of having a child with a mitochondrial disease to procreate. Hence, for the participants, the rationale behind the development of nuclear transfer techniques to prevent transmission of these diseases is that having a genetically own child is of sufficient importance to prospective parents. Some interviewees stated that many people desiring to procreate would *go to extremes* to have their genetically own child and hence be ready to embark on a trajectory involving experimental techniques. According to some of the participants, the desire to have a genetically own child is evolutionary and hardwired, as is explicit in the following quote: 'It is a very complicated situation, it is evolution-based and hardwired in our brain that we want a genetically own child, although you could ask how important that *really* is'. The use of the word *really* in this quote demonstrates that this participant thinks that, although evolution-based, this desire may be overcome. Another respondent indeed suggested that more investigation was needed as to why people would desire a genetically own child so much. One interviewee stressed that she thought that the reluctance to opt for using donor oocytes as a possible alternative form of assisted reproduction was because of the practical difficulties:

> Donating oocytes is a difficult procedure, few do it out of altruistic motives. So I think, what I want to say is in fact, the willingness to opt for oocyte donation will increase if oocyte banks become more readily available, if you do not have to find a donor yourself, if there is some matching with regard to color of the eyes and hair and other stuff that is possible with sperm banks. (BE)

This respondent was clearly of the opinion that the reason why many people do not choose oocyte donation as an alternative for assisted reproductive technology procedures that would allow them to have their genetically own child was at least partially due to difficulties that could be overcome by compensating oocyte donors. Although oocyte

donation is necessary also for nuclear transfer, this interviewee suggested that once donation of the (entire) oocyte becomes standard practice as a fertility treatment, less importance will be attached to having a child of which both parents are genetic partners and the extra step of replacing the nucleus may no longer be considered necessary.

Although all interviewees accepted this new technique to allow people to have their genetically own child, several interviewees suggested that the fact that research groups were pursuing this type of research was primarily because of the prestige it would generate, to be among the first to develop a technique with treatment potential that would imply manipulation of a human embryo, rather than the fact that this was a technique that would help many. As an alternative to helping people conceive a genetically related child free of the disease, one interviewee stated that 'an option would be to try to improve treatment of mitochondrial diseases as an alternative to manipulating the genetic material.' A subset of participants pointed out that the information research on nuclear transfer would yield regarding the functioning of the cell, also perhaps for older women trying to conceive, would partly justify the research into this specific type of manipulation of the embryo. As to the question whether the possible resulting fertility treatment would have to be part of public health care coverage, most participants agreed that this would have to be decided based on the priority with regard to other treatments. One interviewee stated that

> This is clinical care. If you can in a reliable way use nuclear transfer to beget healthy children who would otherwise have a mitochondrial disease, I would say that this is *care* (emphasis mine). The same goes for preimplantation genetic diagnosis. (NL)

So to help people at high risk of transmitting serious disease to have their genetically own children should, according to this interviewee, be part of standard (and reimbursed) care.

Another interviewee, however, stated that:

> I think that we are sometimes stretching it a bit, it is already so with preimplantation genetic diagnosis, it is to some extent an enormous luxury problem. I understand that infertility, you want to do something about it, and it can be extremely burdensome. But if we were to look on a global scale how we are to divide the costs of health care. . .one could voice one's doubts about it. (BE)

So this interviewee, although not as such opposing research and reimbursement of these techniques still questioned whether the distribution of health care money would not be better directed toward other more urgent aims.

The contribution of the mtDNA

In our study we found opposite views on the contribution of mitochondrial DNA. Those participants who considered mtDNA a less important form of DNA also considered it irrelevant to the identity of the resulting child. For example, one interviewee stated that:

> Yes, nuclear DNA defines your characteristics if you think genetics is important. You could say that if you are going to do genetic manipulation on nuclear DNA that the results are passed on from generation to generation and that it affects the individual. Those mitochondria they are also passed on but we assume that a mitochondrion is a very stupid thing with only a limited amount of DNA that just has to maintain a motor and does not define the characteristics of an individual. For me, this is also a moral difference. (BE)

So this interviewee explicitly links the status of mitochondria as non-identity defining to the moral acceptability of techniques that would in principle change the germ line. Other participants, however, did not believe mtDNA was less identity defining as nuclear DNA, as mutations in mtDNA would lead to serious diseases as well, a fact that is as such identity affecting. One interviewee suggested that if the avoidance of disease is the primary concern, this would imply that also techniques to prevent diseases that consist of germ-line nuclear genetic modification would be acceptable. For this interviewee, what was morally acceptable in terms of DNA intervention was based on whether a certain mutation would lead to a diseases (rather than to a variation of a non-medical characteristic), not whether it was situated in the mitochondrial or nuclear DNA.

It follows logically that those who believed that mtDNA was less identity defining than nuclear DNA thought that the term three-parent child as it is used in the media worldwide is exaggerated, as the characteristics of the resulting child that the mtDNA donor contributes was deemed by them too limited. As such, these respondents were strong proponents of donor anonymity also in this context. However, some of those who believed that mitochondria may also contribute substantially to the identity-defining characteristics of the resulting individual did think that the term three-parent child was not completely exaggerated:

> A child with three parents? Yes you cannot deny that. Unless you state that well that little bit of cytoplasm shouldn't have a name, it is the same as a dress or. . .But it is DNA, it is crucial, without it you do not have a human being. It is not a dress, I believe it is even more than a surrogate mother. (NL)

This interviewee subsequently stated that because of the fact that three people contributed to the resulting child, careful counseling of the family regarding how to deal with this situation also after conception and even till the child reaches puberty was needed, as this was typically the time when children started to question their origins. Related, a subset of interviewees was not convinced that the role of the mtDNA donor was trivial, and they made the analogy with donors of entire gametes, where the status of the donor with respect to the resulting child is not yet settled, and with the complex structure of present-day family formation which is moving away from the nuclear family.

Safety as an ethical requirement

All interviewees thought that the nuclear transfer technique was in principle a good technique to prevent the passing on of a disease of the mtDNA. There was some consensus that the nuclear transfer techniques will not fully replace PGD but will either be offered as a second line possibility after PGD is unsuccessful or to those for whom PGD or prenatal diagnosis is not an option, due to homoplasmy or high mutation load:

> If people have a high risk to have an abnormal embryo then you would manipulate, but if this risk is relatively low, but you still want to eliminate those embryos, then you would probably opt for selection. So yes I think you need to juxtapose those options and choose on the basis of the problem. (NL)

However, the main concern of all participants was that the technique would not be safe. If asked which technique she would prefer one respondent stated that 'I would prefer the one with the highest efficiency and safety, and then preferably also the most feasible and accessible one'. This quote suggests that first and foremost technical and economic issues influence the decision whether this technique is an acceptable option, rather than other ethical issues. All interviewees agreed that in order for these techniques to be used efficiently and safely, more

research was needed, both in the form of animal research as well as in the form of preclinical safety research using human embryos. Some explicitly named the cytoplasm transfer which was occasionally done in the 1990s to help older women conceive as a paradigmatic example of why new techniques should not be hastily introduced, as this technique was considered unsafe in view of a higher than expected number of abnormal pregnancies and births.

Participants also all agreed that nuclear transfer is similar to other new fertility technologies in that safety can only be assessed after the first children have been born, and possibly even after the children of these children were born. As one of our interviewees stated, for such techniques 'the proof of the pudding is in the eating'. All agreed that this would require follow-up of pregnancies and children resulting from the use of this technology. Some participants thought that also psychosocial tests should be included, but others thought that this would be not necessary, as they did not believe there would be an effect on psychosocial well-being.

For parents to allow children to be followed up after such procedure was seen as a moral duty by the participants and a prerequisite to be allowed to participate in such experimental procedure. This moral duty was also there for professionals and for funding bodies: if research to develop these techniques were to be funded, the follow-up should be included from the beginning:

> We are under a moral obligation to do a long-term follow-up. You also see it in preterm birth, if you investigate premature children you see a small bar of damage and challenges, but the longer you follow them up the more these bars grow. (BE)

In this quote, the analogy with children created and/or born under other technically new conditions was drawn, and the interviewee explicitly points out the fact that potential damage may only become apparent after quite some time. Interestingly, the potential of such unforeseen damage was not quoted as a sufficient reason not to proceed with the development of these techniques.

The fact that there would be potential transgenerational risks associated with the procedure, which is basically germ-line modification, was not deemed sufficient to disallow the technique altogether, and interviewees stated that the decision-making authority of whether to reproduce using techniques that may have transgenerational effects should ultimately lie with the parents. One solution to the problem that has been suggested in the literature is to allow for the selection of only male embryos, as this would limit any potential risk to the first generation born (Bredenoord *et al.*, 2010). Some interviewees thought this was an acceptable solution and it would fit within the definition of sex selection for medical reasons. Others were more uncomfortable with the suggestion, as this quote suggests:

> I think it would be better to develop to design the technique in such a way that you can have both boys and girls. It would be my preference to do that. So, well, if you say we are going to do boys and not girls, you have a different story. (NL)

So in this quote the interviewee suggests that developing a technique that would only be safe if boys were chosen was still not a satisfactory solution. One interviewee suggested that sex selection could be deployed until the technique was proven safe in the first generation, because she believed that in that case, the transgenerational risk would have decreased to an acceptable level.

Discussion

Although there seems to be a logical link between valuing the fact that people can have their genetically own children and approving not only of research aimed at developing mitochondrial replacement techniques, but also eventually of reimbursement of assisted reproduction using this technology, this seemed not to be so straightforward in the interviews. On the one hand, interviewees thought this technique was worthy of further exploration, and they acknowledged that people would go to extremes to have a genetically own child. This is consistent with the findings in the HFEA consultations where respondents were positive about the new techniques, and related this to the fundamental right of parents to pass on their own genes (HFEA, 2013). On the other hand, many of our interviewees did not believe that to have a genetically own child, although very important to most people, was a right or a sufficient reason to develop and use experimental techniques. Indeed, in this respect, it has been argued in the related debate about research investments aimed at developing stem cell-derived ('artificial') gametes for reproductive use that alleviating the pain of infertile couples should always be balanced against the risks involved for themselves and their future offspring and against other needs in society that may have a more convincing claim on the healthcare budget (Dondorp and De Wert, 2012; Mertes, 2014). This may also apply to the technique of nuclear transfer. Indeed, as Heidi Mertes argues, offering couples insight in the reasons why they prefer genetic parenthood and subsequently discuss with them whether they do not overestimate the importance of genetic parenthood may be a preliminary step before offering them techniques to achieve this goal. Our interviewees thought that the fundamental scientific knowledge and potential alternative applications that would be generated by the development of these techniques, would still make it worthwhile to pursue them. Hence, although the importance of a genetically related child is the primary reason to invest in the development of this technique, our study suggests that this may not be the only reason.

Whether it would be possible to provide a technique that would sufficiently reduce transmission risks was the main moral concern of the participants. They acknowledged that with techniques involving human reproduction, such as this one, safety is never 100% guaranteed and that an assessment of the risks can only be done after the first babies are born and followed up for several years. Even then, there may be transgenerational risks. As a commentator stated: 'The only way to find out about safety is to license the first treatment' (Poulton and Oakeshott, 2012). Pre-clinical research using human embryos was deemed necessary to eliminate harm further down the line as much as possible. As Provoost *et al.* have argued, a framework distinguishing between experimental, innovative and established treatment could help to define milestones to be reached and to decide when the technique is sufficiently proven and safe enough to go to the next stage (Provoost *et al.*, 2014). But interviewees also agreed that long-term follow-up of the children was needed. This is in agreement with the findings of the Nuffield Council of Bioethics who stated that families using such techniques should commit to allowing very long-term follow-up of their children and families (Nuffield Council on Bioethics, 2012). It can be asked, however, how this relates to the right of future children not to be burdened with research. Although this seems an important proportionality-affecting question, the fact that these children, who are already conceived in a nontraditional way, would be more scrutinized and screened than their peers was not mentioned as ethically problematic in our study.

In the current debate on nuclear transfer it has been stated that the fact that these techniques would affect the germ line complicates the matter of follow-up even more. However, this was not seen by our participants as a reason not to proceed with the development of the technique. The right of parents to decide for themselves whether to change the germ line was explicitly mentioned, which is analogous to what was found in the HFEA consultation (HFEA, 2013). Although the fact that sex selection to prevent the birth of girls from this technique has been suggested as a technically feasible approach to avoid transgenerational harm (Bredenoord *et al*., 2010), as mitochondria are transmitted from a mother to her children, not all interviewees thought this was acceptable. They believed that it should in principle be possible for parents to have children of either sex. In this respect, participants also stated that techniques should in principle be safe for anyone before being implemented, although sex selection could be a way to investigate safety further, to avoid risks to be passed to the next generation in the first stages of implementation.

Views on the nature of the contribution of the mtDNA influenced interviewee's opinions on both the acceptability of germ-line modification and on the status of the mtDNA donor. The article in the Dutch Embryos Act that forbids modification of the nuclear DNA is inspired by the view that mitochondria are less linked with essential characteristics of the individual than nuclear DNA. This view was shared by some of our interviewees but not by others, who claimed that mtDNA may have an important contribution in this respect as well. The latter viewpoint is analogous with what Bredenoord *et al*. (2011) have argued about the moral acceptability of germ-line modification for mitochondrial diseases. They argue that this does not depend on whether the intervention alters the identity of the future child or not, because it is not settled in science whether the mtDNA may also be associated with essential characteristics, and that the definition of what are essential characteristics for an individual is not precisely defined (Bredenoord *et al*., 2011; Roubertoux *et al*., 2003). Indeed, one could state that having a pervasive mitochondrial disorder, such as MELAS, may in itself be seen as identity defining, and that its effects on the germ line over several generations may be more profound than some nuclear changes. Some suggest that what is important in the discussion is whether this would eradicate disease and offer the resulting children a life free of disease, and hence a more open future. The idea that the acceptability of germ-line modification, be it nuclear or mitochondrial, depends on whether or not it eliminates disease, was also expressed by some of our interviewees.

Most interviewees rejected the three-parent label, as they considered mitochondria of too limited importance to attribute to them some kind of parental status. This is similar to what was found in the HFEA consultation. However, the views of the respondents in the HFEA consultation on the status of the mtDNA donor were shaped by the information on the amount and the role of mtDNA. This is similar to our findings, where interviewees who did not see the mtDNA as a trivial contribution to the characteristics of an individual would also not consider the contribution of the mtDNA donor as trivial. Hence, this suggests that views regarding impact and acceptability of germ-line modification and the status of the donor of the mitochondria may evolve as more becomes known about the role of mtDNA.

Our study has many limitations. In translating the quotes from Dutch to English some of the linguistic nuances may have been lost. We only interviewed 12 individuals in two countries, whose views should not be regarded as representative of the values and opinions that may be held by professionals worldwide on this matter. Indeed, our study did not include medical professionals with a strong view that there are ethical objections. We had expected that by interviewing professionals both from Belgium and the Netherlands, as these countries have distinct legal backgrounds and traditions in embryo research, we would have found more opposing views with regard to the ethical acceptability. Our sample is however too small to draw any definite conclusions in this respect. To further explore the issue at hand, a subsequent investigation of the opinions of people affected by mitochondrial diseases and of the general public is necessary. This study has shown that, although amongst the professionals we interviewed there was support for the development and deployment of nuclear transfer, this support does not necessarily correspond to uniform opinions about the importance of having children of whom both parents are genetic parents, or the contribution of mtDNA.

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Authors' roles

The project was set up by Guido de Wert and Wybo Dondorp. The interview questions were defined by G.d.W., W.D. and K.H.. K.H. was the interviewer and transcribed the interviews. A first pass analysis of the data was made by K.H. using NVIVO 10. The analysis was double-checked and fine-tuned by G.d.W., W.D. and K.H. K.H. wrote the first draft of the manuscript, which was reviewed, supplemented and corrected by G.d.W. and W.D.

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Conflict of interest

None declared.

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