Ethical questions about mitochondrial replacement in humans

We thus consider it necessary to establish a moratorium on their use in humans, at least until more is known about these aspects. If this knowledge is obtained, ethical questions would still remain to be resolved, among which we consider the most relevant to be those related to the ***dignity and identity of the human embryo.***

Children with two mothers and a father

In January 2017, the prestigious scientific journal Bioethics published a special edition dedicated to the ethical aspects of nuclear transfer techniques aimed at preventing the transmission of mitochondrial diseases, a topic that we have extensively addressed in our Observatory (see HERE).

Its editorial, Ethics of mitochondrial replacement, starts by referring to the recent birth of the first baby resulting from these techniques (see HERE). It then provides a brief description of the main characteristics of mitochondrial diseases, which are inherited exclusively from the mother. It explains that mothers who carry mutations in their mitochondrial DNA (mtDNA) face the uncertainty of not knowing if their genetic children will or will not inherit a serious mitochondrial disease. However the emergence of mitochondrial replacement techniques (MRT) offers these mothers hope, as healthy mitochondria from a donor are used to replace those of the mother. These techniques are maternal spindle transfer (MST) and pronuclear transfer (PNT), which consist, respectively, in removing the nucleus from a healthy egg or zygote, which will keep its mitochondria. The nucleus of the mother's oocyte (patient or carrier of the mutation) or of another zygote obtained by fertilising the mothers egg is then transferred into the enucleated oocyte or zygote. The editorial continues with a second section of legislation, regulation and policy, in which it explains the situation of the United Kingdom (see HERE), where these techniques have already been approved, and the United States, where the Institute of Medicine issued a report for the U.S. Food and Drug Administration (FDA) with a permissive but more cautious approach than in the UK. Finally, the editorial concludes by presenting the six contributions of the different authors, which we have summarised below.

1. Human nuclear genome transfer (so-called mitochondrial replacement)

The first article, by Françoise Baylis, is entitled Human Nuclear Genome Transfer (So-Called Mitochondrial Replacement): Clearing the Underbrush. The author tackles fundamental questions about the accuracy of the term "mitochondrial replacement", about the

value that we should attribute to the genetic relationship, if having a genetically related child of your own is a need or only a want, and about how to assign human and financial resources that are inevitably limited, specifically arguing whether costly reproductive technologies (such as MRTs) do or do not constitute a defensible use.

As regards the accuracy of the term "mitochondrial replacement", the author says that there is good reason to question the relatively recent and almost imperceptible shift (in policy debates and documents, as well as in media reports) away from the terms "germline genetic replacement therapy", "nuclear transfer techniques" and "nuclear genome transplantation" to euphemisms such as "mitochondrial replacement therapy", "mitochondrial manipulation", and "mitochondrial donation". The fact that this shift in language is scientifically inaccurate is indisputable, and we agree with the author that it is ethically misleading, as it leads one to think that what is manipulated are the mitochondria, which make up only a small fraction of the genome (0.1%). This masks the fact that what is really transferred is the nuclear genome (99.9%), and that the micromanipulation techniques involved are the same techniques used for modification of the nuclear DNA (nDNA) in the germline (gametes and embryos) and "human somatic cell nuclear transfer", or, in other words, cloning. Thus, it conceptually separates these techniques from germline genetic modification, furthering their legislative approval and public acceptance.

As regards the supposed need of future parents to have genetically-related children, free from mitochondrial disease, the author argues that this idea "suggests an inappropriate overvaluing of genetic relatedness within families (which in turn wrongly undermines and thereby threatens valuable and meaningful non-genetic family relations)", and contends that this desire, often interpreted as a need, is at most an interest, a preference. Therefore, if the techniques are not safe — and Baylis considers that they are not — they should not be used since they do not respond to a need. It does not follow from this, in our opinion, that if the application of the techniques were 100% safe, their use would not be morally reprehensible in itself (leaving aside the matter of resources). Other questions must also be taken into account, mainly as regards the dignity of the embryo, since today these techniques are carried out together with in vitro fertilisation (IVF).

The third and final point of her argument deals with the advisability of assigning resources that are limited to the development and application of these techniques. The author considers that this topic should be approached from a public health perspective, privileging shared needs over individual wants, so that resources should be invested in preventing and treating diseases in existing persons. Although this seems reasonable, it is not a decisive argument, because it is also true that the freedom of scientific research should be respected, and should not be governed by purely utilitarian criteria. We do not believe that a principle of distributive justice can suppress the allocation of economic resources to try to resolve the problems of specific minorities. If it were so, trying to resolve the problems of all so-called orphan diseases should be abandoned as they affect only a small group of people, something that we consider completely unfair. On the other hand, we can clarify that, we are in agreement with the author in that having a child is not a need per se, neither is it a mere want, but a gift that parents receive.

2. Do mitochondrial replacement techniques affect qualitative or numerical identity?

Identity of the resulting child

The second article, entitled "Do Mitochondrial Replacement Techniques Affect Qualitative or Numerical Identity?" was written by S. The author points out that in the debate on MRTs, one question that has garnered considerable attention is whether these affect the identity of the resulting child and, if so, in what way? He discusses whether they modify the characteristics of an existing individual, or if they result in the "creation" of a new individual, i.e. if they affect the qualitative identity or the numerical or quantitative identity. The essay presents advocates of the different possibilities. Thus, the panel of experts convened by the UK Human Fertilisation and Embryology Authority (HFEA) considers that, since mtDNA mainly affects only energy production, MRTs would not alter the identity or predetermined characteristics of the individual, while the Working Group of the Nuffield Council on Bioethics (NCOB) believes that these change the quantitative identity of the resulting child compared to the child born without the use of these techniques.

The author believes that this question has implications for the ethical assessment of MRTs. Thus, if they affect the qualitative identity, the resulting individual could later claim that these techniques have harmed him in some way, and that he would have been different had they not been applied. If, on the other hand, they affect the quantitative identity, he would be unable to claim any harm, since he would not exist had these techniques not been performed.

Liao then states that MRTs "create" a new and numerically distinct individual, but his arguments are different and preferable to those of the NCOB. He argues that, by replacing the nuclear material in the donor oocyte (in the case of MST) or zygote (in PNT) with the nuclear material of the affected mother or parents, a new oocyte or new zygote is being created, thus affecting the quantitative identity of the resulting child.

The author bases his argument on the concepts of "cellular continuity" and "organismic continuity", i.e. the continued ability in a cell or organism, respectively, to coordinate and regulate the various life processes. In MST, the nucleus is extracted from the oocyte of the mother (X) and the oocyte of the donor (Y), so that both oocytes cease to exist, since "cellular continuity" is disrupted. Subsequent insertion of X's nucleus into Y generates a new oocyte (Z), different from the previous, which will give rise to a numerically different individual. Similarly, in PNT, the nucleus is extracted from the zygote with the affected mitochondria (F), and from the zygote with donor mitochondria (G), so that both zygotes cease to exist, since "organismic continuity" is disrupted. Subsequent insertion of F's nucleus into G generates a new zygote (H), different from the previous, which is a numerically different individual.

NCOB's argument stating that MRTs affect the numerical identity is different. It is based on the fact that the change in the mtDNA could make such a significant difference to the life of the resulting person that it could be said to make him a different person.

However, Liao identifies two problems in this explanation. First, that an oocyte or zygote could be modified to the extent that the effects on the life of the resulting individual were comparable to those of the MRTs and therefore not affect the quantitative identity, for example using CRISPR gene editing. Secondly, even if a procedure has no significant effects, it can affect the quantitative identity. For example, if the nucleus from an oocyte is mistakenly transferred to another enucleated oocyte from the same woman, instead of from the donor, even though the effects of the mitochondrial disease are the same as those that would have existed if the technique had not been carried out, a new individual has indeed been generated.

The author, therefore, concludes that "the enucleation process involved in MST and PNT permanently disrupts the cellular or organismic continuity in an egg or zygote. As a result, MRTs create a numerically distinct egg or zygote, which then lead to the creation of a numerically distinct individual, when implanted".

In our view, Liao's argument is very interesting. The criticism of the NCOB's explanation seems correct. However, in his own argument, his premise — that the concepts of "cellular continuity" and "organismic continuity" delimit the numerical identity of the cell and the organism, respectively — seems questionable. To begin with, it is startling that, according to him, in PNT, from two embryos that have ceased to exist, a new embryo would be generated that does exist, which, simply, cannot happen. The embryo exists only from the moment of its conception, and its existence will continue until its death. If we start from two live embryos and in the end only one remains alive, what has really happened, unquestionably, is that the other has died. But which of the two lives and which dies? In our opinion, the embryo whose nucleus remains is the one that continues its existence, since it is the nDNA that contains the information for its development. Thus, although certainly much remains unknown about the interaction between nDNA and mtDNA, and various studies appear to suggest that the impact of mtDNA is much greater than suggested by the HFEA (see HERE), it seems to us that that what is being affected is not the numerical identity of the zygote, but its qualitative identity. Likewise, we believe that this argument can be extended to the case of MST, in which the oocytes are manipulated.

3. Ethics of mitochondrial replacement techniques: a Habermasian Perspective.

The third article, entitled Ethics of Mitochondrial Replacement Techniques: A Habermasian Perspective, was written by César Palacios-González.

In it, the author applies the bioethical principles of the philosopher Jürgen Habermas on prenatal genetic manipulation to the case of MRTs, in order to provide a philosophically founded guideline for those he calls "bioconservatives", whose "normative conclusions seem to appear out of thin air and to be unsupported by their premises".

After presenting an overview of mitochondrial techniques and how MST and PNT work, Palacios-González goes on to present the three conditions that Habermas establishes to consider prenatal genetic therapeutic interventions as morally permissible.

The first condition is that the intervention be therapeutic and guided by a clinical approach. Habermas argues that the moral consideration of prenatal genetic interventions is different if the objective is therapeutic rather than enhancement, the second being morally unacceptable, and the first only in certain cases. But it also requires that the approach is clinical, which means that informed consent must be taken into account. As the embryo cannot provide it, "justifiable assumed consensus" is presented, which happens when it can be assumed that the embryo would agree to the intervention if it had the required capacities. This leads us to the second condition, that informed consent of the embryo to the intervention can be assumed. Finally, the third condition is that the aim is to prevent extreme evils that would probably be rejected by all.

The author then uses the Habermasian perspective presented to investigate the morality of MRTs. PNT would be morally permissible, since it takes place when the embryo has already been constituted and, therefore, it can be said that it is acting on someone. In MST, in contrast, there are two possibilities. If the male and female gametes are preselected, as they would always give rise to the same individual, it could be said that we are acting therapeutically on someone. In contrast, if the gametes have not been preselected, it cannot be said that we are acting according to the logic of cure, because there is no specific individual to be cured.

However, an additional consideration should be made regarding Habermas's stance with respect to the value of the human embryo. The philosopher argues that the human life of the human embryos possesses a value that, while it does not make it inviolable, nevertheless makes them qualify as beings that "should not be disposed over". Thus, according to this perspective, PNT would be excluded as a morally acceptable option, as it requires the use of embryos to benefit the reproductive purposes of the mother. On the other hand, research to develop MST requires the destruction of human embryos, as scientists must perform MST and then create embryos to perform research on them, for example, embryonic development after application of the technique. Furthermore, these embryos will be discarded. This means that, from a Habermasian perspective, MST must also be rejected, even with preselected gametes.

Although we believe that Palacios-González's argument is developed correctly according to his premises, we think that these assumptions have limited validity. Thus, in our opinion, the evils to prevent do not always have to be extreme, the safety of the procedure should be proven, and the differentiation between somatic genetic modification and germline genetic modification is relevant. Finally, but no less important, we believe that the embryo, from the moment of its conception, has the same dignity as at any other time in its biological development, and that therefore, its life is non-disposable (See our article on the biological status of the human embryo).A mitochondrial story: Mitochondrial replacement, identity and narrative

4. A mitochondrial story: Mitochondrial replacement, identity and narrative

The fourth article, "A Mitochondrial Story: Mitochondrial Replacement, Identity and Narrative" is by Jackie Leach Scully.

In this essay, the author asks how MRTs could affect the identity of the persons *created* and their families. She notes that it is generally said that the effect of these techniques on the identity may be direct, alternating the genetic composition and physical characteristics of the child, or indirect, changing the child's experience of the disease and generating new intrafamilial relationships that shape the sense of self. However, Scully considers that there is a third way in which the identity can be affected, through the mediating influence of the social world, and that this has a greater potential to negatively affect the generation of identity narratives of these children.

As regards the direct effect, she explains that mtDNA, involved in the production of cell energy, does not affect the characteristics that make up the identity, such as facial features, cognitive abilities or personality traits. However, she acknowledges that many aspects of mitochondrial function remain unknown. With respect to the effect on the experience of the disease, she says that certainly this experience will be affected, but that this does not have major implications, and that this is what happens in many other therapeutic interventions. She then analyses the familial effects of these techniques and concludes that, given the evidence (especially anecdotal but in part empirical) that family structures are flexible and that family networks can accommodate a wide variety of relationships between parents and children without causing psychological damage, the identities of children resulting from these techniques will certainly not be affected in this sense.

She later says that in the evaluation of the effect of MRTs on identity, we must also consider the "socially mediated identity", as identity is formed *within* and *by* a social world. She proposes a model of narrative social identity: "A personal sense of self accumulates out of the ascription and recognition, by ourselves and others, of narrative fragments drawn from a slowly evolving repertoire of identity-forming stories". In the case of persons born as a result of these techniques, what will happen, at least at the start, is that they will lack a social narrative that moulds their identity, as they will be unprecedented cases. ***"It follows from this that an important question when evaluating the impact of MRT on identity", says Scully, "is what kind of narratives of conception, birth, parentage and health status will emerge for the child born through MRT and his or her family (and donor) to use".***

The author suggests that several sources can contribute to the development of a collective narrative: fiction, policy documents, public consultation materials, etc. In the case of MRTs, official communications have taken great care to present them as vital therapeutic procedures, and to use the terms "donation" and "donor", which connects with existing social narratives on the virtue of blood or organ donors. However, Scully believes that the most immediate influence is exerted by the popular media, in which the novelty of the technique and the genetic link to three persons are the predominant topics in this respect, which could lead to the development of a damaging narrative of identity.

Thus, the author concludes that, "if identity is created in part through cultural narratives, and can be damaged in a morally significant way by the lack of a 'good story', then ensuring that such good stories are available to MRT children and their families becomes a collective moral responsibility".

In our opinion, *we agree that avoiding the use of expressions like "two mothers and one father" may benefit these children and their families,* but they should only be dispensed with if they are scientifically incorrect, as otherwise, it would be helping to generate public misconception of the issue.

5. Mitochondrial replacement techniques: Who are the potential users and will they benefit?

The fifth article, by Cathy Herbrand, is entitled "Mitochondrial Replacement Techniques: Who are the Potential Users and will they Benefit?"

This article is based on a current study of reproductive options in the context of mitochondrial diseases, using data collected in interviews with women affected and medical experts, as well as by analysing key documents (parliamentary documents, public reports, etc.).

Herbrand notes that in the debate on these techniques, she has seen a notable lack of details on their possible beneficiaries, who are only named in general terms as "patients", "women with mitochondrial disorders" or "women who would otherwise pass on mutated mitochondria through their eggs". She also notes how families affected by mitochondrial disorders have been mainly described as a homogenous group who need MRTs, giving very little information on their state of health and the family situation of the women affected, and if they would be disposed to use the techniques, assuming that any woman affected, or a carrier of the disease, could and would like to benefit.

The author then criticises the fact that bioethics and scientific discussions have dominated debates in this respect, noting the usefulness of providing empirical data from the social sciences. Thus, she analyses empirical data from the aforementioned study to answer four questions: Who will be suitable for MRTs? Who will be entitled to use MRTs? How many will engage with MRTs? Who will be able to afford MRTs?

As regards the first question, the author recalls that mitochondrial diseases are not always due to mutations in the mtDNA, but that on many occasions the mutation is in the nDNA, cases in which MRTs are not applicable. Moreover, even if the mutation is in the mtDNA, the mothers are often asymptomatic carriers with no family history, so it is most likely that transmission will not be prevented in the case of their first child. That being the case, the author is surprised that in official reports and the media, there is no mention made of the size and characteristics of the respective groups affected when these topics are addressed, and that during parliamentary debates, most participants are not even aware of the crucial distinction between nuclear and mitochondrial mutations. She cites the example of British Member of Parliament, Luciana Berger, who had organised a public debate on MRTs the day prior to the vote on the regulations. When asked whether "mitochondrial disease from the nuclear

DNA will remain in our population even after this treatment is licensed", she replied, "it is not something I have been made aware of, and it certainly has not come up in any of the discussions or debates that I have attended".

On who will be entitled to use these techniques, in principle, MRTs will only be accessible to mothers with a high mutation load, in whom the likelihood that the disease will manifest severely in offspring is very high, which excludes many of the women. Moreover, the diversity of symptoms and syndromes associated with alterations in the mtDNA makes it very difficult to predict these probabilities.

As regards the third question, the author uses the data obtained from the study to demonstrate that, unlike what is often assumed in public and parliamentary debates, not all women at risk of passing on the disorders and eligible for the techniques would choose to make use of them. Thus, a series of difficulties were identified: physical or medical (too weak to raise a child or a medical condition that prevented them from becoming pregnant, fear that their condition would worsen, not knowing if they would be able to care for a child later on in life), social or family (due to age, family, work or relationship, some study participants reported that they were no longer, or were still not, in the right circumstances under which to have a child), preference to conceive a child "naturally", religious or ethical reasons, or the acceptance of adoption and donor egg as satisfactory alternatives.

Finally, the author calculates that the cost of treatment would be around €95,000 per child born, which raises doubts about how many people could afford it, unless it were publically funded. Considering that this funding would be considerable, the author classifies as "regrettable" the fact that the financial aspects have not been addressed in more depth during public debates. "In a context of limited health care resources, it could have been worth assessing and discussing the cost/effectiveness of MRTs with respect to other treatments already available or under development", says Herbrand.

Thus, she concludes that there are several medical, legal, individual and financial constraints that may limit the use of MRTs much more than the public have been given to understand.

In our opinion, this essay highlights relevant aspects in the discussion of MRTs that have been considerably ignored in debates on these techniques.

6. Is mitochondrial donation germ-line gene therapy? Classifications and ethical implications.

In the last article, "Is Mitochondrial Donation Germ-Line Gene Therapy? Classifications and Ethical Implications", authors Ainsley J. Newson and Anthony Wrigley try to answer two questions: How should we classify mitochondrial donation techniques? And, what ethical implications surround such a classification?

The authors argue that a sub-class is needed within the field of genetic modification where these techniques can be classified, as they do not fit within existing categories. Specifically, they say that it cannot be considered germline gene therapy for several reasons:

i) the *target* of the genetic modification is not the genetic material, usually a single gene, in the nucleus, but a whole organelle outside;

ii) the *method* is different, as MST and PNT do not involve any alteration at DNA level;iii) the

iii) the *mechanism of inheritance* of the introduced change would not follow Mendelian inheritance in these cases, but would be inherited exclusively through the maternal line (it would therefore only persist though subsequent generations if a female child went on to have daughters);

iv) the *kind* and *degree* of change is different. The substitution/alteration distinction already mentioned could be said to be a difference in kind. Moreover, the size of the mitochondrial genome, which is composed of only 37 genes with a total length of 16.5 kb, may mean a smaller overall change compared with interventions targeted to the nucleus, particularly if a large gene is altered;

v) the *risk* of change many also be relevant. In the approaches that use recombinant DNA methodology to target the nucleus, it could be argued that the risk is higher due to the possibility that a change is produced in the wrong gene; and vi) the *intentionality* of the change may be different. It might be stated that with more traditional forms of germline gene therapy, there is the intention to effect a change in future generations, while MRTs would tend to prevent the defect in the oocyte or embryo, with any change in future generations being an unintentional "by-product". As the authors themselves state, though, this is a contentious variable.

Germline mutation

They therefore propose the term *conditionally inheritable genomic modification* or CIGM. The term "conditionally" recognises the exclusively maternal inheritance of the mitochondria, so-called bottleneck effects (only a limited and a random number of the mother's mitochondria pass to the offspring, which explains the variation in the level of mutation between different generations and between siblings) and the unpredictability in mitochondrial segregation. The use of the term "genomic" instead of "genetic" resolves the fact that these techniques target whole organelles (the mitochondria) instead of genes.

The article concludes that, although classifying the techniques as CIGMs could indicate that their automatic prohibition as germline therapies is not justified, it would not resolve all the ethical questions, since not all depend on the classification. They suggest, for example, that sufficient knowledge would still be needed of the effects of altering the mitochondria of an oocyte to make judgments on possible harms to future generations, and to resolve the ongoing question of whether the therapeutic benefits would exceed the potential harms.

In our opinion, establishing this new category of CIGM is not correct insofar as it tries to be conceptually disassociated from germline gene therapy. Germline gene therapy, in our opinion, is any genetic modification that, since it is carried out in gametes or embryos, will affect all the cells of the organism. The target, method, mechanism of

inheritance, kind and degree of change, risks and intentionality are only associated factors that do not affect this definition. Similarly, the fact that it is transmitted to subsequent generations is only a consequence that, until now, occurred in all cases. The fact that this outcome does not occur in MRTs in which the resulting individual is a male does not mean, therefore, that it is not a germline genetic mutation. Furthermore, as the authors themselves acknowledge, oocytes can contain around 200,000 copies of the mitochondrial genome - only 0.2% of the number of genes, but 50% of the amount of DNA. Moreover, if we take into account the number of genes, more are modified with MRTs, since in therapy targeted at the nucleus, only one or a few genes would be modified, but not 37. It is unjustifiable to look at the length of the modified genome and ignore the total amount and/or a number of genes.

Germline mutation

We think that these techniques would be a particular case of ***germline genetic modification***, and the fact that they do not form part of this category cannot and should stop them from being examined in their singularity.

Conclusion

As can be derived from the different essays, many issues remain unresolved in the debate on the ethics of so-called mitochondrial replacement techniques, not only ethical but also technical, such as the effect of the mitochondrial genome on ***the identity of the individuals, the interactions established with the nuclear genome, and the mechanism of transmission to offspring***.

We thus consider it necessary to establish a moratorium on their use in humans, at least until more is known about these aspects. If this knowledge is obtained, ethical questions would still remain to be resolved, among which we consider the most relevant to be those related to the dignity of the human embryo. PNT, in addition to being necessarily linked with in vitro fertilisation, requires the destruction of a healthy embryo for each embryo requiring treatment, which is an insurmountable ethical impediment; therefore, from a personalist point of view, ***this technique will never be ethically acceptable***. In contrast, MST by itself does seem acceptable, as it acts on the oocyte. Nevertheless, in order for its practical application to also be acceptable, a procedure other than in vitro fertilisation must be used, which, to the best of our knowledge, is not being promoted. If this line of action is investigated and the safety problems are resolved, the use of MST could meet the criteria of personalist bioethics.

[See first child born using this technique]

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