

This response was submitted to the call for evidence by the Nuffield Council on Bioethics on *Emerging techniques to prevent inherited mitochondrial disorders: ethical issues* between January 2012 and February 2012. The views expressed are solely those of the respondent(s) and not those of the Council.

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Pro-nuclear transfer and Maternal spindle transfer (MST)

Summary

1. The proposed procedure is both novel and experimental.
2. Problems of public consultation and misleading media claims.
3. Human embryos destined for implantation in a human being have so far been universally protected from clinical interference. Questions about mother's informed consent.
4. Germline modification of the embryo raises the issue of proxy consent on behalf of the future child and any future descendants of that child.
5. The pioneering nature of the research - genetic modification and further development of the human embryo – involves crossing a line that has so far been regarded as absolutely barred. Once crossed, it may lead to broader applications, including possible modification of the egg's nucleus.
6. The precautionary principle should prevail in relation to entities that are as intrinsic to human existence as genes and the embryo.
7. The need to monitor resulting babies into childhood and beyond will be an intrusive burden.
8. Comparison with organ or tissue transplantation and with donation of other bodily material is inappropriate because of the unique link between genetic material and personal identity.
9. Problem of reaching consensus at the boundary of fertility treatment and scientific research.

1. The novel and experimental nature of the proposal

This is an issue that lies outside our current models for research, drug development and clinical practice and it is right that the Government recognises the need for consultation and reflection. But whether to proceed clinically is more than a matter of tweaking regulation, nor is the general public well equipped to provide an informed response. Hence, a high responsibility lies on advisers such as the HFEA and the Nuffield Council on Bioethics.

2. The possibility of public misunderstanding of the scientific aspects

As far as the public is concerned, the explanation of the procedures involved is complex and genetic aspects can easily be misrepresented or suppressed. For example, media airings of the subject have tended to provide a simplified account, with reports based on highlighting a single case. Figures suggesting the minimal genetic contribution of the unrelated donor [25,000 (99.8%) genes from parents, 13 genes from donor's mitochondrial DNA] are

supplied, making this, the three parent embryo – which would to many people seem the most sensitive and dramatic aspect of the proposal – appear an insignificant or negligible aspect. But the missing context is important: that the greatest part of a person's DNA is, in any case, 'junk' material whose function, if any, is unknown, nor that a single gene in a person's DNA can have enormous significance – there are single gene disorders. Readers of one newspaper (the Times) were told that these 13 mitochondrial genes carry out only basic 'housekeeping' functions and do not confer inherited traits such as appearance and personality. The director of the Wellcome Trust Mark Walport similarly discounted the 'three-parents' angle, likening mitochondria, the powerhouses of a cell, to batteries and saying that what is at issue is 'only a tiny, tiny amount of genetic material.' These claims may need confirmation, since they may well affect the answers we give to practical questions raised about the link between genes and identity, felt or real, and therefore about the *subsequent* significance to the child of its origins, and the possibility of physical, psychological or social effects later in life. These are all practical, i.e., empirical, questions, but they are so far necessarily untested, since the procedures have only been carried to a conclusion in very limited primate research. (A single recorded case (in China) of implanting modified embryos of this kind in a human ended in the failure of the embryos to come to term.) The immediate ethical consideration this highlights is that we are talking here of applying an experimental procedure so far confined to the laboratory directly to human subjects.

3. The question of consent – mothers and their children

A further aspect of the necessarily experimental status of would-be mothers and resulting children is that human embryos destined for implantation in a human being have so far been universally protected from clinical interference. The question of 'consent' is usually linked to the term 'informed' and it is, of course, expected that consent will be needed in this case. But there is a question as to how far people can be genuinely informed on a topic which carries such large implications as this. To really understand what is involved, you need to know something about genetic science, about principles of epidemiology, including a grasp of risks and statistics, and to have a realistic appreciation of possible future developments in medical treatments for the condition that it is intended to avoid. The possibility, though, is that a presumption would develop that ethical objections in relation to consent have been overcome if the procedures are legally permitted. Nor is it certain that the patient would fully appreciate that this is not the only alternative available to her – a donor egg with identity preserved is already legally available as a solution. But the potential mother is not the only experimental subject: there is also the future child, for whom the problematic nature of its own genetic origins may raise questions about identity and welfare.

4. The question of consent – practical issues raised by germline modification of the embryo

The situation is one that places the issue of consent on behalf of the future child and any future descendants of that child in a special light. Parents can give proxy consent on behalf of their child, but consent for an adult can't normally be given by proxy. And yet, if it turns out that some people born as a result of this technique and created from an embryo modified in this way suffer unanticipated undesirable effects the problem will be passed down the line to future generations.

A further consideration is that, if the procedure is carried out under conditions of medical confidentiality and these future people are not informed about their mode of creation, they may be subjected to wrong treatments, or to failures to treat, on the part of geneticists or family doctors who wrongly diagnose their problems. Being unaware of a family hazard to which they are susceptible may significantly affect their lives, their interests and their well-being, just as being aware of it may protect them.

This is where it begins to seem necessary to focus on a wider perspective: the broader consequences that flow from the irreversibility of this step and the unique novelty of the new world from which the clinical community has so far deliberately excluded itself.

5. Taking the lead – pioneering research

The UK takes pride in pioneering scientific research in many areas, and clearly there are potential profits to be made from biotechnological innovation and its medical deployment. But pioneering the clinical application of research that has so far been regarded as an absolute ethical no-go-area – research, that is, that clinicians in the Western democracies have so far regarded as impermissible – should prompt careful thought. There are two aspects to the uniqueness of the proposed procedure: i) that it involves reconstruction (genetic engineering) rather than selection, and ii) that the germline is affected – any effect of the modification will be passed on to future generations (it is anticipated that the effects will be benevolent but prediction is risky). For good reason, then, this is a line that has so far been regarded as not to be crossed. To cross it in this one case is to open a Pandora's box hitherto kept firmly sealed – and it is difficult not to believe that once that box is opened, germline therapy will be regarded as an acceptable option in other cases as well. In other words, we might expect that, once the ethical arguments used to restrain moves toward designer babies have been swept aside in this one instance, momentum would grow to legalise interference with the nucleus of the human egg as well as with the mitochondria. The much-debated 'designer baby' would become a reality.

6. The precautionary principle

The message here is of the need for caution in exercising the new technological power we may now possess over the future of our species. As in other areas where genetic engineering is already applied – animal husbandry, modification of plants - the precautionary principle should prevail. In the end, we should consider whether to continue to hold as inviolable the principle that things that are as intrinsic to human existence as genes and the embryo should maintain their absolute status as protected from manipulation by human science. This, I suggest, is the ethical issue at the heart of this decision-making process.

7. Some further questions about the future child.

I have raised some questions i) about the social and psychological consequences for the child of its triple genetic ancestry, and ii) about the safety risks of interfering with this basic genetic material – the egg. It can be assumed that there will be a need to monitor resulting babies into childhood and beyond, an intrusive burden which would serve to confirm their experimental status.

An important advantage of the proposed procedure is to enable the mother to have a child which is genetically hers. This is an important objective, nor do I agree with some of those

involved in fertility treatment who believe that, once donated, the source of a child's genetic material is irrelevant – that parenthood is a purely social concept. People are increasingly concerned to understand their own complex genetic inheritance and to have access to the world of their genetic relations – a biological family that includes grandparents, aunts, uncles and cousins, as well as forebears and descendants. This fabric of connections has until now formed the webbing underpinning most known cultures and societies. But children born by this procedure would need to be given information about their three genetic sources, and this is likely to be confusing for their sense of personal identity.

8. Unjustified comparison with organ or tissue transplantation

As stated above, people are increasingly concerned to locate themselves in their biological network, which has until now provided the individual's deepest conception of their identity and in many cases offered them the social space within which to find their earliest sense of self. This is why comparison with organ or tissue transplantation and with donation of other bodily material is completely inappropriate. Genetic material has always been assigned a special status in English law (e.g. a condemned pregnant woman could not be put to death but had first to be allowed to give birth).

9. Finding consensus at the boundary of fertility treatment and scientific research

It would seem necessary to draw a much clearer line between fertility treatment and scientific research than is the case at the moment. But what if we find that consensus is impossible to achieve? The alternatives are these: to proceed unsanctioned and possibly risk finding we have earned pariah status in the international scientific community, or to step back in the face of an apparent widespread consensus against interference with the human embryo.

So can the move to clinical application of the scientific research at issue in this debate be ethically defended? Of course, human happiness and the relief of suffering matter morally. However, the reservations of those who fear the commodification and trivialising of human life are understandable, and it might well be that the balance should fall on the side of caution – that we should conclude, that is, that the boundaries of reproductive medicine are rightly narrower than the boundaries that govern scientific research.

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