A slippery slope to human germline modification

The United Kingdom's decision to trial the technique of mitochondrial replacement is premature and ill-conceived, says **Marcy Darnovsky**.

The UK government's recent move towards human trials of mitochondrial-replacement techniques has prompted intense interest among scientists and bioethicists, while the media continue to frame mitochondrial replacement as a matter of 'three-parent babies'. The description is accurate — it would involve a woman affected by mitochondrial disease, whose egg provides a nucleus, a second woman to provide a 'healthy' egg and a man to provide sperm — but this simple framing overshadows profound social and ethical concerns.

Mitochondrial-replacement procedures would constitute germline modification. Were the United Kingdom to grant a regulatory go-ahead, it would unilaterally cross a legal and ethical line on this issue that has been observed by the entire international community. This consensus holds that genetic-engineering tools may be applied, with appropriate care and safeguards, to treat an individual's medical condition, but should not be used to modify gametes or early embryos and so manipulate the characteristics of future children.

Supporters argue that these concerns do not apply to modifications of mitochondrial DNA, which they characterize as an insignificant part of the human genome that does not affect a person's identity. This is scientifically dubious. The genes involved have pervasive effects on development and metabolism. And the permissive record of the UK regulatory authorities raises the prospect that inheritable mitochondrial changes would be used as a door-opening wedge towards full-out germline manipulation, putting a high-tech eugenic social dynamic into play.

Officials say the techniques would save lives. Yet they would do nothing to help people who are living and suffering with mitochondrial disease. Instead, the techniques are aimed at allowing a small number of women, those affected by a particular kind of mitochondrial disease, to have healthy children who are genetically related to them. It is easy to sympathize with their situation: the prospect of a suffering child is devastating. It is important to note, however, that these women have much safer alternatives, including pre-implantation genetic diagnosis and the use of third-party eggs with conventional IVF.

The UK Human Fertilisation and Embryology Authority (HFEA) repeatedly claims that 1 in 200 children is born each year with a form of mitochondrial disease and, unsurprisingly, many media accounts echo this number. The scientific consensus is that the number is more like 1 in 5,000 (R. H. Haas *et al. Pediatrics* **120;**1326–1333; 2007). Among that much smaller group, a significant majority of cases involve mutations in nuclear as well as in mitochondrial DNA, and so could not be helped by mitochondrial replacement.

Although proof of safety is, by definition, impossible in this situation, the evidence submitted up to now on mitochondrial replacement is far from reassuring. Most of the work has been on early-stage embryos; basic research on epigenetic and other interactions among nuclear and mitochondrial genes is lacking; animal studies are preliminary. The HFEA, which had originally asked that the mitochondrial-replacement technique being developed in the United Kingdom, called pro-nuclear transfer, be tested in non-human primates, later dropped that requirement — after US researchers found the technique to be unsuccessful in macaques.

Those opposed to green-lighting mitochondrial replacement have been described in some quarters as religious objectors, against all types of IVF. In fact, many secular and actively pro-choice scientists, bioethicists and women's-health advocates have voiced grave and detailed concerns about the safety and utility of mitochondrial replacement, and about authorizing the intentional genetic modification of children and their descendants.

MITOCHONDRIAL **REPLACEMENT** PROCEDURES WOULD CONSTITUTE **GERMLINE** MODIFICATION.

The HFEA, for its part, has made questionable claims of favourable public opinion about mitochondrial replacement. In 2012, the agency carried out a public consultation, which it said found "broad support" for the technique. Yet the consultation report shows something quite different. Of more than 1,800 respondents to the largest and only publicly open portion of the exercise (the element that in past consultations has been presented as the most significant), a majority opposed mitochondrial replacement.

The HFEA points out that the consultation included other "strands": workshops of 30 people each; a public-opinion survey; two meetings with preselected speakers; and a six-person patient focus group. The sentiment in these strands tended to be more favourable, but this sentiment was encouraged in various ways. When a reference to a study caused uncertainty and concern, for example, it was dropped from subsequent discussions on the grounds that it was not relevant. The report noted that "some participants' trust in the safety of these techniques is relatively fragile, and easily disrupted by new information".

The next step in the United Kingdom will be draft regulations for clinical trials of mitochondrial replacement, expected later this year. A request by US researchers for Food and Drug Administration approval to use a variation of the technique is also likely soon.

The question raised by these proposals is whether a risky technique, which would at best benefit a small number of women, justifies shredding a global agreement with profound significance for the human future. We need a moratorium on procedures based on human germline modification while that question is widely and fairly considered. ■

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