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.

Professor Joanne Poulton et al

Ethical issues in mitochondrial donation

Oocyte donation is the most acceptable and reliable means of preventing maternally inherited mitochondrial DNA disease, and has the advantage that the women carrying mutant mtDNA may be the physiological, even if not the genetic, mother.

We are very supportive of research into the effectiveness and safety of pronuclear transfer and spindle transfer, but feel that it is too early to license these techniques to be used in assisted conception. We note that the MRC and the Wellcome Trust appear to be endorsing these procedures already, which we consider is premature, e.g. press release (14th April 2010) on the Wellcome Trust website which states,

> "What we've done is like changing the battery on a laptop. The energy supply now works properly, but none of the information on the hard drive has been changed," explains Professor Turnbull. "A child born using this method would have correctly functioning mitochondria, but in every other respect would get all their genetic information from their father and mother."

While this approach may well be useful in the long term, especially for families with homoplasmic mtDNA diseases (which is the case for the majority, but not all, cases of Leber Hereditary Optic Neuropathy, henceforth LHON), we have a number of concerns.

- First, insufficient is known about either the biological basis of the processes underlying mitochondrial transmission (the biological bottleneck) or about the effects of nuclear transfer on mitochondrial DNA replication and segregation.
- Secondly, the potential of alternative less invasive methods should be fully exploited before moving on to this method. In particular, preimplantation genetic diagnosis has only recently become available and there is very little experience as yet to determine how applicable it) is to the majority of families with heteroplasmic mtDNA diseases. We note however, that preimplantation sampling may be a less attractive approach for homoplasmic mtDNA disorders. LHON is the commonest of these diseases, but generally only affects the visual system and is hence a relatively mild mitochondrial disease. In LHON, selection of females can be used to reduce the risk that the offspring will be affected. Nevertheless the risk to females remains around 15%.
- Thirdly, emerging research on mitochondrial quality control may provide a relatively non-invasive means of modulating mtDNA mutant load in vitro.
- Finally, the demand for human oocytes for both clinical practice and research into treatments for infertility and the causes of genetic disease, is rising steadily. An increase of donated gametes is essential for research into pronuclear and spindle transfer. Oocyte donation is also the most acceptable and reliable means of preventing maternally inherited mitochondrial DNA disease. But supply has not kept pace with increasing demand disadvantaging both approaches.

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