New safety and efficacy evidence for mitochondrial donation revealed

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A new IVF-based technique is likely to lead to normal pregnancies and reduce the risk that babies born will have mitochondrial disease, according to researchers at the Wellcome Trust Centre for Mitochondrial Disease at Newcastle University.

Published today in the journal *Nature*, scientists report the first in-depth analysis of human embryos created using a new technique designed to reduce the risk of mothers passing on mitochondrial disease to their children, which is debilitating and often life-limiting.

The new technique, called "early pronuclear transfer", involves transplanting the nuclear DNA from a fertilised egg into a donated egg, which contains healthy mitochondria, on the day of fertilisation.

Today researchers, in a study involving over 500 eggs from 64 donor women, publish results that indicate that the new procedure does not adversely affect human development and will greatly reduce the level of faulty mitochondria in the embryo. Their results suggest that the technique will lead to normal pregnancies whilst also reducing the risk of babies having mitochondrial disease.

The results of this study will be considered by the Human Fertilisation and Embryology Authority's (HFEA) Expert Scientific Panel. The HFEA will ultimately decide whether to issue the first licence to a clinic. A licensed clinic would allow couples affected by mitochondrial disease to have the choice of whether to use pronuclear transfer to try and have

healthy children.

Professor Mary Herbert, senior author of the study, said: "Having overcome significant technical and biological challenges, we are optimistic that the technique we have developed will offer affected women the possibility of reducing the risk of transmitting mitochondrial DNA disease to their children."

Extensive studies conducted in collaboration with researchers from University of Oxford and the Francis Crick Institute indicated that embryos created using the new technique are indistinguishable from those created by conventional IVF. Analysis of thousands of genes in single cells detected no difference between the two types of embryos. There was also no increase in chromosomal abnormalities, which can cause miscarriage and birth defects. These findings provide reassurance that the new procedure does not have a harmful effect on early embryonic development.

The research findings also indicate that the new technique will result in a minimal amount (less than 2%) carryover of disease-causing mitochondrial DNA to the embryos. The importance of keeping carryover to a minimum is highlighted by studies on embryonic stem cell lines. The team found that one of five stem cell lines derived from embryos created using the new technique, showed an increase in the percentage of mitochondrial DNA carryover. While stem cells are very different from embryos, the observation raises the possibility that faulty mitochondrial DNA may persist in some cases. However, the research team is optimistic that the new technique will be effective in reducing the risk of disease in children of affected women.

A further important finding of the study is that the technique will work best if patient (rather than donor) eggs are frozen. It will therefore be possible for affected women to have their eggs frozen for future use.

This is likely to increase the success of the treatment by helping to avoid the decline in egg quality as women get older.

Professor Doug Turnbull, Director of the Centre for Mitochondrial Research, and co-author of the paper said: "This study using normal human eggs is a major advance in our work towards preventing transmission of mitochondrial DNA disease. The key message is that we have found no evidence the technique is unsafe. Embryos created by this technique have all the characteristics to lead to a pregnancy."

He added: "Our studies on stem cells does express a cautionary note that it might not be 100% efficient in preventing transmission, but for many women who carry these mutations the risk is far less than conceiving naturally."

In the event of a positive outcome from the Expert Panel, the team at Newcastle Fertility Centre, which is part of the Newcastle Hospitals NHS Foundation Trust, will submit an application for an HFEA license to offer pronuclear transfer to women at high risk of transmitting mitochondrial DNA disease to their children. The team is also working to secure the necessary funding to be able to offer clinical treatments on the NHS.

Professor Herbert said: "Our ongoing research is focussed on refining the techniques to further reduce the risk of transmitting disease."

She added: "I would also like to thank the women who donated eggs for this research. It would not have been possible to do this work without their help."

Dr Beth Thompson, Senior Policy Advisor at the Wellcome Trust said: "This study adds to the extensive body of evidence built up over the past ten years suggesting that mitochondrial replacement therapy is not

unsafe. The results bring the UK closer to being able to offer mitochondrial replacement technique to couples affected by mitochondrial disease. The UK's strong regulatory system will now kick in to decide whether there is enough evidence that this technique is safe enough to be a good choice for families.

"Ultimately, couples affected by mitochondrial disease will be the best placed to decide whether the new technique is right for them, with advice from their doctors."

More information: Louise A. Hyslop et al, Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease, *Nature* (2016). DOI: 10.1038/nature18303

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