RBM ONLINE

ELSEVIER

Letter

# Response: First birth following spindle transfer - should we stay or should we go?

To the Editor

We appreciate the opportunity to respond to the letter by Norbert Gleicher and colleagues (Gleicher et al., 2017) concerning our report 'Live birth derived from oocyte spindle transfer to prevent mitochondrial disease' (Zhang et al., 2017). Just as with the first birth following IVF, this first birth following mitochondrial replacement therapy (MRT) has provoked medical, ethical and legal debates, most of which are addressed in an editorial by Alikani et al. (Alikani et al., 2017) and in a letter from Boiani and Cohen (2017). Here we add some further points of clarification.

Mitochondrial disease is indeed very devastating and the family in question has suffered very much on this account. The mother has had four miscarriages, and two of her children died at a very early age due to Leigh Syndrome from a mitochondrial DNA (mtDNA) mutation. We counselled her extensively before we made the decision to pursue the procedure, supported by our ethical review committee. The couple was fully aware that MRT is a very new and experimental technology, at least as it applies to humans, and they made the decision to proceed on this basis. We applied our best knowledge of nuclear transfer (as was available in 2014) to our internal review board (IRB) protocols and consents. We did not 'rush to use this as treatment' as is quoted in the letter by Gleicher et al. (2017).

The risks to an offspring secondary to nuclear transfer are still unknown. The first monkey generated by spindle transfer is now 8 years old, and the female monkeys thus generated have had babies with no major concerns reported to date (personal communication between Dr. Taosheng Huang and Dr. Shoukhrat Mitalipov). Although several recent publications have suggested that mtDNA drift after nuclear transfer could be a potential risk (Hyslop et al., 2016; Kang et al., 2016; Yamada et al., 2016), these reports are based on *in-vitro* studies of human embryonic stem cell lines and none reveals a convincing mechanism for such a radical drift, making it all but impossible to develop effective measures to prevent drift. So even if these information were to have been available at the time we undertook treatment of this patient, it is difficult for us to know how we could have informed the family regarding the likelihood of this potential adverse outcome. Furthermore, the UK Human Fertilization and Embryology Authority (HFEA) approved application of this technology to selected patients in November of 2016 after the organization had intensively reviewed all relevant publications, including our data.

The most appropriate way to evaluate the safety of MRT is close follow-up of the health of the children born following treatment. In our case, although we had obtained consent for long-term follow-up, due to privacy concerns (particularly after widespread coverage by the world's media) and legal issues (denial of visa application by United States Consulate), the parents decided not to come back to allow follow-up on a regular basis, as is their right. Based on our recent conversation with the parents, the baby seems to be doing well. We hope that once the media's interest lessens, the parents will return and we can follow the protocol as stated in the consent.

In conclusion, we feel it is necessary to consider this case in its appropriate historical context. Similar questions were raised when the first IVF baby was reported many years ago, and, of course, such questions are not without merit. However, an important question for the field is: Should we stay or should we go? When we raise concerns about the safety of MRT, do we have any solid, scientific evidence to support the notion that this procedure is not safe? Do we have other better options to offer similar patients in their quest to have a healthy baby? And if not, at what point does our caution go from due diligence to stagnation?

*Declaration: The authors report no financial or commercial conflicts of interest.*

## REFERENCES

Alikani, M., Fauser, B.C., Garcia-Valesco, J.A., Simpson, J.L., Johnson, M.H., 2017. First birth following spindle transfer for mitochondrial replacement therapy: hope and trepidation. Reprod. Biomed. Online 34, 333–336. doi:10.1016/j.rbmo.2017.02.004.

Funding: The communication received no funding support.
https://doi.org/10.1016/j.rbmo.2017.07.004
1472-6483/© 2017 Reproductive Healthcare Ltd. Published by Elsevier Ltd. All rights reserved.

Boiani, J.A., Cohen, J., 2017. Response: first birth following spindle transfer. Reprod. Biomed. Online 35, 546–547.

Gleicher, N., Kushnir, V.A., Albertini, D.A., Barad, D.H., 2017. Letter to the editor: first birth following spindle transfer. Reprod. Biomed. Online 35, 542–543.

Hyslop, L.A., Blakeley, P., Craven, L., Richardson, J., Fogarty, N.M., Fragouli, E., Lamb, M., Wamaitha, S.E., Prathalingam, N., Zhang, Q., O'Keefe, H., Takeda, Y., Arizzi, L., Alfarawati, S., Tuppen, H.A., Irving, L., Kalleas, D., Choudhary, M., Wells, D., Murdoch, A.P., Turnbull, D.M., Niakan, K.K., Herbert, M., 2016. Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease. Nature 534, 383–386. doi:10.1038/nature18303.

Kang, E., Wu, J., Gutierrez, N.M., Koski, A., Tippner-Hedges, R., Agaronyan, K., Platero-Luengo, A., Martinez-Redondo, P., Ma, H., Lee, Y., Hayama, T., Van Dyken, C., Wang, X., Luo, S., Ahmed, R., Li, Y., Ji, D., Kayali, R., Cinnioglu, C., Olson, S., Jensen, J., Battaglia, D., Lee, D., Wu, D., Huang, T., Wolf, D.P., Temiakov, D., Belmonte, J.C., Amato, P., Mitalipov, S., 2016. Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations. Nature 540, 270–275. doi:10.1038/nature20592.

Yamada, M., Emmanuele, V., Sanchez-Quintero, M.J., Sun, B., Lallos, G., Paull, D., Zimmer, M., Pagett, S., Prosser, R.W., Sauer, M.V., Hirano, M., Egli, D., 2016. Genetic drift can compromise mitochondrial replacement by nuclear transfer in human oocytes. Cell Stem Cell 18, 749–754. doi:10.1016/j.stem.2016.04.001.

Zhang, J., Liu, H., Luo, S., Lu, Z., Chavez-Badiola, A., Liu, Z., Yang, M., Merhi, Z., Silber, S.J., Munne, S., Konstandinidis, M., Wells, D., Huang, T., 2017. Live birth derived from oocyte spindle transfer to prevent mitochondrial disease. Reprod. Biomed. Online 34, 361–368.

Zitao Liu [a], Zaher Merhi [a], John Zhang [a,b]Taosheng Huang [c]

[a]*New Hope Fertility Center, 4 Columbus Circle, New York, NY 10019, USA*

[b]*New Hope Fertility Center, Punto Sao Paulo, Lobby Corporativo, Américas 1545 Providencia, Guadalajara, Mexico*

[c]*Division of Human Genetics, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229, USA.*

*E-mail address:* zitao.liu@nhfc.com