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Letter

First birth following spindle transfer

To the Editor

The very detailed recent editorial in this journal by Alikani et al. (2017) offers clear evidence of how intensely the senior editors of *RBMOnline* must have struggled with a decision to publish the case report by Zhang et al. (2017) detailing a live birth following spindle transfer for mitochondrial replacement therapy (MRT). Including the decision to publish the manuscript, any decision they could have reached would have been controversial. We, therefore, applaud the editors for explaining themselves to the readers of the journal in so much detail.

Acknowledging obvious personal biases in favor of loosening the currently too restrictive prohibitions in the USA and elsewhere against research into nuclear transfer methods and other new technologies permitting the crossing of the human germline, we also sympathize with the editors' rather benevolent views about the reported experience by Zhang et al. Based on our reading of the authors' report (Zhang et al., 2017) and the detailed editorial comments by Alikani et al. (2017), we, however, reached somewhat different conclusions.

We do not see how the scientific community can or should view this case as an 'achievement', because if this example has anything to offer, it is only as a perfect lesson in how responsible research should not be performed – and not only research that potentially crosses the human germline, which carries with it enhanced sensitivities – but all research.

As Alikani et al. (2017) and other observers (e.g. Reardon, 2017) note, informed consent in this case was inadequate. Insufficient informed consent is ethically incompatible with all forms of medical practice. Furthermore, a legal scholar is quoted in the above-mentioned article in *Nature* (Reardon, 2017), making the point that because the newborn boy could not give informed consent himself, 'duties for physicians to protect the best interests of the future child were even bigger'.

This case also demonstrated how incomplete informed consent can invalidate whatever scientific achievement might, otherwise, have been possible. Since his parents now refuse any testing of the child, because no adequate informed consent was obtained in advance, investigators have lost the opportunity to follow the child at least through the early years of his life. Such testing is essential because two separate studies have demonstrated so-called genetic drifting after MRT (Hyslop et al., 2016; Yamada et al., 2016), which increases mutated maternal mitochondrial DNA (mDNA, i.e., heteroplasmy) with increasing numbers of cell cycles. Therefore, if a child at birth demonstrates low levels of heteroplasmy, it does not preclude that at older ages heteroplasmy will reach a critical level, resulting in phenotypical expression of the genetic defect that the MRT was intended to overcome.

Dietrich Egli, whose laboratory was the first to report genetic drift after nuclear transfer (Yamada et al., 2016), was quoted in the above-mentioned *Nature* article (Reardon, 2017) as saying, 'Whatever we learn in a person (human), will be completely new. It looks like a rush to use this as treatment and telling patients that this is the treatment, during a time when we still know very little what the outcomes are.' Why Alikani et al. (2017), therefore, would describe this case as 'the first successful case of MRT' is unclear. It will take years, maybe decades, to determine whether the treatment in this case was successful or not.

We also fail to understand what relevance Alikani et al. find in Zhang et al. attempting to set up a pre-investigational new drug (IND) discussion/application with the Food and Drug Administration (FDA), which in the USA has statutory control over all methods of MRT. That they were rejected by the FDA is not a surprise. Many other groups, including our own, received precisely the same non-response from the FDA. What we, too, consider an inappropriate policy of the FDA is, however, not an excuse for breaching clearly and publically formulated FDA guidelines prohibiting any human experimentation that crosses the human germline and which may lead to birth.

Contrary to initial public statements by Zhang et al., the spindle transfer for MRT was performed in New York City. It, like the embryo transfer, was initially reported to have been performed in Mexico. This change in the description of where events occurred is of great ethical, as well as legal, importance since the MRT, as is now apparent, was performed within the USA with clear intent to transfer any so-created embryos into a uterus to achieve birth. Confirmation of these facts by Zhang's publication and Alikani's editorial, therefore, clearly established intent to breach FDA guidelines, as patient and embryos were then moved to Mexico, where only the embryo transfer was performed in an affiliated IVF center in Guadalajara.

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We were also surprised by the unchallenged acceptance by Alikani et al. (2017) of the authors' representation that they received approval for all of the case-connected procedures (presumably including the spindle transfer for MRT) from the 'Internal Review Board' (IRB) of the Mexican clinic, where allegedly only the embryo transfer took place. Aside from the fact that we do not know of many IVF centers in the USA that have their own IRB, and we certainly do not know of any in Mexico, a Mexican IRB would not be permitted to approve an experimental procedure, such as spindle transfer, that is carried out in an USA-based institution. The spindle transfer performed in New York City, therefore, not only lacked FDA approval but also, likely, was performed without prior IRB review and approval.

Not only is performance of a procedure with such a degree of potential consequences without IRB approval unethical, but international scientific medical publishing guidelines also prohibit the publication of such work without prior IRB approval. *RBMOnline*, therefore, should not have published this case.

We are writing this letter out of concern that opponents of reproductive research will use the irresponsible way in which this research was conducted as example of why all reproductive research should be prohibited outright. It is important to point out that most of the reproductive scientific community is more disciplined and more ethically, as well as legally, astute.

There is, otherwise, only one other lesson to be learned from this case, this time relevant to the FDA and other regulatory agencies around the world. What this case demonstrates so well is that if responsible scientists are prohibited from performing responsible research under appropriate guidelines and safeguards, the research will go elsewhere, where there exist neither guidelines, safeguards, nor responsible researchers.

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