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Letter

Response: Artificial blastocoel collapse of human blastocysts before vitrification and its effect on re-expansion after warming

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To the Editor

Ebner and Shebl (2018) are wondering how we explain the fact that, contrary to other published studies (Coello et al., 2017; Ebner et al., 2017), we did not find a link between re-expansion of warmed blastocysts and clinical results. It should be noted that in each of these studies (including our own), different biomarkers were used to predict the implantation potential (or implantation failure) of warmed blastocysts, but all were based on measurement of blastocyst expansion.

To estimate an increase in blastocyst size over time from warming to transfer, one may use a linear function $y = kx + n$, in which x represents the time interval, k represents the rate of re-expansion, and n the size of the blastocyst immediately after warming. We compared the re-expansion speed using this linear model, whereas Ebner et al. (2017) focused on time to beginning of re-expansion and time taken for completion of re-expansion. Coello et al. (2017) measured blastocyst size immediately after warming and again before transfer. Both groups observed blastocysts at two extreme time points, without considering the morphodynamics occurring between these time points. Since blastocysts rarely re-expand linearly (Kovačič et al., 2018), we also introduced a new parameter of 're-expansion pattern' in our study.

All three studies aimed to identify warmed blastocysts with minimal chance of implantation, which would make warming of another blastocyst necessary. Ebner et al. (2017) identified this characteristic in blastocysts with long delay in initial expansion, while in the study by Coello et al. (2017), very small-sized blastocysts immediately after warming were recognized as a problematic group. In our study, blastocysts from all re-expansion patterns resulted in live births, including small-sized blastocysts that showed slow increase in blastocoel volume during the recovery period; therefore we think that re-expansion time does not serve as a good predictor for implantation failure.

We cannot agree with the findings of Ebner et al. (2017) that it is possible to evaluate the viability of an intact blastocyst less than 1 hour post-warming and so decide whether or not a second embryo should be warmed. In our experience, this time is too short. Blastocysts in our study often needed more than 1 hour to re-activate the fluid-pumping mechanism. Measurement of the time to complete expansion also seems to be questionable, as a large proportion of blastocysts fail to expand fully during the time from warming to transfer.

In theory, the size of the warmed blastocyst measured before transfer also seems to be a good indicator of its quality, but only if the embryo is not in a collapsed or contracted state. Another problem is that the time from warming to transfer varies. In Coello's study, for instance, it varied from 3.5 to 7 h.

We also believe that blastocyst size immediately after warming, as measured by Coello et al. (2017), cannot be used as a standardized general parameter, since it is influenced by the developmental stage of fresh blastocysts, trophectoderm permeability, hatching, artificial collapse (partial or total), vitrification protocol, and so forth. This parameter, however, could be potentially useful in the case of total artificial collapse of blastocysts before vitrification, which, as stated in our study, would help set a standard starting point and thus provide a foundation for further measurements of warmed blastocysts. The question that still exists is whether this intervention is safe or even necessary for the embryo in view of the good clinical results achieved without artificial collapse, as shown by all three cited studies. Why artificial collapse of blastocysts before vitrification works better in some laboratories, but not in others, is difficult to explain. More than blastocoel shrinkage techniques, we speculate that the different vitrification protocols used could be a contributing factor.

In the future, it will be difficult to introduce a standardized model that is based on measuring re-expansion time or blastocyst size differences with time-lapse microscopy that would suggest when to warm another blastocyst. Experience with fresh embryos suggests that time indicators and algorithmic models of embryonic development that have proved to have good predictive value in some IVF laboratories do not work in other laboratories. We can expect the same with warmed re-expanding blastocysts, as evidenced here.

A more demanding issue that requires a separate approach is whether, in the case of warmed blastocysts with low implantation

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potential (14.2% in D category in Coello et al., 2017), an additional blastocyst should be warmed and transferred. From this perspective, attempts to define categories of warmed blastocysts with different implantation potential are worthwhile.

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