Clinical outcomes following selection of human preimplantation embryos with time-lapse monitoring: a systematic review

Sir,

We have read the recent article by Kaser and Racowsky (2014) with great interest and we highly welcome this thorough systematic review. We entirely agree with the main conclusions as presented in the abstract. There are currently no high-quality data to firmly support the clinical use of this technology for selection of preimplantation embryos. Prospective studies are needed to clarify the role.

We would, however, like to discuss the results from the review upon which Drs Kaser and Racowsky base this conclusion.

The authors thoroughly review the time-lapse studies that have presented data on clinical outcome and present the results of their descriptive comparison, including their interpretation of the results from our prospective study (Kirkegaard et al., 2013). Amongst others the authors use the results from our study to argue that there are no differences in timing between the pregnant and the non-pregnant group of all the measured parameters. Our objection is that our study was not powered to test pregnancy as a clinical outcome for all the parameters that the authors review. Accordingly, we specifically desisted from drawing any conclusions on the ability of time-lapse parameters to predict pregnancy in general. This is clearly stated in our paper. Following standard scientific conduct, we did publish timings of all the parameters in the pregnant and non-pregnant group, yet acknowledged that the study was powered only to test the parameters from the targeted logistic regression analysis. We even clarified this in a response to a letter addressing the sample size (Kirkegaard et al., 2014). We believe that the underpowered sample size entails a high risk of falsely concluding that there is no difference. For example, we did not test appearance, abuttal, syngamy, and breakdown of the male and female pronucleus (PN) as predictors of implantation in our logistic regression analysis (as stated in the review), but only PN breakdown. Therefore it is hardly justified to state that we did not find any difference in the above parameters, without acknowledging the lack of power to detect such differences. This is true for several of the conclusions the authors draw from our publication, including the conclusion that we found no difference between implanting and non-implanting embryos in terms of cleavage and blastocyst kinetics in general. We consider it plausible that the majority of the other published studies are far too small to detect any presumed differences in timing with regard to pregnancy. No randomized controlled studies of single embryo transfers have been published so far. We therefore find it very poorly supported, that reliable prediction of blastocyst formation may be the main advantage of TLM, as stated in the review.

It is correct that we conclude that TLM may decrease variability (Sundvall et al., 2013). But as the cited study involved manual, in contrast to computer-assisted annotation, it cannot be stated that the reduced variability is a result of the semi-quantification. The statement that TLM may decrease intra- and inter-observer variability among embryologists, as a result (our underlining) of computer-assisted annotation of developmental milestones and semi-quantitative process for embryo evaluation, is therefore unsupported.

In summary, we entirely agree that larger prospective studies with clinical outcomes are needed to clarify the role of time-lapse. That the existing literature suggests no association with implantation potential is in our opinion so far unjustified due to several factors, most importantly due to lack of power of the studies. This was acknowledged in the original publications, but unfortunately not in the review.

References


Reply: Clinical outcomes following selection of human preimplantation embryos with time-lapse monitoring: a systematic review

Dear Sir,

We thank Drs Kirkegaard and Ingerslev for their interest in our review and for their pioneering work in the field of time-lapse monitoring (TLM). Several points they raise in their Letter to the Editor deserve attention.

First, we would like to clarify that we do not maintain, as they state, that ‘there are no differences in timing between the pregnant and the non-pregnant group of all the measured parameters’ for the included studies—a conclusion that in fact was drawn in the Abstract of the cited Kirkegaard et al. (2013) publication, albeit with their acknowledged limitations in power. Rather, in our collated data we note that some parameters have been shown to be predictive of implantation (e.g. time to pronuclear breakdown, duration of the 2-cell and 3-cell stages,

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doi:10.1093/humupd/dmu044
Advanced Access publication on July 17, 2014