Systematic review on clinical outcomes following selection of human preimplantation embryos with time-lapse monitoring

Thomas Fréour, Natalia Basile, Paul Barriere, Marcos Meseguer

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LETTERS TO THE EDITOR

Systematic review on clinical outcomes following selection of human preimplantation embryos with time-lapse monitoring

Sir,

We have read with great interest the recently published systematic review authored by Kaser and Racowsky (2014). This review enlightens the reader on the problem of utilizing time-lapse technology as a clinical tool based on the absence of 'high quality' data and advises the users to keep it as an experimental tool. Although we agree with the authors' general comment that standardization in embryo annotation is necessary, and that the existing literature does not yet provide any certainty on the improvement in live birth rates permitted by time-lapse monitoring (TLM), we would like to address some issues raised in this paper.

First, the literature described as not having 'high quality' data represents, in our opinion, the irreplaceable starting point of future prospective studies, essential for elaborating relevant randomized controlled trials (RCTs) to demonstrate the clinical usefulness of embryo morphokinetics. First, the morphokinetic differences between implanted and non-implanted embryos have been described and used to build algorithms (Meseguer *et al.*, 2011). The benefit of this strategy over standard morphology has then been confirmed retrospectively (Meseguer *et al.*, 2012), allowing the design of a 'high quality' RCT with the appropriate sample size and power (Rubio *et al.*, 2014).

Second, the authors state that current studies available on TLM demonstrate that faster cleaving embryos have a higher implantation potential, consistently with all previously published studies using conventional morphology, implying that TLM would have limited superiority over morphology. This statement should be nuanced, as there is some evidence that TLM can also provide some relevant exclusion criteria for embryo de-selection, regardless of embryo morphology (Rubio *et al.*, 2012). In this view, one can postulate that future TLM would not only predict which embryo has the highest implantation potential, but also help the embryologist to discard the ones that have very low implantation potential. To go further, preliminary work recently published on the increased possibility of selecting chromosomally normal embryos by TLM paves the way for future studies aiming at identifying morphokinetic markers relevant for both embryo selection and de-selection for transfer (Basile *et al.*, 2014).

Third, we agree that single embryo transfer (SET) is the gold standard for studies aiming at revealing a link between embryological aspects and implantation. However, most studies on TLM used the concept of known implantation data (KID) embryos, embryos with known implantation. Whether excluding cycles with partial implantation negatively impacts validity should be debated, as external validation can be conducted in KID embryos too. One can also argue that any study conducted with a SET policy should not be extrapolated to double embryo transfer cycles, which still represent the large majority of IVF activity throughout the world. It would thus be interesting to check the SET proportion in published studies using the KID concept.

Fourth, the authors mention concerns regarding light exposure in TLM. Embryo exposure to light during incubation in a time-lapse system has already been compared favorably with light exposure on standard microscope (Ottosen *et al.*, 2007).

Fifth, we fully agree that standardization in time-lapse nomenclature is necessary. However, whether t_{cf1} (identification of first cytokinesis furrow) is unequivocally identifiable and should be the standard reference can be debated, as pronucleus fading has been shown to offer an accurate alternative (Cruz *et al.*, 2013).

Sixth, we would like to insist on one aspect of clinical embryology that the authors shortly recall in their introduction. Indeed, conventional morphology assessment only allows moderate prediction of the embryos' implantation capability, and suffers from relatively limited specificity and sensitivity, with significant inter/intra observer variability. We obviously fully agree with this statement, especially as, to our knowledge, no RCT has evaluated the clinical interest of morphology evaluation. Moreover, few studies conducted in humans without any embryo selection, for example for legal reasons, showed that high cumulative pregnancy rates could also be obtained (Ubaldi *et al.*, 2010). It should also be noted that variability is largely present in studies based on conventional morphology (media, atmosphere. . .); however, this has not invalidated its usefulness as the gold standard in embryology. Therefore, if one considers that any embryo assessment method not supported by 'high quality' evidence of its efficiency should be considered an experimental strategy subject to Internal Review Board approval, then all IVF labs across the world should reconsider most of the procedures that are routinely used including the way they choose embryos for transfer. It should also be recalled that morphology represents the first step of TLM-based embryo selection.

In summary, we are confident that some conclusions drawn by the authors of this review will very soon be partially dismissed by 'high quality' clinical prospective studies, ruling out the statement that 'TLM should remain an experimental strategy subject to institutional review and approval'.

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Thomas Freour[1,*], Natalia Basile[2], Paul Barriere[1] and Marcos Meseguer[3]
[1]*Service de médecine et biologie de la reproduction, CHU de Nantes, INSERM UMR1064, Nantes 44093, France*
[2]*IVI Madrid, Avenue Del Talgo 68, Madrid, Spain*
[3]*IVI Valencia, Plaza de la Policía Local, 3, Valencia 46015, Spain*
**Correspondence address. Service de médecine et biologie de la reproduction, CHU de Nantes, 38 boulevard Jean Monnet, Nantes 44093, France. Tel: +33-240084370; fax: +33-240083228; E-mail: thomas.freour@chu-nantes.fr*
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Reply: Clinical outcomes following selection of human preimplantation embryos with time-lapse monitoring: a systematic review

Sir,

We thank Dr Freour and colleagues for their critical read of our review and for their innovative work in the field of time-lapse monitoring (TLM). We likewise share the authors' enthusiasm regarding the potential transformative nature of this technology, and agree with many of their points above, as outlined in our review (Kaser and Racowsky, 2014). However, there is one key point in which we differ: when is it clinically acceptable to apply a new technology or test? That is, what amount of evidence is sufficient?

We agree that well-executed retrospective analyses are essential first steps to define the markers necessary for prospective validation, and certainly recognize the authors' contributions in this regard. In our opinion, though, the lack of prospective data renders it difficult to justify both the broad implementation of the technology and its attendant surcharge, which is apparently being collected by some clinics worldwide.

All too often have retrospective data in this field appeared so promising as to prompt a change in practice, only later to be invalidated by appropriately designed prospective studies. The ART community does not have to reach too far back to cite relevant examples—the use of fluorescence *in situ* hybridization for preimplantation genetic screening or the application of metabolomics as a non-invasive method for embryo selection both come to mind (Mastenbroek *et al.*, 2007; Vergouw *et al.*, 2012).

Just because we have done it incorrectly in the past though, does not mean that we should do it incorrectly in the future. As technologies emerge, it is of the utmost importance that they are vetted and validated with appropriately controlled, prospective studies before routine use in the lab. Otherwise, there is potential not only to misguide the field, but also to do harm to patients. As a community, we have a collective responsibility to learn from previous mistakes.

As stated in our review, 'prospective studies are currently underway and hopefully will clarify the role of TLM'. We look forward to reading the randomized controlled trial from our European colleagues in due time. We sincerely hope that the data show improvement in meaningful clinical outcomes, thereby further elucidating the benefit of this approach. We are very much excited about the promise of TLM; however, experience has shown us that our field and indeed our patients do not always benefit from early adoption of new technologies.

Conflict of interest

C.R. acts as a consultant (scientific advisor) for Auxogyn, Inc.

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Daniel J. Kaser and Catherine Racowsky*
Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
**Correspondence address. cracowsky@partners.org*
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