RBM ONLINE

ELSEVIER

Review

Time-lapse culture with morphokinetic embryo selection improves pregnancy and live birth chances and reduces early pregnancy loss: a meta-analysis

Csaba Pribenszky [a,*], Anna-Maria Nilselid [b], Markus Montag [c]

[a] *University of Veterinary Science, Istvan u. 2., Budapest 1078, Hungary*
[b] *Vitrolife Sweden AB, Box 9080, Göteborg SE-400 92, Sweden*
[c] *ilabcomm GmbH, Eisenachstr. 34, Sankt Augustin 53757, Germany*

Csaba Pribenszky obtained his PhD at the University of Veterinary Science, Budapest, Hungary and worked as senior researcher at EMBRAPA, Brasilia; Uconn, USA; UNCEIA, France; ATIT, Taiwan; University of Aarhus, Denmark and at numerous assisted reproduction technique laboratories worldwide. His main research areas include time-lapse imaging, embryo selection, cell stress and cryopreservation.

KEY MESSAGE

A meta-analysis was conducted on five studies with 1637 patients. The analysis showed that the application of time-lapse monitoring together with an embryo-evaluating algorithm was associated with a significantly higher ongoing pregnancy rate, a significantly lower early pregnancy loss and a significantly higher live birth rate.

A B S T R A C T

Embryo evaluation and selection is fundamental in clinical IVF. Time-lapse follow-up of embryo development comprises undisturbed culture and the application of the visual information to support embryo evaluation. A meta-analysis of randomized controlled trials was carried out to study whether time-lapse monitoring with the prospective use of a morphokinetic algorithm for selection of embryos improves overall clinical outcome (pregnancy, early pregnancy loss, stillbirth and live birth rate) compared with embryo selection based on single time-point morphology in IVF cycles. The meta-analysis of five randomized controlled trials (n = 1637) showed that the application of time-lapse monitoring was associated with a significantly higher ongoing clinical pregnancy rate (51.0% versus 39.9%), with a pooled odds ratio of 1.542 ($P < 0.001$), significantly lower early pregnancy loss (15.3% versus 21.3%; OR: 0.662; $P = 0.019$) and a significantly increased live birth rate (44.2% versus 31.3%; OR 1.668; $P = 0.009$). Difference in stillbirth was not significant between groups (4.7% versus 2.4%). Quality of the evidence was moderate to low owing to inconsistencies across the studies. Selective application and variability were also limitations. Although time-lapse is shown to significantly improve overall clinical outcome, further high-quality evidence is needed before universal conclusions can be drawn.

* Corresponding author.
E-mail address: pribenszky.csaba@univet.hu (C Pribenszky).

http://dx.doi.org/10.1016/j.rbmo.2017.06.022
1472-6483/

Please cite this article in press as: Csaba Pribenszky, Anna-Maria Nilselid, Markus Montag, Time-lapse culture with morphokinetic embryo selection improves pregnancy and live birth chances and reduces early pregnancy loss: a meta-analysis, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.06.022

Introduction

A receptive endometrium, a genetically and metabolically sound embryo and the appropriate synchronization between them are fundamental for achieving a successful ongoing pregnancy and the birth of a healthy baby during the course of IVF for infertility treatment. One of the critical steps limiting success rates in the laboratory phase is the embryo culture and the proper evaluation of the available embryos. It has been generally accepted that, although there are evident correlations, embryo morphology is not always a robust and absolute indicator for implantation potential since sometimes the best looking blastocyst fails to produce pregnancy, or, a morphologically suboptimal embryo can develop into a healthy baby. Finally, on average, only one-third of all cycles result in a pregnancy (Calhaz-Jorge et al., 2016).

Morphological evaluation of the embryos at specific time points has been the method of choice for embryo selection for decades (Cummins et al., 1986; Edwards et al., 1981), although its limitations have later been recognized (Guerif et al., 2007; Racowsky et al., 2009). Morphological evaluation started with the strategy of measuring single features, such as pronuclear size and alignment (Sadowy et al., 1998; Scott et al., 2000; Wright et al., 1990), multinucleation in early cleavage stages (Alikani et al., 2000; Hardy, 1997), blastomere fragmentation (Plachot and Mandelbaum, 1990; reviewed in Munné and Cohen, 1998; Alikani et al., 1999) or blastocyst morphology (Fehilly et al., 1985; Gardner et al., 2000; Hartshorne et al., 1991). Together with classical morphology, timing of cleavages has been also considered to measure the quality of embryos (Johnson and Day, 2000; reviewed in Johnson, 2002). It was shown as early as in the mid-eighties, that embryos with early first and second cleavages can have implantation rates well above 30% (Edwards and Beard, 1999; Edwards et al., 1984). More recent proposals for scoring embryo quality often combine the results of multiple single-point observations (Nagy et al., 2003; Qian et al., 2008; Scott et al., 2007). Consensus guidelines (ALPHA, SART) also propose multiple evaluations; however, they also disclose their limitations in predicting implantation potential (Racowsky et al., 2009; ALPHA, 2011; Hossain et al., 2016). Although multiple observations will increase the robustness of embryo evaluation, it imposes multiple disturbances to the culture environment, possibly stressing the embryo and reducing the embryos' potential to develop and implant. The way to circumvent this 'observational dilemma' is incubation using time-lapse monitoring. This provides information about the development of the embryos in time intervals of 5–10 min, adding up to about 1000 images in each focal plane per embryo during a 5-day culture period compared with the 2–4 static time point observations carried out in normal routine. This imaging procedure alters the basis of embryo evaluation from single discrete time-point observation to continuous observation, changing the timing variable from discrete to continuous. This transition was enabled by the introduction of advanced microscopy for live cell imaging, focusing on the special needs of the human embryo (Cruz et al., 2011; Pribenszky et al., 2010; Wong et al., 2010).

The information obtained through time-lapse monitoring gives us knowledge about the kinetic and morphologic changes and abnormalities an embryo undergoes *in vitro*. Kinetic events can be precisely timed and the correlation of these timings and intervals to blastocyst formation, implantation, live birth and time to pregnancy were investigated in various publications (Castelló *et al.*, 2016 [review]; Ebner *et al.*, 2016). The time-lapse technique puts a time-stamp on all images; such digitalization paves the way for calculated assessments and therefore less subjectivity.

The introduction of time-lapse imaging systems in clinical human IVF, however, has stirred discussions about how new technologies should be implemented in the daily clinical routine. Many reviews and observational studies have discussed the value of time-lapse monitoring in routine laboratory practice (Freour et al., 2015; Kaser and Racowsky, 2014; Kirkegaard et al., 2012, 2014; Montag et al., 2011; Racowsky et al., 2015; Wong et al., 2013). It is as yet unclear, however, whether the observed benefits come from the undisturbed culture or improved selection based on continuous time-lapse images. In short: what is the weight of these benefits in the added value of time-lapse?

Others have suggested that investing in time-lapse and changing the daily routine would not lead to clinical benefits (Armstrong et al., 2015a; Wong et al., 2014). It has been suggested that the clinical benefits of applying new technologies should be verified and documented by randomized controlled trials before general implementation in routine clinical IVF (Harper et al., 2012). A Cochrane review based on three randomized trials (Kahraman et al., 2013; Kovacs et al., 2013; Rubio et al., 2014) with 994 patients concluded that insufficient evidence was available for the benefit of time-lapse imaging (Armstrong et al., 2015b). More recently, another two clinical randomized controlled trials were published (Goodman et al., 2016; Siristatidis et al., 2015), increasing the number of treatment cycles by more than 60%, adding up to 1637 patients, thus justifying a new meta-analysis on this subject. Moreover, from three of the studies we could obtain also data on live birth, which would be worth investigating.

We define time-lapse as an intervention that essentially comprises undisturbed embryo culture and the consideration of the continuous visual information provided by time-lapse imaging for embryo evaluation and selection. We completed a thorough literature search for relevant randomized controlled trials and performed a meta-analysis to see whether time-laps monitoring (TLM) intervention could change clinical outcome.

Materials and methods

Sources

The investigators conducted a literature search in major electronic databases, including *SCOPUS* (the Elsevier database), *Web of Science*, *MEDLINE/PubMed*, *Cochrane Central Register of Controlled Trials (CENTRAL)*, *Latin American and Caribbean Literature on the Health Sciences database* (*LILACS*), *Excerpta Medica database (EMBASE)* and *Cumulative Index to Nursing and Allied Health Literature (CINAHL)* in January 2016 and repeated the search in February 2017 to double-check and augment the original one.

The search strategy aimed to identify prospective randomized controlled trials that randomized patients to time-lapse based embryo culture and assessment or to conventional embryo assessment in IVF cycles. The time period covered in the search was publications up to February 27, 2017. The following keywords for title, abstract and keywords were used to identify relevant studies: 'embryo' and 'time-lapse'. The results were further screened by using the terms 'RCT' or 'clinical trial' or 'randomized' or 'prospective' and by eliminating non-human related and non-English studies or duplicates.

Further efforts were made to identify all available studies, including searching trial registries (ClinicalTrials.gov, WHO International

Please cite this article in press as: Csaba Pribenszky, Anna-Maria Nilselid, Markus Montag, Time-lapse culture with morphokinetic embryo selection improves pregnancy and live birth chances and reduces early pregnancy loss: a meta-analysis, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.06.022