A critical appraisal of time-lapse imaging for embryo selection: where are we and where do we need to go?

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Received: 15 May 2015 / Accepted: 3 June 2015 / Published online: 1 July 2015
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Abstract

Purpose The aim of this study was to undertake a critical appraisal of the available evidence for the use of time-lapse imaging for embryo selection in clinical IVF.

Methods A literature search in PubMed, Scopus, Cochrane Central, ClinicalTrials.gov, Current Controlled Trials, and WHO International Clinical Trials Registry Platform was performed to identify randomized controlled trials that investigated the effect of time-lapse embryo selection and/or the time-lapse incubation system on ongoing pregnancy rate. We then performed a systematic review and assessed the relative risks (RRs) and 95 % confidence intervals (CIs) for ongoing pregnancy rates and the risk of bias of the eligible studies.

Results We identified four eligible randomized studies, three of which investigated the effect of both time-lapse incubation system and selection on ongoing pregnancy rate; the pooled result revealed a benefit of this intervention (relative risk (RR) 1.20; 95 % CI 1.05–1.37). However, the evidence was judged to be of low quality due to study limitations; a beneficial effect was observed in only one study deemed to be at high risk of bias. The single study assessing the effect of only the time-

lapse incubation system revealed a non-significant negative effect (RR 0.71; 95 % CI 0.49–1.03).

Conclusions The findings from this systematic review of the current evidence do not support routine use of time-lapse technology in clinical IVF. We therefore believe that the use of time-lapse imaging for embryo selection should remain experimental and that couples should not be subject to a surcharge for having their embryos cultured in a time-lapse imaging system. Future studies evaluating this technology in well-designed trials should be performed.

Keywords Time-lapse · IVF · ICSI · Embryo · Embryo selection

Background

The technology of in vitro embryo culture has improved significantly in recent years [1]. New culture media and incubators have been developed which enable us to grow embryos routinely to the blastocyst stage [2]. However, progress has been much slower regarding the development of reliable methods for the evaluation and assessment of embryo developmental competency. Despite intensive investigation in the realms of genomics, proteomics, and metabolomics, embryologists routinely still depend on daily static assessments in which standard variables include developmental rate based on cell count on days 2/3, or extent of blastulation on days 5/6, and morphological features such as fragmentation and degree of symmetry in cleavage stage embryos, or quality of the inner cell mass or trophectoderm in blastocysts [3]. Unfortunately, despite a plethora of published studies, technological developments for assessing embryo competence have been modest and have not yet resulted in the desired increase in implantation and pregnancy rates [4, 5].

Capsule A critical appraisal of the current evidence for using time-lapse imaging in clinical IVF.

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Time-lapse analysis was first used more than three decades ago for the study of the developmental progression of bovine embryos *in vitro* [6, 7]. Recent interest in this technology for assessment of clinical embryos was engendered following numerous studies investigating the potential benefit of multi-day scoring of human embryos for improved selection of the most robust embryo(s) for transfer [8]. Despite conflicting findings, it is reasonable to assume that compared with static observations, images captured more frequently will provide substantially more information regarding the association between morphological development and embryo viability, and that a more integrated appraisal of overall developmental kinetics will be acquired.

It is against this background that time-lapse technology has been introduced into the clinical IVF laboratory. Indeed, programs are purchasing these machines, and some are accepting them “on loan” from companies and then charging patients to have their embryos imaged, even before robust data prove efficacy [9]. It is because our field has previously introduced technologies before adequate prospective data support their use [reviewed by 5], that we feel that this article is a necessary and timely contribution. Although a comprehensive and critical assessment of the time-lapse imaging literature was recently published [10], no randomized control trial (RCT) data were available at that time. Here, we present a systematic review of the RCTs now available.

Available time-lapse systems and potential benefits

There are three available time-lapse imaging systems currently used in the clinical embryology laboratory (Primo Vision, EmbryoScope, and Eeva). They all require the use of a digital inverted microscope that acquires images of the embryos at preset intervals which are then integrated to create videos. The EmbryoScope is a compact, self-contained incubator with a built-in camera, while the Eeva and Primo Vision systems comprise a camera that is placed in a traditional chamber incubator. Each of the three systems uses a different light source and differs in the way the embryos are brought into the field of view (no movement of the culture dish vs. constant movement of the dish holding the embryos). The EmbryoScope and Primo Vision systems use bright field technology that allows the assessment of both kinetic parameters and morphology, while the dark field technology used with Eeva allows the assessment of kinetic parameters but provides more limited information on morphology. Although all systems use an oil overlay, they also differ in the way the embryos are cultured: the Eeva dish and the microwell group culture dish for Primo Vision provide “group” culture, in which 12 micro-wells (Eeva) and 9–16 wells (Primo Vision) share a common 50–120 μ l volume of medium. In contrast, the EmbryoScope provides an individual culture set-up, in which the culture dish has 12 unique wells, each holding 20–25 μ l of medium.

What benefits might we expect from time-lapse technology? There are at least two. The first is that the embryos are kept in a less disturbed environment during culture as they are not exposed to changes in gas composition, pH or temperature shifts, or to the movements that accompany daily embryo evaluation under standard conditions, except when changing the culture medium [9]. The second potential benefit relates to the additional developmental kinetic and phenotypic markers that can be acquired as compared with standard evaluation at distinct time-points; it is also known that human embryos do not continuously display morphologic features that are currently used during standard, static morphological grading such as, for example, fragmentation [9].

The timing of key parameters from time-lapse monitoring for predictions of blastocyst formation [11–13] aneuploidy, [14, 15], and, in some cases, implantation [16–18] have been investigated. Various models based on specific developmental milestones and phenotypes have been built [9]. Several of these retrospective studies have shown that the use of certain morphokinetic markers improves prediction of blastocyst formation and embryo selection; higher implantation and pregnancy rates have been reported which, in turn, has propelled many clinical IVF laboratories to acquire time-lapse systems [9]. However, the innate differences among the imaging systems make it difficult to compare the findings of studies using the different technologies. In addition, interpretation of results is further complicated when different oxygen tensions have been used (e.g., 5 % O₂ in the time-lapse imaging system vs. atmospheric O₂ in the control) as some studies have shown improvement in embryo quality and implantation rates when using low O₂ concentration [19–21].

A systematic review of available RCTs

We have performed a systematic review searching for studies in PubMed, Scopus, Cochrane Central, ClinicalTrials.gov, Current Controlled Trials, and WHO International Clinical Trials Registry Platform. Institutional Review Board approval was not sought for this work because this is a review of previously published studies. We considered eligible studies that investigated the effect of the following:

- A) *Both the time-lapse incubation system and time-lapse embryo selection*: time-lapse incubator+time-lapse embryo selection vs. standard incubator+standard embryo selection.
- B) *Only time-lapse embryo selection*: time-lapse incubator+time-lapse embryo selection vs. time-lapse incubator+standard embryo selection.
- C) *Only the time-lapse incubation system*: time-lapse incubator+standard embryo selection vs. standard incubator+standard embryo selection.

We identified four published studies, the main characteristics of which and associated risks of bias assessment are reported in Table 1. Three studies investigated the effect of both the time-lapse incubation system and selection [22–24], while one study investigated the effect of only the time-lapse incubation system, without use of imaging information for embryo selection [25]; we did not identify any published study investigating the effect of only time-lapse embryo selection. Of note, a strength of each of the four studies included in our systematic review was that the same oxygen tension was used for both the time-lapse and control groups: 5 % O₂ [22, 23]; and atmospheric O₂ [24, 25].

The most important reproductive outcome reported by all four studies was ongoing pregnancy, and the results of all four studies regarding ongoing pregnancy rate (per randomized woman) are reported in the forest plot (Fig. 1). The pooled result considering only the three studies that investigated the effect of both the time-lapse incubation system and time-lapse selection revealed a benefit of this intervention: relative risk (RR) 1.20 and 95 % confidence interval (CI) 1.05–1.37 (Fig. 1). In other words, considering the ongoing pregnancy rate of 43 % in women using standard embryo culture and selection, this rate would be in the range of 45 % to 58 % when using time-lapse embryo imaging and selection, indicating that between 6 and 46 women would need to be treated to achieve one additional ongoing pregnancy.

However, this estimate should be interpreted with great caution because it was judged to be of low quality after applying the recommendations by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group [26]. The quality of the evidence was downgraded two levels because of study limitations, since the observed benefit is mainly based on the results from one study [24] judged to be at a high risk of bias for several reasons: for example, approximately 30 women who were originally randomized to the conventional incubator group were excluded because they wished to have their embryos imaged, and although the authors defined ongoing pregnancy as that confirmed at 16–18 weeks' gestation in the trial registration, in the manuscript they considered all pregnancies confirmed by ultrasound in week 12 as ongoing pregnancy. While there is probably little clinically meaningful difference between an ongoing pregnancy rate in week 12 vs. at 16–18 weeks, this reporting discrepancy was, nevertheless, considered as a potential selective reporting bias. Therefore, the most cautious interpretation of available evidence is that uncertainty remains regarding the effect of this intervention on ongoing pregnancy rate.

The one study assessing the effect of only the time-lapse incubation system [25] revealed a non-significant negative effect of this intervention: considering an ongoing pregnancy rate of 28 % in the control group, the estimated ongoing pregnancy in the time-lapse embryo incubation group (also

achieved following standard embryo selection) is in the range of 14 % to 29 % (RR, 0.71; 95 % CI, 0.49–1.03; Fig. 1). This evidence was judged to be of moderate quality, being downgraded one level because of imprecision.

Additionally, we identified three more registered ongoing RCTs: NCT02246309 estimated to be completed in January, 2015; NCT02081859 estimated to be completed in December, 2015; and NCT02218255 estimated to be completed in March, 2016. We hope that future systematic reviews including these studies and potentially others will be able to provide more answers about the effect of time-lapse embryo incubation and selection on reproductive outcomes.

Limitations of existing studies

Despite the increasing number of studies reporting algorithms and models that may assist in selecting the most viable embryos in a cohort, it is likely that timing of development is primarily determined by embryo health, although other variables such as culture conditions, use of ICSI, and type of ovarian stimulation protocol, as well as intrinsic patient characteristics, could also play a role. In addition, there is no universally accepted nomenclature for time-lapse kinetic/morphologic features, which thus limits one's ability to compare the results among studies: a standard nomenclature, as suggested by Kaser and Racowsky [10], would go a long way to ensuring that different research groups are referring to the same event when a certain parameter is being evaluated. It is also important to develop and validate scoring systems that rely on morphologic as well as kinetic features [27] in order to utilize the most benefit offered by the time-lapse systems [28]. Furthermore, some studies rely on kinetic markers only for embryo selection and do not take morphology into account, while others include both. The day of embryo transfer also differs among, and even within, some studies despite our knowledge that cleavage stage and blastocyst stage transfers result in different outcomes [29]. Indeed, there are currently no published data comparing implantation rates following day 3 transfer using time-lapse parameters with those from day 5–6 transfer using standard morphology; this important knowledge gap would address whether the use of early time-lapse markers before day 3 enables equivalent embryo selection (or de-selection) as extended culture to days 5/6. Finally, a short, 2-day embryo culture, such as that performed in one of the included studies [25], is less likely to show the full benefit of an undisturbed embryo culture as the handling of the embryos outside the incubator will not be very different between time-lapse and standard technologies; however, the results from such studies are particularly important for those IVF centers that are considering use of time-lapse to perform embryo transfer in the early cleavage stage.

Table 1 Characteristics of the available randomized controlled trials

Comparison	Time-lapse incubator+time-lapse selection vs. standard incubator+standard selection	Time-lapse incubator+standard selection vs. standard incubator+standard selection		
Study	Kahraman et al., 2013	Rubio et al. 2014	Kovacs et al. 2013	Park et al. 2014
Country	Turkey	Spain	Hungary	Sweden
Study design	Parallel design	Parallel design	Parallel design	Parallel design
Period of enrollment	Dec 2011 to Jun 2012	Feb 2012 to Jul 2013	Jan 2012 (ongoing)	May 2010 to Feb 2014
Eligibility criteria	Age 20-35 years, BMI <28 kg/m ² , ≥8 oocytes retrieved, first or second treatment cycle, no recurrent spontaneous abortions, no severe endometriosis, no PCOS, no hydrosalpinx, no uterine pathology, no severe male factor or very severe morphological sperm defects	Age 20-38 years, first or second ICSI cycle, BMI 18-25 kg/m ² , none of the following: severe male factor, hydrosalpinx, uterine diseases on ultrasound or hysteroscopy, endocrinopathies, thrombophilia, recurrent pregnancy losses, endometriosis, or patients receiving concomitant medication that might interfere with the results of the study	Age 18-36 years, BMI 18-30 kg/m ² , regular menstrual cycles (25-35 days), FSH <10 mIU/L, intact uterus, less than 2 previous failed IVF cycles, no PCOS, sperm not obtained by surgical extraction, no chromosome abnormality, no hydrosalpinx, no stage III/IV endometriosis	Age ≤40 years, undergoing first IVF cycle using ICSI and at least one oocyte was retrieved, and not using egg donation
Exclusion criteria ^a	Unexpected poor embryo development, total freezing due to increased OHSS risk	None	Less than 3 good quality embryos on day 3	None
Interventions	EmbryoScope time-lapse incubator vs. standard monitoring	EmbryoScope time-lapse incubator vs. standard monitoring	Primo Vision time-lapse system vs. standard monitoring	EmbryoScope time-lapse incubator vs. standard monitoring
O ₂ and CO ₂ in the incubator	5 % O ₂ and 6 % CO ₂ in both groups	Atmospheric O ₂ and 5.5 % CO ₂ in both groups	5 % O ₂ and 5-6 % CO ₂ in both groups	Atmospheric O ₂ and 6.0 % CO ₂ in both groups
Cleavage or blastocyst transfer	Blastocyst (day-5)	Cleavage (day-3) and Blastocyst (day-5)	Blastocyst (day-5)	Cleavage (day-2)
Age (years) ^b	28.5±3.32 vs. 28.5±3.72	30.4±5.5 vs. 30.0±5.5	NR	31.8±4.3 vs. 31.8±4.1
BMI (kg/m ²) ^b	23.92±3.79 vs. 23.92±4.42	23.2±3.7 vs. 23.0±2.8	NR	24.4±3.9 vs. 24.3±4.0
Number of oocytes retrieved ^b	13.53±3.45 vs. 14.67±7.07	8.0±2.7 vs. 8.1±3.0	NR	9.5±5.5 vs. 9.5±4.5
Implantation rate (%)	NR	348/775 (44.9 %) vs. 299/699 (37.1 %)	NR	63/226 (27.9 %) vs. 37/117 (31.6 %)
IVF/ICSI	ICSI	ICSI	NR	ICSI
Risk of bias assessment				
Selection bias	Low risk	High risk; the randomization table was handled by the embryologist.	High risk; by using blocks of two, researchers were aware of the allocation group of every even participant before its enrollment.	Low risk
Performance/detection bias	Low risk	Low risk	Low risk	Low risk
Attrition bias	Low risk	High risk; The authors stated in a webinar (https://www.youtube.com/watch?v=y26XhmrALbg) that a proportion of participants in the control group was excluded after randomization	Low risk	Low risk
Selective reporting ^c	Low risk	High risk; The authors did not report clinical pregnancy and the primary outcome (ongoing pregnancy) was not assessed as reported in the trial register (NCT01549262) ^c	Low risk	Low risk
Other bias	Low risk	High risk; IVI was a part owner of and had a long-standing financial interest with Fertiltech which only recently was sold. Fertiltech is the firm that manufactures EmbryoScope	Low risk	Low risk

NR not reported, BMI body mass index, IVF in vitro fertilization, ICSI intracytoplasmic sperm injection, PCOS polycystic ovary syndrome, FSH follicle-stimulating hormone

^a Although the original reports excluded these participants from the final analysis, we were able to analyze all included women respecting the ITT principle

^b Time-lapse vs. standard monitoring, respectively (mean±SD)

^c In the study, ongoing pregnancy was defined as the presence of gestational sacs with fetal heartbeat detected by transvaginal ultrasound examination in 12 weeks, while in the trial register it is reported that this primary outcome would be confirmed 16–18 weeks after embryo transfer

Fig. 1 Forest plot of ongoing pregnancy per randomized woman in the studies comparing time-lapse vs. standard incubator. Risk of bias legend: *A* selection bias, *B* performance bias, *C* detection bias, *D* attrition bias, *E* reporting bias, *F* other bias

Suggestions for future studies

An ideal study would be designed to investigate the effect of both the time-lapse embryo incubation system and the use of imaging data for the selection of transferred embryos. Thus, we believe that researchers should consider a parallel group RCT with the following two arms:

- Time-lapse incubation system and embryo selection with time-lapse markers for embryo selection
- Standard incubation system and embryo selection with standard morphology criteria for embryo selection

However, we feel that there would also be value in investigating possible independent effects of the time-lapse incubation system and time-lapse embryo selection. Therefore, the above design should be expanded to include the following arm:

- Time-lapse incubation system but with standard embryo selection

Therefore, when comparing groups A and B, the effect of both time-lapse embryo incubation system and selection would be investigated; when comparing groups A and C, the effect of only time-lapse embryo selection would be investigated; and when comparing groups B and C, the effect of only time-lapse incubation system would be investigated.

One should also consider including a sufficient number of subjects (at least 300 women per group) while avoiding the most important sources of bias. The study should ideally be a multi-center trial in which all participating centers use the

same culture conditions, day of transfer, and standardized embryo morphological grading and selection.

Conclusions

In summary, time-lapse embryo imaging is a promising technique with several potential advantages; however, current evidence from available randomized controlled trials is still of very low quality, and further studies are warranted. Our opinion is similar to some recently published systematic reviews and opinions [9, 30, 31]: we believe that the available evidence is insufficient to support the use of time-lapse compared with conventional evaluation for embryo selection. Future trials examining time-lapse are necessary and should be encouraged. Based on the available evidence, we believe that embryo selection based on time-lapse imaging should remain an experimental strategy and that couples should not be subject to a surcharge for their embryos to be cultured in a time-lapse imaging system. The ART community has previously depended on retrospective data for the introduction of new technologies (such as preimplantation genetic screening with FISH, metabolomics screening of spent media, and IMSI) only to find a lack of efficacy (and, indeed in some cases, a possible harm) after validation with prospective studies. In the words of Albertini, “the proof of the pudding” for this technology has yet to be established [32].

We hope that well-designed RCTs will be undertaken improving the quality of the evidence regarding the efficacy and safety of time-lapse imaging for embryo selection as well as some cost analyses and evaluation of the acceptability and

feasibility of this intervention; this would permit patients and health care providers to make evidence-based decisions regarding use of time-lapse for embryo culture and selection.

Conflict of interest The authors declare that they have no conflict of interest.

Declaration of authors' roles All three authors participated equally in the content, editing, and finalizing of the manuscript.

Support None.

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