Choosing the best embryo by time lapse versus standard morphology

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Within the past few years the morphological evaluation of in vitro fertilized embryos has been extended to include continuous surveillance, enabled by the introduction of time-lapse incubators developed specifically for IVF treatment. As a result time-lapse monitoring has been implemented in many clinics worldwide. The proposed benefits compared with culture in a standard incubator and fixed time-point evaluation are uninterrupted culture, a flexible workflow in the laboratory, and improved embryo selection. The latter is based on the reasonable assumption that more frequent observations will provide substantially more information on the relationship between development, timing, and embryo viability. Several retrospective studies have confirmed a relationship between time-lapse parameters and embryo viability evaluated by developmental competence, aneuploidy, and clinical pregnancy. Furthermore a much anticipated randomized study has shown improved pregnancy rates (PRs) after culture in a time-lapse incubator combined with selection using a hierarchical time-lapse selection model. At present this is the only randomized study on possible benefits of time lapse in human embryology. Strict evidence may still seem too weak to introduce time lapse in routine clinical setting. This aim of this review is therefore to perform a balanced discussion of the evidence for time-lapse monitoring. (Fertil Steril® 2015;103:323–32. ©2015 by American Society for Reproductive Medicine.)

Key Words: Embryo selection, time-lapse monitoring, ART, human

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Reliable selection of embryos with the highest developmental competence is a prerequisite for successful IVF treatment. Current embryo assessment is based on development rate and morphological features as evaluated under a microscope at certain, distinct time-points. Although embryo grading schemes vary between fertility clinics, most laboratories grade the cleavage stage embryo on the degree of fragmentation, presence and number of nuclei and size, number and symmetry of blastomeres per embryo (1–6). Blastocysts are evaluated with regard to the expansion of the blastocoel and the number and cohesiveness of cells in the inner cell mass (ICM) and trophectoderm (TE) (7). Standardized timing of observations is critical (8). As morphology and developmental competence is not firmly correlated, morphological assessment has limited predictive value in the identification of the most viable embryos (8). This might be explained to some extent by the dependence on timing of the observations (9) and the high degree of interobserver and intraobserver variability (10–12). Models based on sequential early embryo parameters in combination with specific time intervals of inspection have been shown to improve selection and implantation rates (13–15). Therefore it is reasonable to assume that more frequent observations will provide substantially more information on the relationship between development and timing and thereafter embryo viability. This assumption forms the theoretical basis of the potential benefits of time-lapse monitoring (TLM) in human IVF embryo selection. An increasing number of studies report a correlation between timing of key events and implantation potential or surrogate end points such as aneuploidy and development potential. Yet, timing of development depends presumably on both culture conditions, treatment and patient populations, which might complicate the uncritical transferability of any model from one setting to another (16–22). The aim of this review is to discuss the evidence regarding time lapse as a selection method and the role of TLM in the future assisted reproductive technology (ART) laboratory.

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EMBRYO SELECTION USING TIME LAPSE

An increasing number of studies suggest that timing of development differs between embryos with full developmental potential and those with no or limited potential. Based mostly on observational studies, several putative markers of viability have been suggested. Time-lapse variables identified in the literature as positive or negative predictors of development, aneuploidy, or pregnancy are summarized in Tables 1–3. The end points vary greatly and the embryo populations are heterogeneous, which complicate comparisons between the studies. Only a few of the studies have adjusted for, or evaluated, known or potential confounders. Although almost all of the various parameters that are possible to measure have been proposed as candidate markers of viability, only a few clinically applicable models have been proposed (23–25). The end points for prediction models can, in principle, be divided into three categories: prediction of implantation, prediction of aneuploidy, and prediction of developmental competence, mainly blastocyst development. Figure 1 lists examples of time intervals identified as optimal for these three end points.

PREDICTION OF IMPLANTATION POTENTIAL

The first published model aimed at predicting implantation potential was a hierarchical ranking model that used morphological observations and kinetic timings (24). Embryos originated from infertile patients and oocyte donors. The study (24) reported combined baseline data for 522 embryos as a result of intracytoplasmic sperm injection (ICSI) transferred to 247 patients, but to correlate the time-lapse observations to clinical outcome the analysis was restricted to include embryos with known implantation. The model was therefore based on 247 embryos from an unknown number of cycles, consisting of a mixture of transfer of single and multiple embryos. No baseline data were made available that allowed for an evaluation of the distribution of potential confounders for the implanted and nonimplanted group of the embryos and patients included in the model. Morphokinetic data were obtained using the EmbryoScope and the timing of cellular divisions up to five cells were recorded. Median values showed no significant statistical difference between the implanted and nonimplanted embryos, except for four-cell stage (t4)–t3 (s2). The group of implanted embryos displayed a more narrow distribution of timings with a smaller variance compared with nonimplanted embryos, which encouraged the investigators to define optimal time intervals based on quartiles for all annotated parameters, followed by a logistic regression analysis to identify the most predictive parameters. The result was a hierarchical model, where morphologically poor embryos were discarded after an initial screening, followed by a sequential application of the identified criteria. The

TABLE 1

Studies evaluating blastocyst development.

Study	No. of embryos	End point(s)	Predictive parameters	Source of embryos
Payne et al., 1997 (74)	30	Day 3 quality (transfer/freeze or not)	No difference in mean timings. Difference in variation in timing of PB extrusion and PN appearance and abuttal	
Lemmen et al., 2008 (71)	102	Blastomere number on day 2. Images/5 min	First division (t2), PN breakdown	IVF/ICSI
Wong et al., 2010 (39)	100	Blastocyst/nonblastocysts day 5/6	Duration of the first cytokinesis, duration of the 2- and 3-cell stage	Frozen/thawed surplus embryos IVF
Hashimoto et al., 2012 (36)	80	Blastocyst score 96 and 120 h after fertilization High/low score	Timing of the 7/8-cell stage. Duration of 3-cell stage and third cleavage (t8-t5)	Frozen/thawed surplus embryos IVF and ICSI, 5% O_2
Cruz et al., 2012 (34)	834	Blastocyst score on day 5/6 High/low quality	Timing of 4-cell stage (t4), duration of the 3-cell stage (s2), morula, uneven blastomeres, direct cleavage to 3 cells	Donor oocytes, 20% O_2, ICSI Nonselected
Dal Canto et al., 2012 (35)	459	Expandend/nonexpanded blastocysts on day 5	All divisions and durations of cellular stages except first division (t2)	Surplus, nonselected IVF/ICSI patients 5% O_2
Hlinka et al., 2012 (37)	180	Blastocyst development	Time intervals for cleavage cycles and interphases (timely/untimely) Low positive but high negative predictive value	ICSI, 20% O_2, nonselected group
Conaghan et al., 2013 (23)	1,233	Blastocyst quality (freeze/transfer)	Duration of 2- and 3- cell stage	Donor/infertile AFC $\geq$12, FSH $<$10 IU/mL, $\geq$8 2PN oocytes
Kirkegaard et al., 2013 (38)	571	High quality blastocyst	Duration of the first cytokinesis, 3-cell stage, direct cleavage	Prospective cohort (maternal age $<$38 y, $>$7 oocytes), ICSI, 5% O_2

Note: AFC = antral follicle; ICSI = intracytoplasmic sperm injection; PB = polar body; PN = pronuclei.

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