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REVIEW

Effect of embryo selection based morphokinetics on IVF/ICSI outcomes: evidence from a systematic review and meta-analysis of randomized controlled trials

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Abstract

Purpose Debate exists for the optimal tool to select embryos for transfer in assisted reproductive technology (ART). Time-lapse monitoring (TLM) is a noninvasive tool suggested where each embryo can be captured every 5–20 min. Given the inconsistency in the existing studies, we conducted this meta-analysis of RCTs to summarize the evidence available concerning the predictive ability of morphokinetics compared with the routine assessment of embryo development in ART.

Methods The primary databases MEDLINE, EMBASE, Cochrane, NHS, WHO, and Other Non-Indexed Citations were consulted for RCTs that have been published until November 2018, with no language restriction.

Results and conclusion Our review includes 6 RCTs ($n=2057$ patients). The data showed an improvement (~9%) in live birth TLM (OR 1.43; 95% CI 1.10–1.85; $P=0.007$), with low-quality evidence. There was no evidence of a significant difference between both groups concerning ongoing pregnancy, clinical pregnancy and implantation rates. The data further showed that morphokinetics is associated with decreased early pregnancy loss rate. These estimates must be interpreted with caution owing to the statistical and clinical heterogeneities and the consequent difficulty in drawing any meaningful conclusion.

Keywords Time-lapse monitoring · Morphokinetics · Embryo assessment

Introduction

Embryo assessment and selection is still a challenge to increase the current unsatisfactory success rates of in vitro fertilization (IVF), with a live-birth rate to be only around 32% for the first IVF cycle [1]. Around the globe, most IVF clinics assess the developing embryo using conventional morphological selection (CS), microscopic look on a daily base, to choose the embryo(s) of high livelihood for transfer [2]. When evaluating embryos outside the incubator, as in traditional culture incubators, much critical information regarding the cumulative behavior of the in vitro embryonic growth is missed. Moreover, it disrupts the stability of the culture environment. Over the last few years, time-lapse monitoring (TLM) technology has been developed to overcome some of these problems. TLM is provided with a microscope with exceptional optics and a capture system. An image of each embryo is taken every 5–20 min intervals and then kept in a recording system. This provides continuous observation and monitoring of embryo morphokinetic details while leaving the embryos in a "sealed" environment where temperature, pH and humidity are undisturbed. Despite the described advantages of TLM, the periodic exposure to light during the digital imaging process may negatively impact embryo development and the subsequent outcomes [3–5].

Whether TLM is attributed to higher IVF success, remains to be further validated. Time-lapse morphokinetic

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parameters neither influence nor improve the clinical outcomes but may predict or correlate with them. Some studies reported that using TLM is associated with significantly higher clinical pregnancy rate compared with conventional incubators and standard grading system of embryo morphology [6–8]. On the other hand, other studies reported that embryo development, clinical pregnancy, and implantation rates are similar between the two culture and grading systems [9–11].

The effect of time-lapse selection remains inconclusive to be introduced in a routine clinical setting. The current systematic review and meta-analysis aim to review and critically analyze the IVF outcome when comparing the use of morphokinetic details versus the conventional morphological assessment in embryo selection for embryo transfer according to the latest evidence.

Methods

Study design

We conducted a systematic review and meta-analysis of all RCTs investigating the effect of embryo assessment using morphokinetics on ART outcomes. The review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. Study protocol can be assessed at PROSPERO International prospective register of systematic reviews (registration number CRD42019118779). As this study was a systematic review and meta-analysis of published data, formal ethics approval, and informed consent were not required.

Eligibility criteria and search strategy

Criteria for RCTs inclusion/exclusion were established before the initiation of the literature search. The inclusion criteria were as follows: (1) RCTs, whether published or not; (2) RCTs that compare TLM to conventional embryonic grading systems, regardless of embryo stage at transfer (cleavage or blastocyst stage); (3) RCTs that track clinical and ongoing pregnancies; and (4) RCTs that have been published until November 2018, with no language restriction. The exclusion criteria were as follows: (1) nonrandomized studies (quasi or pseudo-randomized trials); (2) randomized studies that used sibling-oocyte or embryo-split; and (3) overlapped or duplicated trials.

The following electronic databases, trial registers, and websites were searched: MEDLINE® In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Central Register of Controlled Trials, the Medical Research Council's Clinical Trials Register, the NHS Centre for Reviews and Dissemination databases, Web of Science, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) portal (www.apps.who.int/trialsearch/), and ClinicalTrials.gov (clinicaltrials.gov/). A search strategy was carried out based on the following keywords and/or Medical Subject Heading (MeSH) terminology: time-lapse, morphokinetics, embryo dynamics, embryo selection, embryoScope, built-in microscope incubator, and time-lapse incubators cinematography, with no language restriction.

Reference lists of primary and review articles were hand searched, and additional articles or unpublished materials that were not captured in the electronic searches were obtained by communicating with trial conductors. Relevant journals and abstracts of conference proceeding of the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) were also hand searched. Studies' investigators were contacted if any additional information needed about their studies.

Selection strategy and study quality assessment

Y.M. and A.S. searched all titles and abstracts, and examined the full texts of all potentially eligible studies, independently, for compliance to inclusion criteria. Disagreement about any eligible study was solved by discussion between reviewers. The selection process was as per PRISMA flow chart.

Data extraction and management

Y.M and A.S independently extracted the data using a data form designed by and piloted the authors on two independent occasions. In case of disagreement, a consensus was reached after discussion. Data retrieval included the study characteristics, methods, participants, interventions, outcomes, adverse events, and finally, any funding source for the studies. Both reviewers counterchecked these extracted data repeatedly.

Risk of bias assessment

Two reviewers (Y.M and A.S) independently evaluated the risk of bias for each eligible RCT using the Cochrane Collaboration Tool for Assessing Risk of Bias [13]. Discrepancies were resolved by discussion with a third investigator. Biases in the following items were evaluated: (1) generation of the allocation sequence; (2) allocation of concealment; (3) blinding including detection and performance, (4) blinding of participants and personnel to outcome assessment; (5) attrition bias for incomplete outcome data; (6) reporting bias in the form of selective outcome reporting; and (7) others. Risks of biases for each RCT were classified as low risk, a high risk, or unclear risk.

Statistical analysis

Statistical analyses were performed using Review Manager version 5.2 (Cochrane Collaboration, Software Update). Dichotomous variables were analyzed using the odds ratio (OR) and 95% confidence interval (95% CI). The significance level was set at $P < .05$. Assessing the heterogeneity was by the I^2 statistic and classified as low (< 30%), moderate (30–50%) or high (> 50%).

Quality of evidence

Validity was assessed based on the reported characteristics, including the method for randomization, the presence of a power calculation, concealments, the use of intention-to-treat analysis, the presence of any potential funding source, and the presence or absence of blinding. Missing data were obtained from the authors when possible.

The evidence for the primary outcome of the meta-analysis was independently assessed by Y.M. and A.S. using GRADE (Grading of Recommendations Assessment Development and Evaluation Working Group) [14] methodology. The GRADE software is available at https://gradepro.org. The GRADE criteria allow the evaluation of certainty of evidence in terms of study design, risk of bias, indirectness, inconsistency, imprecision, large effect size, plausible confounding, dose–response gradient, and publication bias. Disagreements between reviewers were resolved by discussion and adjudication of a third reviewer (M.F.).

Outcome measures

The primary outcome was the live birth per randomized patient, defined as delivery of viable infant ≥ 32 weeks of gestation. Secondary outcomes included: (1) clinical pregnancy; (2) ongoing pregnancy; (3) implantation; and (4) early pregnancy loss (positive β-hCG-positive cycles that did not result in an ongoing pregnancy) per randomized patient.

Results

Study selection

On December 1, 2018, we searched the web, found and retrieved a total of 277 records, where 265 were from database searches and 12 from the hand searching. Of which, 8 were duplicates, and 245 records did not meet the eligibility criteria. We further examined 21 records for eligibility. Fifteen studies (from seventeen records) were excluded for the following reasons: (1) three were ongoing, recruiting participants without preliminary results [15–17]; (2) one was completed with no publication, and the authors did not answer our e-mails [18]; (3) two did not use morphokinetics assessed by time-lapse for embryo selection before embryo transfer [19, 20]; (4) seven studies randomized patient's oocytes and embryos which could interfere with clinical outcome measures [9, 21–26]; (5) one compared two different culture systems rather than assessment criteria [27]; and (6) one study used pseudo-randomization schemes (medical record number) that is why we considered it non randomized trial [28]. In the end, we only had six RCTs (from 7 records) that address the practice of morphokinetics compared with the standard morphology [29–34] (Fig. 1).

Included studies

Main characteristics and quality features of the six included trials are presented in Table 1.

Assessment of the risk of study bias

Selection bias

All of the studies used an adequate method of random sequence generation. However, Study of Rubio et al. [32] was judged with a high risk of selection bias as some of the randomized patients were able to request the intervention, and in some cases, this request was granted. Moreover, the allocation concealment in Kovacs et al. [31] was performed by the principal investigator who was involved in the study, so it was judged to be at high risk of selection bias. The remaining studies [29, 30, 33, 34] were considered at low risk of bias for this domain.

Performance bias

Two studies were considered at high risk of performance bias because the study participants and clinic staff were aware of concealment [31, 34]. Another two studies were considered to have a high risk of bias due to the inability to blind the embryologists to the allocation [32, 33]. The remaining studies [29, 30] were judged to have a low risk of bias.

Detection bias

The outcomes are objective and unlikely to be influenced by the person detecting them. Therefore, all studies were judged to have a low risk of bias.

Attrition bias

Two studies [31, 34] were judged to have high a risk of attrition bias because a large proportion of the randomized

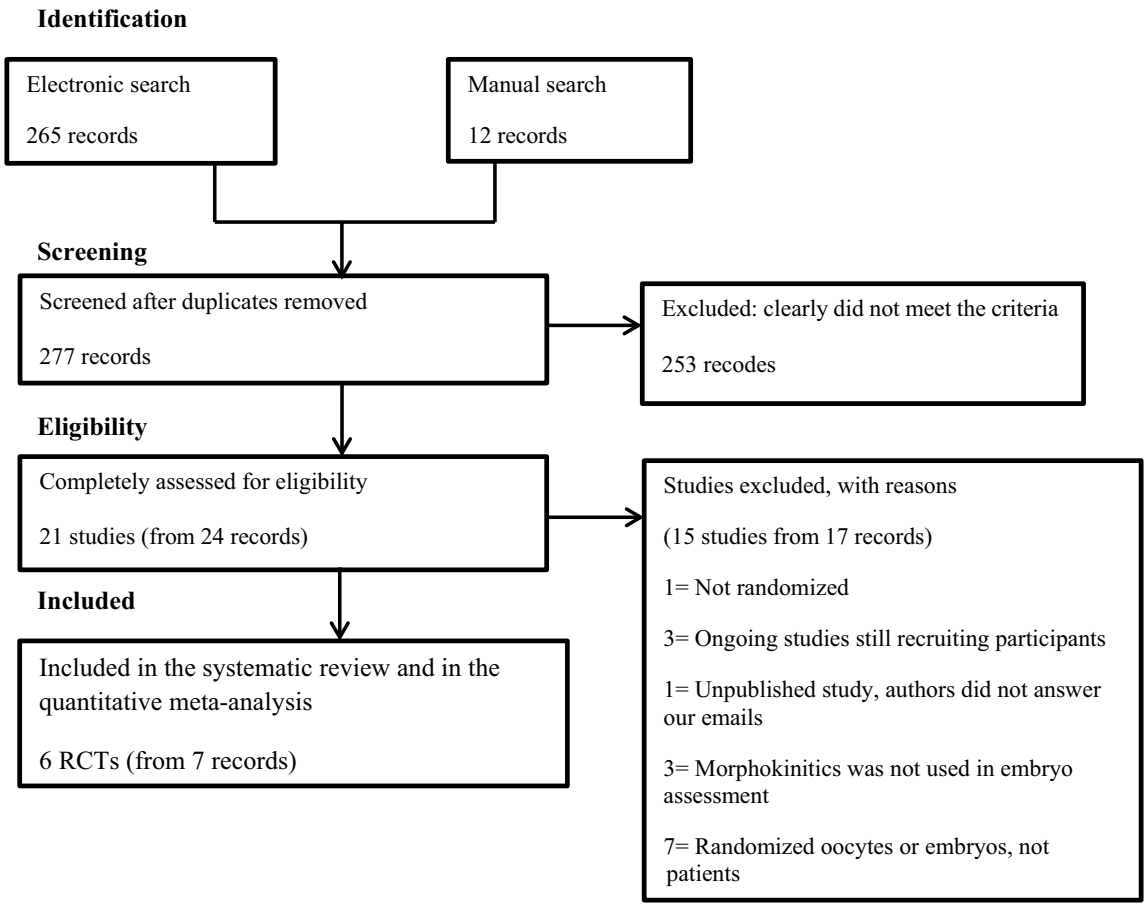


Fig. 1 Study flow diagram

couples recruited was excluded. The other studies were at low risk of attrition bias.

Reporting bias

All included studies assessed the targeted outcomes and were judged to have a low risk for reporting bias.

Other bias

Yang et al. [34] had additional source of bias, which is the variation in the day of embryo transfer (day 3 and day 5), while Kovac et al. [31] had a high risk of bias due to the non-disclosed interim reporting and analysis of results as were planned in ClinicalTrials.gov. The remaining four studies had no additional source for risk of bias was detected.

Outcome measures

Analysis of live birth rate involved 932 women with blastocyst transfer after ICSI ($n=482$ with TLM, and $n=450$ with CS) (only two studies; 30, 32), and resulted in 417 Live births ($n=236$ in TLM arm, and $n=181$ in CS arm). This corresponds to notably higher outcomes in TLM arm (OR 1.43; 95% CI 1.10–1.85; $P=0.007$) without heterogeneity among studies ($I^2=0\%$; Fig. 2a).

Five eligible RCTs evaluated the effect of morphokinetics for embryo transfer compared with the conventional assessment on ongoing pregnancy rate [30–34]. Overall, 882 ongoing pregnancies were reported out of 1757 women were randomized in the trials ($n=464$ ongoing pregnancies in the TLM group, and 418 in the CS group). There was no difference in the incidence of ongoing pregnancy between TLM and CS (control) groups ($I^2=73\%$; fixed effect OR 1.02; 95% CI 0.93–1.12; $P=0.64$; random effect OR 0.99; 95% CI 00.79–1.23; $P=0.9$). Heterogeneity was best resolved by excluding Rubio et al. [32] (Fig. 2b).

Six trials reported clinical pregnancy data (29, 30, 31, 32 33, 34), including 1201 clinical pregnancies in 2057 women. There were 621 clinical pregnancies in the TLM group and 580 in the control group. There was no difference in the rate of clinical pregnancy between TLM and CS groups ($I^2=71\%$; fixed effect: OR 1.01; 95% CI 0.85–1.21; $P=0.88$; random effect OR 1.08; 95% CI 0.73–1.60; $P=0.69$).

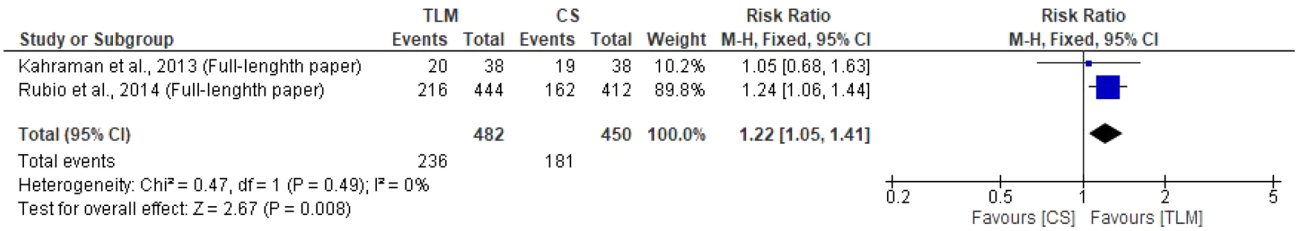
Table 1 Characteristics of included RCTs

RCTs evaluating time-lapse monitoring versus conventional assessment system (control)				
Trial	Participants	Interventions	Outcomes	Quality features
Yang et al. [28]	Design: completed, open-label, active-controlled, non-inferiority, two arms, one centre RCT Population ($n=600$): aged ≤ 36 years, with first or second fresh autologous IVF, oocytes retrieved ≥ 10, and fresh SET Exclusion: patients had underlying uterine conditions, egg donation cycles, PGD and recurrent pregnancy loss	TLM, $n=300$: predictive parameters were t5, cc2 and s2 for ET on day 3 CS, $n=300$: blastocysts were scored according to Gardner's scoring system for ET on day 5	Primary: OPR, secondary: IR, twin pregnancy, ectopic pregnancy and early miscarriage	Randomization: (1:1 ratio), online-generated blocks (www.random.org). Blindness: open label. ITT: yes. Funding: Ferring Pharmaceuticals and the Program for New Century Excellent Talents in University, China
Kaser et al. [33]	Design: pilot, open label, three arms, one centre RCT. Population ($n=163$): aged 18–40 years, autologous IVF cycle with fresh SET Exclusion: prior retrievals without clinical pregnancy > 3; egg donation, a gestational carrier, "freeze all" cycle, or zygotes < 4, PGD/PGS, or in vitro maturation; and presence of uninterrupted hydrosalpinx or intrauterine adhesions	TLM, $n=110$: 56 were randomized to TLM and day 3 ET and 54 were randomized to TLM and day 5 ET. Early TLM markers were annotated manually and embryos exhibiting abnormal cleavage (division of one cell into three cells) or direct cleavage were excluded. The Eeva™test was then applied to assign a blastocyst prediction rating of H, M or L according to durations of P2 and P3: Rating H (P2 = 9.33–11.45 h and P3 = 0–1.73 h); rating M: (if not high and P2 = 9.33–12.65 h and P3 = 0–4 h); or rating L: (if not high or medium) CS, $n=53$: incubation within the TLM incubator and day 5 ET based on conventional morphology with day 5 ET	Primary: CPR, secondary: OPR, IR	Randomization: (1:1 ratio), computer-generated, random number sequence cards enclosed in opaque, serially numbered envelopes. Blindness: Open label. ITT: yes. Funding: Progyny, Inc.
Goodman et al. [26]	Design: completed, parallel design, two arms, one centre RCT Population ($n=300$): aged 18–43 years and undergoing an autologous IVF with fresh multiple ET Exclusion: PGD, fertility preservation, did not undergo fresh transfer or patients with 1–3 zygotes	TLM, $n=150$: embryo selection for day 3 or 5 ET based on TLM score − 0.2:4; negative points: cc2 < 5 h (− 1), presence of multinucleation (− 0.5), presence of irregular division (− 0.5). and positive points: t5 45.8–57.0 HPI (+ 1), s2 0.0–0.1 h (+ 1), s3 1.4–7.0 h (+ 1), tSB < 100 HPI (+ 1) combined with morphological grade CS, $n=150$: embryo selection for day 3 or 5 ET based on conventional once-a-day morphologic criteria	Primary: CPR, secondary: fertilization, IR, and early pregnancy loss rates	Randomization: (1:1 ratio), computer-generated random number sequence. Concealed: yes. Sample size: yes. Blindness: the patients, REI physicians and staff, and sonographers were blinded. ITT: yes. funding: not reported

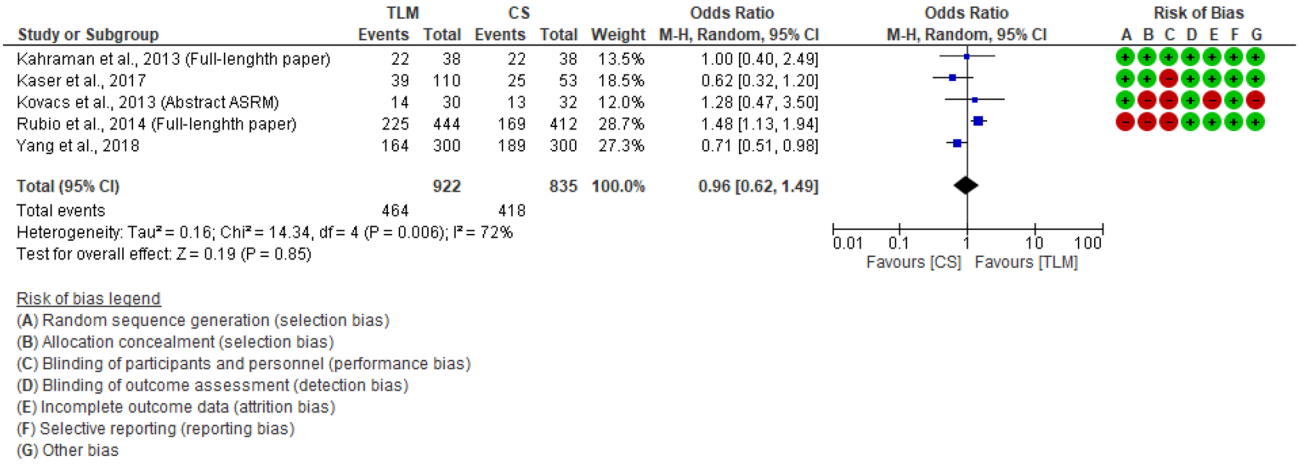
Table 1 (continued)

RCTs evaluating time-lapse monitoring versus conventional assessment system (control)				
Trial	Participants	Interventions	Outcomes	Quality features
Rubio et al. [32]	Design: completed, parallel design, two arms, two center RCT Population ($n=843$): aged < 20–38 years, BMI 18 and < 25, autologous or oocyte donation (OD), first or second ICSI cycle, fresh multiple ET Exclusion: patients with severe male factor, hydrosalpinx, uterine diseases or hysteroscopy, endocrinopathies, recurrent pregnancy losses, endometriosis, or receiving concomitant medication. For autologous treatments, low-responder patients (> 6 MII/cycle) or FSH > 12 or AMH < 1.7 pmol/L	TLM, $n=444$: embryos were selected on day 3 or 5 for ET using the multivariate morphokinetic model using morphokinitic parameters t2, t3, t4, t5, cc2 and s2 CS, $n=412$: embryos were assessed only by conventional morphologic criteria and transferred on day 3 or 5	Primary: OPR, secondary: fertilization rates, embryo development, IR, CPR and early pregnancy loss rates	Randomization: (1:1) computer-generated randomization table. Concealed: no, sample size: yes. Blindness: the gynecologist and the statistician were blinded. ITT: yes. funding: the instrumentation, disposables, and utensils used in this study were fully paid for by IVI. (A minor shareholder in UnisenseFertiliTech)
Kovacs et al. [31]	Design: parallel design, two arms, multicenteric RCT Population ($n=62$): patients eligible for fresh SET in autologous IVF	TLM, $n=30$: TLM observations (composite score based on cleavage kinetics, fragmentation, BC formation) combined with morphological scoring. Embryos were cultured till day 5 in automated time-lapse device inside traditional incubator CS, $n=32$: embryos were developed in a traditional incubator and selected for SET on day 5 using standard daily embryo monitoring	Outcomes: clinical, OPR, IR	Randomization: blocks of two, by selecting TLM or control assignments using closed, opaque envelopes. Concealed: no. Sample size: no. Blindness: single blinded (patients only). ITT: no. funding: no
Kahraman et al. [30]	Design: parallel design, two arms, one centre RCT Population ($n=64$): aged < 35 years, BMI < 28, their first or second autologous IVF, with no recurrent spontaneous abortions, ≥ 8 oocytes retrieved, fresh or frozen SET Exclusion: severe endometriosis, polycystic ovary syndrome, hydrosalpynx, uterine pathology, or severe male factor and very severe morphological sperm defects	TLM, $n=38$: morphology and hierarchical model was used using morphokinetic parameters: t2, t3, t4, t5, t6, t7, t8, t9 + , tM, tB CS, $n=38$: selection was based solely on the morphological score on day 5 according to Gardner's classification (conventional incubator)	Measured parameters: CPR, IR, OPR and miscarriage rate	Randomization: (1:1) list generated on random.org. Concealed: yes, sample size: no. Blindness: not reported. ITT: yes. Funding: not reported

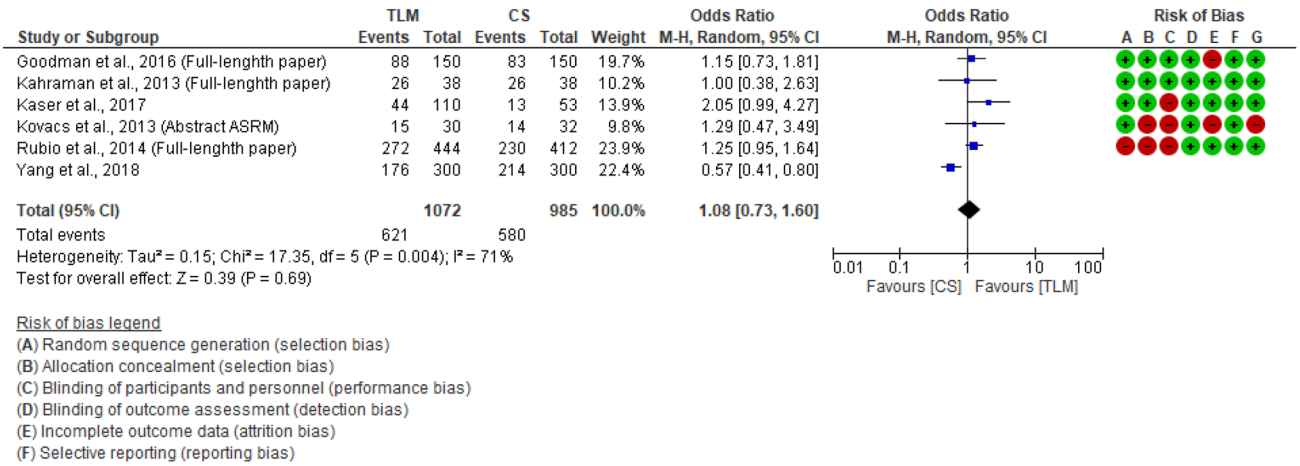
CPR clinical pregnancy rate, *ET* embryo transfer, *IR* implantation rate, *ITT* intention-to-treat, *OPR* ongoing pregnancy rate; *PGD* preimplantation genetic diagnosis, PGS preimplantation genetic screening, *SET* single embryo transfer, *t2* time of cleavage to two-blastomere embryo, *t3* time of cleavage to three blastomere embryo, *t4* time of cleavage to four-blastomere embryo, *t5* time of cleavage to five-blastomere embryo, *cc2* the second cell cycle (the duration of the two-blastomere embryo phase (t3–t2), *s2* synchrony in divisions from a two blastomere embryo to a four-blastomere embryo (t4–t3), *tM* time of morula, *tB* time of blastocyst



Livebirth

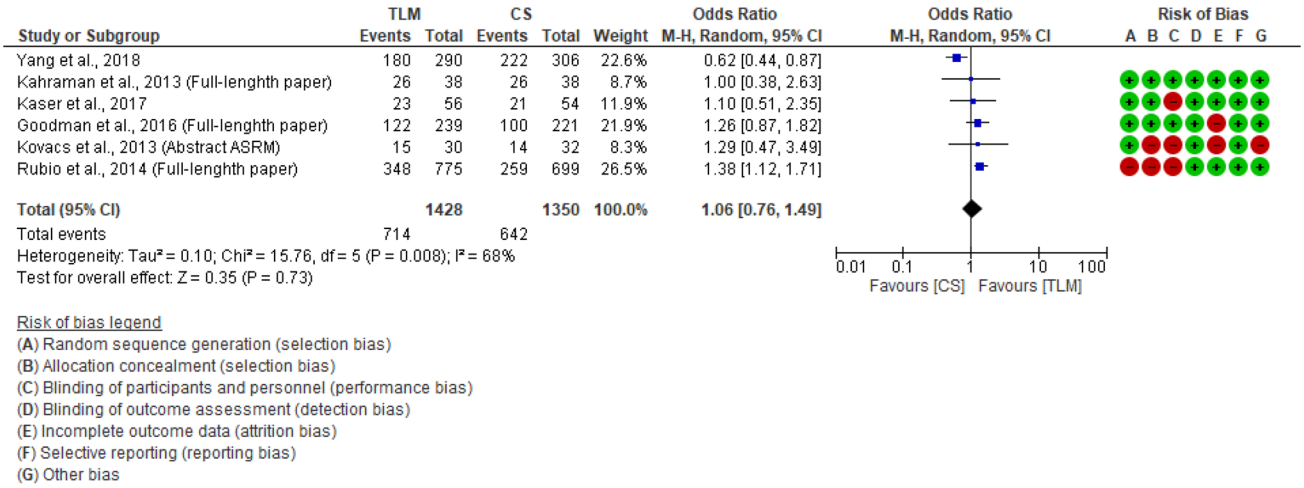


Ongoing pregnancy

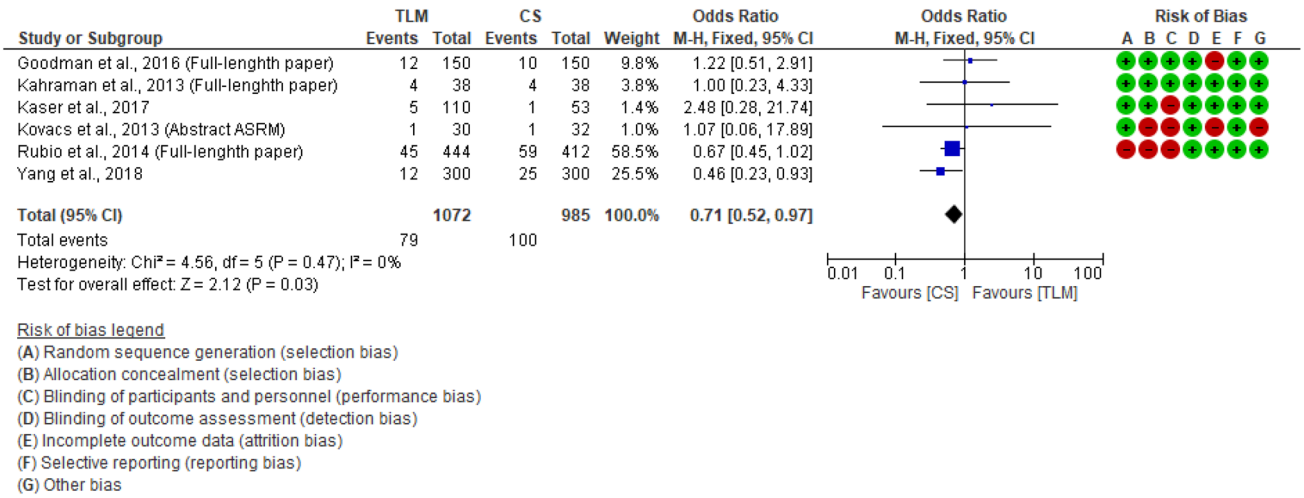


Clinical pregnancy

Fig. 2 Forest plot of comparison TLM utilising embryo selection software versus conventional assessment



Implantation rate



Early pregnancy loss

Fig. 2 (continued)

For the implantation rate, the embryos transferred in the six RCTs [29–34] were 1428 in total for the morphokinetics group compared with 1350 in CS group (Fig. 2d), corresponding to OR of 1.14 (95% CI 0.89–1.33). The pooled data for implantation rate showed no between-group difference, and high heterogeneity between studies for this outcome ($I^2 = 68\%$; fixed effect: OR 1.14; 95% CI 0.98–1.33; $P = 0.1$; random effect OR 1.06; 95% CI 0.76–1.49; $P = 0.73$). Exclusion of Yang et al. [34] resolved this heterogeneity.

Our estimate showed that embryo selection based on morphokinetics was associated with a statistically significantly lower rate of early pregnancy loss compared to embryo selection based on conventional morphological assessment (6 RCTs, 2057 women; OR 0.71, 95% CI 0.52–0.97, $P = 0.03$). There was no detected heterogeneity (Chi squared 0.69, $I^2 = 0\%$) (Fig. 2e).

Subgroup analysis

Subgroup analysis was performed to determine the effect of morphokinetics compared with the conventional assessment on embryo selection using the same culture conditions. Three studies used the same incubators and culture conditions for both groups [29, 33, 34]. The data showed

no difference in the rates of clinical pregnancy (3 RCTs; 1063 women; OR 1.04, 95% CI, 0.52–2.10, $P=0.91$), early pregnancy loss (3 RCTs; 1063 women; OR 0.74, 95% CI, 0.44–1.23, $P=0.24$) and implantation (3 RCTs; 1166 embryos; OR 0.93, 95% CI, 0.55–1.56, $P=0.78$). Two studies reported the ongoing pregnancy rate [33, 34], and showed no between-group difference (763 participants; OR 0.69, 95% CI, 0.51–0.92, $P=0.01$). Data for live birth outcome was not available when similar culture conditions were used for both groups.

Overall quality of evidence

Overall, quality of evidence was rated as low for ongoing pregnancy, clinical pregnancy and implantation, moderate for early pregnancy loss, and very low for live birth rate (Table 2). Between-study heterogeneity was detected for methodology, day of embryo transfer, and culture protocols. Several studies were judged to have high risk of bias for selection [31, 32], performance [27, 32–34], attrition [31, 34], and other bias [31, 34] including a possible publication bias due to small study effect, so that we downgraded the cumulative evidence quality.

Discussion

In this meta-analysis, embryo selection with morphokinetics is associated with considerably higher live birth and considerably lower early pregnancy loss than conventional embryo selection. No evidence exists for of between-group differences on ongoing pregnancy, clinical pregnancy and implantation. It is worth noting, however, that the rate of live birth was poorly reported in the majority of trials.

Comparison with other studies

Four other reviews have been published on this topic. The first review [35] by Polanski et al. was published in 2014 and included only two small randomized studies (138 patients). Polanski et al. found that time-lapse embryo algorithm based on morphokinetics was not associated with live birth, ongoing pregnancy, clinical pregnancy. In 2015, a review from Racowsky et al. [36] did not support the routine use of time-lapse imaging for embryo selection. On the contrary, Pribenszky et al. [37] analyzed 1637 patients from four RCTs and one pseudo-randomized study [28], concluding that time-lapse assessment results in reduced early pregnancy loss, higher ongoing pregnancy and live birth.

Table 2 Evidence profile: embryo selection using morphokinitics compared with conventional morphology in patients undergoing fresh embryo transfer after ICSI

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with Clinical outcome			
Ongoing pregnancy rate	501 per 1000	496 per 1000 (395 to 616)	RR 0.99 (0.79 to 1.23)	1757 (5 RCTs)	⨁⨁◯◯ LOW
Clinical pregnancy rate	589 per 1000	607 per 1000 (511 to 696)	OR 1.08 (0.73 to 1.60)	2057 (6 RCTs)	⨁⨁◯◯ LOW
Early pregnancy loss	102 per 1000	74 per 1000 (55 to 99)	OR 0.71 (0.52 to 0.97)	2057 (6 RCTs)	⨁⨁⨁◯ MODERATE
Implantation rate	476 per 1000	490 per 1000 (408 to 575)	OR 1.06 (0.76 to 1.49)	2778 (6 RCTs)	⨁⨁◯◯ LOW
Livebirth	402 per 1000	490 per 1000 (425 to 555)	OR 1.43 (1.10 to 1.85)	932 (2 RCTs)	⨁◯◯◯ VERY LOW

Intervention morphokinitics assessment, *comparison* conventional morphology, *CI* confidence interval, *OR* odds ratio, *RCT* randomized controlled trial

GRADE working group grades of evidence

High certainty we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

However, the inclusion of 239 women from the pseudo-randomized study [28] may negatively affect the resulted conclusions. Recently, the updated Cochrane review [10] by Armstrong et al. divided the studied that evaluated time-lapse morphokinetics selection of embryos into two groups: TLM versus conventional assessment (in the same TLM incubator and culture conditions) and TLM incubation versus conventional incubation (two different culture conditions systems). The authors reported that insufficient evidence exists to recommend the routine use of TLM in clinical practice.

To our knowledge, no prior meta-analysis on this issue is as large, up to date, or comprehensive. Our review has been evaluating the clinical outcomes, where we added recently published two RCTs (representing ~ 35% of the total number of participants; 763 out of 2057 individuals).

Study strengths and limitations

We used strict inclusion criteria, and rigorous methodology would strengthen the present review. We have tried to select only true RCTs with fresh embryo transfer, aiming to reduce a lower heterogeneity for study designs and population characteristics. We included a large number of randomized women ($n = 2057$) analyzed with intent-to-treat analysis. Where the appropriate, application of both fixed and random effects models was used, resulting in no changes in the overall results. However, the results of this meta-analysis should be interpreted cautiously. This caution owes to the observed flaws in some studies, eventually decreasing the confidence in the estimates. First, using different equipment and culture conditions such as oxygen tension, humidity, temperature stability and recovery time might influence the estimates. One important concern is that the included studies reported different types of incubators and culture conditions. Three RCTs used a single brand of TLM incubator with the same criteria of culture for both intervention and control groups [29, 33, 34], while the other three used different incubators for comparing the effect of morphokinetics of TLM with CS for embryo cultured in standard incubators [30–32]. In a subgroup analysis for embryo culture using the same criteria of culture, both groups showed no difference in the rates of ongoing pregnancy, clinical pregnancy, early pregnancy loss, and implantation. Other concerns include decisions taken by unblinded embryologists, and discrepancies in the type of ET (fresh and frozen), day of embryo transfer (day 3 or day 5), and the number of embryos transferred. Furthermore, prediction models and visual information of the time-lapse devices varied greatly, and the embryo populations were heterogeneous.

The gap exists in the literature as only six studies are available with three of which are relatively underpowered was another encouraging point to conducting our analysis. Also, no uniform definitions exist for the outcomes assessed. Clinical pregnancy is defined as fetal sacs with a heartbeat visualized by ultrasonography at ≥ 4 [30, 32–34] or at ≥ 8 weeks of gestation [29] or as a serum β-hCG level higher than 10 IU/mL on day 14 after ICSI [31]. In addition, definitions of miscarriage and ongoing pregnancy varied markedly among the studies included. These heterogeneous definitions of outcomes could result in a different assessment for the outcomes, thereby affecting the generalizability and applicability of the drawn evidence.

That being said, robust evidence on the effectiveness of TLM remains weak, and the routine use of TLM is still a premature step that will increase the cost of ART treatments with no proven clinical benefit. Therefore, we take the position to say that, at this stage, TLM should be offered in free of charge research-based situations.

Overall completeness and applicability of the evidence

No evidence of between-group differences existed regarding the probability of clinical pregnancy, ongoing pregnancy and implantation. The pooled data from the included studies suggest that TLM may increase the incidence of live birth and reduce the early pregnancy loss, albeit the completeness and applicability of this evidence are limited, which is leaving unanswered questions. Therefore, well-controlled, large-scale, multicenter RCTs with the live birth as a primary outcome are still needed to verify the use of morphokinetics can improve IVF outcomes. It is preferable that these future trials are performed to include also the cumulative live birth, the offspring and the cost-effectiveness of TLM technology. Towards this end, for the time being, the strict evidence seems still to be insufficient to transfer time-lapse imaging into routine clinical.

Conclusions

The effect of TLM for embryo selection awaits further studies. Although the findings of this review reported a significant improvement in live birth favoring morphokinetics evaluation as compared to traditional morphological assessment, the up-to-date evidence remains rather scarce. The resulted live birth and their health to date do not give cause for concern. Large, powered, well-conducted RCTs are required considering live birth as a primary endpoint to establish a shred of adequate evidence on whether TLM can be transferred into clinical practice.

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Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

References

1. Smith AD, Tilling K, Nelson SM, Lawlor DA (2015) Live-birth rate associated with repeat in vitro fertilization treatment cycles. JAMA 314:2654–2662
2. Montag M, Liebenthron J, Köster M (2011) Which morphological scoring system is relevant in human embryo development? Placenta 32:S252–S256
3. VerMilyea MD, Tan L, Anthony JT, Conaghan J, Ivani K, Gvakharia M, Boostanfar R, Baker VL, Suraj V, Chen AA, Mainigi M, Coutifaris C, Shen S (2014) Computer-automated time-lapse analysis results correlate with embryo implantation and clinical pregnancy: a blinded, multi-centre study. Reprod Biomed Online 29:729–736
4. Meseguer M, Herrero J, Tejera A, Hilligsoe KM, Ramsing NB, Remohi J (2011) The use of morphokinetics as a predictor of embryo implantation. Hum Reprod 26:2658–2671
5. Ottosen LD, Hindkjaer J, Ingerslev J (2007) Light exposure of the ovum and preimplantation embryo during ART procedures. J Assist Reprod Genet 24:99–103
6. Meseguer M, Rubio I, Cruz M, Basile N, Marcos J, Requena A (2012) Embryo incubation and selection in a time-lapse monitoring system improves pregnancy outcome compared with a standard incubator: a retrospective cohort study. Fertil Steril 6:1481–1489
7. VerMilyea MD, Tan L, Anthony JT, Conaghan J, Ivani K, Gvakharia M, Boostanfar R, Baker VL, Suraj V, Chen AA, Mainigi M, Coutifaris C, Shen S (2014) Computer-automated time-lapse analysis results correlate with embryo implantation and clinical pregnancy: a blinded, multi-centre study. Reprod Biomed Online 29(6):729–736
8. Mascarenhas M, Fox SJ, Thompson K, Balen AH (2019) Cumulative live birth rates and perinatal outcomes with the use of time-lapse imaging incubators for embryo culture: a retrospective cohort study of 1882 ART cycles. BJOG 126(2):280–286
9. Kirkegaard K, Hindkjaer JJ, Grondahl ML, Kesmodel US, Ingerslev HJ (2012) A randomized clinical trial comparing embryo culture in a conventional incubator with a time-lapse incubator. J Assist Reprod Genet 6:565–572
10. Armstrong S, Arroll N, Cree LM, Jordan V, Farquhar C (2018) Time-lapse systems for embryo incubation and assessment in assisted reproduction. Cochrane Database Syst Rev 1:1. https://doi.org/10.1002/14651858.cd011320.pub3
11. Mio Y, Maeda K (2008) Time-lapse cinematography of dynamic changes occurring during in vitro development of human embryos. Am J Obstet Gynecol 199(6):660 e1–5
12. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6:e1000097
13. Higgins JPT, Green S (eds) (2014) Cochrane handbook for systematic reviews of interventions. Version 5.1.0. http://www.cochrane-handbook.org. Accessed 23 July 2014
14. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, Nasser M, Meerpohl J, Post PN, Kunz R, Brozek J, Vist G, Rind D, Akl EA, Schünemann HJ (2013) GRADE guidelines: 14 Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 66:719–725
15. Quiroga R, Blasco V, González C, Caligara C. Application of MACS and time-lapse technology in good-prognosis patients. https://clinicaltrials.gov/ct2/show/NCT01908569?recrs=aeh&cond=time+lapse&draw=1&rank=2
16. Ronn R, Eldar-Geva T. Time-lapse incubation for embryo culture—morphokinetics and environmental stability. https://clinicaltrials.gov/ct2/show/NCT02657811?recrs=aeh&cond=time+lapse&draw=1&rank=6
17. VerMilyea M. Validation study using a time-lapse morphometry MIRI imaging incubator (TiMMI). https://clinicaltrials.gov/ct2/show/NCT02852356?recrs=aeh&cond=time+lapse&draw=2&rank=12
18. KGaA M. TiLE (time lapse Eeva) clinical trial (TiLE). https://clinicaltrials.gov/ct2/show/NCT02417441?recrs=aeh&cond=time+lapse&draw=1&rank=9
19. Park H, Bergh C, Selleskog U, Thurin-Kjellberg A, Lundin K (2015) No benefit of culturing embryos in a closed system compared with a conventional incubator in terms of number of good quality embryos: results from an RCT. Hum Reprod 30(2):268–275
20. Barberet J, Chammas J, Bruno C, Valot E, Vuillemin C, Jonval L, Choux C, Sagot P, Soudry A, Fauque P (2018) Randomized controlled trial comparing embryo culture in two incubator systems: G185 K-System versus EmbryoScope. Fertil Steril 109(2):302–309
21. Wu Y, Lazzaroni-Tealdi E, Wang Q, Zhang L, Barad DH, Kushnir VA, DarmonSK Albertini DF, Gleicher N (2016) Different effectiveness of closed embryo culture system with time-lapse imaging (EmbryoScopeTM) in comparison to standard manual embryology in good and poor prognosis patients: a prospectively randomized pilot study. Reprod Biol Endocrinol 14(1):49
22. Cruz M, Gadea B, Garrido N, Pedersen KS, Martínez M, Pérez-Cano I, Muñoz M, Meseguer M (2011) Embryo quality, blastocyst and ongoing pregnancy rates in oocyte donation patients whose embryos were monitored by time-lapse imaging. J Assist Reprod Genet 28:569–573
23. Ingerslev HJ, Kirkegaard K, Hindkjaer J, Grondahl ML, Kesmodel US, Agerholm I (2011) Cleavage rates of human embryos randomized to culture in conventional incubator and culture in a time lapse instrument. Hum Reprod 26(Suppl 1):P164
24. Mara C, Nicols G, Inmaculada P-C, Niels R, Manuel M, Marcos M (2010) Comparative study of embryo quality, blastocyst and ongoing pregnancy rates in oocyte donation patients sharing embryoscope and standard incubator. Fertil Steril 94(4 Suppl 1):78 **Abstract no. o-267**
25. Nakahara T, Iwase A, Goto M, Harata T, Suzuki M, Ienaga M, Kobayashi H, Takikawa S, Manabe S, Kikkawa F, Ando H (2010) Evaluation of the safety of time-lapse observations for human embryos. J Assist Reprod Genet 27:93–96
26. Yang Z, Zhang J, Salem S, Liu X, Kuang Y, Salem R, Liu J (2014) Selection of competent blastocysts for transfer by combining time-lapse monitoring and array CGH testing for patients undergoing preimplantation genetic screening: a prospective study with sibling oocytes. BMC Med Genomics 7:38
27. Hardarson T, Bungum M, Conaghan J, Meintjes M, Chantilis SJ, Molnar L, Gunnarsson K, Wikland M (2015) Noninferiority, randomized, controlled trial comparing embryo development using media developed for sequential or undisturbed culture in a time-lapse setup. Fertil Steril 104(6):1452–1459
28. Siristatidis C, Komitopoulou MA, Makris A, Sialakouma A, Botzaki M, Mastorakos G, Salamalekis G, Bettocchi S, Palmer GA

(2015) Morphokinetic parameters of early embryo development via time lapse monitoring and their effect on embryo selection and ICSI outcomes: a prospective cohort study. J Assist Reprod Genet 32(4):563–570
29. Goodman LR, Goldberg J, Falcone T, Austin C, Desai N (2016) Does the addition of time-lapse morphokinetics in the selection of embryos for transfer improve pregnancy rates? A randomized controlled trial. Fertil Steril 105(2):275–285
30. Kahraman S, Çetinkaya M, Pirkevi C, Yelke H, Kumtepe Y (2012) Comparison of blastocyst development and cycle outcome in patients with eSET using either conventional or time lapse incubators. A prospective study of good prognosis patients. J Reprod Biotechnol Infertil 3(2):55–61
31. Kovacs P, Matyas S, Forgacs V, Sajgo A, Rarosi F, Pribenszky C (2013) Time-lapse embryo selection for single blastocyst transfer—results of a multicentre, prospective, randomized clinical trial. Fertil Steril 100(3):90
32. Rubio I, Galan A, Larreategui Z, Ayerdi F, Bellver J, Herrero J, Meseguer M (2014) Clinical validation of embryo culture and selection by morphokinetics analysis: a randomized, controlled trial of the EmbryoScope. Fertil Steril 102(5):1287–1294
33. Kaser DJ, Bormann CL, Missmer SA, Farland LV, Ginsburg ES, Racowsky C (2017) A pilot randomized controlled trial of Day 3 single embryo transfer with adjunctive time-lapse selection versus Day 5 single embryo transfer with or without adjunctive time-lapse selection. Hum Reprod 32(8):1598–1603
34. Yang L, Cai S, Zhang S, Kong X, Gu Y, Lu C, Dai J, Gong F, Lu G, Lin G (2018) Single embryo transfer by Day 3 time-lapse selection versus Day 5 conventional morphological selection: a randomized, open-label, non-inferiority trial. Hum Reprod 33(5):869–876
35. Polanski LT, Coelho Neto MA, Nastri CO, Navarro PA, Ferriani RA, Raine-Fenning N, Martins WP (2014) Time-lapse embryo imaging for improving reproductive outcomes: systematic review and meta-analysis. Ultrasound Obstet Gynecol 44(4):394–401
36. Racowsky C, Kovacs P, Martins WP (2015) A critical appraisal of time-lapse imaging for embryo selection: where are we and where do we need to go? J Assist Reprod Genet 32(7):1025–1030
37. Pribenszky C, Nilselid AM, Montag M (2017) Time-lapse culture with morphokinetic embryo selection improves pregnancy and live birth chances and reduces early pregnancy loss: a meta-analysis. Reprod Biomed Online 35(5):511–520