Does the addition of time-lapse morphokinetics in the selection of embryos for transfer improve pregnancy rates? A randomized controlled trial

Linnea R. Goodman, M.D., Jeffrey Goldberg, M.D., Tommaso Falcone, M.D., Cynthia Austin, M.D., and Nina Desai, Ph.D., H.C.L.D.

Department of Reproductive Endocrinology and Infertility, Cleveland Clinic, Beachwood, Ohio

Objective: To determine if the addition of continuous morphokinetic data improves reproductive outcomes when all embryos are cultured in a closed system.
Design: Prospective, randomized, controlled study.
Setting: Single academic center.
Patient(s): A total of 235 patients undergoing fresh autologous IVF cycles with at least four embryos, cultured in the Embryoscope: 116 patients randomized to conventional once-daily morphologic embryo screening (CS) and 119 to additional time-lapse kinetic monitoring (TLM) for selection.
Intervention(s): TLM versus CS.
Main Outcome Measure(s): Intrauterine clinical pregnancy (CPR) and implantation (IR) rates.
Result(s): CPR and IR were similar overall (TLM vs. CS, respectively: CPR 68% vs. 63%; IR 51% vs. 45%) and with blastocyst transfers (CPR 74% vs. 67%; IR 56% vs. 51%). CPR with day 5 transfer was threefold higher than day 3 transfer, but group (TLM vs. CS) was not a significant predictor of clinical pregnancy or implantation. Significantly more multinucleation was detected when CS embryos were retrospectively reviewed with the use of TLM (7.0% vs. 35.3%), and multinucleation was independently associated with decreased rates of implantation. Time to the start of blastulation of <100 hours after insemination and the morphokinetic scoring system used in the TLM group were independently associated with implantation.
Conclusion(s): The addition of time-lapse morphokinetic data did not significantly improve clinical reproductive outcomes in all patients and in those with blastocyst transfers. Absence of multinucleation, timing of blastulation, and morphokinetic score were found to be associated with blastocyst implantation rates.
Clinical Trial Registration Number: NCT02081859. (Fertil Steril® 2016;105:275–85. ©2016 by American Society for Reproductive Medicine.)
Key Words: Time-lapse monitoring, embryo selection, blastocyst, morphokinetics, implantation, multinucleation

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/goodmanl-time-lapse-embryo-selection/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Embryonic potential for implantation and successful pregnancy in in vitro fertilization (IVF) cycles has traditionally been assessed by means of microscopic examination with the use of a tiered grading system based on morphology (1–5). The visualization of embryonic development has been limited to a brief evaluation once a day owing to the potentially deleterious effects of exposure to ambient temperature and pH conditions outside of the incubator (6).

The goal of frequent monitoring, while maintaining an optimal culture environment, has led to the development of specialized culture systems,

Received August 19, 2015; revised October 9, 2015; accepted October 13, 2015; published online October 29, 2015.
L.R.G. has nothing to disclose. J.G. has nothing to disclose. T.F. has nothing to disclose. C.A. has nothing to disclose. N.D. has nothing to disclose.
Reprint requests: Linnea R. Goodman, M.D., Department of Reproductive Endocrinology and Infertility, Cleveland Clinic, 26900 Cedar Road, Beachwood, Ohio 44122 (E-mail: linnea.goodman@gmail.com).

Fertility and Sterility® Vol. 105, No. 2, February 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.10.013

such as the Embryoscope incubator (Fertilitech) that enables time-lapse photography without removing embryos from the incubator. Retrospective studies evaluating undisturbed culture within the Embryoscope have found that it is safe (7) and may potentially provide a culture environment leading to increased blastocyst formation (7, 8), implantation, and clinical pregnancy rates (7, 9–11) over some conventional forms of culture using large box incubators with atmospheric oxygen concentrations (9).

The use of morphokinetics, or timing of embryonic developmental events and visualization of dynamic morphology, available through continuous time-lapse monitoring, has added another dimension to current traditional morphology classification scores (12–14). Wong et al., using time-lapse imaging, identified three specific cell cycle events occurring before genomic activation that correlated to blastocyst formation (15). Review of the expanding literature on morphokinetics shows that the spectrum of timing of events in embryo development may provide additional clues to embryonic potential. There have been several retrospective studies evaluating the specific cell cycle kinetic parameters associated with blastocyst formation and/or pregnancy (7, 12,15–22). In 2011, Meseguer et al. retrospectively analyzed kinetic data from 247 embryos with known implantation status to create a hierarchy of morphology and timing of events in embryo development visualized by time-lapse monitoring to predict embryo implantation (23). In a follow-up study, that group retrospectively compared pregnancy outcomes in standard culture and conventional embryo grading with outcomes after culture within the Embryoscope and the use of time-lapse parameters to assist in embryos selection, with results favoring higher pregnancy rates in the time-lapse system (9). A more recent randomized controlled trial by Rubio et al. found increased continuing pregnancy rates with the use of continuous time-lapse culture and selection compared with standard embryo culture and was able to validate the model previously described by Meseguer et al. (24). However, a limitation of these studies is the inability to parse out the confounding effect of the different culture systems: There have been no studies to date with the ability to control for variables such as culture dish, gas concentrations, and effects of undisturbed growth and incubation environments. In addition, these studies only focused on early kinetic parameters with ensuing cleavage-stage transfers.

To date, it has not yet been established if adding the morphokinetic data available through continuous time-lapse imaging to conventional embryo selection criteria improves clinical outcomes if all embryos are cultured in a self-contained incubator allowing growth in an optimized environment without disturbance. The goal of the present blinded randomized controlled trial was to compare implantation and clinical pregnancy rates when continuously monitored kinetic parameters and dynamic morphologic events were added to a conventional once-daily morphologic grading system with all embryos cultured in identical conditions within the Embryoscope.

MATERIALS AND METHODS

This study was a prospective randomized controlled clinical trial approved by the Institutional Review Board at the Cleveland Clinic. The study was registered with the Clinical Trials website (NCT02081859). Patients aged 18–43 years undergoing an autologous IVF cycle from March 2014 to May 2015 at the Cleveland Clinic Reproductive Endocrinology and Infertility (REI) clinic with a plan for a fresh embryo transfer were eligible to participate in this trial. Patients were excluded if they had plans to undergo preimplantation genetic testing or were undergoing IVF for fertility preservation. Eligible patients were identified during the course of the IVF cycle and offered the opportunity to participate at the time of oocyte retrieval. All embryos were cultured in the Embryoscope regardless of group. After randomization, patients were excluded from the data analysis phase if they did not undergo fresh transfer owing to previously unforeseen reasons (risk of ovarian hyperstimulation, uterine factors, etc.). Patients with only one to three zygotes were also excluded, because there was little selection and most often all cleaving embryos were transferred.

Consecutive patients eligible for the study were approached by the REI physicians. If the patient agreed to participate, a signed informed consent form was placed on the chart and laboratory personnel added the name to a consecutive list where the group assignment was revealed at time of oocyte retrieval. All patients who agreed to participate were randomized to having embryo selection for transfer based on conventional once-a-day morphologic criteria only or on conventional criteria in conjunction with morphokinetic criteria. Patients were randomized 1:1 to conventional embryo selection (CS) versus Embryoscope time-lapse morphokinetic selection (TLM) with the use of a computer-generated random number sequence. The list was housed in the laboratory, where it was accessible only by research personnel not involved with the recruitment of patients. Patients, REI physicians and staff, and sonographers were blinded to how embryos were selected. Only the embryology laboratory staff were aware of which group the patients were randomized to. The flowchart of included patients is depicted in Figure 1.

Research Procedure

The IVF process was the same for both groups. Controlled ovarian hyperstimulation (COH) protocols were chosen based on patient specific factors, including serum antimüllerian hormone (AMH) levels, antral follicle count, and response to previous stimulation. Protocols included GnRH agonist or antagonist to suppress spontaneous ovulation and FSH with or without the addition of hMG to stimulate follicular growth. Final maturation was triggered when at least two follicles reached a mean diameter of >18 mm with hCG or GnRH agonist based on the COH protocol, and all patients underwent ultrasound-guided transvaginal oocyte retrieval 36 hours later.

Embryo Culture

Upon retrieval, oocytes were placed in 25 μL Global-HTF medium (Life Global) supplemented with 10% human serum albumin (Sage/Cooper-Surgical) in 35-mm dishes under an oil