Obstetric and perinatal outcomes of pregnancies conceived with embryos cultured in a time-lapse monitoring system

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Objective: To compare obstetric and perinatal outcomes of singleton pregnancies resulting from embryos incubated in a time-lapse system (TLS) with those of embryos grown in standard IVF incubators (SI).
Design: Retrospective description of a cohort of patients who conceived during a randomized, controlled trial.
Setting: Private university-affiliated IVF center.
Patient(s): Of 856 randomized patients, 378 gave birth to a live-born infant: 216 of the deliveries originated from embryos incubated in TLS, and 162 deliveries were from embryos cultured in SI.
Intervention(s): Embryo incubation and selection in TLS.
Main Outcome Measure(s): Delivery and neonatal outcomes.
Result(s): No significant differences were observed in the baseline characteristics of the study population. The delivery rate was 49.3% (TLS) vs. 40.0% (SI), and multiple deliveries were higher in the TLS group: 31.0% (67 of 216) vs. 24.7% (40 of 162) in the SI group. When singleton pregnancies were analyzed no differences were found between the two groups in the rate of obstetric problems with respect to weeks at delivery: 38.8 (95% confidence interval [CI] 38.4–39.1) (TLS) vs. 39.5 (95% CI 38.0–39.9) (SI); preterm births (<37 weeks): 10.7% (TLS) vs. 12.3% (SI); and very preterm births (<34 weeks): 2.9% (TLS) vs. 3.3% (SI). No statistical differences were found in neonatal outcomes such as birth weight: 3,163 g (95% CI 3,035–3,292 g) (TLS) vs. 3,074 (95% CI 2,913–3,236) (SI); low birth weight (<2,500 g): 12.8% (TLS) vs. 12.3% (SI); very low birth weight (<1,500 g): 2.0% (TLS) vs. 2.4% (SI); or height: 50.3 cm (95% CI 49.6–50.9 cm) (TLS) vs. 49.7 (95% CI 48.9–50.4 cm) (SI). No major malformations or perinatal mortality were found in either of the two groups.
Conclusion(s): No detrimental effects were observed in obstetric and perinatal outcomes when a time-lapse incubator was used rather than a more widely used conventional incubator. As far as we know this is the first report from a randomized study of the neonatal outcomes of time-lapse monitoring. Our results suggest that this technology is an effective and safe alternative for embryo incubation, though trials of larger numbers of patients are required to further confirm our conclusions.
Clinical Trial Registration Number: NCT01549262. (Fertil Steril® 2017;108:498–504. ©2017 by American Society for Reproductive Medicine.)
Key Words: Obstetric outcome, perinatal outcome, standard incubator, time lapse

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Recent years have seen the development of noninvasive embryo selection methods. In this context, time-lapse systems (TLS) enable a detailed 24-hour evaluation of embryo development, including developmental kinetic parameters that, in combination with morphologic assessment, improves embryo selection and, in turn, IVF outcome and pregnancy rate after IVF (1).

Time-lapse monitoring (TLM) is widely used in clinical practice and is generally considered a safe and effective technology for the continuous monitoring of human embryos cultured for treatment purposes (2–4). However, some scientists raise questions about introducing TLS into routine clinical practice owing to the uncertainty about their clinical and cost-effectiveness and the lack of high-quality studies, recommending it should be considered an experimental strategy (5, 6).

Many studies have compared time-lapse technology and morphokinetics as predictors of embryo implantation success (1, 7, 8), as a method of

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embryo selection (9–12), and with respect to clinical outcomes (1, 13). However, it remains a controversial subject (14, 15) because some studies of live births, clinical pregnancy, or miscarriage have found insufficient evidence on which to base a definitive opinion regarding TLS vs. conventional incubation (16).

This controversy has been fueled by the fact that no outstanding data have been previously published in relation to obstetric and perinatal outcomes of pregnancies achieved with embryos cultured in TLS.

We have previously published a clinical validation of embryo culture and selection by morphokinetic analysis using TLS (13). The aim of the present study was to perform a second analysis of our data, to re-evaluate the safety of this technique by assessing obstetric and perinatal outcomes of pregnancies resulting from embryos conceived in TLS vs. standard IVF incubators (SI). To our knowledge, this is the first report on this topic.

MATERIALS AND METHODS

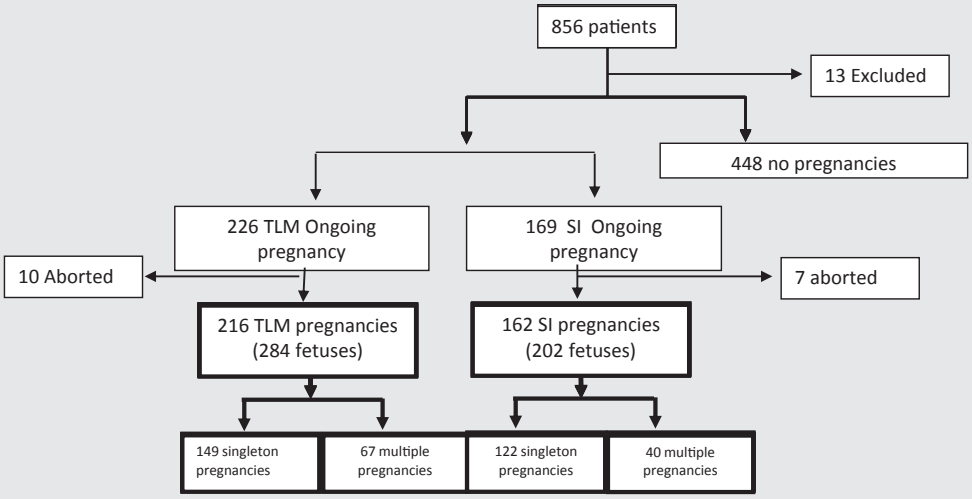
Study Design and Study Population

Obstetric and perinatal data were gathered about newborns conceived using TLS (study group) or SI (control group) from a randomized, controlled trial performed at IVI Valencia and IVI Bilbao from February 2012 to July 2013 (13). This study was approved by the institutional review board of the Instituto Valenciano de Infertilidad, in Valencia, Spain (1009-C-088-IR) (Clinical Trial Registration Number: NCT01549262). All the births for which we had notification during the period October 2012–April 2014 were included in the study. A description of the sample analyzed is shown in Figure 1.

IVF Procedures

In this section we provide a short summary of a previous study published by Rubio et al. (13), in which 856 patients were recruited and served as a platform of the present study. In the previous study embryos randomly cultured in an SI, which were evaluated only by conventional morphologic criteria, and embryos cultured in a time-lapse incubator (EmbryoScope, Vitrolife) and were assessed using our multivariate algorithm. Time-lapse monitoring technology used in this study is Conformité Européene (CE)-certified (i.e., meets the safety and health requirements for equipment in the European Union; certificate number: DGM-673), and its utilization met the purposes for which it was approved. Patients entering the trial were allocated to either TLS (study group) or SI (control group) using a computer-generated randomization table (obtained by SPSS software; IBM), which was handled by an embryologist at the laboratory in charge the day before the oocyte retrieval or oocyte donation. The study is considered double-blind because [1] the gynecologist (evaluating the primary effect) did not know to which group the patients had been assigned, and [2] the statistician evaluating the results only knew the incubators by a binary code and not by type. Ovarian stimulation protocols (autologous and donors) have been described previously (13, 17). Both GnRH-agonist and -antagonist treatments were applied, and hCG (Ovitrelle, Serono Laboratories) was administered SC when at least three leading follicles had reached a mean diameter of 18 mm. Transvaginal oocyte retrieval was scheduled 36 hours later. After ET, all patients received luteal phase support every 12 hours, whereby autologous patients received a daily dose of 400 mg and oocyte recipients a daily dose of 800 mg of vaginal micronized P (Progeffik, Effik). Ovum pickup and intracytoplasmic sperm injection (ICSI) are described elsewhere (13). Immediately after ICSI the injected oocytes for TLS cycles were placed individually in pre-equilibrated culture dishes (EmbryoSlide, Vitrolife) under oil at 37°C and 5.5% CO_2 in air in a time-lapse incubator (EmbryoScope). Zygotes for the conventional incubator (Heraeus, Heracell) cycles were placed in normal Petri

FIGURE 1



Description of the sample analyzed. Study group: pregnancies obtained from embryos incubated in TLS. Control group: pregnancies achieved from embryos incubated in SI.

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