ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Improved outcomes after blastocyst-stage frozen-thawed embryo transfers compared with cleavage stage: a Society for Assisted Reproductive Technologies Clinical Outcomes Reporting System study

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Objective: To investigate whether there is a difference in obstetrical and perinatal outcomes in blastocyst frozen-thawed embryo transfers (FETs) compared with cleavage-stage FET.
Design: A retrospective cohort study.
Setting: Not applicable.
Patient(s): Women undergoing autologous FETs at either the blastocyst stage (n = 118,572) or the cleavage stage (n = 117,619) reported to the Society for Assisted Reproductive Technology in the years 2004–2013.
Intervention(s): None.
Main Outcome Measure(s): Live birth, gestational age, birth weight, miscarriage.
Result(s): After controlling for confounders, there were a 49% increased odds of live birth after blastocyst-stage FET compared with cleavage-stage FET (odds ratio [OR] = 1.49; 95% confidence interval [CI], 1.44, 1.54). Additionally, blastocyst FET was associated with a 68% (OR = 1.68; 95% CI, 1.63, 1.74) increased odds of clinical pregnancy and an 7% (OR = 0.93; 95% CI, 0.88, 0.92) decreased odds of miscarriage. There was also a 16% increased odds of preterm delivery (OR = 1.16; 95% CI, 1.06, 1.27) after blastocyst FET but no difference in birth weights.
Conclusion(s): In patients undergoing FET, blastocyst-stage transfer is associated with higher live-birth rates when compared with cleavage-stage transfers. Furthermore, perinatal outcomes are similar between the groups. (Fertil Steril® 2018;■:■–■. ©2018 by American Society for Reproductive Medicine.)
Key Words: Blastocyst, cleavage, frozen embryo transfer

Assisted reproductive technologies (ART) and IVF specifically have now resulted in many thousands of successful pregnancies each year. In the United States, it is estimated that 1.6% of infants born every year are conceived using ART (1). In recent years, with the advent of vitrification and improved IVF cycle outcomes after blastocyst transfer (2), there has been an increase in blastocyst-stage frozen-thawed embryo transfers (FETs). However, there is little high-quality evidence comparing obstetrical and perinatal outcomes of cleavage-stage FETs to blastocyst-stage FETs, as noted in a 2016 Cochrane review (2).

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Most studies comparing cleavage-stage FET to blastocyst-stage FET suggest no difference in cycle outcomes (3–11). Despite insufficient data to support blastocyst-stage FET, many IVF clinics have implemented blastocyst FET for their patients. It is well known that pregnancies conceived through IVF are at increased risk for obstetrical and neonatal complications including preterm delivery and low birth weight (12). While these risks may be mitigated in FET cycles (13, 14), it is important to determine whether there are significant differences in outcomes between blastocyst-stage and cleavage-stage FETs.

Using the Society for Assisted Reproductive Technologies Clinical Outcomes Reporting System (SART-CORS) database, the aim of this study was to investigate whether there is a difference in obstetrical and perinatal outcomes in FET cycles among cleavage-stage versus blastocyst-stage embryos. We hypothesized that blastocyst-stage FETs have better pregnancy outcomes, specifically higher numbers of live births and fewer preterm deliveries. In addition, we hypothesized that birth weights are higher in live births that resulted from blastocyst-stage FETs.

MATERIAL AND METHODS

All IVF cycles reported to SART-CORS over a 10-year period (2004–13) were evaluated. Data were collected and verified by SART and reported to the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493 [15]). Ninety-five percent of IVF cycles in the United States are reported through the SART registry (16). Validation of the data collected through SART-CORS occurs annually. Some clinics have on-site visits for chart review based on an algorithm for clinic selection. During the site visit, data reported by the clinic were compared with information recorded in patients' charts. In a recent review of validation of site visit results, 90.9% (10/11) of the data fields selected were found to have discrepancy rates of $\leq$5% (17).

Only frozen, autologous cycles were included in the analysis. Exclusion criteria included fresh IVF cycles and IVF cycles using donor oocytes. Furthermore, only cycles with treatment and pregnancy outcomes were included. The primary study outcome assessed was live-birth rate. Secondary study outcomes included clinical pregnancy and miscarriage rates, preterm delivery, birth weights, and stillbirths. Demographic criteria from the cycles were also collected.

The following associated SART-defined terms and definitions were used in this study. *Live birth* is defined as a fetus showing signs of life after delivery. *Clinical intrauterine gestation* is defined as an intrauterine pregnancy visible on ultrasound. *Stillbirth* is defined as a birth at 18 weeks or later from the date of transfer in which no fetus showed signs of life after delivery. *Preterm delivery* is defined as a delivery before 37 weeks of gestation. *Low birth weight* infants are those with a birth weight less than 2,500 g and *very low birth weight* infants are those with a birth weight less than 1,500 g. Analyses also looked at weights greater than 4,000 and 4,500 g.

Statistical analysis was performed using both SAS 9.4, SAS Institute and Microsoft Excel, version 14.7.6. $P<.05$ was considered statistically significant. Adjusted and unadjusted associations between outcomes and blastocyst stage (vs. cleavage stage) were examined using generalized estimating equations using logit links for binary outcomes and identity links for continuous outcomes. These models adjust tests for repeated measures from women with multiple treatment cycles and assume equicorrelation between observations belonging to the same woman. Perinatal outcomes were evaluated among cycles with one live birth. Cochran-Mantel-Haenszel tests examined bivariate associations between perinatal weights and blastocyst (vs. cleavage) stage. Again, generalized linear models examined associations. Sensitivity analyses evaluated all associations adjusted for reporting year to evaluate the possibility that improved outcomes are due to improved medical practices rather than use of blastocyst over cleavage stage. This study was approved by the Rutgers Health Sciences Institutional Review Board and the SART Research Committee before the release of the data to our institution.

RESULTS

A total of 236,191 FET cycles from 171,901 patients (with between one and 13 cycles per patient) that occurred from 2004 through 2013 were analyzed. All cycles performed before 2006 were cleavage-stage FETs. Blastocyst-stage FET cycles were first reported in 2006 and comprised 12% of all FET cycles. Blastocyst-stage FETs continued to increase yearly thereafter, rising to 78% in 2013. Use of blastocyst-stage FETs significantly increased over time ($P<.0001$), as seen in Supplemental Figure 1.

Regional data on FET trends became available in 2010. For the purpose of analyzing regional use of blastocyst FET over time, the United States was broken up into four regions: midwest, northeast, south, and west. The south had the highest use of blastocyst FETs in 2010. The northeast region had the lowest use in 2010 (58%) but grew to the highest by 2013 (81%). Within each of the four regions, rates of blastocyst FET use significantly increased over time ($P<.0001$), as seen in Supplemental Figure 2.

Demographic data from the FET cycles are shown in Table 1. Although there were statistically significant differences in the demographic characteristics between blastocyst-stage and cleavage-stage FET cycles in terms of age, body mass index (BMI), gravidity, parity, maximum serum FSH, and prior IVF cycles ($P<.0001$), differences were not large enough to be clinically meaningful and likely secondary to our large sample size. Cleavage-stage FET cycles were found to have more smokers than blastocyst FET cycles (7.2% compared with 5.25%, $P<.0001$). Cleavage-stage FET cycles also had fewer single ETs compared with the blastocyst FET cycles (5.4% vs. 20.2%, $P<.0001$).

Blastocyst FET cycles had significantly increased cumulative pregnancy rates (60.6% vs. 47.7%), clinical intrauterine gestations (48.5% vs. 37.4%), and live-birth rates (37.9% vs. 28.8%) when compared with cleavage-stage FET cycles ($P<.0001$; Table 2). Improved success for blastocyst-stage FET was achieved using both fewer embryos thawed ($P<.0001$) and fewer embryos transferred ($P<.0001$;