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CLINICAL ARTICLE

Comparison of perinatal outcomes following fresh and frozen-thawed blastocyst transfer☆

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ABSTRACT

Objective: To investigate the effect of ovarian stimulation on endometrial receptivity by comparing singleton pregnancy and perinatal outcomes following fresh or frozen-thawed blastocyst transfers. *Methods:* A retrospective cohort study enrolled patients undergoing fresh or frozen-thawed blastocyst transfers that resulted in live deliveries between January 1, 2010 and September 30, 2013 at a single academic center. Implantation, clinical pregnancy, spontaneous abortion, and live delivery rates were calculated. The incidence of term delivery, preterm delivery, low birth weight, term low birth weight, and very low birth weight were also recorded. To detect a 10% difference in the implantation rate, a minimum sample size of at least 415 transfer cycles in each group was estimated. *Results:* The study included data from 918 fresh and 1273 frozen-thawed cycles. Patients in both groups were of similar age and there was no difference in the grading of blastocysts. No differences were observed in the implantation (37.3% vs 37.7%), clinical pregnancy (50.2% vs 49.4%), spontaneous abortion (7.3% vs 9.3%), and live delivery (42.9% vs 40.6%) rates of the two groups. A sub-analysis of all live singleton and twin deliveries revealed no difference in perinatal outcomes between the two techniques. *Conclusions:* The present study demonstrated equivalent singleton pregnancy and perinatal outcomes when comparing frozen-thawed and fresh blastocyst transfer procedures.

1. Introduction

During the past decade, frozen-thawed embryo transfers (FETs) have contributed to an increase in the proportion of live deliveries that occur following the use of assisted reproductive technology [1]. According to the Society for Assisted Reproductive Technology, the number of FETs has increased by 82.5% between 2006 and 2012, whereas there was an increase of only 3.1% in the number of fresh embryo transfers during the same period [2,3]. Although the increase in FETs can be attributed to factors including improved cryopreservation techniques, specifically vitrification [4], as well as banking of genetically screened embryos [3], there has also been a shift towards FETs in the name of improved endometrial receptivity and perinatal outcomes. Recent data have suggested a detrimental effect of ovarian stimulation on endometrial receptivity during fresh in vitro fertilization (IVF) cycles [5,6], leading to higher rates of low birth weight (LBW) [7], preterm delivery [8], and other adverse perinatal outcomes [5,8,9]. In the context of these epidemiologic findings, preferentially electing to transfer frozen-thawed embryos into a more receptive uterine environment over transferring fresh embryos immediately following ovarian stimulation has been proposed as the new gold standard of care for assisted reproductive technology [5,10]. In an attempt to mimic the natural stimulation process, a physiologic approach to ovarian stimulation has been utilized by the authors, with a step-down protocol and combinations of follicle-stimulating hormone and luteinizing hormone activity. To investigate the effect of ovarian stimulation on endometrial receptivity, the aim of the present study was to compare the singleton pregnancy and perinatal outcomes between fresh and frozen-thawed blastocyst transfers at the study institution.

2. Materials and methods

All patients who began IVF cycles at the Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine, New York, USA, that resulted in live deliveries between January 1, 2010 and September 30, 2013 were analyzed for potential inclusion in the present study. Only fresh and frozen-thawed blastocyst transfers were included. Any live deliveries occurring earlier than 37 weeks of pregnancy were defined as preterm deliveries. Preterm delivery earlier than 34 weeks of pregnancy was defined as early preterm delivery, while preterm delivery between 34 and 37 weeks of pregnancy was defined as late preterm

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delivery [11]. Neonatal weight below 2500 g at delivery, irrespective of gestational age, was defined as LBW [12] and neonatal weight below 1500 g at delivery, irrespective of gestational age, was defined as very low birth weight (VLBW) [12]. The Weill Cornell Medical College institutional review board approved the study design (protocol# 1503016064) and, as the protocol involved the retrospective review of patient charts, the need for individual consent from patients was waived.

Controlled ovarian stimulation was performed to maximize ovarian follicular response while minimizing the overall risk of ovarian hyperstimulation syndrome. Controlled ovarian stimulation, human chorionic gonadotropin (hCG) trigger, oocyte retrieval, embryo culture, and embryo transfer were performed per the standard protocols at the study institution [13]. Patients were downregulated in the preceding luteal phase using either oral contraceptive pills or 0.1 mg (estradiol) E_2 patches. Controlled ovarian stimulation was initiated with gonadotropins (Follistim; Merck, Kenilworth, NJ, USA; Gonal-F; EMD-Serono Inc, Rockland, MA, USA; and/or Menopur; Ferring Pharmaceuticals Inc, Parsippany, NJ, USA). Patients were initially treated with a gonadotropin-releasing hormone antagonist (Ganirelix acetate 0.25 mg; Merck, Kenilworth, NJ, USA) based on a previously described flexible protocol to suppress ovulation [13]. hCG was used to trigger ovulation and was administered according to a sliding scale dosage (10 000 IU for E_2 ≤1500 pg/mL; 5000 IU for E_2 1501–2500 pg/mL; 4000 IU for E_2 2501–3000 pg/mL; and 3300 IU for E_2 ≥3001 pg/mL). In general, the hCG trigger was administered when two lead follicles attained a mean diameter larger than 17 mm. Oocyte retrieval was performed under conscious sedation using transvaginal ultrasonography guidance approximately 35–37 hours after hCG administration. Luteal support was initiated the day after retrieval using 50 mg of intramuscular progesterone daily. IVF was performed using conventional insemination or intracytoplasmic sperm injection based on each patient's partner's semen analysis and the couple's history. All embryos were cultured using a two-step culture media manufactured in the study institution's embryology laboratory. Embryos cultured until the blastocyst stage were then graded based on their degree of expansion, development of the inner cell mass and trophectoderm [14]. Patients underwent fresh blastocyst transfers on day five. Embryo transfers were performed using catheters (Smiths Medical Inc, Norwell, MA, USA) at approximately 1 cm below the uterine depth identified at prior trial transfer. Ultrasonography guidance was only utilized when the transfers were deemed difficult based on the prior trial transfer.

Cryopreservation of day-five blastocysts from fresh IVF cycles was generally performed for either the cryopreservation of supernumerary top-quality blastocysts during the fresh IVF cycle, or the prevention of ovarian hyperstimulation syndrome. All blastocysts were cryopreserved using a previously described protocol [15]. Briefly, embryos were transferred through vitrification solutions containing ethylene glycol, dimethyl sulfoxide and sucrose before being loaded to a vitrification device (Cryolock; Biotech Inc, Cumming, GA, USA) and immersed in liquid nitrogen [15]. Patients underwent either natural or programmed FETs based on menstrual history or prior FET success. Patients with ovulatory menstrual cycles underwent natural FET comprising ultrasonographic and hormonal monitoring for ovulation. Vaginal progesterone supplementation (Endometrin 100 mg twice daily; Ferring Pharmaceuticals Inc, Parsippany, NJ, USA) was started one day after luteinizing hormone surge in some patients based on clinical history and physician preference. Patients with anovulatory menstrual cycles underwent programmed FET, in which patients received 0.1-mg E_2 patches with or without prior downregulation using gonadotropin-releasing hormone antagonist. After confirming the presence of a trilaminar endometrial pattern via ultrasonography, intramuscular progesterone supplementation was initiated. FET was performed in these patients 5 days after the detection of luteinizing hormone surge. Embryo transfers were performed using the same procedure as fresh IVF cycles.

The demographic characteristics included in the analyses were age, parity, body mass index, and the number of previous IVF attempts; patient baseline variables included total days of stimulation, total gonadotropin dose administered, endometrial stripe thickness on day of hCG or peak thickness prior to progesterone administration, number of oocytes retrieved, the number of mature oocytes, and the grade of the transferred blastocyst. The implantation rate was defined as the mean number of sacs observed on ultrasonography divided by the number of embryos transferred for each patient. Clinical pregnancy rate was defined as the number of intrauterine gestations with fetal cardiac activity per cycle. A biochemical pregnancy was defined by positive hCG levels without a gestational sac. Pregnancy loss after visualization of an intrauterine gestation was considered a spontaneous abortion. Any delivery after 24 weeks of pregnancy was considered a live delivery. The perinatal outcomes analyzed included mode of delivery, incidence of term deliveries, incidence of preterm deliveries (including early and late preterm delivery), overall birth weight, LBW, VLBW, and term LBW.

Continuous variables were expressed as mean ± SD, categorical variables were expressed as absolute numbers and percentages, and non-parametric variables were expressed as medians and interquartile ranges. The Student *t* test was utilized to analyze differences between groups for continuous variables, the χ^2 and Fisher exact tests were used for categorical variables, and the Wilcoxon rank-sum test was used for non-parametric variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the incidence of preterm delivery, overall LBW, and term LBW, and adjusted ORs (aOR) were calculated incorporating the Mantzel– Haenszel correction. Statistical significance was set at $P<0.05$ and statistical analyses were performed using STATA version 13 (StataCorp LP; College Station, TX, USA). Assuming an α error of 5% and power of 80%, a minimum sample size of at least 415 transfer cycles in each group was deemed necessary to detect a 10% difference in implantation rates [3].

3. Results

A total of 2191 blastocyst transfer cycles met the inclusion criteria during the study period; 918 were fresh embryo transfers and 1273 were frozen-thawed transfers. Demographic and baseline characteristics of patients who underwent fresh IVF cycles are detailed in Table 1.

When the demographic characteristics and blastocyst grading were compared between patients who underwent fresh or frozen-thawed blastocyst transfers, no significant differences were observed in age, body mass index, specific infertility diagnoses, endometrial stripe thickness, grading of blastocele expansion, inner cell mass, or trophectoderm of the blastocysts transferred (Table 2).

No differences were noted in the implantation, clinical pregnancy, biochemical pregnancy, spontaneous abortion, and live delivery rates between the two groups (Table 3). The rates of singleton and twin deliveries were also comparable. No triplets or other higher-order gestations were recorded in the present study. Table 4 summarizes the perinatal

Table 1
Demographic and baseline characteristics of patients who underwent fresh blastocyst cycles (n = 918). [a]

Variable	Value
Age, y	35.8 ± 5.09
Parity	0.73 ± 0.26
BMI	23.2 ± 4.72
Previous IVF attempts	1.64 ± 0.69
Total stimulation days	9.52 ± 1.72
Total gonadotropins administered, IU	2378.5 ± 1304.9
Peak endometrial stripe thickness, mm	10.7 ± 3.73
E_2 level on day of trigger, pg/mL	2042.4 ± 802.6
No. of oocytes retrieved	15 (11–17)
No. of mature oocytes	12 (9–14)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); IVF, in vitro fertilization; E_2, estradiol.
[a] Values are given as mean ± SD or median (interquartile range).

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