Freeze-all policy: fresh vs. frozen-thawed embryo transfer

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Objective: To compare in vitro fertilization (IVF) outcomes between fresh embryo transfer (ET) and frozen-thawed ET (the "freeze-all" policy), with fresh ET performed only in cases without progesterone (P) elevation.
Design: Prospective, observational, cohort study.
Setting: Private IVF center.
Patient(s): A total of 530 patients submitted to controlled ovarian stimulation (COS) with a gonadotropin-releasing hormone–antagonist protocol, and cleavage-stage, day-3 ET.
Intervention(s): None.
Main Outcome Measure(s): Ongoing pregnancy rates.
Result(s): A total of 530 cycles were included in the analysis: 351 in the fresh ET group (when P levels were $\leq$1.5 ng/mL on the trigger day); and 179 cycles in the freeze-all group (ET performed after endometrial priming with estradiol valerate, at 6 mg/d, taken orally). For the fresh ET group vs. the freeze-all group, respectively, the implantation rate was 19.9% and 26.5%; clinical pregnancy rate was 35.9% and 46.4%; and ongoing pregnancy rate was 31.1% and 39.7%.
Conclusion(s): The IVF outcomes were significantly better in the group using the freeze-all policy, compared with the group using fresh ET. These results suggest that even in a select group of patients that underwent fresh ET (P levels $\leq$1.5 ng/mL), endometrial receptivity may have been impaired by COS, and outcomes may be improved by using the freeze-all policy. (Fertil Steril® 2015;103:1190–3. ©2015 by American Society for Reproductive Medicine.)
Key Words: Freeze-all, frozen-thawed embryo transfer, delayed frozen-thawed embryo transfer, embryo cryopreservation

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Implantation is one of the most important steps to ensure in vitro fertilization (IVF) cycle success (1); its effectiveness depends on embryo quality, the embryo-endometrium interaction, and endometrial receptivity (ER) (2). Growing evidence in the literature shows that controlled ovarian stimulation (COS), with its supraphysiologic hormonal levels, may decrease ER (3, 4). Moreover, endometrial development can be controlled more precisely during its priming for frozen-thawed embryo transfer (ET) vs. for COS (5). Therefore, as the COS may have adverse effects on ER (6), and embryo cryopreservation has become a routine procedure in IVF labs (7), the "freeze-all" policy has emerged as an alternative to fresh ET to improve IVF outcomes (8–10).

With the freeze-all policy, the entire cohort of embryos is cryopreserved, and the ET is performed later in a natural cycle, or in a cycle with hormonal replacement for endometrial priming. The potential advantage of this method is that it provides a more physiologic environment in which ET can occur; this advantage could lead to better pregnancy rates and decrease maternal and perinatal morbidity (11). However, controversies remain regarding patient selection and the threshold at which a cycle becomes supraphysiologic (11).

To date, no effective noninvasive clinical tools are available to evaluate ER that can be used during a fresh cycle as well. The best way to select patients for the freeze-all policy seems to be by assessing progesterone (P) levels on the day of final oocyte maturation, as P-level elevation is related to decreased pregnancy rates in fresh cycles (12–14). To our knowledge, no published studies have used this method to select patients for fresh or frozen ET. Therefore, we performed this study to compare IVF outcomes for patients using fresh ET, performed when P levels were <1.5 ng/dL on the trigger day, vs. patients using the freeze-all policy.

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MATERIALS AND METHODS

A prospective, observational, cohort study was conducted between January 2012 and December 2013, in a private IVF center in Brazil. An institutional review board approved this study, and informed consent was obtained from all patients.

Patient Selection

The following inclusion criteria were established: [1] gonadotropin-releasing hormone (GnRH) antagonist cycles with day-3 ETs; [2] women aged 20–45 years; [3] fresh and frozen-thawed ET performed with good-quality embryos only, i.e., 6–10 cells with ≤20% fragmentation, and equal blastomere size. Exclusion criteria included: [1] patients with a history of recurrent pregnancy loss; [2] implantation failure (≥3 previous ETs without pregnancy); [3] antral follicle count ≤5; [4] severe male factor infertility (oligospermia <1 million/mL, and azoospermia); [5] uterine pathology; [6] patients with a risk of ovarian hyperstimulation syndrome, defined by estradiol (E_2) >3,000 pg/mL, and/or >15 follicles on the trigger day. Pregnant patients were followed for ≤12 weeks of pregnancy, via an ultrasound scan to confirm ongoing pregnancy. Fresh ET was performed only if P was ≤1.5 ng/mL on the trigger day. The freeze-all strategy was implemented in cases in which P was >1.5 ng/mL on the trigger day.

Study Protocol

Patients underwent COS with recombinant follicle-stimulating hormone (FSH) (Gonal-f; Merck Serono) starting on day 2 or 3 of menses, with doses ranging from 150 to 450 international units per day, according to the patient's age, in a step-down protocol. A GnRH antagonist (cetrorelix; Cetrotide, Merck Serono) was used for pituitary suppression when a leading follicle achieved 14 mm. Final oocyte maturation was induced with a "dual trigger": 250 mcg of recombinant human chorionic gonadotropin (hCG) (Ovidrel, Merck Serono) and 0.2 mg of triptorelin (Gonapeptyl Daily; Ferring Pharmaceuticals) when ≥2 follicles reached a diameter of 18 mm (15). The patients underwent transvaginal ultrasound-guided oocyte retrieval 35 hours after the trigger, followed by intracytoplasmic sperm injection (16). On the third day after oocyte retrieval, embryo quality was evaluated, and 1–4 good-quality embryos (6–10 cells with ≤20% fragmentation, and equal blastomere size) were transferred (fresh cycles).

In the freeze-all group, the entire cohort of good-quality embryos was cryopreserved on day 3. Luteal phase support started on the day of oocyte retrieval. All patients received vaginal micronized P in gel form (Crinone 8%, Merck Serono) in a single daily administration. Progesterone was used for ≥13 days, when a pregnancy test was performed, and until 9 weeks if pregnancy was confirmed (17).

Frozen-Thawed Cycles

All embryos were cryopreserved on day 3, by vitrification using an open system. The endometrial priming started on the 2nd day of each patient's menstrual cycle, when E_2 valerate was orally administered at a dose of 6 mg/d. After at least 12 days of E_2 replacement, an ultrasound scan and hormone-level measurements were performed. If the endometrium was ≥7 mm, and the P level was ≤1.5 ng/mL, the frozen-thawed ET was scheduled. The P replacement with vaginal micronized P in gel (Crinone 8%; Merck Serono) for a single daily administration started 3 days before ET. Estradiol valerate and P were continued until the 9th week of pregnancy. If the endometrium was <7 mm and/or the P level was >1.5 ng/mL after endometrial priming, the ET was canceled.

Hormone Analysis

Blood samples were collected on the day of the ovulation trigger, and serum P levels were measured using a chemiluminescent immunoassay for quantitative determination of the hormone (Diagnostics Biochem Canada Inc), with a sensitivity of 0.1 ng/mL.

Outcomes

Pregnancy was determined by hCG levels measured 11 days after ET. Clinical pregnancy was defined by the observation of intrauterine embryo heart motion by 7 weeks of gestation. Ongoing pregnancy was defined as pregnancy proceeding beyond the 12th week of gestation. The implantation rate was calculated as the ratio of the number of observed embryo heart beats to the number of transferred embryos. The main outcome measure was ongoing pregnancy rate, which was shown to be comparable to that for live births, as a measure of efficacy (18). Implantation, pregnancy, and clinical pregnancy rates were the secondary outcome measures.

Statistical Analysis

The data are presented as the mean ± standard deviation (SD), or as a percentage. A comparison of the quantitative variables was performed using Student's *t*-test for independent samples. For a comparison of the categoric data, χ^2 analysis was performed. Differences were considered significant if $P<.05$.

A logistic regression analysis was performed to determine the variables that could be independently associated with ongoing pregnancy, and could affect outcomes. Age, basal FSH level, antral follicle count, number of retrieved oocytes and mature eggs, number that were bipronuclear (2 PN), number of transferred embryos, and cycle type (freeze-all vs. fresh) were included in the analysis. Statistical analysis was done with SPSS version 19.0 for Windows (SPSS, Inc).

RESULTS

During the study period, 1,357 oocyte retrievals were performed, and 530 patients fulfilled the inclusion criteria and agreed to participate in the study. The women's characteristics are shown in Table 1.

A logistic regression analysis was performed, and the variables that were found to be independently associated with