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Freeze-only versus fresh embryo transfer in a multicenter matched cohort study: contribution of progesterone and maternal age to success rates

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Objective: To compare implantation and ongoing pregnancy rates in freeze-only versus fresh transfer cycles.
Design: Retrospective matched cohort study.
Setting: Not applicable.
Patient(s): Women selected using a matching algorithm for similar distributions of clinical characteristics for a total of 2,910 cycles (1,455 fresh cohort and 1,455 freeze-only cohort).
Intervention(s): None.
Main Outcome Measure(s): Implantation and ongoing pregnancy rates.
Result(s): Implantation and ongoing pregnancy rates were statistically significantly higher in the freeze-only transfer cohort than in the matched fresh transfer cohort: ongoing pregnancy rate for freeze-only was 52.0% (95% confidence interval [CI], 49.4–54.6) and for fresh was 45.3% (95% CI, 42.7–47.9), odds ratio (OR) 1.31 (95% CI, 1.13–1.51). In a stratified analysis, the odds of ongoing pregnancy after freeze-only transfer were statistically significantly higher for women both above and below age 35 with progesterone concentration >1.0 ng/mL (age ≤ 35: OR 1.38 [1.11–1.71]; age >35: OR 1.73 [1.34–2.24]). For women with progesterone concentration ≤ 1.0 ng/mL, no statistically significant difference in freeze-only odds of ongoing pregnancy was observed in either age group. The sensitivity analysis revealed that increasing maternal age alone (regardless of progesterone) trended toward a more beneficial effect of freeze-only cycles. A lower progesterone concentration was associated with statistically significantly higher ongoing pregnancy odds for fresh but not freeze-only cycles.
Conclusion(s): Freeze-only transfer protocols are associated with statistically significantly higher ongoing implantation and pregnancy rates compared with fresh transfer cycles. This effect is most pronounced for cycles with progesterone >1.0 ng/mL at trigger and may also be stronger for older patients. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Controlled ovarian stimulation, cryopreservation, freeze-only, fresh transfer, frozen embryo transfer

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In vitro fertilization (IVF) with frozen embryo transfer (FET) has become increasingly common in the United States. According to the Society for Assisted Reproductive Technology (SART), the number of FETs increased by over 80% from 2006 to 2012, which far outpaced the rate of increase for fresh cycles over the same period (1). Advances in cryopreservation of embryos have contributed to this trend, as newer vitrification techniques have improved embryo survival rates compared with slow freezing (2). In addition, there is increasing evidence that FET may lead to more favorable perinatal and live-birth outcomes, including a lower risk of preterm birth, low birth weight, placenta previa, and placental abruption (1, 3–7). As FET has become more common, freeze-only protocols have emerged in which all embryos are electively frozen and transferred in a later natural or medicated cycle.

Despite this growing trend, studies on the impact of freeze-only transfer versus fresh transfer protocols are limited. Two small, randomized, controlled trials (RCTs) by Shapiro et al. (8, 9) in normal and high responders reported increased pregnancy rates in freeze-only versus fresh transfers. Another RCT in patients with polycystic ovary syndrome found that freeze-only transfer was associated with higher live-birth rates compared with fresh transfer (10). A prospective cohort study of cleavage-stage embryos and a retrospective cohort study among women with prior implantation failure also found increased success rates in freeze-only transfer compared with fresh transfer protocols (11, 12).

Given the limited evidence base in the literature and the small cohort sizes of prior studies, we used a large multicenter data set to investigate the effects of freeze-only versus fresh transfer in a retrospective matched cohort. In addition, our study aimed to determine whether maternal age and progesterone (P) affected the relationship between freeze-only versus fresh transfer protocols and pregnancy outcomes. To our knowledge, this study is the largest to investigate outcomes of freeze-only versus fresh transfer and the first to stratify outcomes by maternal age and P concentration on the day of trigger.

MATERIALS AND METHODS

We performed a retrospective matched cohort study on patients from 12 fertility treatment centers in the United States who underwent IVF cycles between 2009 and 2015. We included cycles in which fresh embryo(s) were transferred (fresh) and cycles in which all embryos were frozen, followed by a later transfer (freeze-only). We excluded frozen transfers of supernumerary embryos, cancelled cycles, cycles in which preimplantation genetic screening (PGS) or preimplantation genetic diagnosis was used, and cycles that were missing any data used for matching between the fresh and freeze-only cohorts (patient characteristics, measures of ovarian reserve, and cycle details; see the section "Propensity Score Cohort Matching"). Our analysis included only blastocyst-stage transfers.

Patients underwent controlled ovarian stimulation (COS) according to established practice patterns at each clinic using one of several protocols (antagonist, long agonist, flare) and human chorionic gonadotropin (hCG) or leuprolide acetate (LA; Lupron; AbbVie) trigger. Oocytes were retrieved transvaginally 35 to 36 hours after hCG or LA administration (the trigger was administered when the largest follicle measured 18–24 mm) and were fertilized using either conventional IVF or intracytoplasmic sperm injection (ICSI). The embryos were then cultured to the blastocyst stage.

For fresh cycles, luteal support was initiated after retrieval, and the embryos were transferred into the uterus at the blastocyst stage. For freeze-only cycles, embryos were cryopreserved at the blastocyst stage according to the established practice protocols at each clinic. In a subsequent cycle, patients underwent FET in either a natural or medicated cycle (using estrogen and P supplementation). Indications for freeze-only cycles included, but were not limited to, premature P elevation, patient preference, and ovarian hyperstimulation syndrome (OHSS) risk.

Implantation rate was defined as the number of heartbeats divided by the number of embryos transferred. Ongoing pregnancy was defined as continued pregnancy at the time that the patient transferred care from a reproductive endocrinologist to an obstetrician (usually 8–12 weeks, depending on the clinic).

Propensity Score Cohort Matching

We used a propensity score method to match characteristics between the freeze-only and fresh transfer groups based on factors that may affect success of IVF cycles, using a logistic regression in which the treatment group is the outcome and the factors of interest are the predictors. The propensity score is the estimated probability that a given patient would have been assigned to the treatment group, given a particular set of variables.

Before matching, 13,791 cycles (1,455 freeze-only and 12,336 fresh) were available for analysis. The cycles were matched on characteristics that may influence the success of IVF cycles, including patient characteristics (age, body mass index, diagnosis, clinic, parity, gravidity), measures of ovarian reserve (antral follicle count, day-3 follicle-stimulating hormone [FSH], estradiol [E_2], luteinizing hormone [LH]), and cycle characteristics (gonadotropin dose, P concentration at trigger, oocytes retrieved, number of usable embryos, and number of embryos transferred) (Table 1).

After achieving a balanced cohort through propensity score matching, we performed regression analysis of the treatment groups on the outcome, while controlling for the propensity score. Mixed effects logistic regression was used to compute the odds ratios (ORs) between freeze-only and fresh cycles in the matched data. Clinics and patients were treated as random effects in the mixed model to account for repeated observations on patients and the within-clinic correlation of ongoing pregnancy rates. The distribution of key characteristics before and after matching is shown in Supplemental Table 1 and Supplemental Figure 1 (available online). Most characteristics differed substantially before matching. After matching, all characteristics were similar between the freeze-only and fresh groups.