Matched-cohort comparison of single-embryo transfers in fresh and frozen-thawed embryo transfer cycles

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Objective: To discern the potential effect of ovarian stimulation on implantation potential by comparing ongoing pregnancy rates from matched blastocysts in fresh and frozen-thawed single-embryo-transfer cycles.
Design: Matched cohort study.
Setting: Private fertility center.
Patient(s): Ninety-three matched pairs of single-blastocyst transfer.
Intervention(s): Fresh and frozen-thawed embryo transfers were matched on embryo parameters and patient age.
Main Outcome Measure(s): Ongoing pregnancy at 10 weeks' gestation.
Result(s): The fresh and frozen-thawed groups did not differ significantly in blastocyst diameter, inner cell mass size, trophectoderm cell count, patient age, use of genetic screening, or presence of supernumerary embryos. The ongoing pregnancy rate was significantly greater in the frozen-thawed group than in the fresh group for transfers of day 6 blastocysts (54.3% vs. 17.1%, respectively), but not for day 5 blastocysts (60.9% vs. 56.5%, respectively). This resulted in the overall ongoing pregnancy rate to be significantly greater in the frozen-thawed group than in the fresh group (55.9% vs. 26.9%, respectively).
Conclusion(s): Autologous day 6 blastocysts transferred in frozen-thawed cycles have significantly greater chance of viable implantation than morphologically equivalent embryos transferred in fresh cycles. This advantage appears to result from impaired implantation of day 6 blastocysts in fresh transfers after ovarian stimulation, suggesting that embryo-endometrium asynchrony is a major cause of impaired endometrial receptivity after ovarian stimulation. (Fertil Steril® 2013;99:389–92. ©2013 by American Society for Reproductive Medicine.)
Key Words: Endometrial receptivity, embryo transfer, in vitro fertilization, ovarian stimulation, embryo-endometrium synchrony

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Implantation failure is a common occurrence in cycles of in vitro fertilization (IVF). Success requires a viable embryo synchronous with a receptive endometrium. Controlled ovarian stimulation (COS) is routinely used to obtain numerous oocytes for IVF. However, COS is associated with altered endometrial development (1–3), including advanced histology (4, 5) and impaired endometrial receptivity (6).

Randomized trials have reported reduced implantation and pregnancy rates in autologous fresh cycles compared with cycles using thawed embryos, which is consistent with impaired endometrial receptivity in fresh autologous cycles (6, 7). However, it may be difficult to characterize the endometrial effects and their magnitude from randomized trials in which the experimental units are patients rather than embryos. The potential for transfer of embryos of different quality in the two arms may

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confound the endometrial contribution by introducing embryonic effects. To remove potential embryonic effects, a comparison of transfers of equivalent embryos in fresh and frozen-thawed cycles is necessary.

The present study uses a matched cohort design with embryos transferred in fresh cycles matched with morphologically equivalent embryos transferred in frozen-thawed cycles. The use of only single-embryo transfers (SETs) precludes ambiguous embryonic fate.

MATERIALS AND METHODS

This study included all autologous SET cycles with day 5 or day 6 blastocyst transfer in the 8-year study period ending December 31, 2011. Blastocyst transfer was the standard of care at this center throughout the study period, regardless of cohort size. SET was less common than double-embryo transfer at this center in this period.

The matching algorithm required exact matching by embryo diameter quartile range ($\leq$175 μm, 176–188 μm, 189–205 μm, or $>$205 μm), day of blastulation/transfer (day 5 or day 6), Society for Assisted Reproductive Technology age group ($<$35 y, 35–37 y, 38–40 y, 41–42 y, or $>$42 years), and use of genetic testing. Closest matches by embryo diameter and patient age were preferentially selected within the required ranges. Nonmedical staff blinded to results other than the matching criteria performed the matching. Matched records were used only once.

Patients were stimulated with gonadotropins, typically with the use of urinary FSH (Menopur; Ferring Pharmaceuticals) and recombinant FSH (Follistim; Schering-Plough) in combination. A GnRH antagonist was used for pituitary suppression (ganirelix acetate; Schering-Plough). hCG was used for final oocyte maturation, sometimes in combination with GnRH agonist. Patients triggered with only GnRH agonist were excluded.

Patients with elevated preovulatory P or prior history of implantation failure were offered the option of cohort cryopreservation at the bipronuclear stage. Others accepted that treatment while participating in randomized trials (6, 8). Entire cohorts were thawed in a subsequent cycle. Whether fresh or thawed, embryos were cultured to the blastocyst stage in the same sequential media (Quinn Advantage Protein Plus Cleavage Media and Quinn Advantage Protein Plus Blastocyst Media; Sage) or single-step medium (LifeGlobal), depending on which was in use by this center at the time. In all cases, a single blastocyst was selected for ultrasound-guided transfer. In most cases, the embryo selection was based on morphology alone, but in rare cases, day 3 biopsy and preimplantation genetic screening (PGS) were also used. Supernumerary blastocysts of good morphologic quality were cryopreserved for potential future use.

Blastocysts were measured before transfer. Blastocyst diameter was measured from zona edge to zona edge along the longest axis with an ocular micrometer. Inner cell mass (ICM) was measured along the longest axis and its widest perpendicular axis, and these were multiplied to estimate cross-sectional ICM area. Trophectoderm cell counts were measured along an embryonic "equator" in one plane of focus, counting cells immediately apposed to the surface of the zona pellucida.

Patients using thawed embryos were administered oral E_2 (Estrace, 6.0 mg daily) and E_2 patches as needed beginning 10–14 days before thaw. Daily P injections (typically 100 mg) were initiated the day before thaw. Patients using fresh embryos initiated P and E_2 supplements 1 day after retrieval (through 2008) or 2 days after retrieval (after 2008). All patients received luteal-phase E_2 and P supplements sufficient to sustain serum levels of 200 pg/mL and 15 ng/mL, respectively. Trilaminar endometrial pattern was confirmed before trigger (fresh cycles) or P start (freeze-thaw cycles).

Pregnancy was defined by rising serum hCG titers within 10 days after blastocyst transfer. Clinical pregnancy was defined by sonographic observation of fetal heart motion at 6–7 weeks' gestation. Ongoing pregnancy was defined by viable fetal heart motion observed at 10 weeks' gestation. Early pregnancy losses included all pregnancies failing to achieve ongoing pregnancy. Elective SETs (eSETs) were those in which supernumerary blastocysts were frozen.

JMP version 5.01 (SAS Institute) was used for statistical analyses, except where noted. JMP version 7.02 was used to obtain the confidence intervals for risk ratios. McNemar test was used for comparing nominal variables (Graphpad Software) among matched records, and Fisher exact test was used for other comparisons of nominal variables. Wilcoxon test was used to compare numeric variables. $P<.05$ was considered to be significant. Prior Institutional Review Board approval was obtained for this retrospective study.

RESULTS

There were 377 autologous SET cycles, including 258 fresh and 119 freeze-thaw cycles available for matching. Of these, the matching algorithm was able to match 93 pairs of fresh and freeze-thaw cycles (186 matched transfers, total). The freeze-thaw and fresh transfers included 12 and 5 transfers, respectively, from two randomized trials (6, 8), and another 15 of the fresh transfers were used in a large retrospective analysis (13), so that 32 (17.2%) of the 186 transfers matched here were also used in those previous reports.

Demographics and potential confounding variables are summarized in Table 1. There were no significant differences in patient age, day of blastulation/transfer, embryo diameter,

TABLE 1

Comparison of demographics and potential confounders in matched fresh and freeze-thaw transfers.

	Fresh	Freeze-thaw	*P* value
Transfers	93	93	
Patient age (y)	33.8 ± 4.7	33.8 ± 4.7	NS
Age range (y)	23–45	22–45	
Day 5 blastulation	23 (24.7)	23 (24.7)	NS
Blastocyst diameter (μm)	192.5 ± 17.6	192.6 ± 18.1	NS
Inner cell mass (μm^2)	4,047 ± 1,467	3,939 ± 1,629	NS
Trophectoderm cell count	13.8 ± 4.3	14.0 ± 4.7	NS
eSET	23 (24.7)	19 (20.4)	NS
Genetic screening	4 (4.3)	4 (4.3)	NS
Endometrial thickness (mm)	10.1 ± 2.2	9.1 ± 1.6	.0050

Note: Values are mean ± SD, ranges, or n (%).

Shapiro. Embryo-endometrium asynchrony. Fertil Steril 2013.

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