To delay or not to delay a frozen embryo transfer after a failed fresh embryo transfer attempt?

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Objective: To evaluate if increasing the interval between a failed fresh embryo transfer and a subsequent frozen embryo transfer (FET) cycle has any effect on clinical pregnancy rates (CPRs).
Design: Retrospective cohort study.
Setting: University-based tertiary referral center.
Patient(s): Women who underwent at least one FET after ovarian stimulation for in vitro fertilization (IVF) and a failed fresh embryo transfer attempt from January 2010 to November 2014. We divided our sample according to the "timing" of the first FET (TF-FET), defined by the interval between oocyte retrieval and the FET cycle start date. The start of the FET was classified as either immediate ($\leq$22 days after oocyte retrieval) or delayed (>22 days after oocyte retrieval).
Intervention(s): None.
Main Outcome Measure(s): CPR after the first FET.
Result(s): A total of 1,183 FET cycles (performed in 1,087 women) were included in our study. No significant differences were found between the immediate and delayed FET groups regarding age, number of oocytes retrieved, number of good-quality embryos produced, embryo developmental stage at FET, and number of frozen embryos transferred. Most importantly, the CPRs of the first FET did not differ significantly according to the TF-FET (32.5% after immediate FET vs. 31.7% after delayed FET), even after adjusting for potential confounding with the use of multivariable logistic regression.
Conclusion(s): FETs performed immediately after fresh IVF cycles had CPRs similar to those postponed to a later time. Therefore, deferring FETs may unnecessarily prolong time to pregnancy. (Fertil Steril® 2016;105:1202–7. ©2016 by American Society for Reproductive Medicine.)
Key Words: Frozen embryo transfer, endometrial receptivity, time to pregnancy, assisted reproduction, embryo cryopreservation

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Ever since the first live birth after a frozen embryo transfer (FET) in 1983, the cryopreservation and deferral of embryo transfers has progressively increased, currently accounting for up to one-third of all children born with the use of assisted reproductive technologies (ART) in the United States (1). Meanwhile, the difference between frozen and fresh embryo transfers regarding perinatal outcomes has been a subject of much debate. Although FET cycles have been associated with lower rates of preterm birth, low birth weight (2–5), antepartum hemorrhage (6), and ectopic pregnancy (7–10), they have also been linked to higher rates of large-for-gestational-age infants (3, 11), placental/hypertensive complications (3), and conflicting perinatal mortality rates (6, 11). These results have led many researchers to question whether the overall benefits of routinely performing fresh embryo transfers may not actually be outweighed by these accumulating potential risks (12–15).

Physicians are commonly asked by their patients whether ovarian stimulation may bear any carryover effect on a subsequent treatment (16), and FETs are frequently postponed in an attempt

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to minimize any conceivable residual effect that ovarian stimulation may have on endometrial receptivity (17). However, the literature on this matter is rather scarce (18, 19). For this reason, although this empirical decision may be based on the best of intentions, the elective deferral of FETs may unnecessarily frustrate couples who wish to become pregnant as soon as possible.

The objective of the present study was to evaluate if increasing the interval between a failed fresh embryo transfer and a subsequent FET cycle has any effect on clinical pregnancy rates (CPRs).

MATERIALS AND METHODS

Study Population and Design

We performed a retrospective cohort study including all women who underwent at least one FET after ovarian stimulation for in vitro fertilization (IVF) from January 2010 to November 2014 at our center. Approval to retrieve and analyze the data was provided by the Ethics Committee of Brussels University Hospital (Dutch-Speaking Free University of Brussels).

Only the outcomes of the first FET cycles performed after ovarian stimulation and a failed fresh embryo transfer attempt were assessed. To minimize bias, we included only FETs that followed fresh cycles in which a GnRH antagonist and hCG alone were administered for down-regulation and ovulation triggering, respectively.

Women who were acceptors of donated oocytes or performed either in vitro maturation or blastocyst biopsy for preimplantation genetic diagnosis were excluded from the study. Furthermore, if during the preceding ovarian stimulation cycle ovulation was triggered with a drug other than hCG (e.g., a GnRH agonist, either alone [20] or in combination with hCG [21]) or hCG was administered for reasons other than ovulation triggering (e.g., for late-follicular ovarian stimulation [22] or luteal phase support [23]), those cycles were also disregarded. Finally, FET cycles performed under GnRH agonist down-regulation or with concomitant exogenous ovarian stimulation also were excluded from the sample.

Ovarian Stimulation Performed during the Preceding Failed Fresh Embryo Transfer Cycles

Ovarian stimulation was initiated on day-2 of the menstrual cycle with either recombinant FSH (rFSH; Gonal-F [Merck Serono Pharmaceuticals], Puregon [Merck Sharp and Dohme], or Elonva [Merck Sharp and Dohme]) or highly purified hMG (hp-hMG; Menopur [Ferring Pharmaceuticals]). Pituitary down-regulation was performed by means of daily administrations of either cetrorelix (Cetrotide; Merck Serono Pharmaceuticals) or ganirelix (Orgalutran; Merck Sharp and Dohme) starting from day 7 of the menstrual cycle. Cycles were monitored with the use of serial vaginal ultrasound scans and serum determination of E_2, P, LH, and FSH. Whenever necessary, dose adjustments of rFSH/hp-hMG were performed according to ovarian response.

As soon as three follicles with mean diameters $\geq$17 mm were observed, final oocyte maturation and ovulation were triggered with the use of hCG (5,000–10,000 IU highly purified urinary hCG [Pregnyl; Merck Sharp and Dohme] or 250 UI recombinant hCG [Ovitrelle; Merck Serono Pharmaceuticals]).

Oocyte Retrieval, Insemination, Embryo Quality Assessment, and Cryopreservation

Cumulus-oocyte complexes were collected by means of transvaginal aspiration ~36 hours after triggering. The insemination of the collected oocytes was performed with the use of either conventional IVF or intracytoplasmic sperm injection (ICSI). Fertilization was assessed ~18 hours after insemination, and from then onward embryo development was graded daily until embryo transfer or cryopreservation according to the following parameters: number and size of blastomeres, rate of fragmentation, multinucleation of the blastomeres, and early compaction. Blastocyst quality on day 5/6 was assessed according to the criteria proposed by Schoolcraft et al. (24).

Good-quality embryos that were not used for the failed fresh embryo transfer attempt were cryopreserved by means of vitrification with the use of a closed vitrification system with high-security straws (CBS-ViT-HS; Cryobiosystem) in combination with dimethylsulfoxide and ethylene glycol bis (succinimidyl succinate) as cryoprotectants (Irvine Scientific Freeze Kit; Irvine Scientific), as described by van Landuyt et al. (25). Embryos were vitrified as cleavage-stage embryos on day 3 or full-to-expanded blastocysts on day 5 or 6 of embryo culture. Day 3 embryos were warmed the day before FET and transferred as day 4 embryos in day 4 endometrium. Day 5/6 blastocysts were warmed in the morning of the day of transfer and transferred in day 5 endometrium.

Endometrial Preparation for the FET

The FETs took place in either a natural or an artificially supplemented cycle monitored by both pelvic ultrasound and blood sampling of E_2, P, LH and FSH. In a natural cycle, ovulation occurred either spontaneously (detected by means of serial plasma LH assessments until a LH peak was noted) or artificially triggered (with the use of 5,000 IU hCG, as soon as one follicle $\geq$17 mm and endometrial thickness $\geq$7 mm were observed). In artificially supplemented cycles, preparation of the endometrium consisted of sequential administration of E_2 valerate and micronized vaginal P as previously described (26). In brief, we administered 2 mg E_2 valerate twice per day (Progynova; Bayer-Schering Pharma) for 7 days, followed by 6 days 2 mg E_2 valerate three times per day. On day 13, endometrial thickness was measured by means of ultrasound scan. If the endometrial thickness was $\geq$7 mm, supplementation with 200 mg micronized vaginal P (Utrogestan; Besins) three times per day was initiated. If the endometrial thickness was <7 mm, patients continued to take 2 mg E_2 valerate orally three times per day until the endometrium thickness was $\geq$7 mm, at which point P supplementation was started.