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.

The "Timing" of the First Frozen Embryo Transfer

The "timing" of the first FET (TF-FET) was defined as the interval between oocyte retrieval and the start of the first FET cycle. We divided our sample in cycles with either an immediate (≤22 days after oocyte retrieval) or delayed (>22 days after oocyte retrieval) start of FET cycle (Fig. 1). This cutoff was devised by adding the interval between oocyte retrieval and the first pregnancy test (15 days) to an extra interval of up to 7 days necessary for the patients to have their withdrawal bleeding and begin their first FET cycle. By using these intervals, we essentially divided our sample into: 1) women who had an immediate FET; and 2) women who waited at least one menstrual cycle before having their transfer.

Embryos were transferred under ultrasound guidance with the use of a K-soft-5100 catheter (Cook). The choice to transfer one or two embryos was decided by the clinician depending on patient age and according to Belgian law (27).

Main Outcome Measure and Statistical Analysis

Basic demographic characteristics were compared between the women who underwent immediate and delayed FET, with the use of the Student *t*/Mann-Whitney (for continuous variables) or χ^2 (for categoric variables) tests.

Clinical pregnancy, defined by the International Committee for Monitoring Assisted Reproductive Technology as the visualization of a gestational sac during transvaginal ultrasound at 7 weeks of gestational age (28), was the main outcome of our study. Our secondary outcome was live birth after 24 weeks, with unknown outcomes (patients lost to follow-up) being considered as negative.

CPR and live birth rates per FET were assessed both crudely and with the use of multivariable logistic regression accounting for the following known potential confounders for FET cycle outcome: the woman's age, number of good-quality embryos produced, type of FET cycle, stage and number of embryos transferred, and quality of the best embryo transferred. Crude and adjusted odds ratios (ORs) were estimated, adjusting the standard errors to eventually allow for more than one fresh cycle performed in the same women to be included in the analysis.

A *P* value was considered to be significant at <.05. For the statistical analysis, we used Stata software version 13.1 (Statacorp).

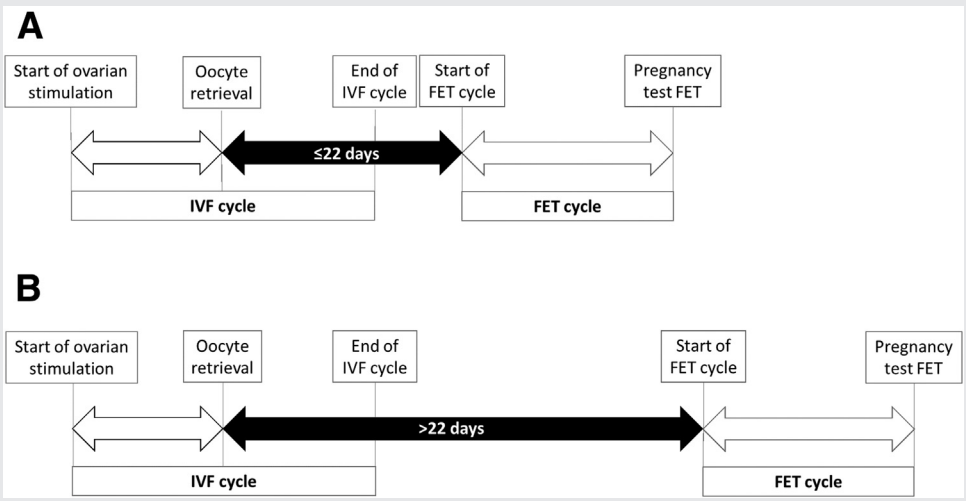
RESULTS

A total of the 1,183 first FET cycles (performed in 1,087 women) were included in the analysis. The indications for IVF included: male-factor infertility (n = 589; 49.8%), tubal-factor infertility (n = 164; 13.9%), ovulatory disorders (n = 109; 9.2%), endometriosis (n = 61; 5.2%), and otherwise unexplained infertility (n = 346; 29.3%). The majority of FET cycles (n = 986; 83.4%) were initiated after a waiting period of >22 days after oocyte retrieval, regardless of the year of treatment (Fig. 2).

Patient Demographics and General Characteristics of the Treatment Protocol

The baseline characteristics of the preceding ovarian stimulation and IVF cycles according to TF-FET are presented in Table 1. No significant differences were found between the groups regarding age, total dose of exogenous FSH administered, number of oocytes retrieved, and number of good-quality embryos either produced or used during the failed fresh embryo transfer attempt.

FIGURE 1



Study groups according to timing of first frozen embryo transfer (FET). The FET cycles were divided in either (**A**) immediate (≤22 days after oocyte retrieval) or (**B**) delayed (>22 days after oocyte retrieval).

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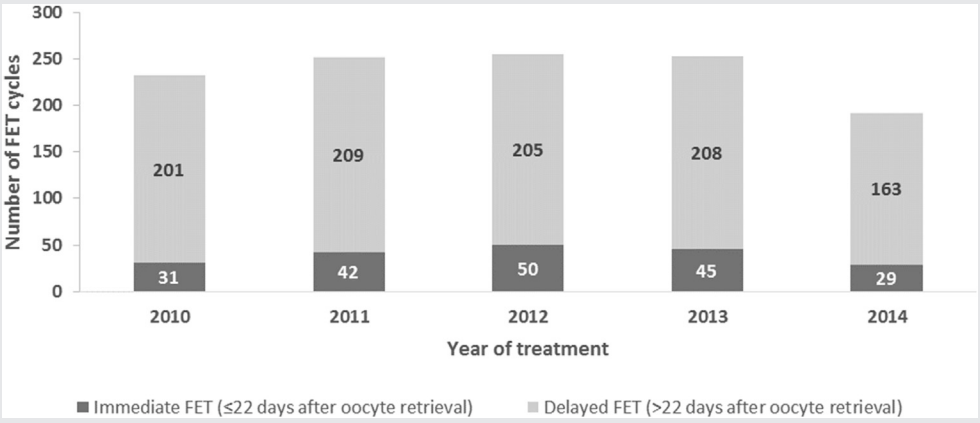
FIGURE 2



Timing of first frozen embryo transfer (FET) cycle according to year of treatment (n = 1,183).

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Relationship between TF-FET and FET Pregnancy Outcomes

Further details regarding the FET cycles are presented in Table 2, including the pregnancy outcome. The embryo developmental stage at transfer, type of FET cycle, and number of embryos transferred did not vary between the immediate and delayed FET groups.

Regarding CPR per FET, these did not differ significantly according to TF-FET (32.5% after immediate FET versus 31.7% after delayed FET, $P=.838$), even after adjusting for age, number of good-quality embryos produced, type of FET cycle, stage and number of embryos transferred, and quality of the best embryo transferred with the use of multivariable logistic regression (predicted probabilities of 32.6% for immediate FET versus 31.7% for delayed FET; $P=.803$; crude and adjusted ORs are presented in Supplemental Table 1 [available online at www.fertstert.org]).

Of the 377 clinical pregnancies in our sample, 286 had a live delivery after 24 weeks, 86 had no live birth, and 5 were lost to follow-up. Live birth rates did not vary significantly between groups (24.4% after immediate FET versus 24.1% after delayed FET; $P=.946$), even after accounting for the potential confounders (predicted probabilities of 24.5% for immediate FET versus 24.1% for delayed FET; $P=.895$).

DISCUSSION

This is, to our knowledge, the first study to comprehensively assess the trends and effects of FET scheduling during ART, revealing that the intentional postponement of FET cycles occurred frequently and did not enhance pregnancy outcomes.

Because delaying FETs may be a potential source for ART-related patient stress and treatment discontinuation (29, 30), we considered that a broader understanding of the motives behind such a frequent decision deserved further scrutiny. Our failure to show any clinical expression of a residual effect of ovarian stimulation on the endometrial receptivity of a subsequent cycle may reassure physicians who might otherwise hesitate to schedule FETs without delay.

On the other hand, patients may opt to purposely delay an FET cycle owing to a number of clinically unrelated reasons. To this extent, a scientific presentation including 271 FET cycles in 2008 was the first to propose that delaying FET cycles might actually even reduce the chances of achieving pregnancy, because delaying embryo transfer was associated with a significant absolute difference of 14.2% in CPR (35.2% for immediate FET versus 21.0% for delayed FET; $P<.01$) (17). However, we consider that our larger sample

TABLE 1

Baseline characteristics of the ovarian stimulation and IVF cycles according to timing of first frozen embryo transfer (FET).

Characteristic	Immediate FET (n = 197)	Delayed FET (n = 986)	*P* value
Woman's age (y)	32.4 ± 4.4	32.5 ± 4.3	.697
Total dose of exogenous FSH (IU)	1,562.5 ± 493.7	1,605.1 ± 553.2	.333
Oocytes retrieved	11.1 ± 6.1	10.4 ± 5.5	.135
Good-quality embryos produced	4.5 ± 2.4	4.4 ± 2.5	.829
Embryos transferred in the failed fresh cycle	1.3 ± 0.5	1.2 ± 0.4	.338

Note: Immediate FET occurred ≤22 days after oocyte retrieval, and delayed FET occurred >22 days after oocyte retrieval.

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TABLE 2

Baseline characteristics of the frozen embryo transfer (FET) cycle according to timing of first FET.

Characteristic	Immediate FET (n = 197)	Delayed FET (n = 986)	*P* value
Embryo developmental stage at transfer, n (%)			
Cleavage stage	95 (48.2)	472 (47.9)	.928
Blastocyst stage	102 (51.8)	514 (52.1)	
Type of FET cyclen, n (%)			.565
Artificially supplemented cycle	35 (17.8)	181 (18.4)	
Natural cycle (hCG trigger)	87 (44.1)	396 (40.1)	
Natural cycle (spontaneous LH peak)	75 (38.1)	409 (41.5)	
Embryo quality of best embryo transferred, n (%)			.854
1	122 (61.9)	603 (61.2)	
2	54 (27.4)	264 (26.8)	
3	21 (10.7)	119 (12.1)	
No. of frozen embryos transferred, mean ± SD	1.4 ± 0.5	1.4 ± 0.5	.665
Pregnancy outcomes, n (%)			
Crude clinical pregnancy rate per FET	64 (32.5)	313 (31.7)	.838
Adjusted clinical pregnancy rate per FET, %[a]	32.6	31.7	.803
Crude live birth delivery rate per FET[b]	48 (24.4)	238 (24.1)	.946
Adjusted live birth delivery rate per FET, %[a,b]	24.5	24.1	.895

Note: Immediate FET occurred ≤22 days after oocyte retrieval, and delayed FET occurred >22 days after oocyte retrieval. Data are presented as n () unless otherwise specified.
[a] Predicted probabilities with the use of multivariable logistic regression and adjusting for woman's age, number of good-quality embryos produced, quality of the best embryo transferred, type of FET cycle, and stage and number of frozen embryos transferred (univariable and multivariable odds ratios are presented in Supplemental Table 1).
[b] Cycles without a live birth outcome (n = 5) were considered to be nonlive births.

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and confounder-adjusted analysis offer a more accurate inference that may serve as a better basis to counsel women seeking to temporarily postpone their next FET cycle. Furthermore, our results agree and add to the already existent body of evidence showing, so far, a lack of an effect of the duration of both embryo cryopreservation (31) and uterine ageing (32) on FET pregnancy outcomes.

Although the present study included a large sample size and adjusted for potentially confounding differences between the groups, it is limited by its retrospective nature and by the possibility of unmeasured confounding. We considered that a retrospective design was the most appropriate for this research hypothesis because we had ethical reservations about performing a prospective study offering a treatment modality which, at first glance, had a biologic plausibility of being detrimental and seemed likely be an inferior alternative. Furthermore, one can also assume that such a clinical trial would be difficult to conduct, because a noninferiority trial capable of detecting even the largest difference we found (1.2%) between immediate and delayed FET (32.5% vs. 31.7%) would require >40,000 cycles per group to achieve a reasonable 80% power with a significance level of 5%. Regarding unmeasured confounding, we were unable to account for all possible confounders, such as smoking and body mass index (BMI). However, it is unlikely that patients with heavy smoking habits or extreme BMIs would be proposed different FET scheduling schemes based on these characteristics alone.

Finally, we should also reiterate that this study evaluated only the effect of TF-FET on CPRs and live birth rates in GnRH antagonist down-regulated cycles and that our results should not be assumed as valid surrogates for the potential carryover effect of ovarian stimulation on other pregnancy outcomes (such as preterm birth, birth weight, and fetal development) nor following GnRH agonist–suppressed ovarian stimulation cycles. To this extent, a previous study providing translational evidence to support that endometrium exposed to ovarian stimulation with the use of GnRH antagonist cotreatment mimics natural endometrium better than one exposed to GnRH agonist down-regulation (33) can not be ignored when attempting to extrapolate our results.

CONCLUSION

This study provides the first potential answer to a very frequent question posed by couples seeking parenthood with the use of IVF: "Will waiting before performing my FET cycle increase my chances to become pregnant?" Ovarian stimulation did not seem to have a carryover effect on CPR per FET, allowing patients to opt to perform their FET cycle either without delay or at their own convenience, potentially reducing the frustration associated with the various waiting periods of IVF treatment.

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SUPPLEMENTAL TABLE 1

Crude and adjusted odds ratios (ORs) for timing of first frozen embryo transfer (FET) and other potential confounders for clinical pregnancy after FET.

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)
Timing of first FET		
Immediate	Reference	Reference
Delayed	0.97 (0.70–1.34)	0.96 (0.68–1.34)
Woman's age		
Per year	1.00 (0.97–1.03)	1.00 (0.97–1.03)
No. of embryos cryopreserved		
Per embryo	1.06 (1.02–1.11)	1.02 (0.97–1.07)
Type of FET cycle		
Artificial cycle	Reference	Reference
Natural cycle (hCG trigger)	0.75 (0.53–1.07)	0.78 (0.54–1.13)
Natural cycle (spontaneous LH peak)	1.28 (0.91–1.81)	1.32 (0.93–1.92)
No. of embryos transferred		
Single	Reference	Reference
Double	1.60 (1.25–2.05)	1.40 (1.06–1.85)
Quality of the best embryo transferred		
1	Reference	Reference
2	0.60 (0.45–0.81)	0.57 (0.42–0.77)
3	0.31 (0.19–0.51)	0.29 (0.18–0.48)
Embryo stage		
Cleavage	Reference	Reference
Blastocyst	1.22 (0.95–1.56)	1.66 (1.27–2.17)

Note: The crude and adjusted OR were estimated using univariable and multivariable logistic regression, respectively. CI = confidence interval.

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