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Protocol Article

Immediate versus postponed blastocyst transfer in stimulated or programmed frozen embryo transfer cycles – a protocol for a non-blinded randomised clinical trial

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ABSTRACT

INTRODUCTION. It is standard clinical practice to postpone frozen embryo transfer (FET) for at least one menstrual cycle after a failed fresh embryo transfer or a freeze-all cycle. Delaying FET has been hypothesised to minimise the negative effect of controlled ovarian stimulation. However, this practice may be associated with increased psychological distress and delayed time to pregnancy. In this clinical study, we aim to investigate whether immediate SC- or PC-FET is non-inferior to postponed SC- and PC-FET in terms of live birth rate (LBR).

METHODS. The study is designed as a multicentre, randomised controlled, non-blinded, non-inferiority trial. A total of 484 women aged 18-45 years who are set to undergo SC- or PC-FET will be included in the trial. Participants will be randomised 1:1 to FET in the first cycle after a failed fresh transfer or freeze all (FET immediate) or to FET in a subsequent cycle (FET postponed). The main outcome will be LBR.

CONCLUSIONS. If immediate FET proves to be as efficient and safe as postponed FET, immediate FET offers various advantages, such as a shorter time to pregnancy for couples who did not conceive in the fresh cycle and lower expenses due to a shorter freezing time.

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TRIAL REGISTRATION. ClinicalTrials.gov (NCT06304792)

The use of frozen embryo transfer (FET) is increasing in Europe [1], and live birth rates (LBR) are similar or even better than those observed in fresh embryo transfer [2, 3]. This may be explained by improved laboratory techniques, vitrification of good quality embryos only and/or suboptimal conditions in the gonadotropin-

stimulated fresh cycles with multiple follicular growth and potential negative effect on the endometrium or endometrial-embryo synchronicity [4, 5].

FET allows for the use of elective single blastocyst transfer without compromising cumulative LBR, thereby reducing the risk of twin pregnancies [6]. In women with a high ovarian reserve, elective freeze-all strategies reduce the risk of ovarian hyperstimulation syndrome (OHSS) [7].

Ovulatory women may undergo FET in a true natural cycle, based on the natural luteinising hormone (LH) peak or in a modified natural cycle (mNC-FET), where ovulation is triggered with human chorionic gonadotropin (hCG) [8]. Oligo-anovulatory women can undergo FET in a programmed cycle (PC), with exogenous oestradiol and progesterone administration, or in a stimulated cycle (SC), where ovarian stimulation (OS) ensures growth of a dominant follicle [8]. For scheduling reasons, or when natural cycles have failed, ovulatory women may undergo SC-FET or PC-FET. A major difference between SC-FET and PC-FET is the presence of at least one corpus luteum (CL) in SC-FET. The risk of hypertensive disorders is significantly increased in pregnancies without a CL [9, 10]. Consequently, oligo-anovulatory women are increasingly offered SC-FET rather than PC-FET [10].

To minimise possible negative effects of OS and subsequent multiple corpora lutea on the receptivity of the endometrium, many clinics postpone FET for at least one menstrual cycle following an unsuccessful fresh transfer or freeze-all. However, this may unnecessarily delay the time to pregnancy and contribute to patient frustration [11].

A systematic review and meta-analysis investigating immediate versus postponed FET found an adjusted OR (aOR) of 1.20 (95% CI: 1.01-1.44) for LBR and an aOR of 1.22 (95% CI: 1.07-1.39) for clinical pregnancy rate (CPR), which indicates a trend towards immediate FET being as effective as postponed FET [12]. However, in subgroup analyses of PC-FET, there were no differences in LBR [13-15]. Another review found no differences when comparing immediate and postponed FET in a mix of SC/PC-FET and NC-FET. A subgroup analysis on endometrial preparation also found no difference [16]. Selection bias is a limitation of these reviews. Recently, two RCTs from China showed a higher CPR in immediate PC-FET than in postponed PC-FET cycles [17, 18], whereas another Chinese RCT on this comparison is still ongoing [19]. No studies have been published comparing immediate FET to postponed FET in a letrozole-SC.

The practice of postponing FET for at least one menstrual cycle after OS and oocyte pick-up (OPU) is poorly supported by evidence. Any unnecessary delay in the time to pregnancy should be avoided as it is not beneficial for patients. This trial, which has a prospective, randomised controlled design, aims to investigate whether immediate SC- and PC-FET is non-inferior to postponed SC- and PC-FET in terms of LBR.

Methods

Trial design

This is a multicentre, non-blinded RCT. Several Danish public fertility clinics participate in enrolling participants and performing treatments according to the Danish Fertility Society and European Society of Human Reproduction and Embryology (ESHRE) guidelines. Inclusion began in 2024 and is ongoing.

Participants and recruitment

A total of 484 patients undergoing either SC- or PC-FET will be included.

Eligible women (**Table 1**) are informed about the study by a doctor or study nurse, and those interested in participation are invited to a baseline visit on cycle days (CD) 2-4 of the first cycle following OPU.

TABLE 1 Overview of eligibility criteria.

Inclusion criteria
Age 18-45 yrs
Oligo-anovulatory women: cycle length > 35 days
Ovulatory women: cycle length < 35 days
Fresh embryo transfer or freeze-all in the previous cycle
Vitrified day 5 or 6 blastocyst
Blastocyst Gardner score > 3BB at the time of vitrification
Exclusion criteria
Uterine malformation or presence of hydrosalpinx
Submucosal uterine myomas
Endometrial polyps
Allergy to standard fertility medication
Contraindications to standard fertility medication
Male or female HIV, hepatitis B or C
Preimplantation Genetic Testing
Severe OHSS[a] with need of ascites drainage
Oocyte donation
TESA/TESE

OHSS = ovarian hyperstimulation syndrome;TESA/TESE = testicular sperm aspiration/testicular sperm extraction.
a) Classified according to the Danish Fertility Society as mild: enlarged ovaries (< 8 cm) and abdominal pain; moderate: ascites, weight gain, nausea, abdominal pain, diarrhoea and enlarged ovaries (> 12 cm); severe: haemoconcentration > 45%, hypovolaemia, massive ascites, multiorgan involvement; critical: haemoconcentration > 55%, leukocytosis and multiorgan failure.

Randomisation

Randomisation occurs on CD 2-4 of the first menstrual bleeding after OPU. The treatment strategy of either SC- or PC-FET is planned by the treating doctor before randomisation and baseline ultrasonography. Stratification on FET type is included in the randomisation model to ensure equal distribution.

Participants will be randomised 1:1 to either:

- FET immediate: SC- or PC-FET in the first cycle immediately following OPU and fresh embryo transfer or freeze-all.

- FET postponed: SC- or PC-FET with at least one cycle between the cycle with OPU, including fresh embryo transfer or freeze-all, and the FET cycle.

Treatment strategies

The FET protocols are described below. Women in the postponed group start their FET cycle after a break of at least one hormone replacement treatment or a natural cycle.

SC-FET (letrozole)/ SC-FET (gonadotropins): Oral letrozole (2.5-)5.0 mg/day for five days or subcutaneous injections with human menopausal gonadotropin/recombinant follicle-stimulating hormone (hMG/rFSH) 50-75 IU/day starting from CD 3-5. Women treated with letrozole may have hMG/rFSH 75 IU per day added in case no dominant follicle on CD 10-14. The hMG/rFSH dose may be increased every 5-7 days if necessary.

Ovulation is triggered by injection of recombinant hCG (6,500 IU) when the dominant follicle is ≥ 17 mm (gonadotropins) or ≥ 18 mm (letrozole). Vaginal progesterone is administered from 3-4 days after trigger and blastocyst transfer is performed 6-7 days after ovulation trigger according to local clinical practice.

PC-FET: Oral oestradiol 6 mg/day is administered from CD 3-5. When the endometrium is ≥ 7 mm thick, progesterone is added, and blastocyst transfer is planned. In case endometrial thickness is < 7 mm after 10-12 days, the oestradiol plasma level is measured, and transdermal oestradiol is added or the oral estradiol dose is increased according to local practice. After 4-6 days of additional oestradiol treatment, progesterone is added regardless of endometrial thickness. Blastocyst transfer is performed on the fifth or sixth day of progesterone supplementation.

In both SC- and PC-FET serum, hCG is measured 11 days (± 1 day) after blastocyst transfer, and in case of pregnancy, hormone treatment is continued until gestational week 10 + 0.

Data collection

An overview of data collection is shown in **Table 2.**

TABLE 2 Overview of study visits.

	Baseline CD 2-4	CD 2-4 postponed group	Trigger[a]/ progesterone[b] day	Day of blastocyst transfer	Blastocyst transfer + 5 days	Pregnancy test	Week 7-8 of gestation	Follow-up after 1 year
Information and signing of consent forms	√							
Data collection	√	√	√	√	√	√	√	√
Randomisation	√							
Transvaginal ultrasound	√	√	√				√	
Blood samples	√	√	√	√[d]		√		
Quality of life questionnaires	√	√[c]			√			

CD = cycle day; FET = frozen embryo transfer; hCG = human chorionic gonadotropin.
a) Refers to the day of hCG-trigger in stimulated cycle FET, blood drawn before hCG administration.
b) Refers to 1st day of progesterone administration in programmed-cycle FET, blood drawn before initiation of progesterone.
c) Only participants in the postponed group.
d) Additional biobank samples.

All data will be collected in accordance with written consent forms. In case of pregnancy, data on obstetric complications, delivery and neonatal outcomes will be collected up to one year after birth. Any deviations from the protocol will be registered.

Blood sample collection and biobank

LH, FSH, progesterone and oestradiol are measured consecutively at all time-points (Table 2), and samples are destroyed immediately after analysis as part of the laboratory routine. HCG is measured 11 (± 1) days after embryo transfer.

If the participant consented, biobank samples are drawn on the day of embryo transfer and stored anonymously

for possible future research. Future use requires approval from the Danish Scientific Ethics Committee. According to standard regulations, biobank samples that are not used will be destroyed five years after the last participant is included.

Transvaginal ultrasound

All women are examined with transvaginal ultrasound (TVUS) at the time points listed in Table 2. Assessed parameters include: i) endometrial thickness, ii) endometrial echogenicity and iii) number of cystic structures > 10 mm (hypoechogenic as well as hyper-/in homogenic) in the ovaries. In case of pregnancy, foetal viability and crown-rump length are assessed at 7-8 weeks of gestation.

Quality of life questionnaires

Participants and their partners are asked to answer two questionnaires regarding quality of life during fertility treatment.

Cancelled cycles and drop-outs

Randomised participants who have their cycle cancelled for medical reasons, such as missing follicular development, are defined as cancelled cycles. Participants who leave the study at their own initiative after randomisation are defined as dropouts. Dropouts will be replaced by the inclusion of a corresponding number of participants. Reasons for dropouts and cancelled cycles will be presented in the final paper. Characteristics of dropouts, cancelled cycles and completers will be compared within and between the treatment groups. A cancellation rate of 5% and a drop-out rate of 5% are expected.

Objectives

The primary objective is to determine whether immediate single blastocyst transfer in SC- or PC-FET is non-inferior to postponed blastocyst transfer in SC- or PC-FET, in terms of LBR per randomised patient (intention-to-treat (ITT) and per-protocol (PP) analyses).

Secondary objectives are listed in **Table 3**.

TABLE 3 Overview of secondary objectives.

Live birth rate per blastocyst transfer
Clinical pregnancy rate
Ongoing pregnancy rate
Miscarriage rate
Cancelled cycle rate and reasons
Reasons for cycle cancellation
Length of the follicular phase: from CD 1 until ovulation trigger in SC-FET and from CD 1 until addition of progesterone in PC-FET
Hormonal levels at predefined time-points
Number of ovarian follicular structures > 10 mm on CD 2-5 of the treatment cycle, on the day of progesterone supplementation: PC-FET, or the day of ovulation trigger: SC-FET
Time to pregnancy and live birth from the start of ovarian stimulation in the fresh cycle
Time to live birth from the start of ovarian stimulation in the fresh cycle to delivery
Pregnancy-related complications, i.e., preeclampsia and pregnancy-related hypertension, medically assisted delivery and post-partum haemorrhage: > 1,000 ml
Neonatal outcomes, i.e., preterm birth, low birth weight, small or large for gestational age and perinatal mortality

CD = cycle day; PC-FET = programmed cycle frozen embryo transfer; SC-FET = stimulated cycle frozen embryo transfer.

Data management and data sharing plan

Data are handled in accordance with the General Data Protection Regulation (GDPR) and in line with the Danish Personal Data Protection Act. Trial data are stored in an online case report form (REDCap), under anonymous identification numbers. Only the primary site has access to the complete dataset. Data processing between each trial site and the primary site follows mutual agreements. A nurse trained in good clinical practice will monitor the study to ensure the quality of the data collection.

Final data from the trial can be shared in an anonymous form according to the International Committee of Medical Journal Editors guidelines. Only groups presenting approved and relevant projects with aims different from ours will be able to obtain data. Data will not be shared until three months after publication of this trial's results. Any expenses will be covered by those requesting data sharing.

Non-inferiority design

The trial was designed as a non-inferiority trial, as we expect the new treatment to be as efficient as the standard treatment in terms of LBR. If so, immediate FET offers various advantages such as shorter time to pregnancy and lower expenses due to the shorter freezing time.

Power calculation and interim analysis

The power calculation was based on an expected LBR of 25% per randomised patient undergoing standard treatment (postponed SC- or PC-FET). A total of 464 patients are needed to be 80% sure that the upper limit of a one-sided 95% CI excludes a difference of more than 10% in favour of the standard treatment. To account for multiple testing in the primary and interim (mentioned below) analyses, we will use an alpha-split of 0.005 and 0.045 for the interim and primary analyses. Thus, the total sample size is increased to n = 484 to ensure 80%

power for our primary outcome, the LBR.

An interim analysis will be conducted after randomisation of 150 patients to assess whether the number of TVUS required for FET immediately before reaching ovulation criteria exceeds the control group. If there is no difference, FET immediate will be considered non-inferior within a two-TVUS margin with 90% power. If FET immediate requires one extra TVUS, it will still be non-inferior with 80% power. If FET immediate requires more than two additional TVUS on average, we will consider terminating the trial due to patient and clinic inconvenience. The total number of patients is adjusted to account for multiple testing after the interim analysis.

Statistical analysis and interpretation

Statistical analyses will be done using the statistical programme R. ITT analyses will include both cancelled cycles and dropouts as previously defined, PP analyses will include cancelled cycles but not dropouts, and per-transfer (PT) analyses will exclude both dropouts and cancelled cycles.

LBR will be compared by risk difference with a one-sided 95% CI or a two-sided 90% Cl. Non-inferiority of the immediate treatment will be concluded if the CI excludes a 10% difference in favour of the standard treatment in the ITT and PP analyses.

The rate of positive pregnancy tests, ongoing pregnancy, miscarriage and cancelled cycles will be calculated by risk difference with a 95% CI in the ITT, PP and PT analyses. Hormone levels will be compared with T-tests. The proportion of cystic ovarian structures > 10 mm will be compared by the χ^2-test. Time to pregnancy will be compared by Kaplan-Meier plots and log-rank tests. Neonatal outcomes and pregnancy complications will be compared using Fisher's exact test.

Patient and public involvement

The trial was developed without patient or public involvement. Patients have expressed a wish for immediate treatment after a failed fresh transfer to minimise time to pregnancy. The results will be shared with participants upon request once the trial is finalised.

Ethics

The intervention arm differs from standard treatment only in the timing of FET after a fresh transfer or freeze-all. There are no anticipated timing-related risks associated with participation.

Trial registration: The trial has been approved by and registered with the Scientific Ethical Committee of the Capital Region of Denmark (H-22030591). The study is registered on ClinicalTrials.gov (NCT06304792).

Discussion

The optimal timing of FET following OS is poorly investigated in SC- and mNC-FET. We hypothesise that SC/PC-FET performed immediately after a fresh cycle is safe and effective. Due to the seemingly decreased risk of HDP if a CL is present in the FET cycle, the strategy of FET treatments in oligo-ovulatory patients is moving towards SC-FET. FET immediate reduces time to pregnancy, relieving patients from burdensome waiting and reducing storage, which would benefit both patients and clinics financially. Additionally, patients at risk of OHSS may be encouraged towards a freeze-all strategy, which will improve safety in these patients.

The trial is designed as a multicentre RCT, limited to SC/PC-FET and single blastocyst transfer, ensuring reproducible and generalisable results. Due to the well-known association between hypertensive disorders in pregnancy and PC-FET, most patients will be treated with letrozole-stimulated FET, unless they are previous non-responders to letrozole or have specific logistical or patient-related concerns.

Double blinding was considered but not applied as differences in ultrasound appearance between the SC- and the PC-FET arm would be recognisable to a physician, with varying actions required in SC-FET and PC-FET. Thus, the study remains unblinded.

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Conflicts of interest AP reports financial support from or interest in Gedeon Richter, Ferring, Merck, Cryos, Organon, IBSA, Ferring, Gedeon Richter, Cryos and Merck. KL reports financial support from or interest in Merck, Gedeon Richter and Ferring. BSOM reports financial support from or interest in Ferring and Gideon Richter. BN reports financial support from or interest in Merck, Ferring and Gedeon Richter. NLCF reports financial support from or interest in Gedeon Richter, Merck, Cryos, Merck, Ferring, IBSA and the Danish Fertility Society. ECLL reports financial support from or interest in Pfizer, Gideon Richter, Dagens Medicin, Merck, Astellas and Radiometer. SJB reports financial support from or interest in Merck and Novo Nordisk. AP, KL, NLCF, MPL, ECLL, BN and MS have all received travel support from different companies. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. These are available together with the article at ugeskriftet.dk/dmj

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