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### **A study protocol for a randomised controlled multicentre trial**

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# BMJ Open Preparation of the endometrium and timing of blastocyst transfer in modified natural cycle frozen-thawed embryo transfers (mNC-FET): a study protocol for a randomised controlled multicentre trial

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## ABSTRACT

**Introduction** Despite the high number of frozen embryo transfer (FET) cycles being conducted (190 000 cycles/year) in Europe, the timing of blastocyst transfer and the use of luteal phase progesterone support in modified natural cycle FET (mNC-FET) in assisted reproductive technologies are controversial. In mNC-FET, the timing of blastocyst warming and transfer is determined according to the time of implantation in a natural cycle, aiming to reach blastocyst endometrial synchronicity. However, the optimal day of blastocyst transfer following ovulation trigger is not determined. In addition, the value of luteal phase support to maintain the endometrium remains uncertain. Thus, there is a need to identify the optimal timing of blastocyst warming and transfer and the effect of luteal phase support in a randomised controlled trial design. The aim of this randomised controlled trial is to investigate if progesterone supplementation from the early luteal phase until gestational age 8 weeks is superior to no progesterone supplementation and to assess if blastocyst warming and transfer 6 days after ovulation trigger is superior to 7 days after ovulation trigger in mNC-FET with live birth rates as the primary outcome.

**Methods and analysis** Multicentre, randomised, controlled, single-blinded trial including 604 normo-ovulatory women aged 18–41 years undergoing mNC-FET with a high-quality blastocyst originating from their first to third in vitro fertilisation/intracytoplasmic sperm injection cycle. Participants are randomised (1:1:1:1) to either luteal phase progesterone or no luteal phase progesterone and to blastocyst warming and transfer on day 6 or 7 after human chorionic gonadotropin trigger. Only single blastocyst transfers will be performed.

**Ethics and dissemination** The study is approved by the Danish Committee on Health Research Ethics (H-18025839), the Danish Medicines Agency (2018061319) and the Danish Data Protection Agency (VD-2018-381). The results of the study will be publicly disseminated.

## Strengths and limitations of the study

- The study will be conducted as a randomised controlled trial concerning both the use of luteal phase progesterone supplementation and timing of blastocyst transfer in modified natural cycle frozen embryo transfer (mNC-FET), providing important information on how to optimise mNC-FET.
- The secondary outcomes of this study will offer insight into the endocrine profile of a cycle with or without conception as well as gynaecological, obstetrical and neonatal outcomes for women using or not using luteal phase progesterone supplementation in mNC-FET.
- The broad inclusion criteria ensure generalisability and a high degree of applicability of the study results.
- Optimising mNC-FET may lead to higher live birth rates, shorter time from start of treatment to pregnancy and a reduction in expenses following FET.
- The study is powered to detect a 10% difference in live birth rates; thus, smaller but clinically relevant differences may be overlooked.

**Trial registration number** The study is registered in EudraCT (2018-002207-34) and on ClinicalTrials.gov (NCT03795220); Pre-results.

## INTRODUCTION

The use of assisted reproductive technology (ART) is increasing and over 5% of the birth cohort in Denmark,<sup>1</sup> and in several other European countries,<sup>2</sup> is conceived by ART. In recent years, the use of frozen-thawed embryo transfer (FET) has become more frequent, exceeding the number of fresh



in vitro fertilisation (IVF) cycles (190 000 FET cycles vs 146 000 fresh IVF cycles/year in Europe).<sup>2</sup> In parallel, the pregnancy rates after FET have increased and may pass those reached with fresh embryo transfer.<sup>3–6</sup> FET has several advantages. With the possibility to freeze all surplus embryos, the need for frequent oocyte retrievals in case of an unsuccessful fresh cycle is reduced. Without the need to stimulate follicle development, the risk of developing ovarian hyperstimulation syndrome, one of the most severe side effects of ART, is eliminated. Furthermore, with FET, single blastocyst transfer can be used without compromising cumulative live birth results, which is a major advantage as singleton pregnancies carry less obstetric and perinatal risks than twin pregnancies.<sup>7</sup> Lastly, singletons conceived after FET have a lower risk of preterm birth, low birth weight and being small for gestational age. However, they do have a higher risk of being large for gestational age compared with singletons conceived after fresh embryo transfer.<sup>8–10</sup> Hypertensive disorders during pregnancy are also reported to be more prevalent after FET versus fresh embryo transfers.<sup>8 10 11</sup>

In women with regular menstrual cycles, FET can be planned in true natural cycles (tNC-FET) with timing based on monitoring of the naturally occurring luteinising hormone (LH) peak or in human chorionic gonadotropin (hCG)–triggered modified natural cycles (mNC-FET). In a natural cycle, the ascending leg of the LH peak starts when the dominant follicle reaches 17 to 18 mm.<sup>12–14</sup> However, in some women, the LH peak is not present until the follicle is 22–23 mm and in others it may be present with a follicle size smaller than 17 mm. Hence, it may be hypothesised that in some patients, an apparent follicle of 17 mm is not a fully mature or healthy follicle and may thus secrete subnormal levels of progesterone and oestradiol from the corpus luteum after hCG triggering. In others, an early endogenous LH peak could cause a premature luteinisation of the endometrium and thereby asynchrony between the endometrium and the transferred blastocyst. Moreover, it has been suggested that the hCG trigger used in a modified natural cycle may affect reproductive outcomes by a negative feedback mechanism that inhibits endogenous GnRH secretion resulting in subnormal LH secretion causing a luteal phase insufficiency.<sup>15 16</sup>

To solve the potential lack of endogenous LH or a suboptimal corpus luteum, many fertility clinics use luteal phase progesterone support to improve implantation rates in FET. Even so, in mNC-FET there is currently no consensus on the effect of luteal phase progesterone supplementation.<sup>17–19</sup> In tNC-FET, a randomised controlled trial (RCT) including 435 patients and a retrospective study with 1972 patients reported higher live birth rates, when vaginal progesterone was added from the day of high-grade blastocyst or day 2 embryo transfers, respectively.<sup>20 21</sup> In mNC-FET, two retrospective studies of 131 and 228 patients reported a higher clinical pregnancy rate and a higher live birth rate when vaginal progesterone was administered.<sup>22 23</sup> Another retrospective study found similar ongoing pregnancy rates in 452 women with or without the use of vaginal progesterone.<sup>24</sup>

Finally, a smaller RCT with 102 patients showed no superiority of intramuscular progesterone versus no treatment in terms of clinical pregnancy rates.<sup>25</sup> However, there was a trend towards a higher clinical pregnancy rate with progesterone supplementation in the latter study. These contradictory and sparse data on the use of luteal phase support in mNC-FET emphasise the importance of a sufficiently powered RCT to assess the efficacy of progesterone in mNC-FET.

To achieve a successful implantation, synchronicity of blastocyst developmental stage and the endometrium is important. The timing of blastocyst warming and transfer in a FET cycle is based on the timing in a natural cycle, with warming and transfer of a day 5 blastocyst 5 days after suspected ovulation. Even so, the optimal day of transfer in mNC-FET has been debated. In the substituted FET cycle, only a few RCTs have tested the optimal day of embryo transfer<sup>26 27</sup>; however, no RCTs have been conducted within tNC-FET or mNC-FET. A recent review based on retrospective studies suggests both warming and transfer of blastocysts on hCG trigger +7 days in mNC-FET,<sup>28</sup> while the standard in Danish fertility clinics is either blastocyst warming and transfer on hCG trigger +6 or +7 days. To explore FET timing in the modified natural cycle, this RCT will assess if warming and transfer 6 days after hCG is superior to warming and transfer 7 days after hCG trigger in terms of live birth rates per transfer.

## OBJECTIVES

### Primary objective

The primary objectives of the study are to investigate if luteal phase progesterone support in mNC-FET is superior to no luteal phase support, and if blastocyst warming+transfer 6 days after hCG trigger is superior to warming+transfer 7 days after hCG trigger, in terms of live birth rates per transfer.

### Secondary objectives

1. To investigate endocrine profiles in blood samples of women undergoing mNC-FET with or without luteal phase progesterone support.
2. To compare treatment outcomes including biochemical and clinical pregnancy rates, miscarriage rates and obstetric complications.
3. To compare neonatal outcomes (birth weight and length, gestational age, malformations and admission to neonatal intensive care unit).
4. To compare self-reported welfare and health of women receiving and not receiving luteal phase progesterone support.

## METHODS AND ANALYSIS

### Study design

The study is designed as a multicentre, randomised, controlled, single-blinded trial with participation of seven public fertility clinics in Denmark. All seven clinics are

part of a University Hospital setting and all hospitals perform standardised treatments according to the public healthcare system in Denmark. Patient enrolment began in January 2019 and continues until January 2021. For a list of the participating hospitals, contact [marte.saupstad@regionh.dk](mailto:marte.saupstad@regionh.dk).

The SPIRIT guidelines were used in development of this protocol.<sup>29</sup>

### Patient and public involvement

Development of this research protocol was done without patient involvement; however, experiences of the first patients included in the study encouraged us to include an assessment of self-reported welfare and health. The final study results will be disseminated to participants on request.

### Study population/participants and recruitment

The study population will consist of 604 women undergoing mNC-FET after IVF or intracytoplasmic sperm injection (ICSI) treatment at one of the seven participating clinics. It is clinical routine that patients scheduled for FET call the fertility clinic on the first day of their menstrual bleeding. Subsequently, a study nurse or a non-treating doctor will identify and contact the patients who fulfil the inclusion and exclusion criteria to invite them to participate in the study. If the patient consents, a mail will be sent containing patient information about the study, and an appointment with a study nurse or a doctor will be set up at cycle days (CD) 2–5. During the first appointment (CD 2–5), the patient will be informed about the study and have the opportunity to ask questions. If she wishes to participate, informed consent forms will be filled out (online supplementary files 1–3). Final screening, including blood samples and an ultrasound examination of the uterus and ovaries, is done during the first consultation, confirming that all inclusion criteria are met.

To further explore how the endocrine profile and metabolism is affected during fertility treatment, a subgroup of 40 patients receiving and 40 patients not receiving vaginal progesterone will have additional blood samples taken twice preovulatory and at four to five timepoints during the luteal phase, to detect endocrine profiles that may or may not be compatible with conception. Study subjects for the substudy analyses will be included consecutively at only two clinics—Rigshospitalet, Copenhagen University Hospital and Horsens Regional Hospital—until the goal of 40 patients in each of the two study groups is met.

### Eligibility criteria

To participate in the study, women will have to meet the following inclusion criteria: age 18–41; regular menstrual cycle (23–35 days); undergoing frozen-thawed blastocyst transfer; vitrified blastocyst derived from first to third IVF/ICSI cycle with Gardner score 3–6 and inner cell mass and trophectoderm quality A and B<sup>30</sup> (table 1). Exclusion criteria are uterine malformations, submucosal uterine

**Table 1** Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age 18–41	Uterine malformations
Regular menstrual cycle (23–35 days)	Submucosal uterine myomas
Undergoing FET	Uterine polyps
Vitrified blastocyst from 1st to 3rd IVF/ICSI cycle in a public hospital	Allergy to study medication
Blastocyst Gardner score 3–6 A/B	Contraindication to study medication
	HIV and hepatitis B/C
	Testicular sperm aspiration
	Preimplantation genetic testing
	Known indication for luteal phase progesterone support

FET, frozen embryo transfer; HIV, Human immunodeficiency virus; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilisation.

myomas, uterine polyps, HIV, hepatitis B/C, testicular sperm aspiration, preimplantation genetic testing, known indication for luteal phase progesterone support, allergy to the study medication and contraindications to the study medication (table 1).

Further, for patients participating in the substudy, treatment for thyroid disorders is an exclusion criterium.

A patient can withdraw from the study at any time. The patient participation in the study can also be interrupted by the non-treating or treating doctors, if one of the following criteria is present:

- ▶ The patient's general condition contraindicates participation in the study.
- ▶ Protocol violation which the investigator considers having influence on the study outcome.

### Treatment and interventions

On cycle day 10–12, the patient undergoes transvaginal ultrasound to measure the dominant follicle and the endometrium. When the dominant follicle measures  $\geq 17$  mm, randomisation is performed and the ovulation trigger (6500 IU hCG s.c.) is administered at 22:00 the same day. If the dominant follicle does not meet the size criteria on cycle days 10–12, subsequent scans are planned, following the patient until the dominant follicle meets the size criterium. Randomisation is carried out by a study nurse or a non-treating doctor using a randomisation programme. Patients are randomised 1:1:1:1 to one of the four groups:

- A. Luteal phase progesterone and warming+transfer 6 days after hCG trigger.
- B. Luteal phase progesterone and warming+transfer 7 days after hCG trigger.
- C. No luteal phase support and warming+transfer 6 days after hCG trigger.
- D. No luteal phase support and warming+transfer 7 days after hCG trigger.

The patients randomised to luteal phase progesterone supplementation will receive the study medication and an instruction in administration of 100 mg vaginal progesterone (Lutinus; Ferring Pharmaceuticals) three times

daily starting the morning of day 4 after hCG trigger. Complete medicine accounts will be kept by the study nurses at each of the trial sites. All medication handed out to the patients will be recorded, and patients are instructed to inform the study personnel about deviations in medicine administration. Concomitant use of prescription medication will be recorded in the study database, and study participants are excluded if they use medication that influences the enzyme CYP3A.

On day 6 or 7 after the hCG trigger, the blastocyst with the highest implantation potential based on morphological criteria is transferred by a treating doctor.

Patients randomised to vaginal progesterone will continue administration of the study medication until hCG trigger+16 days where a pregnancy test will be made. If the test is positive, patients randomised to progesterone support will continue using vaginal progesterone for another 30 days. If the test is negative, all medication will be discontinued.

### Randomisation

The randomisation program (dOxos CDS AB) uses a minimisation algorithm balancing the following variables: study ID (including information about trial site), age, number of previous oocyte retrievals, number of previous FETs and blastocyst Gardner score of the vitrified blastocyst with the highest implantation potential. The treatment arm that provides the optimal balance between the groups, minimising the difference of the means, is selected with high probability. The program also ensures an equal distribution of subjects in each treatment group in the study and at each trial site.

### Blinding procedure

The study is a single-blinded study; therefore, the study medication will be blinded for the treating doctors, but not for the patients, the non-treating doctors or the study nurses. The participants will not take progesterone the morning of the blastocyst transfer, but immediately after, to keep the treating doctors blinded. Patients will be instructed in not disclosing their study group to the treating doctors.

### Data collection

Treatment-related data are collected at the following time points: (1) baseline (CD 2–5), (2) day of hCG trigger, (2a) day of ovulation (hCG trigger+2 days), (3) day of blastocyst transfer (hCG trigger+6/7 days), (4) mid-luteal phase (hCG trigger+11 days) and at (5) hCG trigger+16 days. In case of a pregnancy, outcome data will be collected from the early pregnancy scan and from the patient's and patient's child's medical records up to 1 year after delivery.

### Sample collection

Blood samples will be collected at timepoints 1 to 5 during the treatment period. Patients participating in the substudy will have additional samples taken at all timepoints including samples taken at hCG trigger+14

**Table 2** Overview of blood samples

Baseline (CD 2–5)	AMH Oestradiol FSH LH Progesterone ALAT ASAT	TSH Free T4 TPO antibodies TG antibodies
Day of hCG trigger	Oestradiol FSH LH OH-Progesterone Progesterone	TSH Free T4
Day of ovulation (hCG trigger+2 days)	Oestradiol Progesterone β-hCG	
Day of blastocyst transfer (hCG trigger+6/7 days)	Oestradiol FSH LH OH-Progesterone Progesterone β-hCG	TSH Free T4
Mid-luteal phase (hCG trigger+11 days)	Oestradiol FSH LH OH-Progesterone Progesterone β-hCG	TSH Free T4
hCG trigger+14 days		Oestradiol FSH LH OH-Progesterone Progesterone β-hCG TSH Free T4
Pregnancy test (hCG trigger+16 days)	β-hCG	Oestradiol FSH LH OH-Progesterone Progesterone TSH Free T4
Day hCG trigger+19 days*		Oestradiol FSH LH OH-Progesterone Progesterone β-hCG TSH Free T4

\*Only if pregnancy test at trigger+16 days is positive. ALAT, Alanine aminotransferase; AMH, Anti-Müllerian hormone; ASAT, Aspartate aminotransferase; Free T4, Free thyroxine; FSH, Follicle stimulating hormone; β-hCG, β-human chorionic gonadotropin; LH, Luteinizing hormone; TG antibodies, Thyroglobulin antibodies; TPO antibodies, Thyroid peroxidase antibodies; TSH, Thyroid-stimulating hormone.

days and hCG trigger+19 days, depicted in [table 2](#). Only patients recruited at Rigshospitalet will have samples taken at the day of ovulation (hCG trigger+2 days).

## Research biobank and biobank for prospective research projects

An extra blood sample of 8–14 mL (whole blood, serum and plasma) will be taken at every sampling point, except timepoint 2a, and stored in a freezer. The samples will be stored for prospective analyses of new hormones or endocrine biomarkers related to reproductive medicine in this or future research projects approved by the Danish Committee on Health Research Ethics. When patient inclusion is completed, all biobank samples will be transported to Rigshospitalet.

If samples are not used, they will be destroyed according to the rules of destruction of biological material after end of the study or no later than 5 years after inclusion of the last patient. No biological material will be transferred for analyses outside Denmark.

Patients will sign a separate informed consent form for storage of samples in a biobank for future research projects (online supplementary file 3).

### Transvaginal ultrasound scans

During screening and until the patient meets the criterion for the hCG trigger, transvaginal ultrasound scans will be performed according to the clinical routine in FET cycles. At baseline, an ultrasound examination will estimate the endometrial thickness, the size of the ovaries and the number of antral follicles. On the day of the hCG trigger, endometrial thickness, morphology, echogenicity as well as the presence of one or more follicles  $\geq 17$  mm will be recorded. If in doubt whether a preovulatory follicle is present, endometrial thickness and morphology in addition to serum progesterone level will be considered. If the patient conceives, an early transvaginal pregnancy scan will be made at gestational age 7–8 weeks for estimation of crown–rump length and viability.

### Questionnaires

Having patient well-being as a focus point, the participating women will be asked to fill out questionnaires at timepoints 1 and 4. The questionnaires consist of standardised and validated questions targeted to explore self-assessed health, welfare and the emotional aspects of going through fertility treatment in addition to registration of possible study medication side effects.

### Data management

Data are transferred to an online eCRF; REDCap. The REDCap database has a complete audit trail and is based on anonymous subject ID numbers used in the trial. For numerical values (eg, blood sample values), data ranges are programmed to avoid gross typing errors. Data are backed up daily and stored on a server located in a locked facility in Denmark. Data registered in the trial will be monitored by the Danish Good Clinical Practice Unit.

Only research personnel at Copenhagen University Hospital, Rigshospitalet will have access to the final dataset. Ownership of data is determined by co-operation agreements as well as data processing agreements between

Copenhagen University Hospital, Rigshospitalet (Capital Region of Denmark) and the participating hospitals.

### Data sharing plan

On request, the study protocol and deidentified individual study data collected during the trial, including stored biobank samples, can be shared with research groups with relevant aims and a methodologically sound proposal. Approvals by necessary ethics committees and the Danish Data Protection Agency will be needed before sharing of data. All costs for data sharing will be covered by the party requesting the data. Data cannot be shared with groups working on research projects with the same aims, secondary aims or purposes. Further, no data can be shared until 3 months after publication of first papers on the primary and secondary outcomes in this study. Biobank samples cannot be shared with research groups outside Denmark. Proposals of data sharing should be directed to [anja.bisgaard.pinborg@regionh.dk](mailto:anja.bisgaard.pinborg@regionh.dk). To gain access, the requesting party will need to sign a data sharing agreement.

### Statistics

#### Outcome measurements

The primary endpoint is live birth rate per transfer, comparing the luteal phase progesterone groups with the no luteal phase progesterone groups and the warming+transfer day 6 groups with the warming+transfer day 7 groups. Additional endpoints include assessment of other relevant aspects of mNC-FET including chemical and clinical pregnancy rates, miscarriage rates, and obstetric and neonatal outcomes in the study groups. Furthermore, endocrine blood samples will be collected in all study groups to determine if an endocrine profile compatible and not compatible with conception can be identified. Lastly, self-reported welfare and health of patients receiving and not receiving vaginal luteal phase support will be compared.

#### Sample size calculation

The study is designed as a superiority study that allows detection of an effect size of 10% increase in live birth rates per transfer in

Comparison I: Vaginal progesterone (group A+B) versus no vaginal progesterone (groups C+D), and

Comparison II: Blastocyst warming+transfer day 6 after hCG trigger (group A+C) versus blastocyst warming+transfer day 7 after hCG trigger (group B+D).

Power calculations were performed with SAS Enterprise Guide V.7.1. For a one-sided  $\chi^2$  test comparing groups A+B with group C+D, we found that a total of 604 patients would be needed to detect an increase in live birth rate from 21% in group C+D to 31% in group A+B with 80% power and similarly when comparing group A+C with group B+D. The significance level for the power calculation was set to 2.5% to limit the overall risk of a false-positive result when testing the two co-primary hypotheses to 5% (Bonferroni adjustment). Due to the balanced



study design, mutual adjustment between the two treatments was not considered in the power calculation.

### Statistical analyses

For comparisons between the study groups, Student's t-test for continuous variables and Kruskal-Wallis test, in case of non-parametric data, will be used. For comparisons of proportions, we will use  $\chi^2$  tests. For the adjusted analyses, we will use multiple linear and logistic regression analyses for continuous endpoints and proportions, respectively. A significance level of less than 0.05 will be considered as statistically significant.

### ETHICS AND DISSEMINATION

The safety of participants in all study groups is high. All medication used in the study is part of standard ART care. To ensure patient well-being, the investigators will monitor and evaluate potential side effects of the study medication at every clinical visit until end of progesterone treatment. As late side effects are unlikely with progesterone, there will be no further follow-up.

As the medication is well known, serious adverse reactions (SARs) or suspected unexpected serious adverse reactions (SUSARs) are not expected. However, should a study participant experience a SAR or a SUSAR, the investigator will stop the treatment for that specific study participant immediately and report to the sponsor within 24 hours. The participant will be withdrawn from the study.

No financial incentives exist for participation in the study, as the first three ART treatments with following FETs are covered by the public healthcare system in Denmark. The labelled study medication will be provided to the participants at each of the trial sites for free.

Positive, negative and inconclusive results will be published in international scientific journals and online ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)). The results of the study will be presented at national as well as international scientific congresses and published in high-impact international scientific journals in reproductive medicine such as *Human Reproduction* or *Fertility and Sterility*. Further results of public interest will be reported in the public press.

### DISCUSSION

The increasing use of FET and the lack of consensus regarding use of progesterone supplementation and timing of blastocyst warming and transfer in mNC-FET emphasise the need for additional studies. A major challenge comparing the existing studies on mNC-FET is the many different protocols, methods and traditions. Among the retrospective studies on luteal phase support in mNC-FET, one study used freezing of two pronuclear stage embryos,<sup>22</sup> another used embryos cryopreserved on culture day 3<sup>24</sup> and a third study used data from both embryo and blastocyst transfers,<sup>23</sup> while the only RCT

available used cleavage stage embryos.<sup>25</sup> In the same studies, administration of progesterone was started at different time points after hCG trigger and administered both as vaginal suppositories and as intramuscular injections. Moreover, some of the existing studies are based on multiple embryo transfers, while today's clinical practice in Scandinavia is transfer of a single vitrified/warmed blastocyst.

Regarding the sample size calculation, it has been discussed whether the two interventions can be considered as being independent. As for luteal phase support, it may have a greater effect in patients with an undiscovered corpus luteum insufficiency; however, as a corpus luteum insufficiency would affect the entire luteal phase, the outcome is expected to be independent of the day of the blastocyst transfer. Further, regarding the timing of blastocyst transfer, a surge in LH prior to hCG trigger (dominant follicle  $\geq 17$  mm) carries the risk of premature progesterone synthesis and blastocyst–endometrium asynchrony. However, a premature luteinisation of the endometrium would be independent of introduction of luteal phase support or no luteal phase support at hCG trigger+4 days.

The strengths of this study are the multicentre, randomised, controlled, single-blinded trial design, high generalisability of the study results and publication of the study protocol for increased transparency in research. To further improve the study method, a double-blinded design would have been optimal. However, as no placebo drug was available, it was decided to keep the treating doctors blinded to reduce bias.

Finally, this study may provide the possibility to make new and improved guidelines on mNC-FET for use on a national as well as international basis, the aim being to increase success rates of FET cycles, reduce the time from start of treatment to pregnancy, and reduce the expenses and inconvenience following ART. Furthermore, the investigation of several aspects of success related to ART, from pregnancy to live births, brings forward important information on luteal phase progesterone support and timing of blastocyst transfer in mNC-FET.

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