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PROTOCOL

Is home-based monitoring of ovulation to time frozen embryo transfer a cost-effective alternative for hospital-based monitoring of ovulation? Study protocol of the multicentre, non-inferiority Antarctica-2 randomised controlled trial

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STUDY QUESTION: The objective of this trial is to compare the effectiveness and costs of true natural cycle (true NC-) frozen embryo transfer (FET) using urinary LH tests to modified NC-FET using repeated ultrasound monitoring and ovulation trigger to time FET in the NC. Secondary outcomes are the cancellation rates of FET (ovulation before hCG or no dominant follicle, no ovulation by LH urine test, poor embryo survival), pregnancy outcomes (miscarriage rate, clinical pregnancy rates, multiple ongoing pregnancy rates, live birth rates, costs) and neonatal outcomes (including gestational age, birthweight and sex, congenital abnormalities or diseases of babies born).

WHAT IS KNOWN ALREADY: FET is at the heart of modern IVF. To allow implantation of the thawed embryo, the endometrium must be prepared either by exogenous oestrogen and progesterone supplementation (artificial cycle (AC)-FET) or by using the NC to produce endogenous oestradiol before and progesterone after ovulation to time the transfer of the thawed embryo (NC-FET). During an NC-FET, women visit the hospital repeatedly and receive an ovulation trigger to time FET (i.e. modified (m)NC-FET or hospital-based monitoring). From the woman's point of view, a more natural approach using home-based monitoring of the ovulation with LH urine tests to allow a natural ovulation to time FET may be desired (true NC-FET or home-based monitoring).

STUDY DESIGN, SIZE, DURATION: This is a multicentre, non-inferiority prospective randomised controlled trial design. Consenting women will undergo one FET cycle using either true NC-FET or mNC-FET based on randomisation.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Based on our sample size calculation, the study group will consist of 1464 women between 18 and 45 years old who are scheduled for FET. Women with anovulatory cycles, women who need ovulation induction and women with a contra indication for pregnancy will be excluded. The primary outcome is ongoing pregnancy. Secondary outcomes are cancellation rates of FET, pregnancy outcomes (including miscarriage rate, clinical pregnancy, multiple pregnancy rate and live birth rate). Costs will be estimated by counting resource use and calculating unit prices.

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TRIAL REGISTRATION DATE: 23 July 2017

DATE OF FIRST PATIENT'S ENROLMENT: 10 April 2018

Key words: embryo transfer / ART / freezing / ovulation / LH / randomised controlled trial / chorionic gonadotrophin / ovulation induction / ultrasonography / ovarian follicle

WHAT DOES THIS MEAN FOR PATIENTS?

Frozen-thawed embryo transfer in the natural cycle of a woman is based on the timing of ovulation. There are two methods to monitor the ovulation: the first is home-based monitoring in which the natural ovulation is monitored using urinary LH tests, and the second is hospital-based monitoring using repeated ultrasound monitoring of the dominant follicle followed by hCG triggering for ovulation. The Antarctica-2 randomised controlled trial compares the (cost-) effectiveness of home-based monitoring with hospital-based monitoring of the ovulation.

Introduction

Frozen-thawed embryo transfer (FET) is at the heart of modern IVF and has been made possible by ongoing improvements in laboratory techniques for freezing and thawing of embryos and FET cycle procedures (Wong *et al.*, 2014). The number of FET cycles has increased substantially over the past decade (De Geyter *et al.*, 2018, 2020; Pereira *et al.*, 2019; Wyns *et al.*, 2020). According to ESHRE, FET was the second most commonly performed reproductive technique throughout Europe in 2016, as shown in the recently published annual European data regarding reproductive techniques in Europe . A total of 248 407 FET procedures were performed in Europe in 2016 (De Geyter *et al.*, 2020; Wyns *et al.*, 2020). The published trends in Europe show a growth of the use of FET and an increased effectiveness in terms of pregnancy rate per transfer following FET over time (Ferraretti *et al.*, 2017; De Geyter *et al.*, 2018, 2020; Wyns *et al.*, 2020). Currently, in Europe, one in every 32 babies is born from an IVF or ICSI treatment, of which 43% in the Netherlands is the result of FET (NVOG, 1996-2019). It is to be expected that the relative contribution of FET to the cumulative ongoing pregnancy rates and live birth rates will further increase.

For FET to be effective, the endometrium needs to be synchronised with the developmental stage of the embryo to allow implantation. Two types of methods are mainly used to this aim. First, embryo transfer in an artificial cycle (AC) is used, in which the endometrium is artificially prepared by using exogenous oestrogen and the timing of thaw and transfer is initiated by the start of exogenous progesterone. The second method is embryo transfer in a natural cycle (NC-FET) with repeated ultrasound monitoring of the dominant follicle followed

by hCG triggering for ovulation (modified (m)NC-FET). The recently performed multicentre non-inferiority Antarctica trial showed that mNC-FET is preferred over AC-FET, based on cost-effectiveness (Groenewoud *et al.*, 2016). Two Cochrane reviews have been published evaluating different types of FET cycles.

Ghobara *et al.* (2017) concluded that the evidence is insufficient to support the use of one cycle regimen in preference to another in preparation for FET in subfertile women with regular ovulatory cycles.

The recently published Cochrane review by Glujovsky *et al.* (2020), concluded that there is insufficient evidence on the use of any particular intervention for endometrial preparation in women undergoing fresh donor cycles and FETs.

During an mNC-FET cycle, on average, three hospital visits are needed for ultrasound monitoring (Groenewoud *et al.*, 2016). From the woman's perspective, a more natural approach and less interference with private and working life may be desired (Gerris and De Sutter, 2010). Home-based ultrasound monitoring of follicle growth in fresh IVF cycles indeed improved patient-reported outcomes and experiences such as contentedness, empowerment, discretion and partner participation (Gerris *et al.*, 2014). Therefore, home-based monitoring might be also the preferred treatment for women in FET cycles. Home-based monitoring is feasible by monitoring the natural ovulation using urinary LH tests (also known as true NC-FET). This reduces direct costs—of repeated ultrasound visits and medication—and indirect costs—of transportation to the clinic and productivity loss. Because of these advantages, true NC-FET is increasingly applied in the Netherlands, albeit in the absence of evidence supporting its cost-effectiveness.

We therefore aim to compare true NC-FET with mNC-FET in women scheduled for FET. This randomised trial with a non-inferiority design compares the (cost-) effectiveness of true NC-FET with mNC-FET to time FET in women undergoing IVF.

Materials and methods

Study design

We have set up a multicentre non-inferiority trial carried out in The Netherlands. This study is registered in the Dutch Trial Register (Trial NL6414 (NTR6590), https://www.trialregister.nl/).

Study period

This study is planned to be conducted over 5 years (first participant recruited: 1 April 2018; estimated primary completion date: December 2022). At the time of the manuscript preparation, we have recruited about 1000 women (±68%). As a result of the limiting orders surrounding the current COVID-19 pandemic, the recruitment process was temporarily on hold from 19 March 2020 until 15 May 2020.

Interventions

Women are randomly allocated to either the true NC-FET group (intervention group), or the mNC-FET group (control group).

True NC-FET group (intervention)

The study group provides Clearblue digital ovulation tests (pink cap, SPD Swiss Precision Diagnostics GmbH (SPD), Petit-Lancy, Genève, Switzerland; distributed by BROCACEF Maarssen, the Netherlands) to the fertility centres. The fertility centres hand them to the participating women who are allocated to the true NC-FET group. The subsidising party (The Netherlands Organisation for Health Research and Development ZonMw) pays for the tests; i.e. the tests are not provided nor restrictions are posed by the producer or distributor.

Women allocated to the true NC-FET group will perform urinary LH tests in the morning and evening to identify the LH surge. No ultrasound, not even a baseline ultrasound, will be scheduled since women had more than one ultrasound in the previous fresh cycle or FET cycles. The start of testing will be determined based on the cycle length as stated in the instruction of the LH test kit (instruction leaflet in the box). For example: women with a cycle length of 28 days start on day 11. Women with a variable cycle length (more than 3 days) use the shortest cycle length of the prior 6 months to calculate their start of testing. To determine that the cycle is anovulatory, women will keep testing until at least 7 days after their expected ovulation (longest cycle). No advice is given on first or second morning urine samples; i.e. the instruction of the LH test kit is followed ('It is important to drink normally and not to urinate for 4 h before taking a test'). The woman will interpret the urine monitor kits herself, and no pictures have to be sent to the staff. The test has a digital display which will only show a 'smiley' pictogram when positive. This will prevent interpretation problems for the user. The woman keeps her test results in a study diary (Castor EDC, CIWIT B.V.) with date and time of each test and the test result. In case of positive test result, she is asked to send a message to the clinic staff before 10 a.m. She stops testing after the first positive result. In case of physical signs of ovulation and negative LH tests or unexpected prolonged negative testing, women are allowed to request an ultrasound. In case of follicular development women will continue with LH tests. In case of a post-ovulatory state and the LH rise was missed, the transfer is not scheduled and she reaches her study end point.

Modified NC-FET group (control)

Women allocated to the mNC-FET group will be scheduled for ultrasound monitoring of the dominant follicle followed by a hCG trigger to induce ovulation. Modified NC will be carried out according to local protocol, including which menstrual cycle day to start with ultrasound monitoring. No luteal support will be given. Women are not instructed about the permissibility of LH testing and no LH tests are provided to these women. None of any home testing results are incorporated in clinical decision-making.

Both groups

Women will participate in the randomised intervention for only one FET cycle. The day of thaw and transfer is scheduled according to local protocol in both groups. The IVF or ICSI treatment prior to FET is performed according to local protocol of the participating centre and supernumerary embryos are cryopreserved using standard operating procedures. This includes the choice of pituitary down-regulation (GnRH agonist or antagonist), pre-treatment with oral contraceptive, the choice of gonadotrophins and ovulation trigger and the number of embryos transferred to a maximum of two. For cryopreservation, this

includes choice for the day of cryopreservation, the choice for slow freezing or vitrification and the day of thaw. No luteal support will be given in both groups. All participating centres are prepared to perform embryo transfer 7 days a week, including holidays.

Study population

Women between 18 and 45 years old, who have had IVF/ICSI and who are scheduled for FET and have an ovulatory cycle (as confirmed by either history, basal temperature curve, ultrasound monitoring, serum progesterone or urinary LH tests) are eligible for inclusion. Women with anovulatory cycles, women who are ovulatory with ovulation induction and women with a contra indication for pregnancy will be excluded. The majority of the FETs are single embryo transfer and the majority involve a cleavage-stage embryo. Embryos subjected to biopsy for pre-implantation genetic testing for monogenic or single-gene disorders or structural chromosomal rearrangements are eligible; no preimplantation genetic testing for aneuploidies is carried out in the participating centres.

Settings

Participating centres are university and non-university hospitals and fertility clinics, all located in the Netherlands (a list of participating centres is available at: http://zorgevaluatienederland.nl/antarctica-2). At this moment, there are 22 participating centres. The Antarctica-2 trial is affiliated with the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology, which provides national attention and therefore ensures the right number of participating hospitals to achieve adequate patient enrolment.

It will be performed in centres that collaborate within the Dutch Consortium for Studies in Women's Health and Reproduction. The study will be a pragmatic trial thus covering all practice variations, both in the clinic as well as in the laboratory. This pragmatic design improves generalisability of the study results and no further attempts will be made prior to the start of the study to harmonise the protocols.

Informed consent procedure

Eligible women are counselled by trained fertility doctors or research nurses by means of both oral and written information to ensure that they are fully informed about the content of the study. Those women who agree to participate are asked to sign a written informed consent. The rules of Good Clinical Practice are applied (European Medicines Agency, 2016). All participants must provide their signed informed consent forms before start of the FET cycle. Participants can withdraw from the trial at any time. Eligible women do not need to state a reason for withdrawal.

Randomisation

Consenting eligible women will be randomly allocated to true NC-FET using urinary LH tests or mNC-FET using ultrasound and hCG trigger for ovulation, with a 1:1 allocation using a web-based data system, which is available in our Consortium (Castor EDC, CIWIT B.V.), using a permuted-block design. Because of the large sample size, no stratification will be used. The block sizes will not be disclosed, to ensure concealment. Allocation concealment will be ensured, as the data system will not release the randomisation code until the woman has been recruited into the trial, which takes place after baseline measurements have been entered in the system (consisting of inclusion and exclusion criteria checks). The unique number generated cannot be deleted afterwards. The randomisation sequence will not be accessible by the recruiters. The study is open-label because the nature of the intervention means that masking women to the assigned intervention is not possible. The researchers who analyse the data for pregnancy outcomes will be masked to the assigned intervention, but those who collect the data are not.

Linking personal data to the study number can only be performed in the local participating centres. Written informed consent forms are stored in every centre in a lockable room. All forms will be archived for 15 years in the participating centres.

Patient and public involvement

This study protocol has been designed with active input and feedback of experts and patient representatives from the Dutch patient organization Freya (www.freya.nl).

Outcome measures

Primary outcome measure

The primary outcome for the comparison of the two strategies is ongoing pregnancy, which is defined as the presence of positive heart beat as seen by sonography at 12 weeks gestational age per woman per started cycle (Braakhekke *et al.*, 2014).

Secondary outcome measures

Secondary outcomes are cancellation rates of FET including: ovulation before hCG injection or no development of dominant follicle on ultrasound; no detection of ovulation with LH urine test; and inadequate embryo survival. Other secondary outcomes are pregnancy outcomes including: miscarriage rate, defined as the loss of a pregnancy; clinical pregnancy rates, defined as the presence of a gestational sac seen by transvaginal sonography 5–7 weeks; multiple ongoing pregnancy rates; live birth rates; costs; and neonatal outcomes such as gestational age, birthweight and sex of babies born, congenital abnormalities or diseases of babies born.

Cost data include costs of the intervention and will be registered from clinical patient data. We will also take costs of personnel in week-end days into account. Other health care utilisation, patient and family costs and costs of productivity losses will not be assessed by a questionnaire.

All adverse events (AEs) reported spontaneously by the subject or observed by the investigator or his staff will be recorded. All serious adverse events will be reported to the Medical Ethics Committee.

Sample size calculation

The trial was designed as a non-inferiority trial. The alternative hypothesis assumed that the pregnancy rates would be comparable between both interventions, while the corresponding null hypothesis is that the intervention results in a lower live birth rate than the control arm by more than or equal to the non-inferiority margin. At the time of designing the study, we expected 12% of the couples to have a live birth after one FET. Using a 5% significance level, we need 1390 couples to

exclude a difference of 4% or more to the detriment of true NC-FET. This difference corresponds to a relative risk of 0.67 and a power of 86%. To account for a 5% loss to follow-up, we intend to include 732 couples in each group.

The last European data for 2016 (Wyns *et al.*, 2020) suggest a higher live birth rate following FET of up to 20% compared to 12% in our sample size calculation. We did not adjust our sample size calculation. If the live birth rate turns out to be higher than 12% and/or close to 20%, we will still achieve a similar level of power to answer our research question. With 695 couples in both groups, we will achieve 85% power to detect a ratio of 1, when the non-inferiority ratio is 0.75 and the actual treatment proportion is 20% and alpha is 5%.

Data collection

All data will be systematically recorded using an electronic Clinical Report Form (CRF). These electronic forms will be stored in the same web-based data system as the randomisation (Castor EDC, CIWIT B.V.). Data are handled confidentially and, whenever possible anonymously. A subject identification code list will be used to link the data to the subject, where it is necessary to be able to trace data to an individual subject. The code will not be based on the woman's initials and birth date, the key to the code will be safeguarded by the local investigator. The handling of personal data will comply with the General Data Protection Regulation (in Dutch: de Algemene Verordering Gegevensbescherming, AVG). The medical record files in each participating centre will be used as source for completion of the CRF. Personal data will be stored for a maximum of 15 years in participating centres.

Data analysis

All statistical analyses will be performed according to the intention-to-treat principle. Descriptive analysis will be used to describe the outcome variables. We assume that both study arms will result in comparable ongoing pregnancy rates. We consider true NC-FET inferior when the absolute difference in ongoing pregnancy rate exceeds 4% compared to an expected standard of 12% per woman undergoing one FET cycle—this is comparable to a relative difference of 0.08/0.12 is 0.67. If the left border does not exceed the left border of the 90% CI with the predefined threshold of 0.67 for inferiority we will consider true NC-FET to be non-inferior to mNC-FET. The treatment effect will be expressed as Relative Risk and risk difference with both 90% and 95% CIs. We will investigate interactions ($<$38 years and $\geq$38 years) and assigned treatment with respect to the primary outcome, ongoing pregnancy. A *P*-value of $<$0.05 is regarded as showing an interaction. A per-protocol analysis will also be performed to calculate the true contributions of the interventions to the primary endpoint. With regard to the remaining secondary outcomes, between-group difference of the proportions was expressed as two-sided 95% CIs. We will perform a predefined subgroup analysis to assess whether female age can be used as a treatment selection marker or has prognostic value. We will also plan an exploratory analysis based on prior fresh IVF or prior FET among participants.

Interim analysis

An interim analysis was performed 6 months after 450 inclusions had taken place and completed the 3 months follow-up: this is approximately after 40% of the total inclusion. The interim analysis was performed in March 2020 by an independent statistician, blinded for the treatment allocation. The statistician reported the outcome to the independent Data Safety Management Board (DSMB). The following stopping rule was established using the Peto approach: the trial will be ended using symmetric stopping boundaries at $P < 0.001$ in case at least one of the intervention arms results in a lower pregnancy rate. The trial would not be stopped in case of futility. This stopping rule was verified by the DSMB at the beginning of the trial. After interim analysis, the advice of the DSMB was to continue without any adjustments of the protocol.

Economic evaluation

Both a cost-effectiveness analysis (CEA) and a cost-utility analysis will be performed from a societal and healthcare perspective according to Dutch guidelines (IJzerman *et al.*, 2016) with a time horizon of 1 month. Missing cost and effect data will be imputed using multiple imputation according to the MICE algorithm developed by Van Buuren (1999). Rubin's rules will be used to pool the results from the different multiply imputed datasets. Cost-effectiveness of each strategy will be presented as cost per ongoing pregnancy and costs per live birth as well as average costs per woman. These data will be used to calculate cost-effectiveness ratios. Uncertainty will be around incremental cost-effectiveness, and cost-utility ratios will be estimated using bootstrapping techniques and graphically presented on cost-effectiveness and cost-utility planes (Sullivan *et al.*, 2014). Cost-effectiveness acceptability curves will also be estimated showing the probability that a strategy starting with true NC-FET is cost-effective in comparison with mNC-FET for a range of different ceiling ratios thereby showing decision uncertainty (Fenwick *et al.*, 2004). Cost will be determined until an ongoing pregnancy and will include birth of a child in a secondary analysis.

Ethics and dissemination

This study protocol was designed with input and feedback of patient representatives and experts. This study is conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

This study is approved by the Medical Ethics Committee of AMC Amsterdam (MEC AMC, Code 018) and by the boards of all participating hospitals. All amendments will be notified and need to be approved by the Medical Ethics Committee of AMC Amsterdam (MEC AMC, Code 018). The trial is registered in the Dutch Trial Register (Trial NL6414 (NTR6590), http://www.trialregister.nl). Results will be disseminated through peer-reviewed publications and presentations at international scientific meetings.

Discussion

This protocol describes a multicentre randomised non-inferiority trial where different efficacy, social and economic aspects regarding true NC-FET versus mNC-FET are analysed. No large trials have been published comparing true NC-FET with mNC-FET in terms of ongoing pregnancy rates. If true NC-FET with home-based monitoring of ovulation to time FET is found to result in equal ongoing pregnancy rates compared to mNC-FET with ultrasound monitoring and hCG trigger for ovulation to time FET it would render a costs saving by reducing the required monitoring. We estimate the potential medical cost saving for 2016 to be €4 million euro from the healthcare perspective and between €5 and €6 million from the societal perspective. Since the annual growth rate of FET was as high as 16.3%, the number of FET might further grow to 24 000 in 2020 or 2021. If the cancellation rate would be still 22%, 29 000 FET cycles will be performed. Cost savings in 2021 would be €8 million euro for healthcare and between €11 and €12 million for society.

Participation does not involve additional risks. At the request of the Dutch Patient Organization (Freya) and the funding party ZonMw, the first group of participants were asked to fill out questionnaires concerning patient-reported outcomes and experiences. No negative effects on patient-reported outcomes and experiences were reported in the intervention group (Zaat *et al.*, 2020).

The benefit associated with participation is that women may become pregnant with true NC-FET resulting in less interference with private and working life, and using their natural ovulation with invasive procedures or use of medication withheld. The results may prove beneficial for future couples who need FET. If true NC-FET is cost-effective in women undergoing IVF/ICSI cycles, true NC-FET would inevitably lead to a decrease in burden (less hospital visits and use of medication) and from a societal perspective a decrease in health care costs.

Several limitations also need mentioning. According to ESHRE guidelines, live birth rate should be the primary outcome and we chose ongoing pregnancy as such. This is because ongoing pregnancy is seen as a valid and cost-effective outcome measure of effectiveness (Braakhekke *et al.*, 2014). Nevertheless, we also will report on live birth rate. We are not able to blind this study owing to the type of interventions. We consider it unlikely that this introduces performance bias, since pregnancy outcomes are objective outcome measures. Another potential limitation of this study is that we based our sample size calculation on a 4% difference or more in ongoing pregnancy rate between the two strategies. We can thus not rule out smaller differences.

If this trial shows that true NC-FET is cost-effective compared to mNC-FET, the results may lead to evidence-based changes in national and international guidelines.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Authors' roles

F.M., M.v.W. and M.G. designed the trial, were responsible for the development of the protocol and applied for the grant. T.R.Z., F.M., M.v.W. and J.P.d.B. have overall responsibility for the trial. All authors are responsible for implementation of the study and inclusion of the eligible women. T.R.Z. is responsible for the overall logistical aspects of the trial and drafted the paper. All authors read and approved the final paper.

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Conflict of interest

F.B. reports personal fees from member of the external advisory board for Merck Serono, grants from Research support grant Merck Serono, outside the submitted work. A.E.P.C. reports and Unrestricted grant of Ferring B.V. to the Center for Reproductive medicine, no personal fee. Author up-to-date on Hyperthecosis. Congress meetings 2019 with Ferring B.V. and Theramex B.V. M.G. reports Department research and educational grants from Guerbet, Merck and Ferring (location VUMC) outside the submitted work. E.R.G. reports personal fees from Titus Health Care, outside the submitted work. C.B.L. reports grants from Ferring, grants from Merck, from Guerbet, outside the submitted work. The other authors have none to declare.

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