Fertility preservation in women: exploring clinical dilemmas

Dahhan, T.

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CHAPTER 5

Stimulation of the ovaries in women with breast cancer undergoing fertility preservation: alternative versus standard stimulation protocols; the study protocol of the STIM-trial

T. Dahhan
E.M.E. Balkenende
C.C.M. Beerendonk
K. Fleischer
D. Stoop
A.M.E. Bos
C.B. Lambalk
R. Schats
R.J.T. van Golde
J. Schipper
J.S.E. Laven
L.A. Louwe
A. Hoek
A.E.P. Cantineau
J.M.J. Smeenk
R. Nevedita
Y. Kopeika
F. van der Veen
M. van Wely
S.C. Linn
M. Goddijn

Submitted

Abstract

Background: Chemotherapy for breast cancer may have a negative impact on reproductive function due to gonadotoxic damage. Fertility preservation via banking of oocytes or embryos after controlled ovarian stimulation with FSH (COS) can increase the likelihood of a future successful pregnancy. It has been hypothesized that elevated serum estrogen levels during COS may induce breast tumour growth. This has led to the use of alternative COS protocols with addition of tamoxifen or letrozole. The effectiveness of these COS protocols in terms of oocyte yield is unknown.

Methods/design: Randomized open-label trial comparing COS plus tamoxifen and COS plus letrozole with standard COS in the course of fertility preservation. The study population consists of women with breast cancer who opt for banking of oocytes or embryos, aged 18 – 43 years at randomisation. Primary outcome is the number of oocytes retrieved at follicle aspiration. Secondary outcomes arenumber of mature oocytes retrieved, number of oocytes or embryos banked and peak E2 levels during COS.

Discussion: Concerning the lack of evidence on what stimulation protocol should be used in women with breast cancer and the growing demand for fertility preservation, there is an urgent need to undertake this study. By performing this study, we will be able to closely monitor the effects of various COS protocols in women with breast cancer and pave the way for long term follow up on the safety of this procedure in terms of breast cancer prognosis.

Trial Registration: NTR4108

Keywords: ovarian stimulation, breast cancer, fertility preservation, estradiol, oocytes, cryopreservation, embryos, recurrence, survival.

Background

Breast cancer is the most common malignancy in women of reproductive age [1]. Most young women with breast cancer are advised to undergo chemotherapy, which can be lifesaving, but negatively impacts ovarian reserve [2-6]. The American Society for Clinical Oncology recommends that fertility preservation is discussed early in the trajectory of breast cancer treatment [7]. To bank oocytes or embryos, women have to undergo controlled ovarian stimulation (COS) by follicle stimulating hormone (FSH) to obtain multifollicular growth, and by concurrent pituitary down regulation with GnRH-antagonists or GnRH-agonists to prevent a premature LH surge. Current literature favours COS with GnRH5-antagonists with a GnRH agonist ovulation trigger to minimize the risk of ovarian hyper stimulation syndrome (OHSS) [8-10]. During COS, peak estradiol levels can reach a 2-3 fold increase compared to physiological peri-ovulatory levels [11, 12]. Earlier research showed an association between estrogen exposure and the initiation and promotion of breast cancer [13]. To counterbalance estrogen exposure in breast tissue, adding tamoxifen or letrozole to COS protocols has been suggested. Current clinical practice for fertility preservation therefore varies from standard COS without any anti-estrogenic agents, to adjusted stimulation protocols adding tamoxifen or letrozole to COS [14-16].

Tamoxifen is a non-steroidal selective estrogen receptor modulator, which has an anti-estrogenic effect on breast tissue. Letrozole is an aromatase-inhibitor that systemically prevents the synthesis of estrogen from androgens by competitive reversible binding of the cytochrome P450 enzyme aromatase. The assumption that tamoxifen and letrozole serve a protective role in women with breast cancer undergoing COS is based on data that show an improved prognosis for women with estrogen-receptor positive breast cancer who use tamoxifen or letrozole as long term adjuvant therapy [17-19].

A Cochrane review aiming to compare safety and effectiveness outcomes of tamoxifen or letrozole in addition to standard stimulation protocols in women with ER-positive breast cancer found no randomised controlled trials [20]. One non-randomised prospective study compared oocyte yield for women using tamoxifen alone (n=12) with women using FSH combined with tamoxifen (n=7) with women using FSH combined with letrozole (n=11) [16]. The letrozole-FSH and tamoxifen-FSH protocol had a statistically significant higher number of oocytes compared to the tamoxifen alone protocol (12.3 and 6.9 and 1.7 oocytes respectively). The difference in number of oocytes retrieved between the letrozole-FSH and tamoxifen-FSH was not statistically significant. Follow up (2-10 years) on the safety of COS in women with breast cancer showed similar recur-

rence rates as compared to women with breast cancer who did not undergo COS [16, 21, 22]. However, these studies consisted of a small sample size and were non-randomized. It thus remains unknown whether adjusted COS protocols with tamoxifen and letrozol -suggested to serve a protective role by preventing breast cancer growth during COS -are just as effective in terms of oocyte yield as COS without these agents.
In view of this lack of knowledge, the aim of the current study is to evaluate the effectiveness of COS with tamoxifen or letrozole compared to standard COS on the number of oocytes retrieved in women with breast cancer undergoing COS to bank oocytes or embryos.

Methods/Design

Ethical considerations

This study has been approved by the Institutional Review Board (IRB) of the Academic Medical Center in Amsterdam (MEC 2013_070) and by the board of directors of all participating centres. This study is designed and will be conducted using the guidelines for good clinical practice (GCP) as well as the Declaration of Helsinki.

Study design

This study is a multicentre randomised open-label trial in the Netherlands and Belgium. Women are allocated to one of the three treatment groups: COS-tamoxifen, COS- letrozole or COS alone, (figure 1). Recruitment of women started in January 2014.

Participants

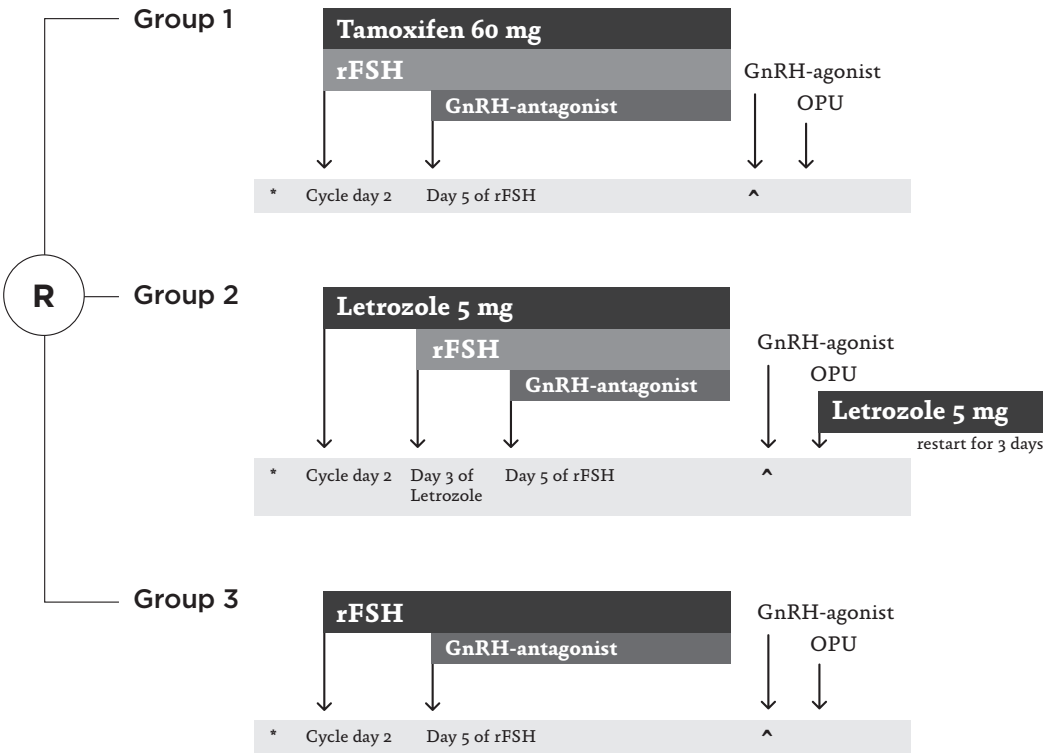
To be eligible to participate in this study, women must meet all of the following inclusion criteria: age 18 – 43 years; confirmed breast cancer (positive estrogen receptor (ER) status, negative ER status or unknown ER status); candidate for cryopreservation of oocytes or embryos (as approved by referring breast cancer specialists and the fertility clinics the women are referred to. Women are excluded if there is a contraindication to use study medication, or if women use medication that opposes the effect of study medication (i.e. paroxetine). In women fulfilling the inclusion criteria, written informed consent is obtained before randomisation. Women are randomised to

either undergoing COS with tamoxifen (group 1) or letrozole (group 2) or COS alone (group 3). Women in all study groups receive standard care concerning COS.

Randomisation

Women are randomised on-line via a web-based facility in a 1:1:1 ratio. They are stratified for oral anticonception use at start COS, for positive estrogen receptor status and positive lymph nodes. The allocated treatment, i.e. group 1, group 2, or group 3, appears directly online and an automatic email with allocation code is sent to the data manager.

Figure 1: Study design STIM-trial



R = randomization
rFSH = recombinant follicle stimulating hormone
* = blood sample for Anti-Müllerian hormone
OPU = ovum pick up
^ = blood sample for peak E2

Outcome measures

Primary outcome is the mean number of oocytes retrieved at follicle aspiration, defined as cumulus oocyte complexes. Secondary outcomes are the number of mature (metaphase II) oocytes, number of oocytes or embryos banked, peak E2 levels, defined as serum E2 level measured on the day of ovulation trigger.

Other study parameters

Baseline characteristics are collected including age, ethnicity, education, body mass-index (BMI), medication, current smoker, menstrual cycle, PCOS, previous pregnancies, past history of subfertility, contraceptive use, and history of ovarian or tubal surgery, family history of premature menopause. Parameters regarding breast cancer: BRCA status, stage and histology, hormone receptor status, and treatment including dose, type, number of cycles of chemotherapy are registered. COS related parameters including follicular or luteal start of COS, antral follicle count, duration of stimulation, total dose of FSH and number of cancelled cycles are collected. This data will be presented descriptively as means with SD as proportion (%) depending on the variable. After finishing the study we will collect data regarding long term outcomes, see appendix 1.

Sample size

We estimate the mean number of oocytes retrieved to be 10±3 in the control group [15, 21]. Based on the available literature we estimate the standard deviation (SD) to be 6 [23]. Based on previous studies we assume that tamoxifen will result in 4 oocytes more and letrozole will result in 4 oocytes less [15, 21]. To prove a two-sided difference of 4 oocytes with an alpha of 5% and a power of 90%, we need to include 48 women in each group. To compensate for 10% lost to follow-up we aim to enroll 53 women in each group, i.e. 159 women in total. This sample size is sufficient to compare both tamoxifen and letrozole with control treatment as well as with each other.

Study procedures

Group 1 - COS-tamoxifen:

Women receive tamoxifen (tablets with a dose of 10-30 milligrams) 60 mg per day orally, starting as soon as they start with 225 IU rFSH on cycle day 2. Women are prescribed to use tamoxifen between 18.00 and 21.00 PM. Tamoxifen is discontinued on the day of GnRHa administration.

Group 2 – COS-letrozole:

Women receive letrozole (tablets with a dose of 2.5 mg) 5 mg per day orally, starting on cycle day 2. Then, on cycle day 4 (day 3 of letrozole) they start with 225 IU rFSH. Women are prescribed to use letrozole between 18.00 and 21.00 PM. Letrozole is discontinued on the day of GnRH-a administration. Women restart letrozole (5 mg per day) at the day of OPU to prevent a rebound increase in E2 levels, and stop after 3 days.

Group 3 – standard COS:

On cycle day 2, or the second day of interruption of the contraceptive pill, 225 IU/day rFSH (Puregon®; Organon, Oss, the Netherlands or Gonal-F®; Merck Serono, Switserland) is used as gonadotrophin. On day 5 of rFSH, a GnRH antagonist (Orgalutran 0,25 mg; Organon, Oss, the Netherlands or Cetrotide 0,25 mg, Merck-Serono, Switserland) is administered to prevent premature LH surge. Gonadotropins should always be administered in the evening (between 18:00 hrs and 21:00 hrs). When one follicle or more reaches 18-20 mm, oocyte maturation is triggered by GnRHa (Decapeptyl®, 0,2 mg; Ferring BV, Hoofddorp or Triptofem ®, 0,2 mg; Goodlife BV Lelystad). Gonadotrophins (r-FSH) are discontinued on the day of the GnRHa trigger. GnRH-antagonists are continued until the day of the GnRHa trigger. The GnRH antagonist injection needs to be given before the GnRHa trigger injection. Oocyte retrieval is performed 34-36 hours after ovulation trigger. Oocytes are frozen in metaphase II or fertilized by ICSI with subsequent embryo banking.

Luteal start of stimulation

When the abovementioned COS-protocols cannot be performed due to extreme time pressing circumstances, women are allowed to start COS in the luteal phase.

Data analysis

Analysis will be on ITT (intention-to-treat) basis, i.e. all women that were randomised will be included in the analysis. We do not expect loss to follow up within this population. Number of oocytes retrieved will be presented as means and SD. Differences in number of oocytes between the groups will be presented as mean differences with 95% confidence intervals and will be compared using ANOVA. The secondary parameters concerning ovarian response i.e. number of mature (metaphase II) oocytes, number of oocytes or embryos banked, peak E2 levels will be presented as mean differences with 95% confidence intervals and will be compared using ANOVA. Differences in number of cancelled cycles will be expressed as a relative risk with 95% confidence interval. Baseline characteristics will be presented in descriptively as means with SD of as proportion (%) depending on the variable. A blinded interim analysis on safety has been performed by a Data Safety Monitoring board, by the time 25% of the sample size was included and they concluded that the study was safe enough to advise continuation of the study.

Discussion

In view of the lack of evidence on what stimulation protocol should be used in women with breast cancer and the growing demand for fertility preservation, there is an urgent need to undertake this study. By performing this study, we will be able to closely monitor the effects of various COS protocols in women with breast cancer and pave the way for long term follow up on the safety of this procedure in terms of breast cancer prognosis. The trial runs under the auspices of the Consortium for Healthcare Evaluation and Research of the Society for Obstetrics and Gynaecology (NVOG Consortium 2.0). The study started including women in January 2014. At present there are seven participating centers in the Netherlands and one center in Belgium (University Hospital of Brussels). In the Netherlands three other centers are preparing start of recruitment: Maastricht Medical Center, Leiden Medical Center

and Medical Center Groningen . In the UK, Guy's Hospital in London is preparing start of recruitment of women. Currently 58 women have been included. The study is still open for additional centres who can recruit women for the study, for which the corresponding author can be contacted. By promotional campaigns among gynaecologists and oncologists, together with the participation of multiple centres, we hope to finish recruitment after 3 years.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

TD, CCMB, KF, DS, AMEB, CBL, RS, SCL, FvdV, MvW, and MG designed the trial protocol and applied for the research grant. TD drafted this manuscript. EMEB is responsible for the logistical aspects of the trial. All authors are responsible for inclusion of the eligible women.

All authors co-authored the manuscript and approved the final version.

Appendix 1: Long term secondary outcomes

Long term outcomes data will be collected for future research purposes. This data is not part of this study.

Data regarding oocyte and embryo banking:

- uptake of oocytes or embryos
- pregnancy rates
- miscarriage rates
- ongoing pregnancy rates
- maternal outcomes
- neonatal outcomes
- congenital malformations

Data regarding breast cancer outcomes:

- 5 and 10 years survival
- 5 and 10 years breast cancer free interval

This data will be obtained by permission of the National Cancer Registry

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