Fertility preservation in women: exploring clinical dilemmas
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CHAPTER 9

This thesis explores clinical dilemmas of fertility preservation, confined to the banking of oocytes or embryos.

In chapter 1 we provide a general introduction of this thesis and describe the objectives of this thesis.

In chapter 2 we describe a quality management project, which aimed to provide insight in how our center for reproductive medicine IVF organized itself to manage fertility preservation-care. The dominant clinical pathway in IVF clinics is elective IVF/ICSI, consisting of controlled ovarian stimulation, follicle aspiration and fresh embryo-transfer, which may take 2–6 weeks. If women have cancer and have to start their cancer treatment soon, controlled ovarian stimulation followed by cryopreservation of oocytes or embryos has become an acute treatment modality. IVF-clinics have therefore been challenged to organize reproductive care within a short period of time.

Our study is the first to describe how an IVF-clinic has set up a fertility preservation-program. To do so, we used a practical tool: Strengths, Weaknesses, Opportunities and Threats (SWOT) analysis. SWOT analysis has been used extensively in business settings to uncover new outlooks and to identify problems that would impede progress. The project used a four-step strategy: first we monitored the baseline referral process during three months. We did so by asking all health care providers from the center for reproductive medicine of the AMC to fill out a notification form once they received a request for fertility preservation from either a patient or a health care professional. Regardless of whether women requesting fertility preservation did eventually pursue with fertility preservation or not, the form recorded the origin i.e. who referred the patient, the indication of the request and suggestions to improve organisational handling of that specific incoming request.

After this monitoring period, the second step of the project was performed. This consisted of a SWOT analysis, performed by an expert-team, which aimed to explore the then existing fertility preservation-care i.e. the “baseline fertility preservation-program” and ways to improve that fertility preservation care. The third-step of the project consisted of setting up a new fertility preservation-program within the center for reproductive medicine for women referred for acute cryopreservation of oocytes or embryos.

We set up the new fertility preservation-program based on the data from the three-months monitoring period of the baseline referral process and the results of the
SWOT analysis. Then, two years after the set-up of this fertility preservation-program, we performed the last step of this quality management project consisting of the evaluation of the program by a final SWOT analysis, performed during a structured brainstorm session. The three-months monitoring period showed that a total of 126 women requested fertility preservation, of which 90 women (71%) wished to cryopreserve oocytes because of age-related decline of fertility. Twenty-eight (22%) women requested fertility preservation for acute reasons, of which 16 (57%) women did so because of breast cancer. The SWOT analysis of the baseline fertility preservation-program revealed that logistics of acute fertility preservation care were not yet incorporated into daily practice and delays in planning a first consult were common. The new fertility preservation-program set up after this SWOT analysis took four general measures. Firstly, information about fertility preservation for patients was developed and was spread through leaflets and the internet. Secondly, potential referring physicians were informed by letters, our website and by information sessions. Thirdly, organisational tools such as a pre-consultation fertility preservation-questionnaire were developed to reduce time of first consultation. Lastly, a checklist for the first consultation was developed that covers relevant fertility preservation items. When we evaluated the organisation of fertility preservation two years after the set-up of the new fertility preservation-program by a final SWOT analysis, we found that consultation was less time-consuming by introducing a pre-consultation fertility preservation-questionnaire for patients and a checklist for doctors to use during consultation. We conclude that our new fertility preservation-program can be used as an example for other IVF-clinics on how to manage acute fertility preservation care and can offer insight in how to use SWOT analysis as a practical tool to improve or start fertility preservation care.

In chapter 3 we report a prospective case-series in which we assessed tamoxifen and tamoxifen metabolite levels (endoxifen) in four women with estrogen receptor (ER) positive breast cancer who cryopreserved oocytes. All women in this study received high doses of tamoxifen (60 mg per day) to modulate the ER of the breast tumour and therefore hypothetically prevent extra tumour growth during controlled ovarian stimulation. The aim of this study was to assess whether endoxifen levels considered high enough for ER inhibition (>7 ng/ml) could be reached. Throughout controlled ovarian stimulation, blood samples were collected and serum levels of estradiol (E2), tamoxifen and endoxifen determined. The average number of vitrified oocytes was 11 (range 5–14). There was a large inter-individual variability in serum endoxifen levels
between the women at time of follicle aspiration (range 5.9–44.5 ng/ml). Of note, three out of four women achieved endoxifen levels considered high enough for ER inhibition (>7 ng/ml). Although it is unknown what the clinical relevance is of high endoxifen levels for this particular group of women, we can conclude that, when dosages of tamoxifen are used like the ones commonly used in the adjuvant setting, endoxifen serum levels similar to those in the adjuvant setting can be reached in the setting of controlled ovarian stimulation for fertility preservation. To further explore and understand the mechanism of how tamoxifen metabolizes in the setting of controlled ovarian stimulation a prospective study in a larger group of women is warranted.

In chapter 4 we present a systematic review which aimed to assess the effects of adding tamoxifen or letrozole to standard controlled ovarian stimulation protocols on the breast cancer free interval in young women with estrogen receptor positive breast cancer who banked oocytes or embryos. Alternative controlled ovarian stimulation protocols with tamoxifen or letrozole are being used based on the idea that standard controlled ovarian stimulation promotes breast cancer growth. We searched for randomised trials comparing controlled ovarian stimulation protocols with additional tamoxifen or letrozole in women with breast cancer. Two review authors independently screened 262 titles and abstracts that were identified by the conducted searches but no randomised controlled trials were identified. Although no randomized controlled trials were found, we identified one prospective cohort study that compared three controlled ovarian stimulation protocols: recombinant follicular stimulating hormone (recFSH) with extra tamoxifen (60 mg per day), a protocol using only tamoxifen as ovarian stimulant (60 mg per day) and a protocol using recFSH with letrozole (5 mg per day). These protocols were compared in 60 women with breast cancer who were banking embryos. A total of 29 women who underwent 33 cycles were compared with a control group of 31 women with breast cancer who did not undergo fertility preservation. Compared with women who received tamoxifen alone, women who received the combination recFSH-tamoxifen or recFSH-letrozole, had a greater number of follicles. Peak E2 levels in the recFSH-letrozole group were significantly lower than in the group receiving tamoxifen alone or recFSH-tamoxifen. After an average of 554 ± 31 days (range 153 to 1441 days) of follow-up for all women including controls, the cancer recurrence rate was similar between women undergoing controlled ovarian stimulation and the women who did not undergo fertility preservation (the control group) (three of 29 versus three of 31
women, respectively; hazard ratio, 1.5; 95% CI 0.29 to 7.4). Thus, the only study that compared controlled ovarian stimulation protocols including tamoxifen or letrozole used a non randomised approach in which small groups of women were compared without power-calculation and the control group consisted of women who did not undergo fertility preservation, in stead of women receiving controlled ovarian stimulation without additional letrozole or tamoxifen. In addition, the study failed to provide long-term follow up for women undergoing controlled ovarian stimulation with tamoxifen or letrozole. For this systematic review, we concluded that there are no randomised controlled trials comparing protocols with extra tamoxifen or letrozole.

Given this lack of evidence, we suggest that controlled ovarian stimulation protocols that include tamoxifen or letrozole should be restricted to the setting of randomised controlled trials.

In chapter 5 we present the study-protocol of the STIM-trial (trial register number: NTR4108): “Stimulation of the ovaries in women with breast cancer undergoing fertility preservation: alternative versus standard stimulation protocols”. To counterbalance estrogen exposure in breast tissue, it has been suggested to add tamoxifen or letrozole to controlled ovarian stimulation protocols. Current clinical practice for fertility preservation therefore varies from standard controlled ovarian stimulation without any anti-estrogenic agents, to adjusted stimulation protocols adding tamoxifen or letrozole to controlled ovarian stimulation. The assumption that tamoxifen and letrozole serve a protective role in women with breast cancer undergoing controlled ovarian stimulation is based on a generalization of data that show an improved prognosis for women with estrogen-receptor positive breast cancer who use tamoxifen or letrozole as long term adjuvant therapy. Follow up (2-10 years) on the safety of controlled ovarian stimulation in women with breast cancer showed similar recurrence rates as compared to women with breast cancer who did not undergo fertility preservation. Although these studies consisted of a small sample size (between 29 and 71 women) and did not compare different controlled ovarian stimulation protocols with each other but only with controls who had not received controlled ovarian stimulation, it seems that thus far controlled ovarian stimulation with extra tamoxifen or letrozole has no harmful effect on long term outcomes for women with breast cancer. However, a larger cohort study is necessary to compare the effects of different controlled ovarian stimulation protocols (with and without extra tamoxifen or letrozole). Besides safety, insight into what stimulation protocol is most effective in terms of oocyte yield is also necessary. One study comparing a
standard controlled ovarian stimulation protocol with a controlled ovarian stimulation protocol with extra letrozole showed a significantly lower yield of oocytes for cryopreservation as compared to a standard controlled stimulation protocol (6.6 ± 3.5 versus 8 ± 5, p=0.038). Another study compared three controlled ovarian stimulation protocols: recombinant follicular stimulating hormone (recFSH) with extra tamoxifen (60 mg per day), a protocol using only tamoxifen as ovarian stimulant (60 mg per day) and a protocol using recFSH with letrozole (5 mg per day). This study found that women who received the protocol containing recFSH and tamoxifen or letrozole had a higher number of mature oocytes as compared with the women receiving a protocol with tamoxifen only (1.5 +/- 0.3 versus 5.1 +/- 1.1 and 8.5 +/- 1.6, respectively; P < .001). Because the quintessence of fertility preservation is to yield a high number of mature oocytes, as a possible proxy for future chances of conception, it is warranted to know which stimulation protocol suits women with breast cancer best in terms of oocyte yield. By conducting the STIM-trial we aim to evaluate the effectiveness of controlled ovarian stimulation with tamoxifen or letrozole compared to standard controlled ovarian stimulation on the number of oocytes retrieved in women with breast cancer undergoing controlled ovarian stimulation to bank oocytes or embryos. Meanwhile, we aim to collect data on the safety of controlled ovarian stimulation by conducting long-term follow up of the women enrolled. The STIM-trial is a multicenter open-label randomised controlled trial. 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 are the number of mature oocytes retrieved, the number of oocytes or embryos banked and peak E2 levels during controlled ovarian stimulation. 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. The study started including women in January 2014. Currently 58 women are included.

In chapter 6 we present a qualitative study that aimed to explore how women experience oocyte or embryo banking when they have just been diagnosed with breast cancer. Although there are studies on the perspectives of breast cancer survivors on childbearing, and decision-making for or against fertility preservation, the experience of going through fertility preservation has not been studied. This lack of knowledge
may not be to the benefit of our patients, as insight into women's experiences and needs during treatment is necessary to provide appropriate psychosocial care during infertility treatment. Psychosocial care by all fertility staff members is a prerequisite for high-quality fertility care, as recently stated by the European Society of Human Reproductive and Embryology (ESHRE). This study therefore aimed to explore how women experience oocyte or embryo banking when they have just been diagnosed with breast cancer. A phenomenological design was chosen as phenomenology is a specific qualitative research methodology devoted to exploring and understanding experiences. All women aged between 18 and 43 years with newly diagnosed breast cancer who banked their oocytes or embryos in the Centres for Reproductive Medicine of the Academic Medical Center or the University Medical Center Utrecht between January 2013 and July 2014 were eligible for inclusion. After obtaining written informed consent, we collected data on demographics and on medical background with the aid of a questionnaire. Then, we conducted face-to-face in-depth interviews, which lasted 45-90 minutes. In total, we invited twenty-eight women of whom twenty-one women consented to participate. The 21 interviewed women had a mean age of 32 years. They banked oocytes (n=15), embryos (n=5) or stopped before follicle aspiration (n=1). Fifteen women had time for only one cycle of banking oocytes or embryos. Fertility preservation was experienced as a burden, mainly because of time pressure and the fear for complications that could result in a delay for chemotherapy. Through fertility preservation women experienced a new identity as a fertility patient, which was sometimes reported as difficult because being different from regular fertility patients further emphasized women's unpleasant identity as a breast cancer patient. On the other hand, women felt relieved to see 'regular' infertility patients in the fertility clinic because this made them realize that they were not the only ones struggling to have a future with children. Women also described coping with breast cancer through fertility preservation as it allowed them to take action in a time when they were not yet able to start with cancer treatment. Their diagnosis had induced a strong survival mode and an eagerness to 'act' and to push emotions aside. For these women, fertility preservation was the 'start' and therefore an integrated part of their breast cancer trajectory. In conclusion, this study provides in-depth insight in the experiences of women with breast cancer undergoing fertility preservation. This insight can be used to increase clinicians understanding, empathy and psychosocial care for these women. Future studies are necessary to investigate ways to incorporate these findings into routine psychosocial care, and to measure its effect on women's wellbeing or even treatment outcome.
In chapter 7 we present a follow-up study on the reproductive choices women make after they have cryopreserved oocytes for medical reasons. There have been efforts to increase awareness about fertility preservation, by organizations like the American Society for Clinical Oncology, Fertile Hope, the International Society for Fertility Preservation, the Oncofertility Consortium and local initiatives i.e. the Dutch Network for fertility preservation. It may be that more women know of their risk of premature ovarian insufficiency and may wish to freeze their oocytes. Since it is known that many of these women will retain ovarian function, chances of natural conception will be present while their oocytes are banked. The added value of banked oocytes to reproductive outcomes is unknown in these women, as there is a lack of a comprehensive follow-up of women who have banked oocytes for medical reasons. This follow up study included a cohort of 85 women who banked their oocytes for medical reasons between 2009 and 2012 in the Academic Medical Center in Amsterdam. We extracted medical data from medical files and disseminated self-report questionnaires. The collected data consisted of demographics, outcomes of ovarian stimulation, type of fertility-threatening treatments, changes in the menstrual cycle, attempts to become pregnant and the outcomes of a possible pregnancy attempt, and intended plans for future use of banked oocytes. A total of 68 women, followed up for an average 25.3 months, returned the questionnaire (response rate: 80%). None of the women had used her cryopreserved oocytes. Sixteen women had tried to conceive. Of these 16 women, eight were trying to conceive naturally, five had conceived naturally within 2 months and three had conceived with medically assisted reproduction not requiring cryopreserved oocytes; two women with conventional IVF because of tubal pathology and endometriosis and one woman with IUI because of polycystic ovary syndrome. Three out of the eight pregnancies had resulted in live births, two resulted in miscarriages and three were ongoing. Most women (71%) intended to conceive naturally and only wished to use their cryopreserved oocytes as a last resource option. The results of our study emphasize the importance of taking the chances of getting pregnant without use of cryopreserved oocytes e.g. by natural conception into account when counseling women on live birth rates after cryopreserving oocytes and when designing new studies that evaluate pregnancy rates in the setting of oocyte cryopreservation.

In chapter 8 we discuss the findings of this thesis and reflect on the clinical implications of our studies. We describe the necessity to design and perform evaluation research within the field of fertility preservation and we reflect on research ideas that incorporate long-term follow up to reach this goal.