Female fertility preservation: clinical challenges

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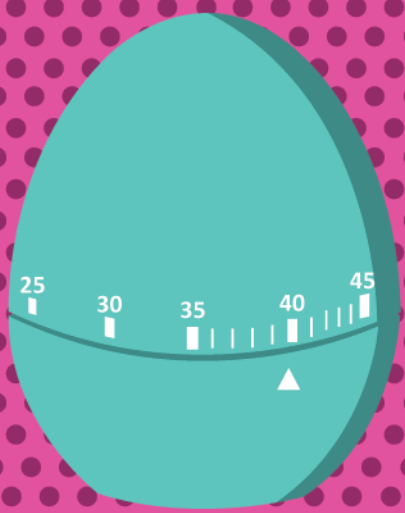
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Summary

This thesis describes several studies focused on clinical challenges in female fertility preservation.

In **chapter 1** we provide a general introduction and outline of this thesis.

In **chapter 2** we present a cross-sectional study that shows an overview of the reasons women banked oocytes in our centre for reproductive medicine between May 2006 and December 2013. During the study period 298 women banked oocytes. Indications for oocyte banking were age-related decline of fertility (n=98, 33%), planned gonadotoxic treatment (n=81, 27%), no sperm available during IVF or ICSI treatment (n=67, 23%), other risk on premature ovarian insufficiency (n=25, 8%) ovarian surgery (n=14, 5%) and previous chemotherapy (n=13, 4%). This study provided insight in the actual reasons why women opt for oocyte banking and revealed that most women did so because of age-related decline of fertility. It is difficult to predict which women will use their banked oocytes because of future infertility.

In **chapter 3** we present a qualitative study in women who face age-related fertility decline to explore their preferences and factors influencing their decisions about two fertility preservation methods: oocyte banking or ovarian tissue banking. Women were recruited through monthly information sessions at our centre on oocyte banking, postings on social media, websites and newsletters and snowball sampling. Women had to be 35 years or older, single, childless and with a possible future desire for motherhood. Interviews were audiotaped and transcribed verbatim. The 'Health Belief Model' -a psychological model used for understanding individuals' health intentions and decision making- was used to analyse which method women prefer, the ultimate trade-off they make, and which factors determine decision-making. Fifteen women participated in the study. The mean age was 36 years and 13 women (87%) were highly educated. For oocyte banking, women mentioned chances of success, extra time and reassurance that they had created a back-up plan and faith in the technique and healthcare professionals as benefits. Risks for themselves, risks for their future children and costs were considered as barriers in decision making. For ovarian tissue banking, the chances of success, the possibility of natural conception, the time investment and effect on menopausal symptoms were seen as benefits, and lack of experience and lack of information were considered barriers for themselves or their future children. Overall, women considered oocyte banking as relatively 'easy', whereas ovarian tissue banking was seen as a more invasive procedure and therefore most women preferred oocyte banking over ovarian tissue banking. Our findings contribute to understanding women's attitudes and concern's about fertility preservation. This information can be used to counsel women better prior to fertility preservation.

In **chapter 4** we report a follow-up study on reproductive outcomes of women who banked oocytes for fertility preservation. Until then, most studies did not systematically

address reproductive follow-up of women who banked oocytes. The aim of this study was to evaluate the reproductive status and outcomes of a large cohort of women who banked oocytes. In this prospective cohort study, 327 women who banked oocytes between July 2009 and August 2015 at our centre received a questionnaire with questions about gonadotoxic treatment after oocyte banking, attempts to conceive and pregnancies after oocyte banking and intended plan for their banked oocytes. In total, 228 (70%) consented to participate and returned the questionnaire. The median time of follow-up was 31 months. A total of 101 women (44%) were trying, or had tried, to become pregnant after oocyte banking, of which 66 became pregnant (65%). Five women reported an unintended pregnancy. Of these, 71 women became pregnant: 54 women (76%) conceived naturally, 5 women (7%) through intracytoplasmic sperm injection with their vitrified–warmed oocytes and 12 women (17%) by other medically assisted reproduction treatments. Of the women who became pregnant with their thawed oocytes, six pregnancies were achieved in five women of which two (40%) resulted in a live birth. A total of 38 women reported a live birth at the time of follow-up. Six women attempted to achieve a pregnancy using their banked oocytes. Our results emphasize that oocyte banking represents a form of risk management: on the one hand, the a-priori unknown risk of absolute infertility and on the other hand the possibility that banked oocytes are unnecessary. This non-committal concept should be discussed during counselling, especially for those women whose treatment is not reimbursed by their healthcare insurance.

In **chapter 5** we provide guidance for handling a new type of intra familial medically assisted reproduction: fertility preservation by mother-to-daughter oocyte donation. For girls diagnosed with premature ovarian insufficiency, banking of their mothers' oocytes can preserve the option of having genetically related offspring. Through a comparison of fertility preservation for mother-to-daughter oocyte donation with reproductive practices in which similar concerns were raised (i.e. donation between family members), we argue that fertility preservation for mother-to-daughter oocyte donation can be acceptable under certain conditions. The moral acceptability of fertility preservation for mother-to-daughter oocyte donation will have to be determined on a case-by-case basis. Our paper provides guidance by recommendations for handling fertility preservation for mother-to-daughter oocyte donation requests, including different options for the legal construction of this form of oocyte donation.

In **chapter 6** we present a prospective case series of four women with estrogen positive breast cancer in which we assessed their tamoxifen metabolite levels during ovarian stimulation with additional tamoxifen for oocyte or embryo banking. During ovarian stimulation for banking of oocytes or embryos, these women may receive high doses of tamoxifen (60 mg) to modulate the estrogen receptor and prevent extra growth of estrogen responsive tumours during ovarian stimulation. The aim of this study was to evaluate whether the tamoxifen dose used in an ovarian stimulation with tamoxifen

combined schedule for women with estrogen receptor positive breast cancer is high enough to reach endoxifen levels (7 ng/ml) that are considered therapeutically effective to inhibit breast cancer growth. The four women with estrogen receptor positive breast cancer who underwent ovarian stimulation for banking of oocytes were prospectively studied at our centre. Throughout ovarian stimulation, blood samples were collected and tamoxifen and endoxifen levels were determined. The four women with estrogen receptor positive breast cancer underwent a total of five ovarian stimulation cycles, while additionally using tamoxifen 60 mg daily. The tamoxifen and endoxifen levels showed a large variability between the women, with endoxifen levels during the whole period of ovarian stimulation varying between 3.96 and 41.0 ng/ml. The average number of vitrified oocytes was 11 (range 5–14). We concluded that therapeutically effective endoxifen serum levels can be reached when tamoxifen is used to counteract estrogen levels during ovarian stimulation for fertility preservation, but not in all women, although large variations of tamoxifen and endoxifen levels between the women were observed.

In **chapter 7** we present the results of a randomized controlled trial on the effectiveness of various controlled ovarian stimulation protocols in terms of oocyte yield in women with breast cancer undergoing fertility preservation. Women aged between 18-43 years were eligible for the study if they had a diagnosis of breast cancer and opted for banking of oocytes or embryos, regardless of estrogen receptor status. Women were randomly assigned to one of three treatment arms: ovarian stimulation plus 60 mg of tamoxifen daily, ovarian stimulation plus 5 mg of letrozole daily or standard ovarian stimulation. The primary outcome measure was the mean number of cumulus oocyte complexes retrieved at follicle aspiration. Secondary outcomes were the number of metaphase II oocytes, number of oocytes or embryos banked, peak estradiol levels defined as serum estradiol level measured on the day of ovulation trigger, and number of women with cancelled cycles. The mean (±SD) number of cumulus oocyte complexes was 12.5 (10.4) after ovarian stimulation plus tamoxifen, 14.2 (9.4) after ovarian stimulation plus letrozole and 13.6 (11.6) after standard ovarian stimulation (mean difference -1.13, 95% CI -5.70 to 3.43 for tamoxifen versus standard ovarian stimulation and 0.58, 95% CI -4.03 to 5.20 for letrozole versus standard ovarian stimulation). There were also no differences in the number of metaphase II oocytes and oocytes or embryos banked. Peak estradiol was significantly lower in ovarian stimulation plus letrozole compared to standard ovarian stimulation. Since the number of cumulus oocyte complexes retrieved and number of oocytes or embryos banked in our study were not affected by the alternative protocols, there are -from the perspective of fertility preservation- no arguments to add or withhold tamoxifen or letrozole to standard ovarian stimulation in women with breast cancer.

In **chapter 8** we provide a general discussion of this thesis with implications for clinical practice and future research.