Chapter 1

General Introduction

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Breast cancer, treatment and fertility

Breast cancer is the most prevalent type of cancer in women. In the Netherlands, every one in eight women will get breast cancer at some point during her life. The yearly incidence of breast cancer is 12.000. Of these 12.000 new cases, about 25% involve premenopausal women, and 8-12% are women between 18-40 years old. Indicating that yearly, about 960 women between 18-40 years old receive a diagnosis of breast cancer in the Netherlands[1].

Treatment options for breast cancer consist of surgical removal of the tumor, often complemented with systemic chemotherapy (adjuvant or neo-adjuvant) to make sure there are no remaining cancer cells elsewhere in the body. In case of hormone receptor positive types of breast cancer, when the tumor growth is initiated by high levels of female hormones in the body (estrogen, progesterone), treatment can also be supplemented with hormonal therapy. Hormonal treatment for breast cancer involves daily oral intake of hormone supplements to suppress natural menstrual cycles, and thereby preventing tumor growth. In general, hormonal therapy is given for at least 3-5 years after finishing with the chemotherapy treatment.

Due to the above mentioned treatment options, the survival chance for breast cancer is high. Five-year survival rates have increased to up to 90% [1;2]. Since survival chances have increased, quality of life after treatment has become more important for patients[3;4]. For many young women, fertility is an important aspect of quality of life [5-7]. Unfortunately, the improved treatment options (involving chemotherapy with often aggressive alkylating agents such as cyclophosphamide) can have a negative effect on fertility[3;8;9], especially when given to (“older” but still below age 40) women with less ovarian reserve[10]. In case of hormonal therapy there is no direct gonadotoxic effect of treatment, but due to the relatively long treatment period, the natural decrease of a women’s ovarian reserve must be taken into account. Therefore, interest in fertility preservation (FP) has increased, so that patients may both survive the cancer, and (try to) remain fertile after treatment.

Fertility preservation options

In the Netherlands, it is possible to try to preserve fertility by cryopreserving embryos, cryopreserving ovarian tissue and cryopreserving oocytes.

Cryopreservation of embryos

Cryopreservation of embryos is up till now the most successful option to preserve fertility before start of oncologic treatment. For many years, the technique has been used in regular fertility treatment for couples with problems getting pregnant. Since 2005 it is performed for oncologic indications as well. In the Netherlands, for cryopreservation of embryos it is necessary that patients have a male partner. In other countries, donor sperm can be used as well. The treatment consists of an in vitro fertilization (ivf) treatment, after which embryos are cryopreserved. The ivf treatment involves the following. First, patients receive hormonal stimulation to increase the number of oocytes that can be harvested. This involves injecting themselves with hormones (follicle stimulation hormone – FSH, and a gonadotrophic releasing hormone agonist (GnRH)-agonist to down regulate ovulation), for a period of two weeks following

their last menstruation. Injections can be done either intramuscularly or subcutaneously in the abdomen. Hormone levels are controlled very strictly, with an ultrasound of the ovaries and blood samples every other day. On day 12, the patient receives an extra injection with GnRH to induce ovulation within 36 hours. After these 36 hours the oocytes are harvested and tried to be fertilized with the male sperm. All fertilized oocytes (embryos) that are matured up to 8 cells are cryopreserved at -196o Celsius. When the patient has finished her oncologic treatment, embryos can be thawed and placed in the uterus with the hope a pregnancy will occur. Cryopreservation of embryos has a success rate of about 20% per embryo, which is the highest of all FP options[11]. However, since hormonal stimulation is required, the procedure of obtaining and cryopreserving the embryos takes at minimum between two and six weeks (depending on in which phase of the menstrual cycle a woman is at diagnosis), which is not always possible with respect to the oncologic treatment that has to start.

Cryopreservation of ovarian tissue

Cryopreservation of ovarian tissue is available in the Netherlands since 2002. This technique is performed in four hospitals in the Netherlands. With this technique, one of the ovaries is surgically removed (laparoscopic surgery under general anesthesia). The ovarian cortex (the outer layer of the ovary) is then cut into pieces (10x1x5mm) that are frozen in vials at -196o Celsius. Oncologic treatment can start within 2-3 days after surgery. When oncologic treatment is finished, the pieces of ovarian tissue can be thawed and replaced in the remaining ovary, where revascularization will restart a cell cycle in the replaced tissues, hopefully leading to a menstrual cycle again. A natural pregnancy may then be a possibility. At this moment, 24 children have been born worldwide after thawing and replacing ovarian tissue [12-17]. Since it is not known how often tissue is replaced, a success rate of the treatment cannot be defined. In the Netherlands, the first replacement of ovarian tissue took place in November 2012. At this moment it has been done three times. No pregnancies have been reported yet in the Netherlands, but in one woman the menstrual cycle has returned.

Cryopreservation of oocytes

Cryopreservation of oocytes is available in the Netherlands since 2011, and is performed in twelve hospitals. Like cryopreservation of embryos, it involves hormonal stimulation to increase the number of oocytes to harvest. However, the harvested oocytes are now frozen immediately instead of being fertilized first. Cryopreservation of oocytes requires special freezing protocols compared to embryo cryopreservation, because oocytes are very susceptible to the freezing process due to their size, plasma membrane permeability and chromosomal structure [18;19]. The slow-freezing protocols used in cryopreservation of embryos would cause oocytes to form ice crystals and get damaged. Therefore a so called fast-freezing protocol is used to cryopreserve oocytes, which took years to be developed. At this moment, cryopreservation of oocytes is still experimental. The success rate is about 3-5% per oocyte[20].

Ovarian suppression

Another option is ovarian suppression with medication (GnRH antagonists) during chemotherapy treatment. It is thought that by suppressing the ovaries, oocytes will not be in division during chemotherapy so chemotherapy cannot damage them. However, this has yet to be proven. Results of studies on the effectiveness of this technique are still ambiguous [21;22]. Therefore this technique is only offered in research settings in some Dutch hospitals.

Most fertility preservation techniques have to be performed in the short time frame between diagnosis of cancer and start of the oncologic treatment. The decision whether or not to pursue FP has therefore to be made shortly after the diagnosis of breast cancer. Obviously, at this moment there are many competing demands for patients with regard to decisions about oncologic treatments and precautions that have to be made before start of this treatment (buying a wig, special diets, head cooling, etc). Furthermore, emotions may be of great significance at this moment. Hearing about possible chemotherapy induced infertility on top of the diagnosis of cancer, and consequently being forced to think about a future child wish will not make this process easier. It means another decision to make, and more information to absorb.

A preference sensitive decision

Since there is from medical perspective no best fertility preservation option, the decision whether or not to pursue in fertility preservation is considered preference sensitive[23], indicating that a form of shared decision making should be adopted between patients and clinicians. Clinicians should inform patients about all options so that patients can form preferences, and together with the clinician (or multiple clinicians from different disciplines) decide what the best treatment option is. However, the information provision necessary for this is often lacking [24-28]. It seems that the developments in FP techniques are going faster than incorporation of these developments in the information provision for patients.

Information provision about fertility preservation

Over the last decades it has been noticed that information provision about FP is not sufficient. Information provision is often late or not at all, and referral for FP inadequate [25;27;29;30]. When information is provided, it is not always presented in a neutral and objective way [31].

Clinicians' barriers for providing information are a lack of knowledge [28;32;33], the difficult timing and complexity of the information [28;34], disease characteristics [32;35-37], and the experimental character and ethical issues regarding the treatments [28;32;33]. When clinicians do provide patients with information, the way they communicate the options is of great importance. In preference sensitive decisions, it is important that the information provision to patients is not already steered into the direction of one of the treatment options. Peddie et al (2012) found the way in which information is provided to patients to be a barrier *for patients* to undergo fertility preservation [31]. Patients had the feeling that oncologists steered them already in a direction of not undergoing FP.

Clinicians felt justified to do this because of their belief in urgent need for oncologic treatment instead of FP, the experimental character of the FP options, and the chance that the oncologic treatment does not harm fertility [31].

It has been found that *not* receiving information about FP, or not pursuing it might lead to more regret, lower physical quality of life and trends of lower psychological quality of life for cancer survivors, than when they do receive information or pursue FP [38]. Thus indicating a need for adequate information about FP. Internationally, a few studies have been conducted on experiences with information provision about FP and on how to improve information provision [24-26;39-42]. Since then, several informational sources, mainly in brochure-format, have been developed internationally [43]. Yet, it still seems that information provision (and especially with regard to decision making about FP) is not always sufficient. Obviously, in the information provision about FP there is still some room for improvement left.

Possibilities for improving information provision; the role of a decision aid

In case of preference sensitive decisions, such as that about FP, decision aids (DAs) are often good alternatives to provide patients with information and help them in decision making[23]. DAs are tools that provide at minimum some information about the (medical) problem, possible solutions including an option to wait and see, information about risks and uncertainties, and a balanced overview of advantages and disadvantages of each option[44]. It is thought that, with a DA, patients can make up their mind before the consultation, which facilitates decision making with the physician. Decision aids can, for example, be leaflets, booklets, CD-ROMs, or websites. Many (types of) DAs have proven to be effective in increasing knowledge, reducing decisional conflict, and increasing satisfaction with the decision[44].

In order to decide, it is important that patients are aware of their own values and their opinions on the treatment options. Some DAs therefore contain values clarification methods which are meant to implicitly or explicitly clarify a patients' personal values in order to facilitate decision making processes. In implicit value clarification, patients value the treatments after reading or viewing information in the DA (non-interactive and passive). In explicit values clarification, patients are asked to actively consider the importance of benefits and risks of the treatments or options, in order to structure and provide insights in how values affect decision making (interactive; e.g. rating options)[45]. Explicit values clarification methods come in many different formats, with different ways of rating the importance of benefits and risks [46;47], e.g. by comparing benefits and risks of one treatment option at the time, or comparing different treatment options with each other[47]. For implicit clarification, sometimes narratives of other patients are used with whom one can identify oneself [48-50]. However, there is much we do not know about the effectiveness of various specific DA aspects (such as values clarification methods), since the few studies that have tried to assess this, have different results [47;51-54]. A review on DAs in general concluded that more research is needed to study specific aspects of DAs [55]. Moreover, it might be the case that the effectiveness of (certain aspects of) DAs differs in different situations or diseases[54].

Therefore, it is recommended to study the effectiveness of DAs, and specific features, in the setting for which it was originally developed, and to not just rely on effects found in other studies or populations.

Unfortunately, many (effective) DAs or interventions are infrequently used in clinical care after trial periods are over[56]. In order to prevent this from happening, it is important to involve possible end users in developing DAs. In case of a DA about FP these would for example be patients and clinicians. Involvement of end users is deemed necessary, not only for their expert opinion on content and feasibility, but also to create awareness of the existence of the DA, and to motivate them to use the DA once it would become publicly available. Involving end-users at an early stage of development may facilitate implementation and maintenance of the DA in clinical practice.

Objectives and outline of this thesis

In the Netherlands, information provision about fertility preservation (FP) for young women with breast cancer is not sufficient. Since an increasing number of Dutch breast cancer patients will face this preference-sensitive decision each year, there is a clear need for improvement of information provision about FP. The overall aim of this thesis is therefore to (a) develop and (b) evaluate a Decision Aid (DA) about FP that is targeted to improve information provision and decision making about FP for young women with breast cancer.

This thesis describes consecutively the development and evaluation of such a DA with values clarification exercise (VCE). As part of the development, we conducted qualitative interviews with patients who had received a counseling consultation about fertility preservation in the past *(chapter 2)*. The primary aim of this needs assessment was to evaluate the information provision as it was, and to find starting points for development of improved information. Subsequently, we developed a draft DA and presented it to healthy women, patients and clinicians in order to test acceptability and understandability *(chapter 3)*. Next, we presented it to a Delphi panel of patients and clinicians in order to determine an optimal procedure of informing patients (with use of the DA) relevant for the implementation of the DA in clinical practice *(chapter 4)*.

Before evaluating effectiveness of the DA in newly diagnosed patients *(chapter 7)*, experiments were conducted with healthy participants *(chapter 5)*, and a validation study was carried out for one of the questionnaires to be used as outcome measure in the actual effect evaluation *(chapter 6)*. The primary aim of *chapter 5* was to assess the effectiveness of the VCE in the DA, in a population of healthy women who made a hypothetical decision about FP. The primary aim of *chapter 6* was to validate the Reproductive Concerns Scale as a measure for reproductive concerns in Dutch women with breast cancer. This instrument for oncologic populations at risk for infertility is increasingly used worldwide, but has never been validated internationally. By assessing the psychometric properties of the instrument in Dutch breast cancer patients we were able to use it as a validated measure to investigate reproductive concerns of Dutch breast cancer patients in our effect evaluation (RCT) of the DA *(chapter 7)*.

The primary aim of *chapter 7* was the effect evaluation of the DA in recently diagnosed breast cancer patients. Patients were randomized to the DA or information brochures, and completed questionnaires at three measurement moments (diagnosis,

6 weeks later, 6 months later). We assessed decision making outcomes (such as decisional conflict, knowledge), decision making processes (such as preparation for decision making) and health outcomes (such as reproductive concerns, quality of life). Secondarily, respondents were compared to a historical control group who received no information additional to counseling, to assess the effect of both information sources in addition to counseling only.

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