Informing patients about fertility preservation

Development and Evaluation of a Decision Aid about Fertility Preservation for Dutch Breast Cancer Patients

M.M. Garvelink

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Colophon

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“Maar uit de stronk van Isaï schiet een telg op, een scheut van zijn wortels komt tot bloei” (Jesaja 11:1)

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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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Part I: Development of a Fertility Preservation Decision Aid

Chapter 2

Women's experiences with information provision and deciding about fertility preservation in the Netherlands: 'satisfaction in general, but unmet needs'

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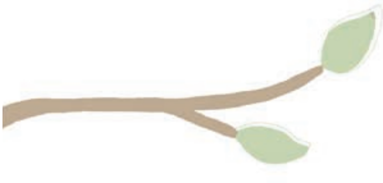


Abstract

Background It is not well known how women receiving counseling consultation about fertility preservation (FP) in the Netherlands perceive the information provision about and referral for FP in the oncology setting. The aim of this study was to qualitatively explore women's experiences with the (process of) information provision about the gonadotoxic effects of cancer treatment and about FP and the decision-making process, and to obtain their recommendation for improvements.

Methods Semi-structured interviews with female cancer patients who had received a counseling consultation on FP (at 18-40 years of age).

Results Thirty-four interviews were held (response rate 64%). Information provision was considered to be important. Overall, women were satisfied with the timing and the content of the information, but women were less positive about the need to be assertive to get information, and the multiplicity of decisions and actions to be carried out in a very short time frame.

Conclusions Information provision on gonadotoxic effects of cancer treatment and about FP was overall deemed sufficient, timely and important. Women recommended standardization of the information provision, improvement of communication among clinicians and medical centers, and availability of FP-specific patient information materials in order to improve future information provision processes.

Introduction

Due to improvements in oncologic treatment, survival for women with cancer has increased. Unfortunately, oncologic treatment is associated with decreased fertility or infertility, as a result of direct gonadotoxic effects of treatment or a delay in childbearing until after treatment is complete [1-3]. The risk of treatment-induced infertility depends on women's age, and type and dosage of the oncologic treatment [4].

Infertility or concerns about fertility due to cancer treatment can be very distressing, leading to a decreased quality of life [5-9]. Therefore, interest in fertility preservation (FP) has risen. Currently, the techniques available include embryo and oocyte cryopreservation, ovarian tissue cryopreservation and ovarian suppression or -transposition. Except for embryo cryopreservation, FP techniques are still experimental.

Despite an increasing number of studies, and guidelines from the Netherlands [10], Europe [11], and the United States of America [4;12] demonstrating the need for discussion of fertility related issues with cancer patients, only about 30-75% of the female cancer patients of fertile age report having discussed these issues with the oncologist [13-17]. Furthermore, the information provision and the process of referral are often inadequate [15;18;19], and not all women are satisfied with all aspects of the information provision [20;21].

Sufficient and clear information is necessary to enable effective patient decision making. Involvement of patients in decision making is especially important in deciding on treatments with possible long-term consequences for quality of life, such as gonadotoxic and FP treatments. It has been found that not receiving sufficient information about FP, not seeing a fertility specialist, and deciding to "wait and see" (expectant management) were related to more regret and decisional conflict [22;23]. Furthermore, receiving counseling about reproductive loss and pursuing FP has been found to be associated with less regret, greater physical QOL and trends of greater psychological QOL [24].

At this moment, it is not known whether the information women in the Netherlands receive about FP is sufficient for them to engage in decision making with their physicians. Therefore it is necessary to explore patient's experiences with the current information provision about FP and with the decision making process.

This study describes the experiences of women who had received at least one counseling consultation on FP in relation to the procedure of information provision and decision making about FP, and their recommendations for improvement of these processes. Research questions were:

1) What are women's experiences with the information provided to them in the past about gonadotoxic effects of oncologic therapy and about FP?
2) What are women's experiences with the process of information provision and decision making about FP?
3) How do women think the information provision and decision-making processes can be improved?

Methods

Sample

Since July 2002 techniques have been available at the Leiden University Medical Center (LUMC) to cryopreserve ovarian tissue, and since October 2005 to cryopreserve embryos on oncologic indication. From 2002 - 2007, these techniques (FP) were discussed with 61 women at risk for gonadotoxic effects of oncologic treatment. Women were eligible for this study when they had had at least one counseling consultation about FP between 2002 and 2007, as registered in a LUMC database for FP, were between 18-40 years of age at the time of the counselling, and had sufficient knowledge of the Dutch language. Eligible women were approached by means of a personal invitation letter, signed by a team of gynecologists. Two weeks after the letter was sent they were contacted by phone to make an appointment for the interview. Our study was approved by the Medical Ethical Committee of the LUMC.

Data collection

Data was collected by means of retrospective semi-structured interviews between November 2007 and April 2008. The topic list for the interviews is presented in Box 1.

Demographic characteristics were both obtained during the interview (Box 1) and by medical record searches (type of malignancy, type of cryopreservation).

All interviews were conducted at the women's homes or at the LUMC (depending on the women's preference) by a researcher not involved in the treatment or counseling of the women (EJ), one interview was conducted by a clinician (LL). Both interviewers had acquired their interview skills during medical training. They were not involved in the treatment of the women they had interviewed.

Data analysis

All interviews were audiotaped, transcribed, and content coded. Qualitative data was analyzed using Nvivo® software. For the qualitative analysis we relied on the steps identified as the Framework Approach [25], indicating identification of themes (a framework) using our a priori coding scheme as a framework (based on the structuring of the interview questions; Box 1). Respondents were anonymized in the analysis. The first fifteen interviews were deductively content coded by two independent researchers thus building an a priori code book (MG and RB). At that point no new codes emerged, and one researcher continued coding the other interviews using the a priori code book (MG). Additionally, specific subthemes and subcodes were allocated to the initial coding. Subthemes were double coded in all interviews (RB, MG) to ensure reliability. Dissimilarities in coding were continuously discussed and adapted based on consensus, in order to find the code that best described the experiences of the respondents. The definite coding scheme with all its subcodes was checked with the other project members. Interpretations of the data were discussed first by two researchers (MG, RB), and secondly in the project group.

In order to compare responders and non-responders, a non-response analysis was conducted on data regarding demographic or medical characteristics, using SPSS version 16.0.

Box 1. *Topic list*

Demographic characteristics
Date of birth/ partner status/ parity/ pregnancies/ menses/ oncologic treatment/ desire for children (yes/no/maybe)

Information provision about treatment induced infertility & fertility preservation (FP)
Can you describe when and by whom the information provision about FP was initiated? What is your opinion about the moment chosen to inform you? What is your opinion about the information received? What is your opinion about the conversation, and the way the information was given to you? What effect did receiving information have on you? How important did you think receiving information about FP was at that time? How important was the possibility of losing your fertility compared to the diagnosis of cancer for you at that time vs now?

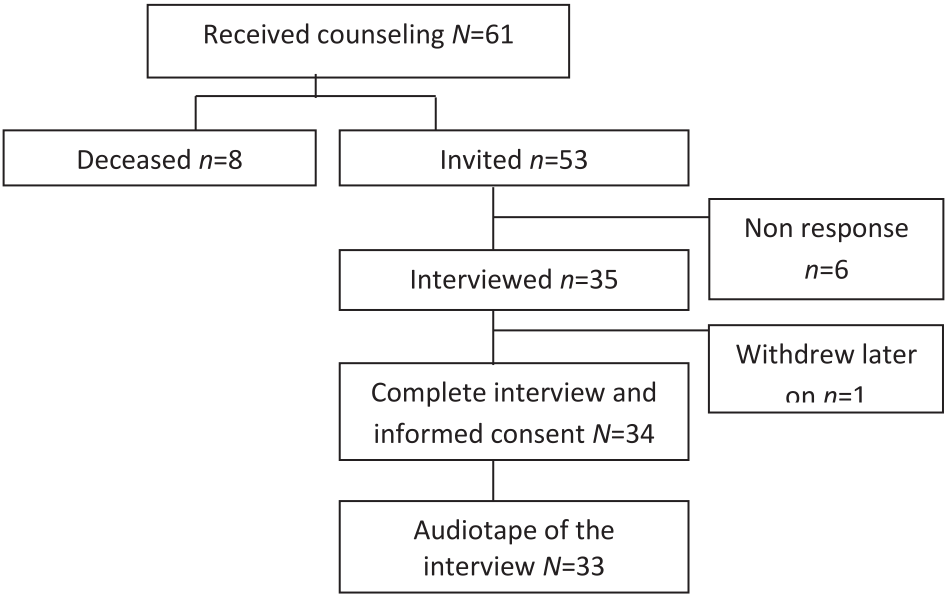
Improvements for future patient information procedure about FP
What did you miss in the information provision about FP? Which patients should be informed about FP? What type of physician would be best to inform patients about FP?
Who should make the decision whether or not to undergo FP (patient, physician, both)?
Do you have recommendations for future information provision?

Decision-making on FP
Who made the decision? What were considerations in decision-making? How did this decision made you feel (effect)? Were you sufficiently informed to make a decision? Did you discuss your decision with others, who? What did you think about the attitude of your physician in the issue of FP? Would you make the same decision now?

Results

Fifty-three women were eligible and invited for the study (Figure 1). Thirteen women (25%) refused to participate, six did not respond to the invitation (11%). Reasons for refusal were no interest in participating in the study (*n*=5), lack of time (*n*=3) or unknown (*n*=5). Eventually, thirty-four interviews (*response rate*= 64%) were held with an average duration of 51 min. (*sd*=17; *range*: 23 – 88 min.). Mean time since the counseling session was 24 months (*sd*=13). Significantly more women in the response group (*n*= 28, 82%) were diagnosed with breast cancer ($\chi 2(2,53)=11.23$; *p*=0.001), than in the non-response group (*n*=11, 58%). Otherwise no significant differences were found between responders and non-responders in demographic and medical characteristics.

Figure 1. Description of the study population



Characteristics of the participants

(Table 1) Sixty-two percent of the women (*n*=21) had had either embryo (*n*=9, 26%) or ovarian tissue (*n*=12, 35%) cryopreservation. The remainder had chosen to “wait and see” (*n*=13, 38%). The majority of the women had been diagnosed with breast cancer (*n*=28, 82%). Other diagnoses were Hodgkin (*n*=2) and non-Hodgkin lymphoma (*n*=2), and metastasized myxoid liposarcoma (*n*=1). Women had been treated with chemotherapy, local or total body irradiation, surgery, stem cell transplantation, or a combination of these. One respondent had not received any treatment, because of a pregnancy. No differences were found in women’s evaluation of the process of information provision or decision making between those who were diagnosed at different years, or with different types of cancer.

Seventy-nine percent of the respondents had no children at the time of the FP consult. Seventy-four percent of the respondents had had a desire for children, either at that time (47%, *n*=16) or later (27%, *n*=9). Five women (15%) had become pregnant spontaneously after therapy, resulting in one miscarriage, one live birth, and three ongoing pregnancies at the time of the interview. One woman who was pregnant at the time of the interview had made use of her cryopreserved embryos to become pregnant. No differences were found in responses of women with or without children before diagnosis, except in their opinions about FP (see opinions about FP).

Thirty women (88%) were in total remission at the time of the interview, one (3%) in partial remission and one (3%) had metastases.

Table 1. *Demographic and medical characteristics of the study population (n=34)*

	FP (*n*=21)	**No FP (*n*=13)**	**Total (*n*=34)**
Age at the time of the interview in years, *Mdn (range)*	32 (22-37)	34 (24-41)	33 (22-41)
Age at FP consultation, *Mdn (range)*	31 (21–35)	31 (22–40)	31 (21-40)
Partner (yes), *n (%)*	17 (81)	10 (77)	27 (79)
Type of malignancy, *n (%)*			
Breast cancer	18 (86)	10 (77)	28 (82)
Other malignancies	2 (10)	3 (23)	5 (15)
Recurrence malignancy	1 (5)		1 (3)
Parity *n (%)*			
0 children before diagnosis	18 (86)	9 (69)	27 (79)
1 child before diagnosis	2 (10)	4 (31)	6 (18)
Menses during/after therapy, *n (%)*			
Never absent	3 (14)	4 (31)	7 (21)
Absent during therapy, returned afterwards	10 (48)	4 (31)	15 (44)
Absent since therapy	7 (33)	3 (23)	10 (27)
Pregnancy after treatment, *n (%)*	4 (19)	1 (8)	5 (15)

FP= fertility preservation, Mdn=median

Initiation and timing of the information provision

The discussion of possible gonadotoxic side-effects of cancer treatment and FP options had either been initiated by a medical oncologist (*n*=16; 49%), the patient herself (*n*=10; 30%), a surgeon (*n*=3; 9%), a nurse (*n*=3; 9%) or a general practitioner (*n*=1; 3%). The initial information provision took place at the time of diagnosis (*n*=1, 3%), soon after diagnosis but before discussion of the cancer therapy (*n*=13; 40%), or during or after discussion of the cancer therapy (*n*=18; 55%). Initial information about gonadotoxic effects of chemotherapy often included mentioning of the options to preserve fertility as well. However, for detailed content information about FP, women were referred to a gynaecologist or IVF-specialist, if necessary in another medical centre.

The appreciation of the timing of the initial information provision was comparable between women who had been informed at different moments, and by different initiators. Nine women appreciated the moment of the information provision without any criticism:

> Quote 1: *"I liked it* [the moment]*, because it gave me the opportunity to think about it [FP] before my treatment started. [..] If you are told about FP too late, it is probably of no use anymore."* (R13, ovarian tissue cryopreservation, age 21)

Twelve women liked the moment the information was given, but gave comments, such as that the information provision was fairly late (*n*=6), that it was too much information at once, or that the procedure of information provision and start of the FP or oncologic treatment went very fast (*n*=6).

Seven women really disliked the moment, because too much information was given at once (i.e. diagnosis, treatments, side effects, fertility issues), or the information was given too late. For the latter, there had been ample time between diagnosis and start of adjuvant chemotherapy to decide and undergo FP, but information provision had been delayed (either because the oncologist was late or referral to the gynecologist was late), which resulted in fewer or no possibilities for FP:

> Quote 2: *"What I didn't appreciate was that you first see a surgeon, and then you have to decide on your surgery. That took a while for me because they said I had that time, just think about it, so I requested for a second opinion. [..] Then my surgery was in January [about 2 months later] and I heard in the second half of January that I would have chemotherapy. [..] If I had known before, perhaps I would have been able to start an IVF procedure in an earlier menstrual cycle."* (R20, embryo cryopreservation, age 31)

Opinions about the information received

Women were ambivalent about the information they received about FP; they seemed positive, but they mentioned negative characteristics of the information as well. In relation to the evaluation of the information women received, they spoke about the content of the information, informants' characteristics, and the importance of the information.

The content of the information

In first instance, 31 women thought the information was sufficient, understandable, or of sufficient quantity. Interestingly, later on in the interview, 19 women additionally mentioned some negative aspects of the information. For example, they emphasized issues that remained unclear, the actual little amount of information that was available, and/or that they missed information. Issues that needed clarification were for example procedural aspects of IVF and cryopreservation of ovarian tissue (e.g. related to the surgery for ovarian tissue cryopreservation, or to aspects of the IVF) side effects, the complete range of available FP options, inclusion criteria for FP, alternative options to have children after chemotherapy when FP is not possible (such as adoption), and ethical aspects. For some, the information was already unclear at the moment of deciding about FP, for others (additional) questions came up afterwards (e.g. about transplantation of the ovarian tissue, or re-implantation of an embryo).

> Quote 3: *"Well, that was not very clear.. [..] It was clear that there were no possibilities and that I needed other information. But I did not have the information I needed..* [about why an age of 40 was an exclusion criterion]" (R1, no cryopreservation, age 40)

Two women were mainly negative about the information received, because they received incorrect information. Both were first told that they were eligible for FP (by an oncologist or gynecologist), but heard later on that they were not. They experienced this as burdensome and of significant (negative) impact.

Informants' characteristics

Many women mentioned the informant (gynecologist or oncologist) to be likable, or the tone of the counseling consultation to be pleasant. Moreover, 10 women appreciated the clinicians' understanding, and willingness to help or think along with them; they mentioned clinicians were often open for questions during the consultation or even accessible for questions or advice after the consultation.

Only few (*n*=4) women thought the conversation was unpleasant, and mentioned the informant to be distant or not empathetic.

Importance of the information provision

Though the majority of the women focused more on surviving the cancer than on fertility at the time, receiving information on the gonadotoxic effects of chemotherapy and FP in addition to all other information on cancer was valued important for almost all women (*n*=27, Quote 4, 5). Receiving information was mentioned to enable women to have a choice in this matter (FP), and therefore in ones own future, which was desired by many respondents. It was suggested that women should be provided with some information, after which they could decide for themselves whether they would like more information.

Some women thought it was merely a secondary issue (oncologic treatment first), or only recently realized how important information about FP had been for them.

> Quote 4: *"Of course I thought it was important to find out that I was going to be infertile. Of course, at least, I think it is not that important compared to surviving the cancer. But when something like this [FP] is being offered to you, I say go for it!"* (R7, ovarian tissue cryopreservation, age 31)
>
> Quote 5: *"[..] You hear something terrible, but you also hear that there are still possibilities. I liked that balance"* (R2, ovarian tissue cryopreservation, age 35)

Decision making about FP

Women had decided about FP by themselves (*n* =15), with their partner (*n*=14), or the physician had made the decision for them (*n*=5). Some women added that talking with significant others helped them in decision making. When the physician had made the decision, FP had not been possible because of unfulfilled inclusion criteria, like being too old or having a poor prognosis.

Women spoke about their opinions about the FP options, considerations in decision making, effects of decision making, and post-decisional satisfaction.

Opinions about FP

Most women were happy about the availability of possibilities to spare their fertility. Moreover, the options were often associated with positive feelings such as hope, a reason to live, relief, feeling good about trying to preserve fertility, and amazement about what is possible nowadays.

> Quote 6: *"It gave me hope that there will be stored something there [in the freezer] that I can use in the future. This gave me so much hope for recovery [of the cancer] that I thought: "we should not miss this opportunity, we have to take this chance"."* (R63, ovarian tissue cryopreservation, age 34)

Four other women were merely neutral (*n*=2) or more negative about the options (*n*=2, both had had one child before diagnosis of cancer) and mentioned as reason the insecurities associated with the success rates of the options.

> Quote 7: *"I have mixed feelings about it, especially because it is no insurance [of your fertility] at all"* (R25, no cryopreservation, age 33)

When no(t all) options were possible, women mentioned either feelings of acceptation (*n*=3), or frustration (*n*=8; these include the two women who received incorrect information, mentioned before):

> Quote 8: *"There you go.., you see it, tears.."* (R25, no cryopreservation, respondent cries because there were no possibilities to spare her fertility at her diagnosis)

Considerations

For most of the women, the main reason for undergoing FP was to have done everything to ensure future fertility. Several other factors that were taken into consideration were: the necessity of FP (having a small chance of infertility), (un)/willingness to undergo surgery, whether there is time for hormonal stimulation in case of IVF, risk for metastasis with cryopreservation of ovarian tissue, no choice/impossibilities regarding FP (e.g. ineligibility), the experimental character of cryopreservation of ovarian tissue (uncertainties), success rates, ethical aspects, not want to be stuck with embryo's from the current partner, and costs or insurance.

One woman mentioned that she made an emotional decision because rationally she had no reasons not to pursue FP, but it did not feel right to her, so she chose not to.

Effects of Decision Making

It was often emphasized that deciding about FP was just one of many decisions to be made. For some, this made it easier to decide on FP because they were already in a decision making "mode", for others it made decision making on FP harder (especially in an emotional sense). Some additionally mentioned that the nice thing about this decision is that this was actually one of the few decisions that they could make themselves, next to all decisions related to the cancer treatments.

For many women decision making felt good or peaceful (relaxed):

> Quote 9: *"Looking back, I have the feeling that I made the right decision. It makes me feel good to know what the possibilities are and to make an informed decision. It was not easy, but it felt good, as if we made the right decision for us, yes."* (R20, embryo cryopreservation, age 31).

Only few mentioned a very hard time decision making, feeling preoccupied with it at the time they had to decide, or burdensome emotions that came with decision making (*n*=6):

> Quote 10: *"I remember I was nonstop talking about it".* (R10, ovarian tissue cryopreservation, age 25)

Post decision-making satisfaction
Of the women who decided about FP by themselves (*n*=29), seventeen women who underwent FP (1 unknown) and six women, who decided to wait and see, would still choose the same FP option, irrespective of the procedure:

> Quote 11: *"I would do it again ten times in a row. [..] I was so happy that I was able to do it!"* (R16, embryo cryopreservation, age 34)

Five women experienced post decision making *dis*satisfaction. Of these 5 women, 4 women actually underwent FP (1 chose to wait and see). Two women (ovarian tissue cryopreservation) were dissatisfied because they knew or thought they had remained fertile after the oncologic treatment so FP had not been necessary (one was pregnant at the moment of the interview). One woman (cryopreservation of embryos) was dissatisfied because of the side effects of the IVF medication. Another woman (ovarian tissue cryopreservation) now knew that by the time her treatment finished, she will be too old to have the pieces of ovarian tissue replaced into the remaining ovary.

Process of information provision and decision making

The majority of respondents were, in general, satisfied with the procedure of information provision and decision making. However, there seemed to be room for improvements. Typical procedural aspects that were mentioned by many respondents were the assertiveness necessary to receive information in the first place, the amount of information one receives, in combination with the speed at which multiple decisions had to be made in a short time frame (timing), and the multiple medical centers that need to be visited to get information about FP, because only few centers are specialized in FP-issues.

Assertiveness

Many women had to be assertive in some way to get the topic fertility on the physician's agenda or to get information they required about FP (*n*=15). Women had to be assertive either to get initial information about FP, to receive additional information, to be referred, or to get the right treatments (schedules, hormones etc).

Only few women mentioned specific resulting emotions (anger, frustration). However, from the way women expressed themselves, it emerged that they were unhappy.

> Quote 12: *"You had to be very assertive [..], I thought that was poor. Not all information is [publicly] available, and at that moment you think about different things [than fertility]. Yes, I think many people have missed opportunities as a result of poor information provision."* (R11, embryo cryopreservation, age 31)

Amount of information and number of decisions, in relation to timing

For many women (*n*=12), the process of information provision and decision making about FP went very fast, or the combination of cancer, information about FP, and the need for decision making was very much at the same time. This speed at which much information is given and multiple decisions had to be made between cancer diagnosis and start of the cancer treatment was often negatively evaluated. Sometimes, women therefore compared the process to "being on an ongoing train" or "in a rotating mill".

Multiple medical centers

Twenty women commented on the fact that they had to go to a different medical center to receive detailed information about FP because this information was only available at specialized medical centers in the Netherlands or Belgium (for this study: LUMC, RdGG, or a medical center in Belgium). Half of the women had no problems with visiting multiple centers to receive adequate information about FP, for example, because they were prepared to make this offer in order to receive the best available information about FP. The other half of the women were more negative about the multiple locations because of poor communication between the centers (Quote 13) with unclear or even wrong information as a consequence, the need to tell their story over and over again, and administrative hassle such as having to register as a patient in each hospital and inconvenience with regard to travel expenses.

> Quote 13: *"Because there were two hospitals, I noticed [..] that the communication was really poor. I often had to give additional details and then they needed consent, they had to fill in forms and did not have the right information. The hormone levels I had to request myself with the gynecologist because things were too separated between the centers. I understand that it is privacy, but this was very inconvenient."* (R2, ovarian tissue cryopreservation, age 35).

Recommendations regarding the process of information provision and DM

With regard to the question who should decide about FP, many women preferred some form of shared decision making between physicians and them (*n*=7), or at least emphasized the importance of the provision of reliable information by a physician, after which women can decide for themselves (*n*=13).

Three women suggested that only women with a good prognosis should be informed about FP. The majority of the women (*n*=26) reported that all (eligible) women should be informed, regardless of their prognosis (quote 14), and that all available information should be given.

> Quote 14: *"Hope makes one feel alive. And a prognosis.., well, there are women who defeat the prognosis!!"* (R23, embryo cryopreservation, age 27, in reaction to whether or not women with a poor prognosis should receive information about FP)

Three women, who did not receive the information face-to-face, mentioned providing face-to-face information as an improvement. Many others preferred to receive information they could take home, either before the consultation with the fertility specialist in order to prepare themselves for it, or after the consultation to be able to read it again. Brochures, websites and checklists (both for patients and clinicians) were mentioned. Further, better communication between clinicians were mentioned, more information about FP, and referral addresses for clinicians to enable them to better inform their patients, attention for FP in social media, and implementation of information provision about FP as structural part in the medical trajectory between diagnosis and start of cancer treatment.

Discussion

This study describes women’s experiences with information provision about gonadotoxic effects of oncologic treatment and FP, and with decision making about FP, and presents women’s recommendations for improvement of information provision and decision making. The conclusions that can be drawn are that information provision on both topics was overall deemed sufficient, timely and important for the majority of women. However, women often had to be assertive, visit multiple medical centers and process much information in a very short time frame. As improvements, women suggested standardization of the information provision, better communication between clinicians or medical centers, and availability of FP-specific patient information materials.

The results of the current study have to be interpreted with caution in view of the study design and method used. First, results will have been subject to selection bias as the study population consisted of women who attended counseling consultation about FP. These will likely be more positive about FP than other women who turned down the offer for counseling or who missed the opportunity. Since we had no information on whether eligible women who did not attend counseling had been offered counseling, we felt it unethical to approach all women of fertile age. Further, findings may have been affected by recall bias, as the study reports on women’s feelings and thoughts on a past procedure (0.6 – 4.1 years ago). Most women were in remission at the time of the interview, and some had given birth to a healthy child or were pregnant at the time of the interview. Additionally, more responders than non-responders were diagnosed with breast cancer. However in both groups more than half of the diagnoses were breast cancer, which can be explained by the higher prevalence of breast cancer than other diagnoses in women between 18 and 40 years of age [26]. The interviewers had no specific training in conducting qualitative interviews other than what was learned during their medical training. Although the attention given to communication, shared decision making and asking further is fairly good in the medical training in the Netherlands, it would have been better when the interviewers had also been specifically trained to qualitative interviewing. The possible lack of specific interview skills may have led to going less deeply into specific answers given by the respondents, which in turn may have led to less depth in the interviews.

Interestingly, the themes we have found were very similar to unstructured open comments from respondents in a quantitative study about improvements in the referral processes of oncologists and in the counseling consultation by the FP specialist [21]. In our study, as much as one third of the women initiated the topic themselves, or that they at least had to be quite assertive to get the information they needed (irrespective of the year they were diagnosed). Yet, women were satisfied with the information received, though for some improved information could have lead to better expectations regarding the FP treatments and more knowledge about other ways to fulfil a pregnancy in the future. Furthermore, some women thought that too much information was provided at the same time. Therefore, the information should not always be given all at once, and ideally tailored to the individual in an individual consultation with a fertility specialist [15]. Generally, women were also satisfied with the timing of the information provision. However, it was emphasized that early information provision is necessary to enable women to decide about FP and to undergo FP treatment [21;27;28].

Consistent with other research [8;29], some women were more preoccupied with surviving (the majority), others were focusing on life after cancer. Interestingly, both groups thought information provision about FP was important. Therefore, women should be able to decide for themselves what they want in FP. Moreover, they should not be pushed into a decision in favour of FP, and all possibilities (including "wait-and-see") and impossibilities should be clarified [30].

Similar to other studies, this study found a majority of women thought all women should be informed about FP [5;7;31]. In practice, this is currently not the case. One explanation may be that some physicians feel hesitant about informing women with a poor prognosis or advanced disease [19;32]. On the contrary, in our study only a few women thought women with a poor prognosis should *not* be informed about FP. Furthermore, women think medical personnel should have more knowledge about FP and referral addresses, to be able to better inform patients. Lack of knowledge has indeed been identified as a barrier to informing (and referring) women [32;33]. Attention should be paid to the communication between medical centers or specialists as well. Other suggestions were to increase attention for FP in social media and to make sure information provision about FP is a structural part in the patient trajectory.

Unsurprisingly, the majority of women had a favorable opinion about FP. Other retrospective surveys on adolescents and women with a diagnosis of cancer have also found that women have a positive attitude towards FP [34;35]. Two women with a more negative opinion about FP, both already had a child at diagnosis, and, consistently with their opinion, chose to wait and see. Additionally, in deciding whether or not to choose for FP, most women mentioned rational considerations that were congruent with the option they chose. Although we are not sure whether women had sufficient knowledge to decide, our data indicates that the first requirements for informed decision making were met (attitude and values, here considerations, were congruent with the decision) [36]. However, some women decided more intuitively with emotion as their primary guide [37].

Most women who underwent FP and all women who decided to "wait and see", were still satisfied with the decision made, two or more years post decision making. Other qualitative research has found that decisional conflict and regret resulted mostly from deciding *not* to receive FP treatment (i.e. wait and see) [23;38]. These different results may be due to differences in counseling consultations on FP. Other studies found that receiving counseling about FP and pursing in FP is associated with less regret [24], and that use of a webbased decision aid leads to reduced decisional conflict, and reduced regret at 1 year post decision making [39].

Lastly, an often mentioned recommendation was to develop patient brochures, checklists, or a website with information about FP [15;40]. Women value additional information to read prior to, or after, the counseling consultation with a gynecologist or ivf-specialist. A quantitative study by Hill et al also found that women required relevant information both before and after the counseling consultation [21]. Balthazar et al (2012) found that women's knowledge about FP after a counseling consultation only is still limited, and therefore recommended development of educational material [41]. Nowadays, web-based information is also used more often, as an adjunct to the information that is handed out by the physician [42].

Future quantitative research should focus on the exact effects of the (perceived) amount of information and satisfaction on decision making processes, and outcomes of decision making in light of relevant existing decision making theories, such as informed- or shared decision making, which also take into account knowledge, attitudes and value congruence, and are measured with validated quantitative measures.

Based on the results of this article we recommend health care providers to inform all eligible women about FP in a timely manner. The amount and timing of information should be adjusted to the patients' individual preferences. It appears that, in the case of breast cancer, often enough time is available between diagnosis and start of adjuvant treatment to underwent one (or more) cycles for cryopreservation of embryos, or a surgery for cryopreservation of ovarian tissue. If information is provided soon after diagnosis, this time can be used optimally for FP. Some women value information to read at home before or after the consultation so better patient information should be developed. Internationally, many websites and some decision aid (DA) websites about FP have been developed (see overview Kelvin et al 2012)[43]. Like many DAs on other topics, the DA website myoncofertility has been found to improve decision making outcomes, compared to brochures [39;44]. Webbased information is accessible at any moment in the trajectory, and seems a viable format for this population [45;46]. Therefore, we think a Dutch webbased DA about FP could be a valuable addition to current information provision. Because few Dutch patients have sufficient knowledge of the English language to consult existing (DA) websites, and not all patient information is the same internationally, a Dutch Decision Aid website should be developed as well. The information gathered through these interviews has therefore been used to develop patient information brochures and a web-based decision aid about FP, which will soon be evaluated.

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Chapter 3

Development of a decision aid about fertility preservation for women with breast cancer in the Netherlands

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Abstract

Background To improve information provision about fertility preservation for breast cancer patients in the Netherlands, a web-based decision aid (DA) with additional values clarification exercise was developed according to the International Patient Decision Aid Standards criteria. This study reports on development of the DA.

Methods Development consisted of four stages: I) development of a draft DA, II) acceptability of the draft DA to patients, III) understanding (knowledge) in healthy populations, IV) acceptability of the revised DA among patients and physicians. The study population consisted of 185 participants: 20 patients, 17 physicians, 148 healthy volunteers.

Results The draft DA was considered to be relevant and understandable by patients, physicians and healthy volunteers. The values clarification exercise needed adaptation in explanation and navigation, which was done after stage II. Knowledge scores improved by 18% for lower educated women (from 4.1 (41%) to 5.9 (59%) correct answers), and by 34% for higher educated women after viewing the website (from 3.9(39%) to 7.3 (73%) correct answers). Design of the DA was evaluated to be clear, but not always very appealing.

Conclusions The DA was regarded as a relevant source of information that seemed coherent and understandable.

Introduction

For many cancer patients, fertility is an important aspect of quality of life [1-3]. As a result of better survival rates after cancer and the known side effects of cancer treatment on fertility, interest in fertility preservation (FP) has increased over the last decade. In the Netherlands, FP-options for women with breast cancer currently comprise cryopreservation of embryos, cryopreservation of ovarian tissue, and cryopreservation of oocytes[1]. Embryo cryopreservation has already been performed routinely for some years, and ovarian tissue and oocyte cryopreservation are experimental but regularly offered.

Information provision about FP is not always sufficient and is often (too) late [4-8]. Known reasons are lack of knowledge among clinicians [8-10], the difficult timing and complexity of the information [8;11], and the experimental character and ethical issues regarding the treatments [8-10;12].

In order to explore patients' experiences with the current information provision and decision making process about FP in the Netherlands, a needs assessment was conducted [13]. Interviews were held with 33 patients who had received a counseling consultation about FP and had made a decision regarding FP in the past. Results indicated that the information provision was overall deemed to be sufficient, timely and important. However, women recommended standardization of the information provision, improvement of communication among clinicians and medical centers, and availability of FP-specific patient information materials (before and after the consultation) [13].

Other studies have also found that patients wanted more information earlier in the trajectory [14] (preferably education materials to read before and after the counseling consultation with the gynecologist [15]), and wanted to have more time for decision making [15]. Therefore, internationally, initiatives have been taken to improve information provision by means of brochures, websites and Decision Aids (DAs) [16].

Decision aids 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 the advantages and disadvantages of each option [17]. Over the last decade, DAs have been increasingly applied to inform patients and help them to decide about preference-sensitive decisions (i.e. where there is more than one option to choose from, with no specific best option for everyone [18]). 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 [17].

Internationally, many English websites, brochures, and some DAs about FP have been developed (see overview Kelvin et al. [16]). Effectiveness has been studied for one of those, the DA-booklet of Peate et al (2012), which has been found to reduce decisional conflict, and increase knowledge about FP for breast cancer patients [19].

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[1] In some hospitals ovarian suppression with GnRH-antagonists is offered to patients, but only in research settings.

A disadvantage of this is that it is a linear booklet, and does not have the advantages of an interactive decision aid. To our knowledge, no other trials have been conducted after the effectiveness of DAs about FP.

Further, few Dutch patients have sufficient knowledge of the English language to consult existing (DA) websites, and countries differ in their medical guidelines with regard to cancer treatment and fertility preservation options. Therefore, a Dutch evidence-based web-based DA (website) about FP for women with breast cancer was developed (www.borstkankerenkinderwens.nl) in order to improve and standardize information provision in the Netherlands. The aim of the DA is to inform patients about FP, to prepare patients for a counseling consultation about FP with a physician who could then provide additional personalized information, and to enable decision making about FP. This article reports on all stages of the development of this DA.

Methods

Stage I: Initial development of the DA

Following the needs assessment (summarized in the introduction of this paper [13]), we aimed to develop a tool to improve patient information provision which would be able to contain large amounts of information, be easily accessible, and could be updated easily. Therefore, a web-based DA (www.borstkankerenkinderwens.nl) was systematically developed in accordance with the International Patient Decision Aid Standards (IPDAS) criteria for development and content of DAs [20], with additional use of international and national guidelines (respectively, a workbook on developing and evaluating patient decision aids [21], and a manual for the development of decision aids [22]). A website designer was responsible for the layout and design of the website and a website developer for building the website and programming functional requirements (such as the values clarification exercise (VCE), a print and enlarge text option, and a web statistics tracking system for research purposes).

Medical content

The website consists of 5 chapters, with a total of 26 informational pages (Box 1). This content was determined through literature review, Dutch guidelines [23], and in consultation with a multidisciplinary team consisting of medical oncologists, radiotherapists, gynecologists, fertility specialists, embryologists, psychologists, clinical geneticists, medical decision making experts, and researchers from our hospital. Patients were consulted prior to the development of the DA, and after a concept DA was developed (stage I-II). All texts were written in cooperation with a linguistic expert in writing medical texts aimed at less-educated patients, in order to increase understandability for a broad public. Probabilities are given in proportions (e.g. 3 out of 100)(13;14). Literature references are provided in a separate chapter, as well as a disclaimer with potential conflicts of interests.

Values clarification exercise (VCE)

In accordance with the IPDAS criteria and Dutch DA guidelines, our DA contains a VCE. Values clarification can be either implicit or explicit. In implicit values clarification patients value the treatments after reading or viewing the information in the DA (non-interactive). In explicit values clarification patients are asked to explicitly consider the importance of benefits and risks of the treatments or outcomes, in order to structure and provide insights in how values affect decision making (interactive; e.g. rating options) [21].

Few studies have evaluated the impact of VCEs [24]. Yet, there are indications that explicit VCEs are more effective in decision making than implicit VCEs. A systematic review comparing DAs with and without VCEs, found that DAs with explicit VCEs led to a higher percentage of patients who made an informed decision that was in agreement with their personal values [17], and to higher congruence between values and treatment [17;25]. More recent studies found that explicit VCEs lead to more satisfaction with preparation for decision making [26] and lower decisional conflict [27]. However, some studies did not find significant improvements in decision making when adding an explicit VCE to a DA [28].

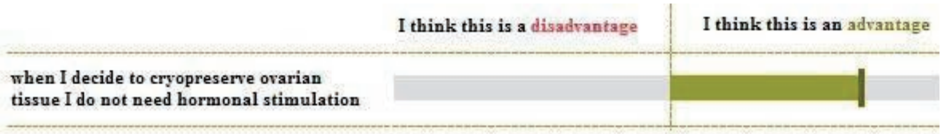
Based on the above mentioned effects of explicit VCEs we decided to add an explicit VCE to our DA [27]. In the literature, several types of explicit VCEs are mentioned, with different ways of assigning importance to the treatments or other decision outcomes, such as five-point Likert scales (not at all to very much), three-point Likert scales with the options advantage/disadvantage/no advantage nor disadvantage to choose from, and Visual Analogue Scales (VAS) [21;29]. On a VAS, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points. Based on considerations mentioned by Feldman-Stewart et al. (2006)[29], we chose a combination of the latter two, consisting of statements about the consequences of each FP option, for which patients were asked to indicate whether it was an advantage or disadvantage and the extent to which the (dis)advantange was considered to be important in decision making about FP (Figure 1,2). We used an additive exercise [29], as we wanted patients to choose only between pursuing (or not) the options for which they are eligible. Patients have the option to add arguments and rate these as well. After rating the importance of the separate statements, the website generates a summary that provides an overview of patients' answers in descending order from most important to least important (as indicated by the patient). This overview, rather than a summary bar indicating how much someone is in favor of one of the treatments [29], was chosen because we did not want to steer patients towards one of the treatments. Instead, patients were provided with a leaning scale on which they were asked to indicate on a 5-point scale their attitude towards a specific FP option ranging from very negative to very positive (adapted from Feldman-Stewart et al 2006 [29](Figure 3).

Question prompt sheet

To offer structured guidance in deliberation and communication, the website provides a list of questions to ask the physician (which can be supplemented with extra questions). These questions need a tailored answer, which could not have been provided on the website, like "what is my personal risk of becoming infertile after breast cancer treatment?", and "how long after my breast cancer treatment will I know whether I still am fertile or not?".

Visual content (illustrations, graphs)

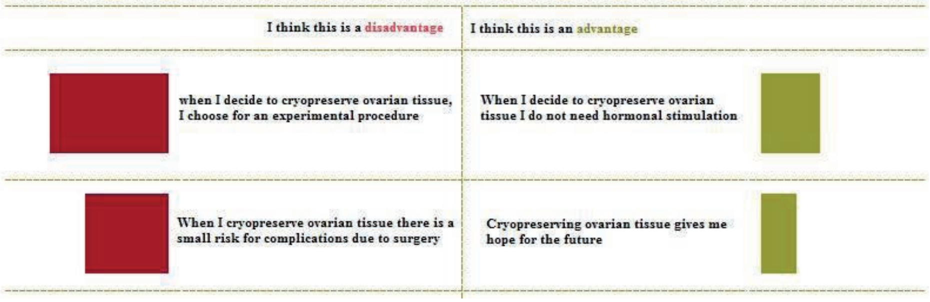
IPDAS criteria suggest visualizing information about outcomes, and to describe treatment procedures and outcomes [30]. Drawings of the cryopreservation procedure were therefore used to increase understanding of the FP processes. Furthermore, a flowchart indicates the possible FP options per age category, tables and graphs indicate the risks of several treatment regimens to become menopausal. No videos were used because this would require software that not all computers (in our hospital) have. No narratives or patient testimonials were used, because these may influence decision making [31-33].



I think this is a disadvantage | I think this is an advantage

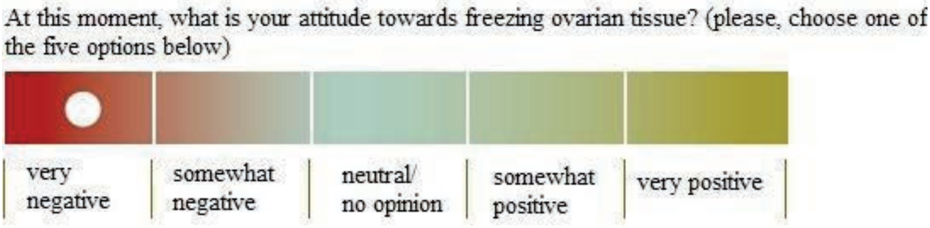
when I decide to cryopreserve ovarian tissue I do not need hormonal stimulation

Figure 1. Example of a statement in the value clarification exercise (cryopreservation of ovarian tissue) For each statement in the value clarification exercise, patient rate whether it is an advantage (green; right side of the figure) or disadvantage (red; left side of the figure) and the extent to which the statement is considered important in decision making about FP.



I think this is a disadvantage	I think this is an advantage
when I decide to cryopreserve ovarian tissue, I choose for an experimental procedure	When I decide to cryopreserve ovarian tissue I do not need hormonal stimulation
When I cryopreserve ovarian tissue there is a small risk for complications due to surgery	Cryopreserving ovarian tissue gives me hope for the future

Figure 2. Example of the summary of given ratings (cryopreservation of ovarian tissue). The *red* boxes in the column with *disadvantages* (left side of the figure) represent the extent to which each rated disadvantage is important in the decision whether or not to opt for a certain FP option (in this case cryopreservation of ovarian tissue), as indicated by the patient herself in the previous step (figure 1). The *green* boxes in the column with *advantages* (right side of the figure) represent the extent to which each rated advantage is important in the decision whether or not to opt for a certain FP option (in this case cryopreservation of ovarian tissue), as indicated by the patient herself in the previous step (figure 1).



At this moment, what is your attitude towards freezing ovarian tissue? (please, choose one of the five options below)

●				
very negative	somewhat negative	neutral/ no opinion	somewhat positive	very positive

Figure 3. Example of a leaning scale (cryopreservation of ovarian tissue)

Box 1. Content of the web-based decision aid "Breast Cancer and Wish for Children"

1. Can I still achieve a pregnancy (after my treatment for breast cancer)?
    a. Chemotherapy
    b. Hormonal therapy
    c. Other treatments
2. What can I do now to be able to have children later?
    a. Wait and see
    b. Cryopreservation of embryos
    c. Cryopreservation of ovarian tissue
    d. Cryopreservation of oocytes
3. What if I cannot achieve a pregnancy later?
    a. No children
    b. Oocyte donation
    c. Adoption
    d. Foster parenting
4. Background information
    a. Fertility
    b. Pregnancy and breast cancer
    c. Genetics and breast cancer
5. Deciding about fertility preservation
    a. What is important to me?
        i. Wait and see
        ii. Cryopreservation of embryos
        iii. Cryopreservation of oocytes
        iv. Cryopreservation of ovarian tissue
    b. Question prompt list

Studies conducted for developing and optimizing the DA (Stages II-IV)

After a draft of the DA had been developed, acceptability and understandability of the website were assessed with patients, physicians, and healthy volunteers in the following three stages (II-IV). All stages were approved by the Medical Ethics Committee of the Leiden University Medical Center.

Stage II Acceptability I: patients

To assess acceptability of the website, structured interviews were undertaken with 10 breast cancer patients between the ages of 18 and 45 who had made a decision about FP at least one year ago. We chose to include former patients since they already had experience with information provision about FP, and were therefore expected to be better able to oversee what this DA would add to the information provision as it was. In addition, it would be unethical to offer a DA that has not been (pilot) tested to patients who are actually facing the decision. Respondents were identified through a database for FP-counseling consultations in our hospital, and were invited by mail, after which they could return an opt-out form within two weeks. When they did not return an opt-out form they were called by the researcher; they were further informed about the study and asked if they wanted to participate after which an appointment was made. Informed consent was obtained before the interview started. During the interviews, respondents were asked to go through the web-based DA while thinking aloud. Additionally, women were asked some overall evaluation questions, and what improvements could be made to the DA. The topic list consisted of questions regarding difficulty in understanding the information, relevance, length, and the use of figures/illustrations for each chapter in the DA. During the interviews, answers were written down on a structured answer form. Additionally, all interviews were audiotaped to check for relevant comments, mumbling, or background information later on. However, the structured answers allowed for quantitative data analysis using Statistical Package for Social Sciences (SPSS, IBM version 20.0).

All interviews were conducted at the women's homes or in our hospital (depending on the women's preference) by a researcher not involved in the treatment or counselling of the women (MG, MF). Two interviews were held by both a researcher (MG or MF) and a clinician (LL). Women received a 15 euro incentive for their participation.

Based on the acceptability test for patients, the website was adapted and used in the next stages (stages III-IV).

Stage III Understandability of the information

Less-educated women

To assess whether women with lower levels of education understood the information on the website, we undertook a knowledge test with 8 less-educated women (lower vocational training; Mean=10.5 years (yrs) of education, range 10-14 yrs.), who were 18-40 years old. Respondents were invited through flyers distributed in local shops. Women were asked to imagine themselves in the situation of having breast cancer and having to decide about FP by reading a hypothetical script before viewing the website. The knowledge test consisted of 10 statements about FP (for example: "Cryopreservation of embryos is possible until the age of 40 (true)", or; "Surgery is necessary to be able to freeze ovarian tissue (true)"), with answering categories "true", "false", or "do not know", which had to be completed before and within one week after viewing the website. All answers could be found on the DA. Internal consistency of the knowledge scale was satisfactory at T0 (α=0.76). Differences in women's knowledge were calculated using the Wilcoxon Signed-Rank Test.

More-highly-educated women

To assess whether women with higher levels of education (higher vocational training or higher; Mean=14.1 yrs of education, range 12-15 yrs) understood the information on the website, we asked 140 healthy students to view the website and make a hypothetical decision regarding FP as part of a one hour psychological experiment in which the effectiveness of aspects of the DA was evaluated [paper in preparation]. Women were randomized to the DA with information only, or to the DA with information + VCE (the type used in all other studies). Before and after viewing the website and making a decision, we assessed knowledge with 10 statements about FP (see above). Internal consistency of the knowledge scale was satisfactory at T0 (α=0.69). Knowledge increase was assessed using a General Linear Model (GLM) for repeated measures.

Stage IV Acceptability II: patients and physicians

As part of a Delphi-study about implementation of the DA for FP [12], acceptability of the website was assessed among 17 clinicians (breast cancer nurses, oncologists (medical, surgical, and radiotherapy) and gynecologists specialized in fertility issues) and 10 breast cancer patients who had decided about FP in the past. Participants were asked to view the website and rate 13 statements about the layout and content (table 2). Agreement was assessed on a five-point Likert scale ranging from 1 (totally disagree) to 5 (totally agree), which were recoded to disagree (scores 1-2), do not know (score 3), and agree (scores 4-5). Percentages of (dis-)agreement are described. Differences between patients and clinicians were tested with χ^2-tests. Furthermore, respondents were asked to value the website with a school mark (grade) from 1-10 (1=poor, 10=excellent, a 6 or higher is judged sufficient in the Netherlands– comparable to a C, B, or A, in USA).

Results

Participants

One-hundred and eighty-five participants took part in the development studies, of whom 20 were patients (stages II n=10, and IV n=10), 17 physicians (stage IV), 8 healthy less-educated volunteers, and 140 healthy more-highly-educated volunteers (stage III). For characteristics of the participants see Table 1.

Stage II

Ten interviews were undertaken (mean duration=106 minutes, range 67-143 minutes). For socio-demographic characteristics and decisions regarding FP, see table 1. In general, respondents appreciated the fact that a DA for fertility preservation had been developed. Eight women thought that the length of the form was just right, one thought it was too short and one thought it was too long.

Table 1. Socio-demographic characteristics of the study participants

	Stage II Patients N=10	**Stage IIIa Healthy volunteers** N=8	**Stage IIIb Healthy volunteers** N=140	**Stage IV Patients** N=10	**Stage IV Physicians** N=17
Mean age, years (range)	33(26-38)	26(18-37)	20(18-36)	34(31-38)	46(35-58)
Partner yes, n(%)	6[a](60)	5(63)	76 (54)	8 (80)	n/a
Children yes, n(%)	6	3(38)	3 (2.1)	2 (20)	14 (82)
FP option chosen					
Cryopreservation of embryos, n(%)	8(80)	n/a	n/a	5(50)	n/a
Cryopreservation of ovarian tissue, n(%)	1(10)	n/a	n/a	3(30)	n/a
None, n(%)	1(10)	n/a	n/a	2(20)	n/a
Education					
Low-intermediate, n(%)	0	8 (100)	0	1 (10)	0
High, n(%)	5[b](50)	0	140(100)	9 (90)	17 (100)
Country of birth, the Netherlands, n(%)		7(88)	126 (90)	10 (100)	16 (94)

FP= fertility preservation, II=acceptability test, III= knowledge test, IV= pre-implementation study, n/a= not applicable, [a]=2 missing, [b]=5 missing.

Nine women thought that there was enough information on the website to decide about FP, and thought that the website would have helped them in decision-making if they had been able to use it. Furthermore, they thought that the presentation of the options was balanced. The design of the website and its division in chapters were highly valued, though the colors of the website were evaluated as somewhat sober.

Evaluation of the textual information (chapters 1-4)

All informative chapters were thought to be (very) relevant and most information was understandable to all respondents. However, some women thought that too much medical jargon was used (ductal/lobular cancer, laparoscopic surgery). Regarding the length of the text, suggestions were made as to divide texts in subheadings, and to provide more links to extra information on other external websites; these would provide more information, but also make the texts look more comprehensibly organized. Some respondents missed information about aspects of FP treatments (such as guidelines, side effects, success rates, replacement of cryopreserved material). The figures and illustrations were considered to be acceptable, though references between the text and figures could be improved. Figures that were illustrative of the FP procedures were thought to be nice and, especially in combination with the text, informative.

Evaluation of the chapter "decision making"

The VCE was thought to be relevant, but most women had trouble understanding what they had to do with the VCE, and how to navigate within it. Moreover, there were too many statements, and some were double negatives. The "continue" button which would lead to a summary of the statements was not prominent enough, so women did not click it (unless the researcher emphasized it). The question prompt sheet was valued highly by all respondents.

The final DA

Content of the DA was adapted based on the comments made in stage II with focus on increasing understandability, by simplifying medical jargon used in the informational chapters. Missed information that was relevant for this website was added. Links to external websites were added for missed information that was not directly relevant to this website, but related to fertility and cancer.

References to figures and illustrations were made clearer in the text. Additionally, one figure was deleted, because it was judged by the participants to be misleading and unclear. The decision making chapter with VCE was adapted with an explanation about how to use the VCE above each FP-option instead of centered on one introduction page, because it is important that women who miss the introduction page for the VCE, still know what to do with it. Furthermore, the introduction to the VCE was shortened, so that women did not have to click through multiple pages before they could start with the VCE. Statements that had been judged to be confusing were adapted. Screenshots (translated) of the final DA are provided in Figures 1-3.

Stage III

Less-educated women

Participants had spent on average 22 min on the website (range 2-51 min), and had viewed on average 16 pages (range 1-30; some pages were viewed more than once). At baseline, participants had correctly answered on average 4 out of 10 questions (41%), which increased to an average of 5.9 correct answers (59%) after viewing the website, an absolute increase in knowledge of 18% (Z=-2.263 p=0.024).

More-highly-educated women

There were no differences with regard to DA-use between participants in the DA+VCE group (*n*=70) and the information only group (*n*=70). Participants spent on average 8.3 minutes on the informational pages, 2.5 minutes on the VCE (only DA+VCE), and viewed on average 13 pages (range 2-38). There were no differences in knowledge scores between women in the information only and information+VCE groups at both measurement moments. At baseline, participants had correctly answered on average 3.9 out of 10 questions (39%), which increased to an average of 7.3 correct answers (73%) after viewing the website, an increase of 34% ($F(1,138)=324.38$, $p<0.001$; Cohen's $d=1.79$).

Table 2. Statements about layout and content of the decision aid addressed to patients and physicians (N=27) [12]

I think..	**Disagree n (%)**	**Do not know n (%)**	**Agree n (%)**
..the amount of information is too much (C)	**22 (81)**	5 (19)	-
..the website will do more harm than good (R)	**25 (93)**	2 (7)	-
..the website does not contain information that can help a patient decide about FP (R)	**24 (89)**	2 (7)	1 (4)
..the information is relevant (R)	-	1 (4)	**26 (96)**
..there is a clear red line through the website (A)	1 (4)	2 (7)	**24 (89)**
..the website is very easy to use (A)	4 (15)	1 (4)	**22 (81)**
..the division of chapters and paragraphs are presented in a clear manner (A)	2 (7)	-	**25 (93)**
..the chapter "deciding about FP" is a good supplement to the information (C)	2 (7)	5 (19)	**20 (74)**
..the information is understandable (U)	-	3 (11)	**24 (89)**
..the FP treatments are explained in a clear manner (U)	3 (11)	3 (11)	**21 (78)**
..the pros and cons of FP are presented in a clear manner (U)	3 (11)	6 (22)	**18 (67)**
..the website looks attractive (L)	8 (30)	4 (15)	**15 (55)**
..the font and font size are clear (L)	8 (30)	2 (7)	**17 (63)**

L=layout, A=accessibility, C=content/length, R=relevance, U=understandability,

Stage IV

The average school mark (grade) given to the website was 7.4 (B in USA; range 5-9). Both patients and physicians were positive about the website. An overwhelming consensus was reached on all statements, apart from the visual attractiveness of the website, while a minority disagreed. Because no significant differences were found between the opinions of physicians and patients with regard to all topics asked, results are presented for both groups together (Table 2).

Discussion

This article outlined the development of a DA about FP for premenopausal women (18-40 yrs) with breast cancer. Conclusions that can be drawn from this study are that after simplifying medical jargon and improving navigation and explanations in the VCE, the DA was seen as a relevant source of information, which seemed coherent and understandable, and was found to be acceptable to patients and physicians. Respondents appreciated the attention that is paid to improving information provision about FP and development of such tools.

Although this website was developed in accordance with the IPDAS criteria, some criteria (5/48 criteria) with regard to the content and development process of DAs could not be met. Three of these five criteria that were not met, were related to tailoring information; in our DA there is no option to enter personal health information and receive feedback regarding fertility status or any exact numeric outcomes, because we cannot give personalized risks and advice without feedback from a physician. We added a question prompt list for patients to make sure that those questions that need a personalized answer are asked in the counseling consultation. The other two unmet criteria were related to reporting of the quality of scientific evidence, and reporting of the stages in reviewing the literature. We reported a list of references, but not the steps in searching this, because we did not think this would be relevant for patients.

In the knowledge test, the increase in knowledge after viewing the website was 18% for less-educated, and 34% for more-highly-educated women. More-highly-educated and less-educated women both reported low knowledge scores at baseline (3-4 out of 10 correct answers). This may be explained by the fact that participants were healthy volunteers. Differences in knowledge scores between less-educated and more-highly-educated women after viewing the website, may be explained by differences in study design (eg. follow-up time). The absolute increase in knowledge scores of more-highly-educated healthy women was comparable to knowledge increase in other patient populations after viewing several kinds of DAs [17;34]. However, relative knowledge increase from baseline to follow-up in populations with patients or persons who are close to patients (relatives, carers) is often smaller than the 18% and 33% we found, ranging from 6%-9% in studies after decisions other than FP [17;34-37], possibly due to higher baseline knowledge in those studies. This might be explained by the fact that patients (or persons who are close to patients) often already know more about their disease or treatment options than healthy volunteers do. A study of Peate et al. (2012) which measured baseline knowledge in patients about FP and knowledge after viewing a DA booklet, found a significant increase (with a large effect size of Cohen's *d*=0.83) from baseline to follow-up, comparable to ours [19]. This might be a result of the relative paucity of available information about FP (thus resulting in lower baseline knowledge) compared to availability of information about other more common medical decisions for which DAs have been developed. Additionally, although some studies used knowledge measures that had been used in multiple studies [19;36], due to the specificity of studied decisions, most knowledge scales, including ours, had been developed by the authors, and were not validated [34;35;37]. Therefore, caution should be taken in interpreting scores of these knowledge scales.

Differences in DA-use between less-educated and more-highly-educated women (time taken to read materials, number and type of pages visited) may be explained by differences in study design as well. For the less-educated women the whole study consisted of a baseline knowledge test, one week time to view the DA, and a follow-up knowledge test after one week. For the more-highly-educated women the knowledge test was part of a one-hour experiment in which a larger set of measurements both before and after viewing the DA were measured [paper in preparation]. It is likely that the latter group spent less time on the DA because they wanted to make sure that they were ready in time. Both samples were not actually facing the decision of whether or not to preserve fertility, so the information should have been just as relevant for both samples.

Patients in acceptability study I (stage II) thought that the information on the website was relevant, necessary and comprehensible, but the VCE was less clear. The IPDAS advocate the addition of a values clarification exercise, but with our method of evaluating acceptability (interviews), we indicated that a VCE can also confuse patients. Previous studies have found varying effects of different kinds of VCEs [10;17;19-21], it is therefore currently not known which type of VCE is most effective in facilitating decision making (processes), if at all. Part of the confusion with our VCE may be because we have combined two types of VCEs; women both have to indicate whether a statement is an advantage or disadvantage for them, and rate their importance. To improve understanding of the VCE we have added instructions on how to use it above each VCE and adapted some statements after stage II. Other aspects of the original VCE were maintained. Caution should be adopted with conclusions about the VCE. Even though patients in the different developmental stages of this DA thought the VCE was relevant, this does not have to indicate that patients will use it, nor that the VCE has a beneficial effect. A study by Peate et al (2013) also found that women indicated that the VCE in the DA about FP was useful, but in practice, in a subsequent trial, the majority (77%) did not use it [19;38]. In our samples, the VCE was used by five of the eight less-educated women who logged into the website (63%), and by 33 of the 70 more-highly-educated women who were randomized to the information + VCE group and logged into the website (47%) [19]. Further research is necessary to investigate the additional value of a VCE in actual decision making about FP.

The design and colors of the website were not always highly-valued. We have used basic colors (green, blue, red) because they were considered to be appropriate regarding the topic of the website. The aim of the website is to be a reliable source for information about FP, and to offer assistance in decision making. The layout should not draw attention away from the content. However, in development of future DAs, more attention could be paid to design and color issues, because this topic seems to be relevant to patients.

The results of the current studies have to be interpreted with caution in view of the small sample sizes per stage (total n=160; stage II n=10; stage III n=8/n=115; stage IV n=27). Although these sample sizes should be sufficient for research related to developing and reviewing DAs [21], the knowledge test with less-educated women (stage III) would have benefitted from more participants. We chose only 8 participants, since we first thought of the study as an extension of the acceptability test with patients (stage II, *n*=10). Later on we decided to test knowledge in a large, more-highly-educated sample as well. Furthermore, patients that participated in this stage were not currently facing the decision to undergo FP. We thought they would be better able to evaluate newly-developed materials than recently diagnosed patients, because they could compare the situation with their own experiences with information provision about FP.

Since medicine continuously strives to improve options to preserve fertility, and information provision for patients is not always sufficient, this DA may be very important for young breast cancer patients in the Netherlands. It is important that before the DA will be widely available, its efficacy in decision making processes and outcomes is studied in a patient population. When the effectiveness of the DA in newly-diagnosed patients has been confirmed, the website should become nationally available in order to prepare patients for counseling about FP with a gynecologist or fertility specialist.

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Chapter 4

A Delphi consensus study among patients and clinicians on the procedure of informing young breast cancer patients about Fertility Preservation

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Abstract

Background The aim of this study was to obtain feedback from, and reach consensus among different experts who are or have been involved in information provision about FP, regarding the (procedure of) information provision about Fertility Preservation (FP) and use of a webbased decision aid (DA) about FP to create optimal conditions for the implementation of the DA-website, as we prepare to implement a DA about FP in the Netherlands.

Methods A two round Delphi study in which experts (patients and clinicians) rated their (dis)agreement with a list of statements (Rounds 1, 2), and additional online forum to discuss dissensus (Round 3). We assessed opinions about FP, web-based DAs, and about the procedure of informing patients. Answer categories ranged from 1 (totally disagree) to 5 (totally agree). Consensus was considered significant when at least 80% of the experts scored either the lowest or the highest two categories.

Results Experts reached rapid consensus on all five statements about the use of a DA (5/5; 100%), and all 8 statements about which patients should be offered information about FP (8/8; 100%). However opinions about FP (4/11 statements; 36%), and procedural aspects such as who should inform the patient (6/10 statements; 60%) and when (3/10 statements; 30%) remained for discussion in round 3. In the online discussion some level of agreement was reached for these statements after all.

Conclusions It was deemed important that FP options exist. Every eligible patient should receive at least some (general) information about FP, soon after diagnosis. Detailed information should be provided by a fertility expert at a later moment. Exact timing and amount of information should be adjusted to patient’s needs and situational context. A DA-website can offer a fair contribution to this.

Background

Due to improved treatment options for young women with breast cancer, survival rates have improved, and quality of life after treatment has became more important. As a result, interest in fertility preservation (FP) has increased in the last decade. In the Netherlands, options for preserving the fertility of women with breast cancer are currently embryo-, ovarian tissue-, and oocyte cryopreservation. Embryo cryopreservation has already been performed routinely for some years, ovarian and oocyte cryopreservation are still experimental.

Information provision about FP is not always sufficient and often late [1-7]. Reasons mentioned for this lack of information are for example related to the experimental character of some of the FP treatments [8;9], ethical issues [10], the difficult timing or the complexity of informing about FP [8;11], and the lack of knowledge about FP [8-10]. Factors associated with withholding information are patient characteristics such as disease stage or prognosis [8;12;13], parental status [8;13], and sexual orientation [12].

Worldwide, there have been some initiatives to improve information provision, by the development of brochures and websites (for example Fertilehope, by the Lance Armstrong Foundation, or Myoncofertility by the Oncofertility Consortium). In order to improve information provision for patients in the Netherlands we also developed a web-based Decision Aid (DA- website) in Dutch about FP for women with breast cancer. The interactive website provides information on different FP options and other ways to fulfill a desire to have children. We assume that a website is a useful method of improving information provision, because it can contain large amounts of information, is accessible at any moment, and can easily be updated to include recent developments. However, before such a website can be implemented in practice, it is necessary to assess experts' opinions about FP, about informing patients about it, and about whether a DA-website could be helpful in improving information provision to patients.

The aim of this study was to obtain feedback from, and reach consensus among different experts who are or have been involved in information provision about FP to create optimal conditions for the implementation of the DA-website, as we prepare to implement a DA about FP in the Netherlands. We assessed their opinions on FP and the possible use of a DA-website, and the procedure of informing patients. We used the Delphi method; a structured process that uses multiple (in this case: 2) rounds of questionnaires to gather information and to reach consensus among participants [14;15]. Furthermore, we used an additional online focus group to explain instances where no consensus was reached in the Delphi rounds.

This paper describes the results of a two round Delphi study and additional online focus group. We report the topics on which the experts reached rapid consensus, and those on which they did not. In those instances where no consensus was reached we explain why this happened. Recommendations are made as to how to embed the results of this study in practice, in order to improve information provision about FP.

Material and methods

Respondents

Respondents were breast cancer patients, breast cancer nurses, oncologists (medical, surgical, and radiotherapy) and gynecologists specialized in fertility issues. Exclusion criteria were no access to the Internet, and insufficient command of the Dutch language (judged by the principal researcher during a telephone call before the start of the study).

Eligible *patients* were female, had received counseling about FP in the past, and had finished their oncologic treatment at least six months ago. Patients were identified through the database of FP patients at the Leiden University Medical Center (LUMC), and approached by means of a personal invitation letter. After two weeks, they were contacted by phone to further explain the study design, and asked for their informed consent. Date and time for this appointment were stated in the invitation letter. All patients who had answered their telephone on the appointed moment were included in the study.

Eligible *clinicians* were nurses and physicians who had completed the appropriate education and were registered as such, who were involved in the treatment of breast cancer patients, who had experience with FP, and who expected themselves to be able to finish all three rounds of the study. They were identified by making use of member lists of special interest groups, Internet searches, acquaintances of members of the project group, and snowballing. We tried to include clinicians from all parts of the Netherlands, and both advocates and opponents of FP (based on previous experiences of the project members with these clinicians). Clinicians were approached by phone and were asked to give informed consent for participation by email.

Beforehand we agreed that the panel should be composed of at least 8 patients, 4 breast cancer nurses, 4 medical oncologists, 2 radiotherapists, 2 surgeons, and 4 gynecologists.

Respondents received a 20-euro incentive for participation. Our study was approved by the Medical Ethical Committee of the LUMC.

Design

An online Delphi study was conducted, consisting of two rounds in which experts rated their (dis)agreement with a list of statements. In an additional online focus group statements for which consensus had not been reached in the Delphi rounds were discussed. Since there are no strict guidelines for the number of rounds in a Delphi study (on average 2-4 rounds), we have chosen for two Delphi rounds in anticipation on the little available time of medical specialists, due to their busy schedules. With the addition of an online focus group we expected to obtain maximal information on dissensus and consensus, with a minimal number of Delphi rounds.

Rounds 1 and 2: Delphi

Round 1 consisted of 48 statements in 6 categories. Statements had been composed by making use of available literature on FP and implementation science, as well as clinicians' and patients' experiences with FP [7-10;12;16;17].

Respondents were asked to rate their (dis)agreement with these statements on a 5-point Likert scale, ranging from 1 (totally disagree) to 5 (totally agree). Demographic and/or practice-related characteristics were also obtained. Respondents had access to the newly developed DA-website.

After Round 1, the degree of consensus was assessed. Consensus on a statement was considered to be reached when at least 80% of the respondents rated either the lowest or highest two categories [18]. This cut-off was chosen because we wanted to achieve the highest consensus possible with both advocates and opponents in one panel (unlikely to be 100%).

Statements for which no consensus was reached were again presented to the respondents in Round 2, together with medians and ranges of the total group responses from Round 1 (Figure 1;[14]). Respondents were then asked to rate their (dis)agreement with the statements in light of others' responses. Furthermore, they were encouraged to provide arguments for their choices.

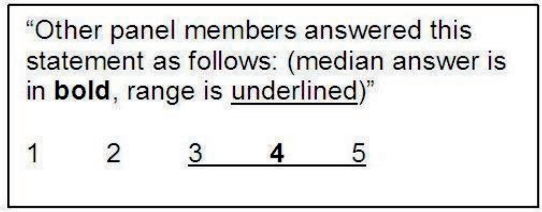
Round 3: Online focus group

Round 3 consisted of an online focus group to discuss statements for which no consensus was reached in previous rounds. These statements had been adapted, based on the open responses of the panel members, to create more vivid discussions (Table 4). When the arguments supplied by participants in Round 2 sufficiently clarified the difference (dissensus) in rating for a particular statement, that statement was not offered for discussion in Round 3.

The online discussion was entirely text-based (forum-like). Panelists were able to login whenever suited them and not necessarily at the same moment. They were not able to see each other, and except for the label "patient" or "clinician", panelists were anonymous in the discussions. Every two days another statement was posted, leaving discussions on previous statements open for comments as well.

Statistical analysis

Medians and ranges are described. Differences in respondents' responses to the statements were tested with Fisher exact tests. All statistical analyses were done using the Statistical Package for the Social Sciences (SPSS) version 17.0.



"Other panel members answered this statement as follows: (median answer is in **bold**, range is underlined)"

1 2 3 **4** 5

Figure 1. Example of the feedback given between Rounds 1 and 2

Results

Participants

We approached 25 clinicians, and 20 patients. Seventeen clinicians were included in the study (response rate 68%; reasons for declining: no time (*n*=5), unreasonable demands for reimbursement (*n*=1), or non-response (*n*=1). One clinician agreed but did not complete rounds 1 and 2 and was excluded afterwards (*n*=1)), and 10 patients (response rate = 50%, 9 declined without stating a reason, 1 had died). The total panel thus consisted of 27 "experts" (Table 1).

Mean age of the patients was 34.4 years old (SD=2.8). Eighty percent of the patients (*n*=8) had a male partner with whom they cohabited. With respect to fertility preservation procedures two patients had chosen to wait and see (20%), five had had cryopreservation of embryos (50%), and three had cryopreservation of ovarian tissue (30%). Two patients had children, of which one before, and one after cryopreservation (without using the cryopreserved material). Nine patients were higher educated (≥15 years of education), one was lower educated (≤10 years of education).

Mean age of the clinicians was 46.7 years old (SD=6.8). They were mostly female (*n*=10, 60%), and had children (*n*=14, 83%). We included clinicians from hospitals in all parts of the Netherlands (North, East, South, West, and Center). Years of clinical experience varied from <1 to >15 years (M=3.8, SD=1.3). Furthermore, the number of breast cancer patients under age 40 they reported to treat annually varied from 1-10 (*n*=8, 47%), 11-30 (*n*=3, 18%), to >30 (*n*=6, 35%).

Table 1. Description of the study population

		Round 1	**Round 2**	**Round 3**
Patients	Patients	10	10	9 (90%)
Clinicians	Medical oncologists	4	4	2 (50%)
	Gynecologists	4	4	3 (75%)
	Radiotherapists	2	2	2 (100%)
	Surgeons	3	3	2 (66%)
	Breast cancer nurses	4	4	3 (75%)
Total	**All experts**	**27 (100%)**	**27 (100%)**	**21 (78%)**

Consensus

Rounds 1 and 2 consisted of respectively 48 and 26 statements. The agreement on the statements is presented, per category and round, in Figure 2, and Tables 2 and 3. For seventeen statements, consensus was not reached in the first two rounds. Sixteen statements were adapted based on open responses of the experts, to form ten statements that were presented in Round 3 (Table 4). For one statement, the arguments supplied by participants in Round 2 already indicated consensus, so these arguments were used to explain dissensus in ratings.

Consensus Round 1

For 22/48 statements (46%) consensus was reached in Round 1 (Table 2).

Experts thought it was important that FP exists, and it was important and acceptable that patients are informed about FP as early as possible. In general, talking about fertility after breast cancer was not thought to give false hope to women. However, based on success rates, experts thought it was only justifiable to offer embryo cryopreservation to patients.

All women in the reproductive age who are at risk of losing their fertility should receive information about FP, independent of marital status, sexual orientation, parity, expressed child wish, and whether women introduced the subject “fertility” or not.

Table 2. Statements that reached consensus in Round 1

	Opinions about FP and DAs	**% disagree**	**% do not know**	**% agree**
1	Talking about fertility after BC gives false hope	100	0	0
2	Success rates of embryo cryopreservation are too low to justify offering it	82	19	0
3	Early information provision about FP is important	96	0	4
4	Offering information about FP upsets patients	96	0	4
5	Offering information about FP would delay BC treatment	89	0	11
6	Offering information about FP can make patients decide not to want BC treatment	96	0	4
7	A website does not contribute to patient education	93	4	4
8	It is important that FP is possible	4	0	96
9	The availability of a website is important	0	4	96
10	Information of the website should be printable	0	7	93
	Which patients should be informed?			
11	Women who already have children	0	4	96
12	All women with breast cancer of fertile age, who are at risk of losing their fertility	7	4	89
13	Lesbian women	0	7	93
14	*Only* women in a steady relationship	93	7	0
15	*Only* women who themselves express their child wish	96	4	0
16	*Only* when a patient brings up the subject "fertility" herself	96	4	0
	By which clinician, and when?			
17	Clinicians should not be forced to offer FP to their patients	96	0	4
18	The website with information about FP should only be offered in hospitals where FP is possible	93	4	4
19	The opinion of a clinician about FP should not matter in offering information about FP to patients	11	0	89
20	The hospitals view about FP should not matter in offering information about FP to patients	7	4	89
21	The best moment to introduce the subject fertility is when the treatment plan is explained	11	7	82
22	The information on the website about FP makes it more easy to talk about FP *for patients*	4	4	93

Furthermore, any personal opinions of clinicians as well as the hospital's general view should not have any bearing on the provision of information about FP to patients.

The availability of the DA-website was regarded as important to inform patients, and to enable patients to talk about FP more easily.

Consensus round 2

Many statements for which no consensus was reached in Round 1 already leaned towards consensus. Nine additional statements reached consensus in Round 2 (Table 3). Experts agreed that the moment at which the information is given to patients should be adjusted to the patient and not to the hospital. Furthermore, women with a poor prognosis for long-term survival should also be informed about FP.

Handing out information (e.g. a DA-website) *after* the consultation with the oncologist, and *before* the consultation with the fertility specialist was thought to save time in both these consultations.

Experts thought the DA-website would decrease the load on patients (e.g. in travel expenses), and would enable clinicians to talk about FP. Questions about FP should be addressed to a fertility specialist.

Round 3 (discussion of dissensus Rounds 1 and 2)

For seventeen statements consensus was not reached after two rounds. Sixteen of these statements were adapted or combined to form 10 new statements for the online discussion (Table 4).

No consensus was reached on whether or not it would be acceptable to give less effective treatment for breast cancer in order to preserve fertility. In Round 2 patients and nurses thought it would not be acceptable (n=7, 50%), while specialists often did not know (n=7, 54%). In the discussion, the majority of the panelists agreed that the acceptability of giving less effective treatment for breast cancer depends on patients' and clinicians' preferences.

It was not clear whether or not FP was promising. Patients and specialists either did not know (n=14, 61%) or agreed that the options were promising (1 disagreed); breast cancer nurses tended to disagree more often (n=2, 50%; p=0.07). Experts stated that it was promising that attention is given to FP, but that FP options as they are now (especially cryopreservation of ovarian tissue and of oocytes) are not very promising. However, it was emphasized that the field of FP is developing quickly, and that the options can *become* promising. Decisions about FP should be based on qualitatively good information, and on weighting the pros and cons of each FP option. Discussion among the experts revealed that informing patients about ovarian tissue- and oocyte cryopreservation is acceptable as long as no false hope is given, and low success rates are communicated to patients.

It was difficult to establish the best moment for informing patients. Experts stated that information should be provided as soon as possible. This does not have to be at the time of diagnosis; as long as it is no later than the moment the treatment plan is discussed with the patient. Furthermore, the information should be adjusted to the patient's informational needs at that moment.

Table 3. Statements that shifted towards consensus in Round 2

		Delphi round	**% disagree**	**% do not know**	**% agree**
	Attitude DA				
1	A website will decrease the load on patients (e.g. in travel expenses)	1	19	15	67
		2	7	7	85
2	The website should be generalized to other types of cancer	1	15	22	63
		2	4	4	93
	Procedure- which patients should be informed, by which clinician, when?				
3	Only patients with a prognosis for long-term survival (>50%)	1	78	15	7
		2	85	7	7
4	Patients should address questions about FP to a gynecologist/ fertility expert	1	7	19	74
		2	4	4	93
5	Timing of the information about FP should be adjusted to the patient	1	26	15	59
		2	11	7	82
6	Timing of the information about FP should be adjusted to the hospital	1	74	15	11
		2	82	11	7
7	Giving information about FP prior to the consultation with the gynecologist/fertility clinician saves time in the consultation	1	11	15	74
		2	4	11	85
8	The possibility to refer patients to a website would save much time in the consultation with the oncologist	1	15	19	67
		2	7	7	85
9	The information on the website about FP makes it more easy to talk about FP *for specialists*	1	0	33	67
		2	0	7	93

FP=fertility preservation

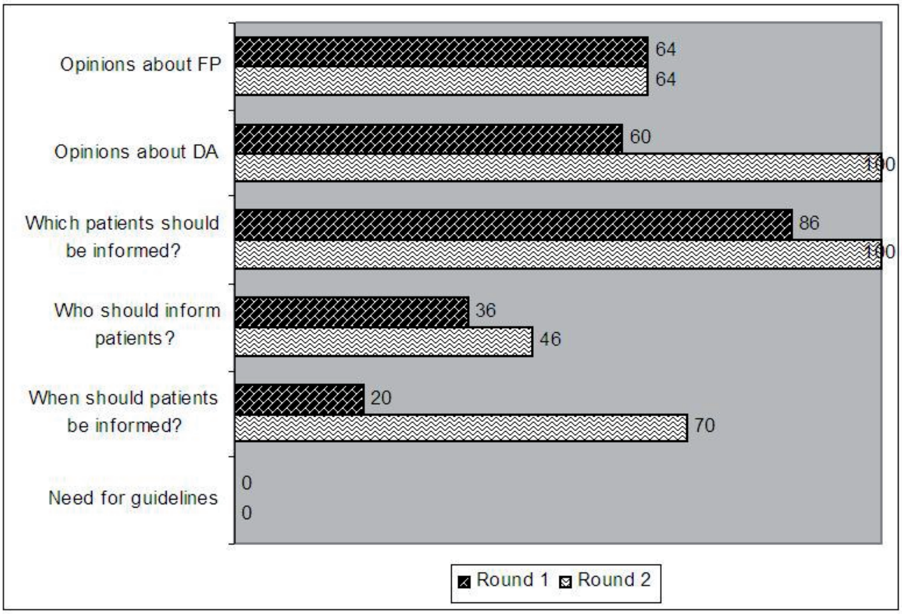


Figure 2. Percentage of concensus per category, Rounds 1 and 2

There was much ambiguity about which clinician should inform patients about FP and to whom patients should address questions about FP. It appeared that there is no single type of clinician who should inform patients and be available for questions. Moreover, a distinction was made between introducing the subject and providing more detailed information. In the discussion, experts agreed that the introduction of the information (or referral to a website) can be done by any health professional, as long as detailed information about FP is given by an FP expert at a point in time not too much later.

When patients have already been in contact with a fertility expert, they can address questions about FP to that person. If not, patients should address their questions to an oncologist, nurse, or other specialist in the (multidisciplinary) breast cancer team who can refer them on to more specialized staff.

Many patients were in favor of using the DA-website in the consultation with the fertility specialist. Specialists and breast cancer nurses mentioned that this depends on the clinician’s preference.

Seventy-eight percent of the experts agreed that guidelines are needed to structure the procedure for informing patients. However, it was unclear which specific procedural aspect this concerned, and whether guidelines should be local or national.

Forty-seven percent of the clinicians thought their clinic did not provide enough information about FP at present (*n*=8).

Table 4. Statements for the online discussion in Round 3

	Statements
1	The fertility preservation options are promising
2	The success rates of experimental treatments such as cryopreservation of ovarian tissue and oocytes are too low to justify offering it to patients
3	It is acceptable to give a less effective treatment for BC to preserve fertility
4	The information about FP can be introduced by anyone
5	Detailed information about FP should only be given by a gynecologist or fertility specialist
6	As soon as it is known that a patient is eligible for FP because of a risk of infertility due to treatment for breast cancer, it is important to introduce the options soon
7	Detailed content information about FP can be given later on to the patient, by a FP specialist
8	Patients should address questions about FP to their treating oncologist
9	When patients have already seen a fertility specialist they should address their further questions to this specialist
10	A checklist and clear agreement about the procedure of informing patients about FP for each medical center is better than a national guideline

Discussion

A Delphi study with online discussion was conducted with experts involved in information provision about FP, to reach consensus on (the procedure for) informing patients about it. Experts thought it was important that every eligible woman receives clear, objective information about FP. General information should be introduced soon after diagnosis (by any health professional), and details later on (by a fertility expert).

As expected, experts valued the more experimental FP treatments differently from embryo cryopreservation [9] There was no consensus on whether or not cryopreservation of oocytes and ovarian tissue could justifiably be offered (8% pro, 76% contra). This is comparable to findings from Kohler et al (2011) who found that only a minority of oncologists (46%) agreed that all pubertal females (13-18 years of age) should be offered ovarian tissue cryopreservation [7]. The experimental character of FP has been found to be a barrier to informing women [8;9], but experts in our study thought that patients should be informed about all options (incl. experimental ones), as long as the information is objective and complete.

Interestingly, different experts made different value trade-offs when formulating their opinions about FP. This underlines that the decision about whether or not to undergo FP is a preference-sensitive decision [19]. The literature suggests that preference-sensitive decisions should be based on good quality information, and on weighting the pros and cons and patients' values [19]. Similar suggestions were mentioned by the experts.

Experts agreed that it is important that all eligible patients are informed about FP. However, similar to many other studies [1-7], 47% of the experts indicated that the information their clinic provides about FP is insufficient at present. A majority of panelists welcomed guidelines to structure the information provision about FP, but they were unable to indicate for which procedural aspects. Increased knowledge of FP among medical professionals in terms of information provision may therefore be more important than in terms of structuring the information provision. With the involvement of patients and clinicians in this study we hope to have created awareness, and thereby supported the implementation of a DA about FP that we have developed.

Panelists reached rapid consensus that *all* women of reproductive age who are at risk of treatment-induced infertility should receive information about FP. Similar to Kohler et al (2011), none of the barriers mentioned in previous literature [8-13] held true for our experts [7]. However, these studies were conducted in 2007-2009, so it is possible that these barriers were resolved by time.

The DA-website was thought to decrease the load for patients (e.g. in travel expenses), to enable patients and clinicians to talk about FP, and to save time in the consultation with the oncologist (who introduces the subject and refers to the website) as well as with the fertility specialist (who has less explaining to do). In previous studies, DAs have been found to be helpful in involving patients more actively [20], and to decrease the length of a counseling consultation when given *prior* to counseling [21]. Experts mentioned that specialists could use the DA-website *in* the consultation as well, but they should decide for themselves whether or not they would like that.

Regarding the issue of who should inform patients, experts distinguished between introducing the information and providing detailed counseling. The available literature and guidelines have suggested a role for oncologists [16;22], gynecologists [16], or (oncologic) nurses [23] in informing women about FP. Panelists suggested a role for oncologists and nurses in introducing the information, and for fertility experts in providing more detailed counseling.

Some limitations have to be taken into account when interpreting these results. We defined consensus at 80% agreement. Most other recent studies have used lower margins, varying from less than 30% in both scale ends [24], to 80% [18]. If we had used a lower margin, more statements would have reached consensus early in the Delphi process (since the least “agreement” we found was 47%), so we would not have been able to obtain experts’ considerations in formulating their opinions, as we have been now. Despite our efforts to include both opponents and advocates of FP, most experts were in favor of FP. With our strict definition of consensus we were nevertheless able to distinguish opposing opinions to some extent. Some statements did not reach consensus because they were not stated sufficiently explicitly for the experts. In the online discussion we were able to obtain consensus on these statements anyway. It is unclear what caused the shifts in opinion between rounds: the opinions of others, or simply participation in this study that caused experts to think more thoroughly about it. Lastly, 78% (*n*=21) of the experts participated in Round 3. Experts who remained active had possibly more affinity with FP or may have had more time to actively participate in an online discussion. It would be interesting to know the opinions of the more busy clinicians, because attention to FP is important in busy schedules as well.

In conclusion; it is important that every eligible woman receives qualitatively good information about FP soon after diagnosis, in order to have enough time to make a decision regarding FP. The exact procedure for informing women should be adjusted to patients’ informational needs as well as the local situation. The web-based DA about FP that we have developed can contribute to this information provision.

Future research should focus on evaluating the effectiveness of the DA-website for newly diagnosed patients who have to decide on FP. Furthermore, since this website is meant for patients and not clinicians, it could be valuable to increase clinicians’ knowledge about FP as well, and make sure they have up-to-date information about FP to help their patients decide.

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Part II: Evaluation of a Fertility Preservation Decision Aid

Chapter 5

Values Clarification in a decision aid about fertility preservation: does it add to information provision?

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(Submitted, 2013)

Abstract

Background To improve information provision and decision making about fertility preservation for breast cancer patients, a web based decision aid (DA) with values clarification exercise (VCE) was developed. We aimed to evaluate the effect of a DA with information only compared to a DA with VCE, and to study the relation between personality and information seeking style on DA-use, decisional conflict and knowledge.

Methods Two scenario-based experiments were conducted with two different groups of healthy female participants. Dependent measures were: decisional conflict score (DCS), knowledge, and DA-use (time spent, pages viewed, VCE used). Respondents were randomized between a DA with information only (VCE-) and a DA with information plus a VCE (VCE+) (*experiment 1*), or between information only (VCE-), information plus VCE without referral to VCE (VCE+), and information plus a VCE with referral to VCE (VCE++) (*experiment 2*). In experiment 2 we additionally measured personality (neuroticism/ conscientiousness) and information seeking style (monitoring/blunting).

Results *Experiment 1*. There were no differences in DCS, knowledge or DA-use between VCE- (n=70) and VCE+ (n=70). Both DAs lead to a mean gain in knowledge from 39% at baseline to 73% after viewing the DA . Within VCE+, VCE-users (n=32, 46%) reported less DCS compared to non-users. Since there was no difference in DCS between VCE- and VCE+, it is unlikely that the VCE caused this difference. *Experiment 2*. There were no differences in DCS or knowledge between VCE-(n=65), VCE+ (n=68), VCE++ (n=66). In all groups, knowledge increased on average from 42% at baseline to 72% after viewing the DA. Blunters viewed less DA-pages (R=0.36). More neurotic women were less certain (R=0.18) and felt less supported in decision making (R=0.15); conscientious women felt more certain (R=-0.15) and had more knowledge after viewing the DA (R=0.15).

Discussion Results indicate that (the information on) both DAs leads to increased knowledge in healthy populations making hypothetical decisions, but that use of the VCE does not seem to improve knowledge or decisional conflict. Personality characteristics were slightly associated with DA-use, information seeking styles with aspects of decisional conflict.

Background

Preference sensitive decision making

An increasing number of medical decisions are preference sensitive, indicating that the "best" decision or treatment option does not only depend on what is best from a medical point of view, but depends on patient preferences with regard to the treatment options as well, and should therefore take into account the values a patient attaches to the advantages and disadvantages of those option(s). In other words, with preference sensitive decisions, patients should be actively invited to participate in decision making [1-3].

Decision aids (DAs)

In order to increase participation in decision making and improve decision making processes and outcomes for preference sensitive decisions, decision aids (DAs) are increasingly used. 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[4].

Despite availability of quality criteria for the development and evaluation of DAs [5], which are used by most DA developers, DAs differ with regard to the type of medium (e.g. brochures, booklets, DVD's, CD-ROMs, websites), their content, and the offered decision making support [6-8]. Some DAs provide patients with information only, summaries, or patient narratives, with which patients can implicitly clarify what is important for them. Others combine information with explicit values clarification methods (VCM), in which patients are supported in active deliberation about what is important to them.

In general, DAs as a whole have been found to be effective in reducing decisional conflict, increase knowledge on the subject, lead to more realistic expectations, and to lead to a higher percentage of patients who are able to decide on a course of action [4]. However, the effect of specific aspects, such as VCMs (if effective at all) is less clear [4;7;9-12]. Two patient studies that have evaluated the effect of DAs with several types of VCM compared to DAs without VCM or information only, did find that VCMs in the form of an explicit values clarification exercise (VCE) lead to a higher percentage of patients who made an informed decision that was in agreement with their personal values [4], a higher congruence between values and treatment [4], and lead to feeling better prepared for decision making [13]. One scenario based study in healthy participants found no significant beneficial effects of VCMs compared to information only [10], one did [7]. When comparing explicit with implicit VCM [7;12], explicit VCM were more effective in healthy participants [7], but no improvements were found in patient populations [12]. Additionally, in theory, deliberation (with VCM) and analytical reasoning may not always be beneficial for decision making [11], since deliberation may overshadow important intuitive feelings that are more difficult to formulate but may be just as important in decision making[11].

The decision

A good example of a preference sensitive decision with a difficult decision making process is the decision whether or not to undergo fertility preserving procedures (fertility preservation, FP) before the start of the cancer treatment when diagnosed with breast cancer. The last decades, chemotherapy for breast cancer has increased survival chances, but with an increased possibility of losing fertility as a consequence [14]. Since many young cancer patients have a future child wish, interest has risen in possibilities to preserve fertility before undergoing cancer treatment. At this moment one can try to spare fertility by cryopreserving embryos, oocytes, or ovarian tissue [15]. However, since chances to become infertile are never 100%, not undergoing any fertility sparing treatment (wait and see) is also an option [14;16]. All these FP options come with risks and success rates [15;16]. For some years, FP is offered to young women with breast cancer (18-40 years old). Not only are there many aspects to consider in deciding about FP, but the decision also has to be made in the short time frame (often a few days to a week) between diagnosis and start of the chemotherapy treatment, with competing demands from other breast cancer-related decisions and emotions [17].

In order to assist decision making about FP, we have developed a DA for women with breast cancer who have to decide about FP treatments [18]. The DA consists of information, and a fine grained, explicit VCE. The VCE consists of statements about the consequences of each FP option, for which patients are asked to indicate the extent to which they were considered a benefit or disadvantage. Additionally, patients have the option to add arguments and rate these as well. After rating the importance of the separate statements, the DA generates a summary that provides an overview of patients' answers in descending order from most important to least important (as indicated by the patient). Moreover, patients can indicate the extent to which they are in favor of the treatment options, and make a decision based on their own values. Patients are not provided with a clear-cut advice about which treatment to choose. The effect of DAs with VCEs on decision making is largely unknown. We hypothesized that the use of our DA with VCE in deciding about FP would decrease decisional conflict compared to information only [7;13].

Emotions, coping styles and personal characteristics may influence decision processes and the extent to which informational sources are used [19-22]. Since patients may react with feelings of anxiety and depression to the news about a diagnosis with a life threatening disease such as breast cancer and the prospect of a fertility threatening cancer treatment [23-25], it may be important to acknowledge these emotions. Furthermore, emotions may affect values related to the decision, and risk perception [26]. Additionally, patients may have their own coping styles when it comes to getting informed about threatening medical situations, which is reflected in their preferred role in decision making and consequently their behavior with regard to seeking information. For example, patients with monitoring coping styles have been found to ask more questions in the consultation, and to prefer more detailed information [27]. Moreover, it has been suggested that patients with a more neurotic personality preferred less participation in decision making about treatment, while more conscientious patients preferred more participation and deliberation [28]. We therefore hypothesized that having a monitoring coping style or a more conscientious personality would be associated with more extensive use of the DA and VCE, less decisional conflict, and more knowledge after viewing the DA. Blunting coping styles and neurotic personalities were thought to be associated with less use of the DA and VCE, more decisional conflict and less knowledge after viewing the DA.

The current research

In order to test the above mentioned hypotheses, two experiments were performed with healthy participants making hypothetical decisions about FP. In order to make participants more similar to patients, we have induced them with neutral, sad and anxious emotions. Although we are well aware of the limitations of including healthy participants instead of patients we chose for healthy participants to be able to include enough participants to reach sufficient power. Additionally, we thought it would be unethical to test these specific hypotheses in a patient population, before they were tested hypothetically in non-patients.

In experiment 1 we studied the effect of type of DA (information only versus information+VCE) on DA-use, decisional conflict, and knowledge. Additionally we assessed the effect of VCE-use on decisional conflict and knowledge.

In experiment 2 we assessed associations between several personality characteristics and information seeking styles with the extent to which the DA was used and on decisional conflict and knowledge.

Experiment 1

Methods

Study design

The study was a 2 (type of DA: DA with information only or DA with information and a VCE) by 3 (emotion: neutral, anxious, or sad) between subjects factorial design, stratified by location (Leiden University – location 1, Tilburg University – location 2). The DA with information only consists of textual information (consisting of 20 separate webpages) and the DA with VCE additionally consists of a VCE for each FP option (consisting of six separate webpages).

Participants

Participants were healthy women between 18-36 years old (*M*=20.8, *SD*=3.4), who had sufficient understanding of the Dutch language. Participants were invited by advertisements at universities, in libraries and on websites (including social media). Participants participated in exchange for either money (location 1; 8 euros) or course credits (location 2) . Participants at location 1 had to actively approach the researcher and had to make an appointment to participate. Participants at location 2 could easily subscribe through an online system.

Procedure

Measurements

The study was completely computerized, outcomes were measured with questionnaires and web statistics. All measures were measured immediately after viewing the DA, except for knowledge which was measured both before and after viewing the DA.

The primary outcome measure was decisional conflict. This was measured with a Dutch translation of the decisional conflict scale (DCS) (including the subscales values clarity, informed decision making, effective decision making, decision making support, decision making uncertainty) [29]. The total scale consists of 16 items measured on a

5 point Likert scale ranging from 0 (totally disagree) 4 (totally agree). A total decisional conflict score is obtained by adding up the scores on the items, dividing them by the number of items and rescoring them from 0-100. A higher score on the DCS, or one of its subscales, indicates more decisional conflict.

Other outcomes were knowledge about FP, measured with 10 statements about FP options with the answer categories “true”, “false”, or “I do not know”. Furthermore, we measured preferred FP option (5 categories: wait and see (not undergoing a fertility sparing treatment), cryopreservation of embryo’s, oocytes, ovarian tissue, do not know), socio-demographic characteristics (age, child wish, parity, experience with (breast) cancer in relatives and peers, relational status, cohabiting, education, ethnicity, religious affiliation), and web statistics such as total time spent on the DA and number of informational- and VCE-pages viewed.

Emotion induction

Emotions were induced by a combination of a short film fragment and background music during the entire experiment, two methods that have previously been found to be successful for inducing moods[30].

Directly after emotions were induced, respondents read a hypothetical script in which they were asked to imagine that they were at a consultation with their oncologist and just received the diagnosis of breast cancer, for which they would be treated with chemotherapy. Since chemotherapy might influence their fertility, they are offered the chance to preserve their fertility before undergoing chemotherapy. At the end of the script women were referred to a DA website to prepare them for making a decision. Respondents were then actually referred to the DA. They were instructed to spend as much time, and view as many pages on the DA as they thought was necessary to make a decision, there was no minimum or maximum.

In order to test whether the emotion induction was successful, participants were asked before (pre induction - I), immediately after emotion induction and after reading the script (post induction - II), and after viewing the DA (post DA - III), to what extent they felt happy, anxious and sad at that moment on a 7-point Likert scale (i.e. “to what extent do you feel happy at this moment”?). This emotion manipulation check indicated that all participants felt more sad ($\Delta M = 2.1$) and anxious ($\Delta M=2.1$) after induction, and less happy ($\Delta M=-2.0$). No differences were observed between the three emotion induction conditions. Likely, the hypothetical script, which all participants had to read following the emotion induction and before measurement of emotions, and the decision itself, may have evoked feelings of sadness and anxiety in all participants. Since no differences on perceived emotions were found between emotion induction conditions, we controlled for emotion induction condition in all analyses but no further analyses were conducted with emotions.

Statistics

Analyses were conducted with SPSS 20.0. Differences between the DAs in continuous outcomes with only one measurement moment (e.g. DCS,) were tested with one-way ANOVAs with DA-type (VCE +/-) as between-subjects factor. Differences in knowledge scores at baseline and after viewing the DA were tested with a General Linear Model

(GLM) for repeated measures, with DA-type (VCE +/-) as between-subjects factor.

Since not all participants randomized to information plus VCE actually used the VCE, we conducted secondary analyses with a new grouping variable, consisting of three arms: information only (VCE-), information plus a VCE which was not used (VCE+-), and information plus a VCE which was used (VCE ++). This variable replaced the fixed variable "DA-type" in the ANOVA and GLM for repeated measures as described above. All the analyses were done, while controlling for the effect of emotion induction condition and location.

Power calculation

A sample size of 64 participants per treatment arm was considered sufficient to analyze main effects on decisional conflict with a power of 0.8 (Cohen's d=0.5; β=0.2; α=0.05). Within the two DA-conditions respondents were equally randomized among the three different emotion conditions.

Results

Participants and socio-demographic characteristics

One-hundred fifty-one women participated. We excluded 11 women because of incomplete data on main outcomes due to problems with internet or the questionnaire. The total population used for data analyses consisted of 140 participants, 39 in location 1, and 101 women in location 2.

At baseline there were no differences in socio-demographic characteristics between the locations (data not shown). Furthermore, randomized conditions (DA-types) were comparable on most socio-demographic characteristics. With regard to child wish (for the future) we found that women in the information only condition somewhat less often had a child wish than women in the VCE+ conditions (χ^2=7.17, *p*<.01; Table 1).

Effect of type of DA on decision making, DA use, decisional conflict, knowledge

Of the total population, 114 women (81%) were able to make a decision whether or not to preserve fertility, of which 24 women (21%) wanted to wait and see, and 90 women (79%) chose to cryopreserve either embryos (*n*=45), oocytes (*n*=34) or ovarian tissue (*n*=11).

There were no effects of DA-type (information with or without VCE) on time spent on the DA or number of pages viewed (Table 1). Mean number of pages viewed for the total group was 13.4 (*SD*=7.7) and mean time spent on the DA was 8.9 minutes (*SD*=7.9). The correlation between time spent on DA and pages viewed was high (*r*=.75, *p*<.001), therefore we chose to use only "time spent" in further analyses.

There were no significant differences in decisional conflict scores (including scores on all subscales) or knowledge between women who received the DA with information only (VCE-) or with information and a VCE (VCE+) (Table 1). In both conditions, the DA led to a significant increase in knowledge (*F*(1, 127)=264.96, *p*<.001). At baseline, mean knowledge score for the total group was 4.2, after viewing the DA it was 7.6; a relative increase of 81%. Moreover, after adjustment for baseline knowledge there was a significant positive relation between knowledge after viewing the DA and time spent on the DA (*r*=0.33 *p*<.001).

Effect of using the VCE on total DA use, decisional conflict

Of the women in the VCE+ condition (*n*=70), only 33 women (47%) had viewed the VCE (VCE++, table 1). These women spent on average 2.49 minutes (range 10 seconds – 8 minutes) on the VCE. There was a significant difference in time spent on the DA between women who did or did not use the VCE (*F*(2,122)=9.01, *p*<.001). Women who had used the VCE spent more time on the DA than women who did not.

There was a significant difference between women who received information only (VCE-), and those who received a DA with VCE and did (VCE++) or did not (VCE+-) use the VCE, with regard to decisional conflict (*F*(2, 122)=6.4, *p*<.01), values clarity (*F*(2,122)=9.4, *p*<.001), and informed decision making (*F*(2, 122)=3.2, *p*<.05). Women who used the VCE reporting the best (lowest) scores, followed by women who received information only (who were not able to use the VCE); women who were able to but did not use the VCE reported the worst (highest) scores. Furthermore, women who had used the VCE reported better (lower) scores on effective decision making (*F*(2, 122)=4.4, *p*<.05) and decisional support (*F*(2, 122)=3.4, *p*<.05) than those who did not use it (Table 1).

Conclusion experiment 1

Experiment 1 showed no difference in knowledge or decisional conflict between women who received a DA with or without a VCE. Secondary analyses within women who received a DA with VCE revealed less decisional conflict for women who *used* the VCE compared to those who did not use it, but with no certainty that it was the VCE that caused this difference, since there was no difference when VCE-users were compared to women who received a DA with information only (without VCE).

Table 1. Socio-demographic characteristics**,** differences in decision-making, decisional conflict, knowledge and DA use between women who received a DA with information only or a DA with information and an explicit VCE (subdivided by whether they used the VCE or not), controlled for emotion induction condition

	DA with information only (VCE-)	**DA with information plus VCE (VCE+)**				
	Total Group VCE- (N= 70)	**Total Group VCE+ (N= 70)**	VCE used (VCE++) N=33	VCE not used (VCE+-) n= 37	**F-(condition) or χ2-value**	**Post hoc analysis**
Age, Mean (SD)	20.7(3.3)	20.9 (3.5)	20.4(3.5)	21.6(3.5)	1.3	
Child wish, yes, n (%)	56(80)	64 (91)	34(91)	30(91)	7.17*	VCE-<VCE+-=VCE++
Children, yes, n (%)	3 (4)	-	-	-	-	
Partner, yes, n (%)	34(49)	42 (60)	24(65)	18(55)	2.59	
Decisional conflict						
Total DCS, Mean (SD)	40.9 (11.6)	43.6 (14.2)	37.9 (15.7)	48.6 (10.6)	6.4**	VCE-<VCE+->VCE++
Values clarity, Mean (SD)	27.7 (14.5)	32.0 (18.4)	22.7 (16.4)	40.3 (16.1)	9.4**	VCE-<VCE+->VCE++
Decisional support, Mean (SD)	44.7 (14.2)	45.9(16.7)	38.4 (18.2)	52.7 (11.9)	3.4*	VCE+->VCE++
Effective DM, Mean (SD)	32.8(15.7)	33.6 (18.7)	27.3 (19.9)	39.2 (15.9)	4.4*	VCE+->VCE++
Uncertainty, Mean (SD)	36.6 (17.8)	40.3 (16.8)	40.9 (20.3)	39.8 (13.2)	0.97	
Informed DM, Mean (SD)	65.2 (22.6)	69.6 (22.9)	64.1 (26.6)	74.5 (17.9)	3.1*	VCE-<VCE+->VCE++
Knowledge						
Knowledge post DA, Mean (SD)	7.3 (1.9)	7.2 (1.7)	7.4 (1.7)	6.9 (1.8)	0.36	

*=p<0.05 **=p<0.01. VCE-=DA with information only; VCE+= DA with information and VCE; VCE+-=DA with information and VCE, VCE not used; VCE++=DA with information and VCE, VCE used. Δ some pages were viewed repeatedly by the respondents.

(table 1 continued)	**DA with information only (VCE-)**	**DA with information plus VCE (VCE+)**				
	Total Group VCE- (N= 70)	**Total Group VCE+ (N= 70)**	VCE used (VCE++) N=33	VCE not used (VCE+-) n= 37	**F-(condition) or χ2-value**	**Post hoc analysis**
Time spent (seconds)						
Total time spent, Mean (SD)	510.2(443.9)	558.9(506.9)	856.3 (551.9)	293.6(261.6)	9.2**	VCE->VCE+-<VCE++
Time spent on information only, Mean (SD)	510.2(443.9)	499.3 (436.5)	706.6 (481.7)	293.6(261.6)	3.9 *	VCE->VCE+-<VCE++
Pages viewed Δ	12.5 (2-38)	14.4 (3-36)	21 (9-36)	8.5 (3-17)	27.61**	VCE+-<VCE++
Made a decision, yes, n (%)	56 (80)	58 (82.8)			4.18*	

*=p<0.05 **=p<0.01. VCE-=DA with information only; VCE+= DA with information and VCE; VCE+-=DA with information and VCE, VCE not used; VCE++=DA with information and VCE, VCE used. Δ some pages were viewed repeatedly by the respondents.

Experiment 2

Since experiment 1 showed a beneficial effect of VCE-use on decisional conflict within women who received a DA with VCE, but not when compared to women who received information only, we were interested in finding explanations for this difference. In the first experiment, only a minority of respondents who received a DA with VCE, accessed the VCE. Since no emphasis was put on the availability of the VCE in their DA, it is possible that some did not see the VCE. Therefore, to increase the number of VCE-users in Experiment 2, we added a third condition to the experiment: information plus VCE, with explicitly referring to the VCE. Furthermore personality characteristics were measured to investigate whether DA- and VCE-use and effectiveness of DA- and VCE-use were associated with certain personality characteristics.

Methods

Study design

Participants were randomly assigned to a DA with information only (VCE-), a DA with information and a VCE without referring to the VCE (VCE+), and a DA with information and a VCE with explicitly referring to the VCE (VCE++), stratified by location (Leiden University – location 1, Tilburg University – location 2).

Participants

Participants were healthy women between 18-32 years old (*M*=21.4), with sufficient understanding of the Dutch language. Participants were invited by advertisements at the same universities of experiment 1. Participants participated in exchange for either course credits/hours or money (6 Euros) at both study locations.

Procedure

The study consisted of two parts. Part I consisted of completing questions about personality and information seeking style. Part II consisted of reading a hypothetical script (see experiment 1) after which respondents viewed a version of the DA (according their randomization) and completed questionnaires related to their decision making (process). Both parts were presented as independent studies of different researchers.

Measurements

Measures were as in experiment 1, with addition of the following scales:

Information seeking styles were measured with a short version of the Threatening Medical Situations Inventory (TMSI) of Miller, 1987 [31], after the example of Ong et al [27]. Respondents were asked to read two hypothetical situations (1-vague suspicious headache complaints and 2-choosing for uncertain heart surgery) and complete three monitoring and three blunting items on a five point Likert scale ranging from 1-5 (not at all to strongly applicable to me) for each scenario. Total monitoring and blunting scores were calculated by adding up all relevant items.

Personality traits were measured with the neuroticism (8 items) and conscientiousness subscales (9 items) of the Dutch translation of the Big Five Inventory [32]. Participants were asked to rate their agreement with statements about their perception of themselves in varying situations, on a five-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Total scores were calculated by adding up all relevant items, dividing by the total number of items per scale.

Statistics

Differences in knowledge scores at baseline and after viewing the DA were tested with a General Linear Model (GLM) for repeated measures. Differences in other continuous outcomes were tested with ANOVAs. Associations between personality characteristics and DA-use were studied with Pearson's product moment correlations (PPMC) and GLMs. All the analyses were done, while controlling for the effect of location.

Power calculation

Presuming a medium effect size (*f*=0.25), we needed a total of 179 participants in three groups to reach a power of 0.8 (α=0.05, β=0.2, with 1 covariate).

Results

Participants and socio-demographic characteristics

One hundred ninety-nine eligible women participated. Due to missing data on some questions, the total population used for data analyses consisted of 197 participants, 91 women in location 1, and 106 women in location 2.

At baseline, there were no significant differences with regard to socio-demographic characteristics between conditions. Mean age of the respondents was 21.4 years old (range 18-32), 179 women (90%) had a future desire for children, and nobody had children.

Effect of type of DA and VCE-use on decision making, DA use, decisional conflict, knowledge

One hundred fifty-two women (77%) were able to make a decision whether or not to preserve fertility, of which 31 (20%) women wanted to wait and see, and 121 (80%) women chose to cryopreserve either embryos (*n*=67), oocytes (*n*=47) or ovarian tissue (*n*=7).

There were no differences between the 3 conditions in total time spent on the DA and the extent to which the informational pages were used (Table 2). However, we did find differences in the extent to which the VCE was used; women who were referred to the VCE significantly more often used the VCE (*F*(2,129)=3.8 *p*<.05), viewed more VCE pages (*F*(2,129)=9.6, *p*<.001), and spent more time on the VCE (*F*(2,129)=5.6, *p*<.01) than women in the VCE+ condition who were not referred.

Of the women in the VCE+ conditions (with and without referral, *n*=134), 84 viewed the VCE (63%). Women who made use of the VCE spent more time on the total DA (*F*(2,130)=17.9 *p*<.001), and on the informational pages of the DA (*F*(2,130)=5.8, *p*<.01) and viewed more informational pages (*F*(2,130)=8.7, *p*<.001) than those who did not, indicating that they used the whole DA more thoroughly.

No significant differences were found between randomization conditions with regard to decisional conflict (or subscales of the DCS)(Table 2). Additionally, within VCE+ (with and without referral), there were no significant differences in DCS or any of the subscales between women who did (VCE++) or did not use the VCE (VCE+-), indicating that VCE-use was not related to differences in decisional conflict between the conditions (Table 2).

Use of the DA lead to a relative increase in knowledge of 71% (*M*=4.2 to *M*=7.2) in the total population (*F*(1,193)=20.9 *p*<.001). No differences in knowledge were found between the randomization conditions, or between women who did or did not use the VCE. Moreover, after adjustment for baseline knowledge score there were significant positive relations between knowledge after viewing the DA, time spent on the DA (*r*=.38 *p*<.001), and time spent on the informational pages (*r*=.36, *p*<.001).

Effect of personality characteristics and information seeking style on DA use, decision making, decisional conflict and knowledge

Personality characteristics and information seeking styles were equally distributed (Table 2). Blunting (with regard to information seeking) was associated with viewing less informational pages (*r*=-.36, *p*<.001) and less total pages (*r*=-.29, *p*<.001). None of the personality traits were significantly associated to the extent to which the DAs were used (time spent, pages viewed). With regard to decisional conflict, being more neurotic was associated with a more decision making uncertainty (*r*=.18 *p*<.01), and decision making support (*r*=.15, *p*<.05) and being more conscientious was associated with less decision making uncertainty (*r*=-.15, *p*<.05). None of the information seeking styles were associated with aspects of decisional conflict.

Knowledge after viewing the DA was associated with more conscientious personality (*r*=.15, *p*<.05) and more monitoring information seeking style (*r*=.15, *p*<.05) (corrected for baseline knowledge).

Table 2 Differences in decision-making, decisional conflict, knowledge and DA use between women who received information only or information plus VCE (subdivided by referral to the VCE, and use of the VCE) (n=197)

		Information plus VCE (VCE+) (N=134)									
		no referral (n=68)			**with referral (n=66)**						
	Information only n=65 VCE- **A**	**VCE not used n=33** VCE+- **B**	**VCE used n=35** VCE++ **C**	**Total (no referral) D**	**VCE not used n=17** VCE+- **E**	**VCE used n=49** VCE++ **F**	**Total (with referral) G**	**Total VCE not used n=49** VCE+- **H**	**Total VCE used n=84** VCE++ **I**	**F-value**	**Post hoc analysis**
Time spent (sec)	464 (333)	362 (387)	669 (360)	520 (401)	287 (303)	663 (407)	566 (416)	363 (387)	665 (386)	17.9**	H<I
Time on informational pages	464 (333)	362 (387)	537 (312)	451 (359)	287 (303)	471 (334)	423 (334)	363 (387)	498 (325)	5.8*	H<I
Pages viewed (incl vce pages)	13.3 (8.7)	10.4 (5.3)	20.4 (10.9)	15.6 (9.9)	7.7 (3.6)	20.7 (11.5)	17.4 (11.4)	10.6 (5.4)	20.5 (11.2)	23.3**	H<I
Informational pages	13.3 (8.7)	10.4 (5.3)	15.1 (6.6)	12.8 (6.4)	7.7 (3.6)	13.3 (7.3)	11.9 (6.9)	10.4 (5.3)	14.1 (7.0)	8.7**	H<I
Knowledge										NS	
After viewing the DA	7.5 (1.6)	7.1 (2.1)	6.9 (2.0)	6.9 (2.0)	6.5 (2.4)	7.5 (1.5)	7.2 (1.8)	7.1 (2.1)	7.2 (1.8)		

*p<0.05; **p<0.001, NS=not significant M=mean, SD=standard deviation DA=decision aid VCE=values clarification exercise

Table 2 Differences in decision-making, decisional conflict, knowledge and DA use between women who received information only or information plus VCE (subdivided by referral to the VCE, and use of the VCE) (n=197)

		Information plus VCE (VCE+) (N=134)									
		no referral (n=68)			**with referral (n=66)**						
	Information only n=65 VCE- **A**	**VCE not used n=33** VCE+- **B**	**VCE used n=35** VCE++ **C**	**Total (no referral) D**	**VCE not used n=17** VCE+- **E**	**VCE used n=49** VCE++ **F**	**Total (with referral) G**	**Total VCE not used n=49** VCE+- **H**	**Total VCE used n=84** VCE++ **I**	**F-value**	**Post hoc analysis**
Time spent (sec)	464 (333)	362 (387)	669 (360)	520 (401)	287 (303)	663 (407)	566 (416)	363 (387)	665 (386)	17.9**	H<I
Time on informational pages	464 (333)	362 (387)	537 (312)	451 (359)	287 (303)	471 (334)	423 (334)	363 (387)	498 (325)	5.8*	H<I
Pages viewed (incl vce pages)	13.3 (8.7)	10.4 (5.3)	20.4 (10.9)	15.6 (9.9)	7.7 (3.6)	20.7 (11.5)	17.4 (11.4)	10.6 (5.4)	20.5 (11.2)	23.3**	H<I
Informational pages	13.3 (8.7)	10.4 (5.3)	15.1 (6.6)	12.8 (6.4)	7.7 (3.6)	13.3 (7.3)	11.9 (6.9)	10.4 (5.3)	14.1 (7.0)	8.7**	H<I
Knowledge										NS	
After viewing the DA	7.5 (1.6)	7.1 (2.1)	6.9 (2.0)	6.9 (2.0)	6.5 (2.4)	7.5 (1.5)	7.2 (1.8)	7.1 (2.1)	7.2 (1.8)		

*p<0.05; **p<0.001, NS=not significant M=mean, SD=standard deviation DA=decision aid VCE=values clarification exercise

Discussion

In the above mentioned experiments we assessed the effectiveness of a DA with information only or with additional VCE with regard to knowledge and decisional conflict, and the effect of personality characteristics on DA use and effectiveness. Additionally, we assessed differences in effect between women who did or did not use the VCE. Experiment 1 showed no difference in knowledge or decisional conflict between DAs with or without a VCE. Additional analyses revealed less decisional conflict for women who used the VCE compared to those who did not use the VCE, but it was unlikely that the VCE had caused this difference, since there was no difference in decisional conflict between women who received information plus VCE and used the VCE and women who received information only. In experiment 2 personality characteristics were measured to investigate whether DA- and VCE-use and effectiveness were affected by personality characteristics. Experiment 2 confirmed that there was no association between VCE-use and decisional conflict or knowledge, and showed that information seeking style affected DA use (number of pages viewed), but not VCE-use. Personality traits were to some extent associated with aspects of decisional conflict. In both experiments there was a large knowledge increase of both DAs, indicating that the information in the DA is beneficial with regard to knowledge, especially for women who use the DA more thoroughly, highly conscientious women and women with more monitoring information seeking styles.

Since quality criteria for DAs anticipate on the addition of a VCM to DAs [33], but the results between studies on the effectiveness of VCM vary from beneficial to no (significant) effects [4;7;11-13], we thought it was important to study the effect of our DA plus VCE before implementing it in patient care. However, it seems that not all patients or participants tend to use a VCE when available. In both our experiments there were women who had used the information on the DA, but not the VCE. Although active referral to the VCE increased use of the VCE, independent of personality or information seeking style, still 17 women (15%) who were referred to the VCE did not use it (*experiment 2*). In the condition without referral about half of the women used the VCE in both experiments. A study with patients who were actually facing the decision to undergo FP found even lower percentages of patients (23%) that used their VCE [34;35]. Although VCE-use does not have to take much extra time (in our experiments: ±5 minutes), it is an extra effort in the already short time patients have to get informed and make a decision, so it should be considered whether active referral is appropriate. The hereby conducted experiments did not show a direct beneficial effect of VCE-use with regard to knowledge or decisional conflict. Therefore, we found no obvious reason to recommend *increasing* VCE-use by actively referring patients to it. Since other VCM were not always beneficial either, quality criteria should perhaps be more cautious regarding VCM recommendation as well [36].

We did find a beneficial effect of both DAs (with or without VCE) on knowledge, since use of the DA lead to a relative knowledge increase of 71-81% compared to baseline (respectively *experiment 2 and 1*), and time spent on the DA was related to knowledge increase after using the DA. It is likely that the increase in knowledge is mostly related to the informational pages.

None of the personality characteristics or information seeking styles were associated with VCE-use; information seeking styles were only associated with DA-use in general, and personality was only associated with decisional conflict. However, effect sizes were small (<.3). Consistent with the literature, women with more blunting coping styles viewed less pages on the DA website [27;37]. More neurotic women reported to be more uncertain about the decision. However, Case et al (2005) mention that information seeking style does not only depend on personality, but also on the threat and controllability that is experienced, and on the desired effect of the information. I.e., information can be used to do something about a potential threat, or to be reassured that there is no threat [38]. Additionally, anticipated emotions that are imagined with potential outcomes of decision making may affect the decision [26]. It is possible that our healthy participants did not really experience the threat, or a desired emotion, which affected their information seeking style and their decision making process. Also, it is likely that actual patients are sadder than healthy participants, and therefore elaborate more on information [39;40]. However, in the current experiments we were not able to study this properly. It is possible that participants in experiment 1 were more similar to patients because of their emotion induction with sad and anxious emotions.

In these experiments, levels of decisional conflict were relatively high (worse) compared to other studies with patients [12;41-43] and healthy participants [10], but comparable to studies with healthy students as participants [7;44]. Possibly, in contrast to what we would have expected, not actually facing the decision made decision making harder. Moreover, most studies who assessed decisional conflict in patients studied primary treatment decisions, which are different decisions than the decision to undergo FP or not, which is an “extra” decision that has to be made in an emotionally challenging period between diagnosis and start of the oncologic treatment [45;46]. For patients it is often a decision between their chances for survival, the extent of their desire for children and their possibilities for FP (related to personal characteristics)[47]; factors that often exclude some FP options and therefore might facilitate decision making. Likely, healthy students did not take these factors into account which may have increased their decisional conflict scores. Additionally, students are high educated and may therefore approach the decision more analytically which may increase decisional conflict scores. Interestingly, other studies with actual patients [4;13] more often found beneficial effects of VCEs than studies with healthy participants[7;10].

These results have to be interpreted with caution due to some limitations. The DA used in this study was originally designed for patients, who make the decision in consultation with a physician, not directly after viewing the DA, so results of a healthy population making the decision by themselves, directly after viewing the DA may not be completely generalizable to patients that are actually facing this decision. Moreover, it is possible that a DA has more effect on decisional conflict and preparation for decision making sometime after the decision is made[13]. In experiment 1, fewer women than expected used the VCE, which reduced our power. Therefore we added a third condition to the second experiment, in which women were actively referred to the VCE.

Conclusions

The above mentioned experiments indicate that our DA about FP for breast cancer patients seems beneficial with regard to knowledge increase, but that the VCE does not seem to improve knowledge or decisional conflict. Additionally, it is important to understand that personality characteristics and information seeking style may be important factors in determining the extent to which DAs are used and helpful for women. It is of utmost importance that these findings are assessed in patients as well, since results may be different when actually facing the decision to preserve fertility.

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Chapter 6

Psychometric properties of the Reproductive Concerns Scale in three populations of women.

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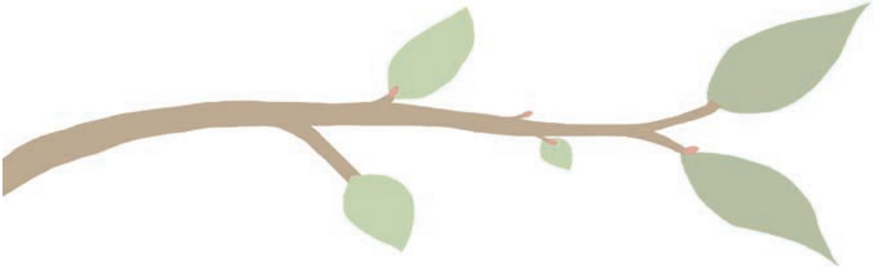


Abstract

We investigated the psychometric properties of a Dutch version of the Reproductive Concerns Scale (RCS). Questionnaires (*N*=547) were administered to 90 women with breast cancer, 231 women with fertility problems and 226 healthy controls. Principal Axis Factor Analysis suggested a one-factor structure with 11 items (breast cancer patients R^2=.48, α=.87, *ICC*=.95; women with fertility problems R^2=.45, α=.86, *ICC*=.86). Women with fertility problems reported most concerns (*M*=21.7,*SD*=9.6), followed by breast cancer patients (*M*=14.8,*SD*=9.7) and healthy controls(*M*=6.2,*SD*=6.7). Theoretically related constructs were correlated to the RCS ($.33 < r > .72$). The RCS seems a valid tool to assess women's reproductive concerns.

Introduction

Because of increased survival rates for breast cancer, quality of life after treatment has become increasingly important. For many women, fertility is an important aspect of quality of life. Unfortunately, chemotherapy, an almost inevitable treatment option for young women with breast cancer, is associated with a negative effect on fertility. Since many young women have not yet started or completed their family at the time of diagnosis, the impact of chemotherapy on their fertility may be of great concern[1].

In the last decade, an increasing number of scientific studies have been conducted on concerns with regard to fertility of young cancer survivors and found that women with cancer, who are of reproductive age, indeed have elevated reproductive concerns compared to healthy women. Reproductive concerns have been associated with lower quality of life [2;3], for example by increasing (infertility-related) distress [4] and depressive symptoms [5]. These studies indicate that it is important to assess reproductive concerns, in order to improve quality of life for these women who have already to cope with so much because of their diagnosis of cancer.

A frequently used instrument for fertility related concerns [2;5;6] is the Reproductive Concerns Scale (RCS), developed by Wenzel et al. (2005) [2] for cancer survivors. The RCS is short (14 items) and specifically designed for an oncologic population. To our knowledge, the Reproductive Concerns Scale (RCS) is the only available English questionnaire that measures reproductive concerns in oncologic populations. Wenzel et al. (2005) used the RCS in 231 cancer survivors [2]. As expected, greater reproductive concerns were significantly associated with lower quality of life scores. Women who reported wanting to conceive after cancer, but were not able to, reported significantly greater reproductive concerns than those who were able to. Furthermore, healthy women reported fewer reproductive concerns than cancer survivors. These between-group differences suggest support for the construct validity of the RCS, but further validation remains important. The factor structure of the RCS has never been formally assessed and further construct validation (e.g. convergent validity with other psychological measures) has not been conducted. The internal consistency (Cronbach's alpha) of the scale was excellent, .91, but test-retest reliability remains to be proven. Further, the RCS has not been validated for use in other languages.

Therefore, our aim was to assess the psychometric properties of the RCS in a Dutch population of women with breast cancer in the Netherlands. We further wished to broaden the applicability of the RCS and not only evaluated the scale in cancer patients, but also in women with fertility problems. We assessed construct validity in various ways. First, we expected that women with fertility problems would report the most reproductive concerns, a control group of healthy women the lowest, and women with breast cancer would be in between [6]. We also expected that younger women [5-7], without children [5;8], or with a desire to have a child [3;5;8;9] would experience higher levels of reproductive concerns. With regard to convergent validity we expected women who report more reproductive concerns to perceive higher levels of helplessness about and less acceptance of their fertility problems. Moreover, reproductive concerns may, in turn, be associated with anxious and depressive symptoms. We also assessed the reliability and stability of the RCS.

Methods

Participants

Eligible participants were female, between 18-45 years old (since women of these ages are considered premenopausal), had sufficient knowledge of the Dutch language, and had either had breast cancer, been diagnosed with fertility problems, or were healthy volunteers.

Women with breast cancer were actively approached through the Department of Clinical Oncology of two hospitals (university and local) in the Netherlands. We included women in all phases between diagnosis and finishing of the treatment. Women with fertility problems were actively approached through the outpatient clinic for fertility of the Department of Gynecology of a university hospital in the Netherlands. The women recruited either visited the outpatient clinic during the study period and were invited during their consultation, or they had visited the outpatient clinic in the past year and were invited by mail. We included all women with a fertility problem with a known cause (either related to themselves or to their partner), irrespective of the duration of the period they had been living with the issue. Women received an information package consisting of an invitation letter, an information brochure about the study, an informed consent form, a return envelope, and the questionnaire. Reminders were not sent. Additionally, women were able to volunteer through websites aimed at women with breast cancer or fertility problems (www.amazones.com, www.borstkanker.nl, www.freya.nl).

Healthy women were recruited by means of advertisements at the university, in libraries, gyms, and by snowballing. Eligible healthy controls received a digital link to the questionnaire. Additionally, women were invited to participate during a visit to an obstetrics practice, because of a pregnancy. Healthy women were offered a five-euro incentive.

Based on the answers to the questions of whether the women had had breast cancer, fertility problems, or none, we allocated them to groups accordingly (Figure 1). However, exceptions were: when additional open comments indicated that women in the control group did have fertility problems, women were allocated to the fertility group. When additional information about women in the fertility group indicated that women did not had fertility problems anymore, or when healthy controls indicated in open comments that they did have fertility problems but the cause of the problems was unknown, women were excluded.

Measurements

Data was obtained by self-report questionnaires. For test-retest purposes of the RCS, women could self-select whether they were willing to complete an additional questionnaire consisting of the RCS only, within two weeks after the primary questionnaire. In the primary questionnaire, we measured additional socio-demographic and medical characteristics:

Reproductive concerns. Reproductive concerns were measured with the Reproductive Concerns Scale (RCS). The original RCS is a 14-item scale, constructed to measure 1 concept; reproductive concerns, among women whose reproductive ability may have been impaired due to disease and/or treatment [2]. The RCS was translated into Dutch by three independent persons. When the translators disagreed, the final text was agreed after extensive discussion. In the translation “problems with reproduction” was substituted with "problems with fertility", because it is not common in Dutch to use the exact translation of reproduction ("voortplanting"). The RCS was back-translated twice by native English speakers. All items were scored on a 5-point scale with answer categories (0) "Not at all", (1) "A little bit", (2) "Somewhat", (3)" Quite a bit" and (4) "Very much". Items 2,6,9 were formulated in an opposite direction, and were reversed.

Symptoms of anxiety and depression. Anxiety and Depression were measured with the Hospital Anxiety and Depression Scale (HADS)[10]. The HADS was previously translated and validated for use in the Netherlands in several Dutch samples, with good psychometric properties to measure the presence and severity of anxiety and depressive symptoms for research purposes [11]. The scale consists of a 7-item subscale anxiety, and a 7-item subscale depression. A higher score indicates more anxiety and/or depressive symptoms. In the current study sample, Cronbach's alphas for the HADS subscales were good (Depression α=.85 and Anxiety=.83).

Illness Appraisals. Illness appraisals were measured with two subscales: the subscales acceptance (6 Items) and helplessness (6 Items) of the Illness Cognitions Questionnaire (ICQ)[12]. The ICQ was previously translated and validated for use in the Netherlands in samples of patients with rheumatoid arthritis and multiple sclerosis, with good validity and reliability [12]. As in a study of Verhaak et al. (2005), we rephrased both subscales to the situation of women facing fertility problems [13]. Higher scores indicate a higher level of the specific belief measured [12]. In this study, Cronbach's alphas for both subscales were good (α=.85 and α=.91).

Statistical analysis

We used SPSS 20.0 for Windows for the analyses. For all analyses, a significance level of $p \leq .05$ was used. Prior to analysis, the normality assumption was examined in all continuous variables. Subscales with skewed distributions (-1 < *skewness* > 1) were transformed using the square root or logarithmic scale to approach a normal distribution.

Factor structure and internal consistency were assessed separately in women with breast cancer and women with fertility problems. Prior to analysis of factor structure, frequencies of endorsement of the RCS items were assessed. Frequencies of endorsement of each single response category were not allowed to exceed 80% in both patient groups. Although no factor analysis has been performed on the RCS, all items were constructed to measure one concept and previous studies that used the RCS all assumed a one-factor structure. Hence, we conducted a Principal Axis Factor Analysis (PA), with a one-factor solution on the correlation matrix of the items. Besides theoretical underpinnings, we took into account eigenvalues (above 1) and scree plots to derive at the final number of factors. Internal consistency was assessed by Cronbach's alpha coefficient and corrected item-total correlations. A value of .7 is an acceptable value for Cronbach's alpha [14]. Corrected item-total correlations were sufficient when they were above .3. Test-retest reliability was calculated by use of the Intraclass correlation coefficient between the RCS test score and the RCS re-test score in all groups separately. Stability coefficients were sufficient when they were above .8 [15].

Construct validity was assessed by examining the relationship between the RCS and relevant socio-demographic variables that have been found to be related to wanting to conceive (age [5-7], living with partner, having children [5;8], desire to have a child

[3;5;8;9]), using t-tests, ANOVAs and Pearson's product moment correlations (*PPMC*), in women with breast cancer and women with fertility problems. Additionally, we compared total RCS scores of women with breast cancer, women with fertility problems, and healthy controls. The convergent validity of the RCS was examined in the samples of women with breast cancer and women with fertility problems by assessing *PPMC*s between the total RCS score, and the scores on instruments measuring theoretically related constructs (anxiety, depression, helplessness, acceptance). For this we used Beck's cognitive behavioural model as theoretical framework [16]. This model states that negative appraisals/cognitions (such as reproductive concerns and related feelings, such as feeling helpless and not accepting the fertility problem), can precede development of anxious and depressive symptoms [16]. Effect sizes between .10 < *r* < .30 were considered as small, between .30 < *r* < .50 medium, and *r* > .50 as large [17]. If significant associations with the RCS were found, stepwise multiple regression analysis was performed with reproductive concerns as dependent variable and theoretically related constructs as independent variables, while controlling for relevant socio-demographic characteristics (*p*-value in = .05/ *p*-value out = .10).

Results

Selection of the participants

The total sample (*N*=547) consisted of 90 (16%) women with breast cancer, 231 (42%) women with fertility problems, and 226 (41%) healthy women (Figure 1).

Characteristics of the participants

Table 1 presents socio-demographic characteristics of the participants. Women in the breast cancer group were diagnosed with cancer between 0-14 years ago (M=3.6 years, SD=2.7 years) and were significantly older than women in the fertility group and healthy women. Most women had a male partner with whom they lived. A significantly larger percentage of women in the fertility group had a partner and were living together than women in the breast cancer group and than healthy women. The majority of women were not religious. A minority of women had children. A significantly larger percentage of the women with breast cancer had children than healthy women, and more healthy women had children than women with fertility problems. This difference in having children remained, even after controlling for differences in age between the groups. Furthermore, a significantly larger percentage of women in the fertility group had a desire to have a child than healthy women and women with breast cancer.

Item analysis

Item analysis was conducted in the breast cancer and fertility group separately. One item (7:"Others are to blame for my reproductive problems") had frequencies of endorsement "not at all" of more than 80% in women with breast cancer and in women with fertility problems (respectively *M* =.21, *SD*=.72, and *M* =.34, *SD*=.38), and was not retained for factor analysis in subsequent groups. Furthermore, two items (6:"I am able to talk openly about fertility or reproductive concerns" *M*=1.97, *SD* =1.31 and *M* =2.16, *SD* =1.21; and 9: "I have had control over my reproductive future" *M* =3.07, *SD*=1.24 and *M* =2.98, *SD*=1.33) had very low correlations (-.002< *r* >.21) with other items (paired) and were eliminated

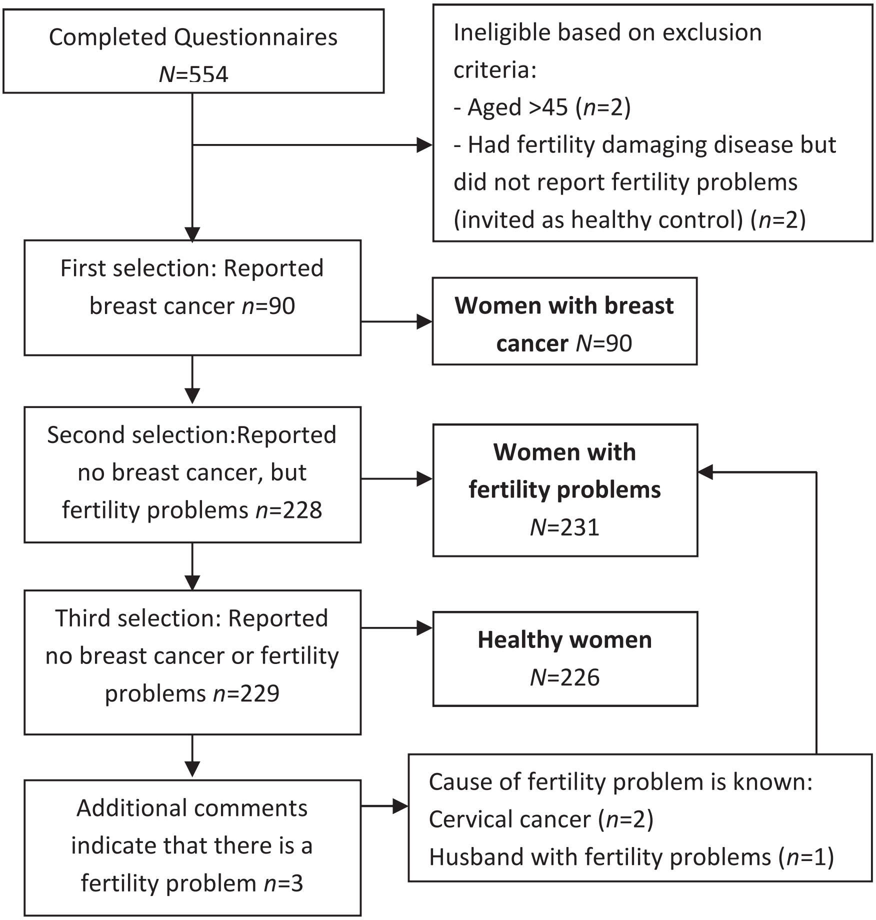


Figure 1. Selection procedure.

from our factor analysis. Additionally, five RCS items (3, 10, 11, 12, 14) were positively skewed in the breast cancer group, indicating that women with breast cancer scored relatively low on these five items. Skewed items were retained for transformation. After transformations items 3, 11 and 14 met the criteria for normality in the breast cancer group. Transformations did not work for items 10 and 12. For reasons of comparability of the RCS structure in women with breast cancer and women with fertility problems these items were retained for factor analysis.

In the fertility group, two items were positively skewed (2, 12) indicating that women with fertility problems scored relatively low on these items. Skewed items were retained for transformation. After transformations item 12 met the criteria for normality. Transformations did not work for item 2. This item was retained for factor analysis.

Subsequently, factor analysis was performed with 11 items (Table 2), in both groups separately. Appendix 1 provides inter-item correlations of the 11 items for the breast cancer group (KMO=.863, Barlett's test=.000) and for the fertility group (KMO=.873, Barlett's test=.000).

Table 1 *Participants' socio-demographic and medical characteristics, N=547*

	Breast cancer group[1] *n*=90, (16%)	Fertility group[2] *n*=231 (42%)	Healthy group[3] *n*=226 (41%)	Total group *N*=547 (100%)	*F*-value / *χ2*-value	Post-hoc test
Age, *M*(*SD*)	36.6(5)	32.4(5)	31.9(7)	32.9(6)	*F*=21.3**	BC>F=HC
Male partner Yes, *n*(%)	78(87)	219(95)	189(84)	484(88)	*χ2*=21.2**	F>BC=HC
Of whom cohabiting, *n(%)*	68(87)	215(93)	158(70)	441(81)	*χ2*=25.3**	F>BC=HC
Having children Yes, *n(%)*	51(59)	40(17)	47(21)	138(25)	*χ2*=44.1**	BC>HC>F
Current pregnancy, *n(%)*	-	4(2)	28(12)	32(6)		
Education						
Low, *n(%)*	8(9)	7(3)	13(6)	28(5)	NS	
Middle, *n(%)*	24(28)	71(31)	64(28)	159(29)	NS	
High, *n(%)*	55(63)	149(66)	148(65)	352(65)	NS	
Religion Not at all, *n(%)*	57(66)	147(64)	144(64)	348(64)	NS	
Present child wish Yes, *n*(%)	59(66)	219(95)	157(70)	435(80)	*χ2*=65.3**	F>BC=HC
Reproductive concerns score *M(SD)*	14.8(10)	21.7(10)	6.1(7)	14.2(11)	*F*=186.8**	F>BC>HC

***=p <0.01 *=p<0.05. Education: Low =primary school, lower vocational education, secondary education; middle=intermediate vocational education, higher general continued education; High = higher vocational education, university education, post-university education. Having children: Respectively n=3(3%), n=36(15%) en n=45(20%) missing.*

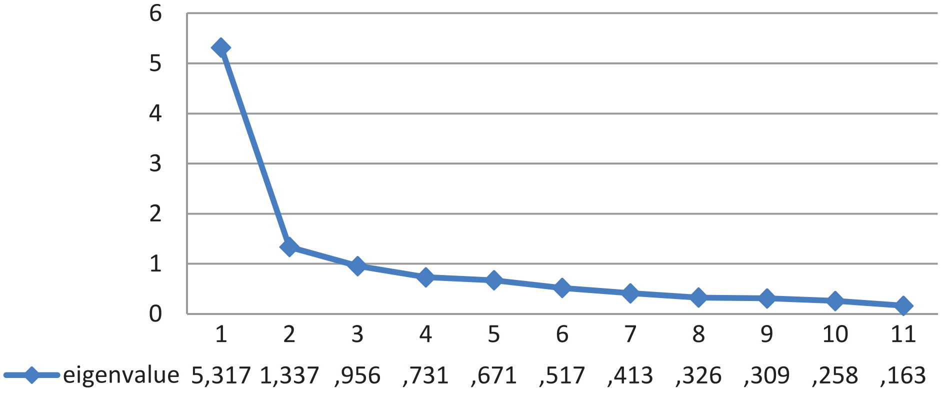
Factor analysis

A principal axis factor analysis was performed in the breast cancer and fertility group separately. The scree test indicated a one-factor solution for both groups (Figure 2). The eigenvalues above 1 indicated that a two-factor solution was preferable in the breast cancer group and a three-factor solution in the fertility group, which were both difficult to interpret. Therefore we decided to conduct a confirmatory factor analysis with one factor, also to follow the original scale. The one-factor solution with 11 items showed theoretical consistency in both the breast cancer and fertility groups and accounted for respectively 48% and 45% of the explained variance (Table 2). In both groups, all of the 11 items had a component loading between .45–.82, except item 4 in women with fertility problems with a factor loading of .36. Because the one-factor solution of the a priori one-factor RCS scale replicated fairly well, we computed a RCS score by adding the 11 items. All 11 items are related to reproductive problems/concerns, so the scale is thought to measure one construct: concerns about fertility. A higher RCS score represents more reproductive concerns.

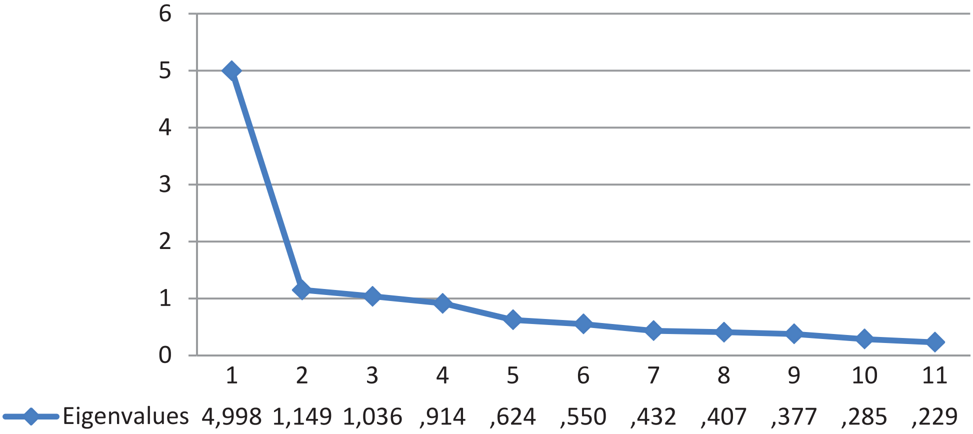
Reliability

Cronbach's α of the 11 items was assessed in women with breast cancer and women with fertility problems and was good in both groups (Table 2), indicating high internal consistency. All items had item-total correlations above .3, which is in an acceptable range, except for item 4 in the fertility group (.297). It is logical that item 4 had higher loadings and item-total correlations in the breast cancer group, since their risk for infertility was indeed caused by illness/disease, which is not always the case for women in the fertility group.

The RCS scale has good levels of stability over a period of approximately 2 weeks in the samples of women with breast cancer (ICC=.95 p<.0001, n=18), women with fertility problems (ICC= .86 p <.0001, n=83), and healthy controls (ICC= .94 p < .0001, n=60).



Scree plot Breast cancer group



Scree plot Fertility group

Figure 2. Scree plots and eigenvalues in the breast cancer and fertility group separately.

Table 2 *Factor loadings of the items of the reproductive concerns scale in women with breast cancer and women with fertility problems (PCA)*

		Breast cancer group		Fertility group	
	Item on the reproductive concerns scale	***Mean(SD)***	**Factor loadings**	***Mean(SD)***	**Factor loadings**
14	I am less satisfied with my life because of reproductive problems	.93(1.17)	**.859**	1.89(1.35)	**.817**
13	I am frustrated that my ability to have children has been affected	1.19(1.36)	**.847**	2.38(1.33)	**.799**
8	I am sad that my ability to have children has been affected	1.96(1.56)	**.832**	2.65(1.31)	**.781**
5	I am angry that my ability to have children has been affected	1.47(1.41)	**.809**	1.90(1.41)	**.741**
1	I have concerns about my ability to have children	1.53(1.56)	**.736**	2.70(1.28)	**.716**
3	I feel less of a woman because of reproductive problems	0.72(0.99)	**.661**	1.51(1.30)	**.718**
2	I am content with the number of children that I have	2.50(1.53)	**.655**	3.58(0.94)	**.468**
11	I have mourned the loss of my ability to have children	1.08(1.30)	**.627**	1.47(1.43)	**.586**
10	I feel guilt about my reproductive problems	0.40(0.88)	**.514**	1.16(1.22)	**.669**
12	I blame myself for my reproductive problems	0.28(0.70)	**.494**	1.06(1.27)	**.606**
4	An illness/disease has affected my ability to have children	2.78(1.52)	**.454**	1.43(1.57)	.364
	Explained variance		*48.3*		*45.5*
	Crohnbach's α		*.87*		*.86*

Construct validity

We examined the relation between socio-demographic characteristics and reproductive concerns in the combined groups of women with breast cancer and women with fertility problems and found that women with higher levels of reproductive concerns were significantly younger in age (*r*(320)= -.228 p<.001), more often living together with a partner (*t*(295) = -2.07, *p* < .05), less often had children (*t*(280) = 6.29, *p*<.001), and more often had a desire to have a child (*t*(314) = -7.85, *p* < .001). Moreover, there was a significant difference in the RCS score between the three respondent groups (*F*(2,545) = 185.48, *p* < .001 (Table 1)). Women in the fertility group had a significantly higher RCS mean score than women in the breast cancer group, and women in the breast cancer group had a significantly higher RCS mean score than women in the healthy group.

In a stepwise multiple regression analysis controlling for group (breast cancer or fertility), reproductive concerns were independently associated with not having children (ß = -.26, 95% CI (-8.0;-2.9) *p* < .001), more often cohabiting (ß =.11, *95% CI* (.1; 9.8), *p*<.05), and having a desire to have a child (ß =.293, *95% CI* (5.4; 12.7), *p*<.001). Together these explained 49% of the variance in reproductive concerns. The difference in RCS between the groups also remained significant after controlling for desire to have a child, cohabiting, and having children (β=-.41, *SE*=.62, *95% CI*: (-7.4; -4.9) *p*<.001).

In the combined group, women with breast cancer and women with fertility problems higher levels of reproductive concerns were associated with higher levels of depression (*r*(304)=.45 *p*<.001), and anxiety (*r*(304)=.33 *p*<.001), more feelings of “helplessness’’ (*r*(275)=.73, *p*<.001) and lower levels of acceptance (*r*(275)=-.59, *p*<.001). These findings indicate that women with higher levels of reproductive concerns have more often depressive or anxious symptoms, and perceive themselves as more helpless. Additionally, women who accepted their fertility problems less reported more reproductive concerns. After controlling for group, desire to have a child, having children and cohabiting, higher levels of reproductive concerns were significantly associated with feeling more “helplessness” (β=.46, *95% CI*: (.8;1.5), *p*<.0001) lower acceptance of the fertility problems (β=-.16, *95% CI*: (-.57; -.1), *p*<.01), and feeling more depressed (β=.16, *95% CI*: (.50;2.48), *p*<.01).

Discussion

In this study we aimed to assess the psychometric properties of the Reproductive Concerns Scale (RCS) in a Dutch population of women with breast cancer (of reproductive age), and women with fertility problems. Results show that the one-factor RCS consisting of 11 items has good internal consistency (reliability) in women with breast cancer, which was confirmed in women with fertility problems, good stability over two weeks, distinguishes between breast cancer patients, fertility patients and healthy controls, and correlates in the expected direction with theoretically related constructs in women with breast cancer and women with fertility problems. Considering these good psychometric properties, we recommend the use of the RCS to measure reproductive concerns in women of oncologic populations with threatened fertility.

In order to pay sufficient attention to reproductive concerns, it is important to have a good instrument to assess them. The RCS seems a reliable and valid instrument for measuring reproductive concerns.

With this study, we have shown that reproductive concerns were higher in younger women, with a desire to have a child, who were living together with a partner and who did not have children. Furthermore, reproductive concerns were positively associated with feelings of anxiety and depression. With the availability of data about reproductive concerns in at-risk groups, we can focus on women who are at risk of having reproductive concerns and address their concerns. For example, by offering them (more) information about fertility preservation, which may support clinical processes such as counseling and referral for fertility related information or fertility preservation treatment. Offering (information about) a way to preserve fertility before start of the oncologic treatment has been found to improve quality of life for oncologic patients [18-20]. It is possible that it may reduce reproductive concerns as well. Especially in case of breast cancer, where there is often enough time to pursue fertility preservation options, offering information about the options might be beneficial.

This study focussed on women with breast cancer and fertility problems only, but since the items in the RCS are not illness-dependent and factor structure was comparable in the two groups studied, it is reasonable that the RCS is a good measure of reproductive concerns in other female (oncologic) populations as well. Although previous studies have used the RCS in other female oncologic populations as well [2;3;6], more research is needed to officially validate the RCS for other oncologic populations. The focus of this study was only on breast cancer patients as oncologic population, as this study is part of a line of research into fertility related issues in breast cancer patients.

With regard to relations between reproductive concerns and theoretically related constructs, we have found medium to large correlations (.33< *r* >.73) between the RCS and all theorethically related constructs. Moreover, we have found that women with higher levels of reproductive concerns have more often depressive symptoms, perceive themselves as more helpless, and are less accepting of their fertility problems. The relation between reproductive concerns and psychological distress has been suggested by other researchers as well[2;3]. Moreover, our findings are in line with the cognitive behavioural model of Beck [16],which states that negative appraisals/cognitions (such as reproductive concerns) can precede the development of depressive symptoms.

The results of this study have to be interpreted with caution due to some limitations. Despite efforts to match groups on the most significant variables, groups differed significantly with regard to age, partner status, living together with a partner, having children, and the desire to have a child. However, in the analysis of construct validity we have controlled for the variables: having children, having the desire to have a child and cohabiting. Furthermore, recruitment of the participants was both active, by personal invitation, and passive, through advertisements on the Internet. The partial self-selection of participants may have induced selection bias because women who volunteered may have more reproductive problems or more interest in the subject, since they were already actively searching for information about it on the Internet. Additionally, due to a missing question on "having children" in the questionnaires in an early phase of the study, there were relatively many missing values on that variable. Later, this question was added or an answer was imputed with information on other questions, but this may have resulted in loss of information. We also did not elicit the phase of treatment in the breast cancer group, or the time since diagnosis of fertility problems in the fertility group.

Lastly, since the RCS has never been formally validated before, we are not certain whether our results can be generalized to other populations. Therefore, the structure of the RCS should be assessed in other populations as well. However, the one-factor solution that could be applied in both women with breast cancer and women with fertility problems does permit some generalizability of our results. Content validity was well assessed in the English version of the RCS, and we therefore decided to limit assessment to the experts in our team, and did not assess it in the target samples.

In conclusion, considering the good construct validity, reliability, and stability of the Dutch version of the RCS, the RCS seems to be a useful instrument for research purposes to recognize reproductive concerns in oncologic populations. We expect the one-factor structure of the RCS to be similar in other populations, although more research would need to be conducted to ascertain that. It is specifically designed for reproductive concerns in oncologic populations and is short and easy to use.

For future research we suggest that reproductive concerns should be studied in other oncologic populations as well as relations between (time that has passed since) diagnosis and treatment and severity of reproductive concerns.

Appendix 1. Inter-item correlation matrices of the 11 items in the a) breast cancer group, b) fertility group

a)	1	2	3	4	5	8	10	11	12	13	14
1	1	.43*	.22*	.45**	.62**	.54**	.57**	.59**	.37**	.39**	.28**
2		1	.28**	.46**	.33**	.50**	.54**	.48**	.34**	.38**	.24*
3			1	.35**	.18*	.37***	.27**	.29*	.35*	.22*	.17*
4				1	.46**	.72**	.76**	.67**	.56**	.23*	.24*
5					1	.43**	.46**	.55**	.35**	.24*	.28*
8						1	.70**	.67**	.55**	.31**	.32**
10							1	.75**	.42**	.34**	.35**
11								1	.52**	.39**	.39**
12									1	.09	.14**
13										1	.61
14											1

*=p≥0.05, ** p≥0.001

b)	1	2	3	4	5	8	10	11	12	13	14
1	1	.13*	.40**	.55**	.55**	.56**	.39**	.43**	.32**	.34**	.51**
2		1	.36**	.25**	.17*	.21*	.16**	.38**	.14*	.16*	.09*
3			1	.64**	.59**	.50**	.39**	.51**	.35**	.43**	.16**
4				1	.65**	.59**	.41**	.39**	.31**	.44**	.34**
5					1	.736**	.45**	.48**	.39**	.41**	.34**
8						1	.41**	.53**	.37**	.42**	.34**
10							1	.49**	.61**	.34**	.24**
11								1	.48**	.35**	.25**
12									1	.29**	.22**
13										1	.1
14											1

*=p≥0.05, ** p≥0.001

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Chapter 7

Additional value of decision aids in complex clinical situations: Effectiveness of a decision aid about Fertility Preservation for breast cancer patients.

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Abstract

Background A web-based decision aid (DA) was developed to improve information provision about fertility preservation (FP) in breast cancer patients. We aimed to assess the effect of this DA compared to brochures and usual care with regard to decision-making about FP.

Methods Multicentre RCT with female breast cancer patients, aged 18-40, randomized between DA or informational brochures; brochures were publicly available. Additionally, results were compared to usual care (no additional information). Measures were self-report questionnaires at diagnosis(T0), six weeks(T1), and six months(T2) on: decisional conflict, knowledge, regret.

Results Twenty-six women were randomized to brochures (n=13) or DA (n=13) and completed T0, 24 completed T1(12/12), 23 completed T2(11/12). Most women (91%) read brochures. Overall, knowledge increased between T0-T2 (22%). Women who received brochures reported more effective decision-making(T1) than women who received the DA. Otherwise there were no differences.

Ten women received usual care. They reported more decisional conflict, less values clarity, less support and less knowledge than women who received brochures, and less knowledge and support than women who received the DA.

Conclusions DA and brochures both increased knowledge. Compared to usual care, the information materials improved knowledge and feeling supported, but the DA introduced slightly more decisional conflict than brochures.

Introduction

Because survival rates for women with breast cancer have increased, quality of life after treatment is becoming more important. Infertility or concerns about (in)fertility due to cancer treatment have a negative influence on quality of life [1;2]. Therefore, interest in possibilities for fertility preservation (FP) has risen. At this moment, options to try to preserve fertility prior to oncologic treatment in the Netherlands are cryopreservation of in vitro fertilized embryos, oocytes and ovarian tissue, and suppression of the ovaries. Success rates of the options range from 5-25%. Despite an increasing number of studies and guidelines demonstrating the need for discussion of FP issues with young cancer patients, information provision about treatment-induced infertility and FP techniques and referral for FP is still not sufficient and often too late [3-10]. Adequate information fulfils psychosocial needs [11], increases women's coping with cancer[12] and enables informed decision making (DM) [13]. An informed decision is a decision based on relevant, good quality information that reflects the decision maker's values [14]. Informed DM is especially important in deciding on treatments with possible long term consequences for quality of life. Gonadotoxic treatments and FP options are such treatments.

To support informed DM and improve information provision about FP, a web-based Decision Aid (DA) was developed, with both textual information and an explicit values clarification exercise to clarify patients' values regarding the FP options[15]. With the availability of this DA, every patient who is eligible for counselling about FP can obtain optimal information about FP at any time and on any location in the Netherlands.

We conducted a randomized controlled trial to evaluate the DA on its effectiveness compared to brochures regarding outcomes of DM and the DM process. We hypothesize that use of the DA leads to an improved *decision process* (patients are better prepared to make a decision; and have less decisional conflict and better knowledge (primary outcome) [16]), which in turn leads to improved *decision outcomes* (more satisfaction with the decision made[17;18], decreased decisional regret), and improved health outcomes (reduced reproductive concerns; better quality of life). Since both arms were offered qualitatively good information about FP we secondarily compared both arms to an observational control group (historical) with women who did not receive additional written information about FP other than that provided orally by the oncologist and/or gynaecologist. We hypothesise that women who have not received additional information (besides a counselling consultation) report more decisional conflict, less knowledge, and worse preparation for DM.

Methods

Participants

Eligible participants for the RCT were female breast cancer patients (stage I-III), who were in prospect of receiving chemotherapy treatment, and who were eligible for FP. Patients had to be aged between 18-40 years old, to have sufficient knowledge of the Dutch language, and internet access/email at home to be able to view the DA and to complete online questionnaires.

Eligible patients for the usual care group were women (aged 18-40 years) who were diagnosed and treated for breast cancer in one of the participating medical centres, in the year before their medical centre started recruiting patients for the KEEP-study.

Study design

The study design was a multicentre randomized controlled trial, with randomization between informational brochures about FP only or a web-based DA in addition to informational brochures, stratified by medical centre. Additionally, results from both groups were compared to an (observational) usual care group. The study was approved by the Medical Ethics Committee of Leiden University Medical Centre (P11.027).

Procedure

Participants were invited for the study by their surgeon, oncologist or breast cancer nurse soon after diagnosis of breast cancer and before they were referred for counselling about FP. Additionally, some specialized gynaecologists and fertility specialists invited patients as well (as long as the final decision about FP was not taken yet).

Eligible patients received an envelope containing an invitation letter, a study brochure, a general brochure about breast cancer and fertility, a decline form and a return envelope. Patients either signed-up themselves, or let their breast cancer nurse/clinician sign them up. After signing up, they received the baseline questionnaire by e-mail. All patients gave their informed consent prior to their inclusion in the study. Randomization took place after completion of the baseline questionnaire with either a link to the DA or to the brochures. All brochures were also publicly available, since we did not want to withhold relevant information for patients who did not participate in this study. Most participating medical centres handed out the brochures to all eligible patients, including those in the DA group. Respondents received a 10 euro incentive for completing three questionnaires.

Twenty-six medical centres in the Netherlands recruited patients for this study, of which 13 included patients. Three centres additionally recruited patients via their gynaecology department (one centre via gynaecology only). Data were collected between June 2011 and December 2012. With the incidence for breast cancer in young women in the Netherlands being almost 1000 women a year, we expected to be able to include enough participants to find small effects in decisional conflict (Cohen's $d=0.2$; $\beta=0.2$; $\alpha=0.05$) between randomization groups within 18 months. After 18 months we stopped randomization for reasons of funding.

Women in the additional usual care group were sent invitations by mail, including the questionnaire, a decline form and a return envelope. They were asked to complete one questionnaire, similar to the T2 questionnaire, for which they received a 10 euro incentive. Data were collected between January and June 2013.

Measurements

Outcomes were assessed with online self-reported questionnaires at baseline (T0), 6 weeks later, since we then expected a decision to have been made (T1), and 6 months after diagnosis, since we expected women to be able to look back at the decision from this time on (T2).

Socio-demographic (age, marital status, parity, child wish, religion, ethnicity, and education) and *medical characteristics* (date of diagnosis, treatment, past fertility problems, FP preference and uptake).

Decisional conflict was measured with the 16-item Decisional Conflict Scale (DCS;

including its subscales DM uncertainty, informed DM, values clarity, DM support, effective DM), validated for a Dutch population [19;20]. The items are measured on a 5-point Likert scale ranging from 0 (totally disagree) to 4 (totally agree). Total scores range from 0-100. A higher score indicates more decisional conflict. Cronbach's α of the total decisional conflict scale (T1) was .82.

Knowledge about FP was measured with 10 statements about FP, with answering categories "true", "false", or "do not know" (for example: "Cryopreservation of embryos is possible until the age of 40 (true)"), with answering categories "true", "false", or "do not know". Total scores range from 0-10. Cronbach's α of the knowledge scale (T0) was 0.62.

Preparation for decision making was measured with the 10-item Preparation for DM scale [21], about the extent to which the available information was sufficient to decide about FP. Answering categories were a 5 point Likert scale ranging from 1 "not at all" to 5 "very much". Total scores range from 0-100. Cronbach's α for the scale was .94.

Risk perception was measured with one item asking respondents to indicate on a 10 point scale 'how large do you think your risk is to lose your fertility due to chemotherapy treatment' (1=very low, 10=very high).

Reproductive concerns were measured with a Dutch version of the Reproductive concerns scale[2;22](Garvelink et al submitted 2013). The Dutch version of the scale consists of 8 of the 14 original items, measured on a 5-point Likert scale ranging from 0 (not at all) to 4 (very much)[2]. Total scores range from 0-40. Cronbach's α (T0) was .79.

Decisional regret with regard to decisions related to FP was measured with a 5-item decision regret scale[23], adapted to the FP-decision. Items were measured on a 5-point Likert scale ranging from 0 (totally disagree) to 4 (totally agree). Total scores range from 0-20. Regret was measured at T1 and T2. At baseline we measured *anticipated* regret, since we did not expect anyone to have made the decision yet. Anticipated regret was measured with 2 items asking after the extent to which women expected to have regret if they did/did not pursue FP now, when they would/would not appear to be fertile after cancer treatment (after van Dijk et al 2008[24]). Cronbach's α of the decisional regret scale (T1) was .61.

Symptoms of anxiety were measured with the 7-item subscale anxiety of the Hospital Anxiety and Depression Scale (HADS) [5;36]. A higher score indicates more anxious symptoms. Cronbach's alpha was good (T0 α=.87).

Use of the study materials Individual website statistics used. We measured time spent on each page and on the total DA, and number and type of pages viewed during the visit.

Analyses

To perform analyses on as many participants as possible, missing data on outcome measures at T1 and T2 were handled using Multiple Imputation[25;26]. This procedure uses linear regression to estimate a value for missing data on continuous variables, using the other variables as predictors. We used data on randomization, risk perception, reproductive concerns score, knowledge, preparation for DM, anxiety, decisional conflict score as predictors in the imputation model. Data were imputed 5 times, and combined using Rubin's (1987) rules for multiple imputation[27].

Differences between participants who completed all measurements and those who missed measurements were calculated with Mann Whitney or Wilcoxon rank-sum tests (continuous outcomes), and χ^2 –tests (ordinal/categorical outcomes) between baseline characteristics.

Due to the small number of participants we used nonparametric tests for all statistical analyses. Data analyses were done with SPSS 20.0 for Windows. Outcomes were considered significant when $p \leq 0.05$. Means (*M*) and standard deviations (*SD*) or medians (*Mdn*), point estimates and p-values are reported.

Differences between randomization groups were calculated using Mann Whitney (continuous outcomes), and χ^2 –tests (ordinal/categorical outcomes). Differences between measurement moments were assessed with the Wilcoxon signed rank-tests. Effect sizes were calculated as Cohen's d ($d=Z/\sqrt{n}$).

Differences between the three groups (secondary analyses) were analysed using Kruskall Wallis tests, using Mann Whitney tests for post-hoc analyses.

Results

Respondents RCT

Thirty-six patients participated, of whom six did not start the baseline questionnaire, two gave no informed consent and two did not complete the baseline questionnaire and could therefore not be randomized. Finally, 26 women (response rate 72%) completed the baseline questionnaire and were randomized to brochures (n=13) or the DA (n=13) (Figure 1). Eleven women were invited after they had spoken to a gynaecologist, 17 women before (just after seeing an oncologist/surgeon).

In both groups 12 women (92%) completed the T1 questionnaire, and respectively 12 (92%) and 11 (85%) women completed the T2 questionnaire (Figure 1). Women who completed all questionnaires were somewhat higher educated ($p<0.05$) than women who missed measurements.

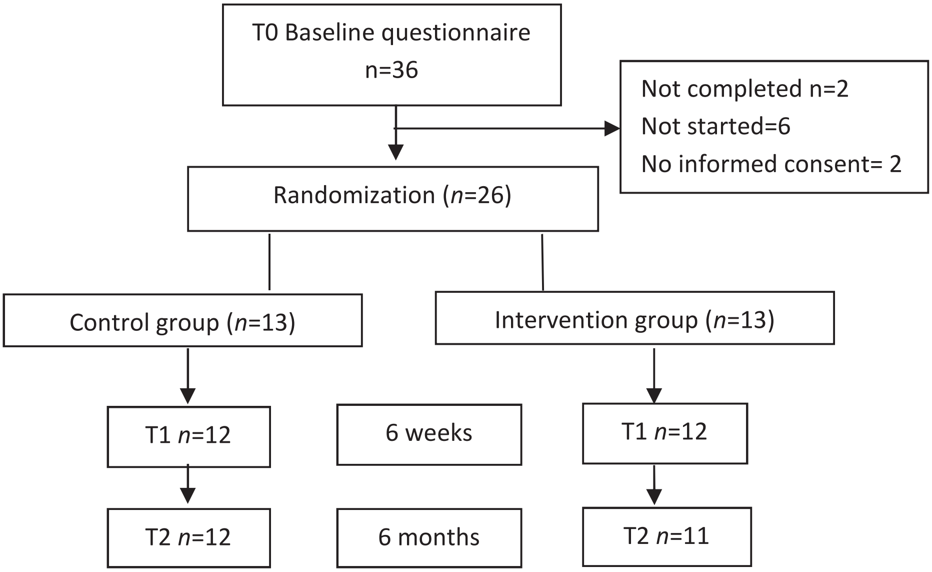

Figure 1. Flow chart of in- and exclusion of patients

Otherwise, we did not find differences between women who did or did not complete all questionnaires with regard to socio-demographic characteristics, or baseline outcome measures. Data on relevant outcome measures were therefore imputed for missing data at T1 (n=5) and T2 (n=5).

At baseline, there were no differences with regard to socio-demographic and medical characteristics between the randomization groups (Table 1). Women who received brochures had lower risk perception (p=.05) when compared to women who received the DA, otherwise there were no differences.

Table 1 Socio-demographic and medical characteristics of the participants

	Brochure (n=13)	**DA group (n=13)**	**Usual care group (n=10)**
Age, M (range)	32.9(28-39)	35.8 (30-40)	34.2 (27-39)
Male partner, n (%)	12/13 (92)	12/13 (92)	9/10 (90)
Of whom cohabiting n (%)	10/12 (83)	12/12 (100)	8/9 (88)
Parity 0<, n (%)	7/13 (54)	7/13 (54)	5/10 (50)
Child wish, yes (%)	13/13 (100)	13/13 (100)	10/10 (100)
Religious, no (%)	7/13 (54)	8/13 (62)	8/10 (80)
Cryopreservation option chosen*			
Embryos	6/12 (50)	5/11 (45)	1/10 (10)
Oocytes	1/12 (8)	-	-
Embryos+oocytes	-	1/11 (9)	-
Ovarian tissue	-	-	-
Wait and see	5/12 (42)	5/11 (45)	9/10 (90)
Educational level			
Low	1/13 (7)	-	-
Middle	3/13 (23)	3/13 (23)	3/10 (30)
High	9/13 (69)	10/13 (77)	7/10 (70)
Self reported breast cancer treatment*			
Surgery	12/12 (100)	11/11 (100)	10/10 (100)
Chemotherapy	12/12 (100)	8/11 (73)	10/10 (100)
Radiotherapy	7/12 (58)	10/11 (91)	6/10 (60)
Endocrine therapy	7/12 (58)	10/11 (91)	6/10(60)
immunotherapy	3/12 (25)	1/11 (9)	1/10(10)
Had a choice (yes)	10(91)**	8(80)***	7 (70)

*Due to missing values, percentages are calculated on a total of resp. 12 and 11 women in the brochure and DA groups (this data could not be imputed). **2 missings. ***3 missings.

Differences between women who received the DA or brochures

Use of the informational sources

Twenty-one women reported to have used any of the brochures about FP (91%; 3 missing) (Table 2). Five women used all available brochures. Of the 13 women who were randomized in the DA group, seven logged in to the DA, of whom 6 used the VCE. Mean time spent on the DA was 29 minutes (1 – 74 minutes). Women viewed on average 15 of the 26 informational pages (range 0-53), and 9 of the 9 VCE-pages (0-21; some pages were viewed more than once).

Preferences and decision making

At baseline 16 women (62%) had a preference regarding FP. At T1 21 women (88%) reported to have a preference, and 23 women (96%) to have made a decision. At T2 all women (*n*=23) reported to have made a decision about FP: ten women chose not to pursue FP (43%), 11 cryopreserved embryos (48%), one cryopreserved oocytes (4%), and one cryopreserved both oocytes and embryos (4%). There were no differences in choices between study arms. Five women (22%) mentioned not to have had a choice in this.

Decisional conflict, Knowledge, Preparation for decision making

Women who received brochures perceived DM at T1 as more effective (an informed, values based decision that is likely to be implemented, and with which they are satisfied) than women who received the DA in addition to brochures (5.4 versus 16.1, p=.03). At T2 there was a trend towards more Decisional Conflict in the DA group (24 versus 14, p=.12). Otherwise there were no significant differences (Table 3).

With regard to knowledge, we found a significant difference between baseline and T1(ΔM=1.35, p=.002; d=-.59), and baseline and T2 (ΔM=1.25, p=.004; -.56), indicating a relative knowledge increase of 22%. There were no differences between the groups within measurement moments.

There were no significant differences in preparation for DM between groups at T1. At T2, there was a trend towards better preparation for DM in the brochure group (81 versus 69, p=.12) (Table 3).

Regret

There were no significant differences in *anticipated* regret between measurement moments, nor were there differences in *regret* between groups. For both groups, there was a trend for a minor increase in regret between measurement moments T1 and T2 (ΔM=4.9; p=.15; d=-.29). At baseline, both groups *anticipated* more regret when not undergoing FP and turning infertile, than when undergoing it and remaining fertile (indicating that it had not been necessary to pursue FP). Anticipated regret at baseline was correlated with deciding to undergo FP at T1 (Spearman's Rho=.55, p<.01). Decisional regret at T1 was correlated with T2-scores (Spearman's Rho=.44 p=.03). When comparing women who opted for FP to those who did not, we found that those who did not opt for FP reported higher regret scores at T1 (23.8 versus 10.4, p=.04; d=-.44) and T2 (32 versus 12.7, p=.02; d=-.54).

Reproductive concerns, Risk perception, Anxiety

There were no significant differences between groups or measurement moments with regard to reproductive concerns or risk perception (Table 3).

Levels of anxiety decreased significantly from baseline to T1 (p=0; d=-.75) and to T2 (p=.001; d=-.67). There were no differences in anxiety between groups at T1, but at T2 women who received the DA had significantly higher anxiety scores than women who received brochures only (9.5 versus 6.1, p=.02)(Table 3).

Comparison with usual care

Forty women who received usual care were approached; twenty-two responded (55%), of whom 8 were eligible. Additionally, two women completed the questionnaire spontaneously online.

Women in the usual care group (n=10) were comparable to the other groups with regard to socio-demographic characteristics, although more women reported to be religious. They opted less often for FP; nine women chose to wait and see (90%), and one chose to cryopreserve embryos (10%; Table 1).

Women in the brochure group (M=6.6) and women in the DA group (M=7.1) reported better knowledge than women in the usual care group (M=4.8; p=.01). Furthermore we found differences in decisional conflict (ΔM=17.1 p=.025) and values clarity (ΔM=19.7, p=.03), with women who received brochures scoring better than usual care, and in decisional support (p=.02) with both women who received brochures (M=12.6) or the DA in addition to brochures (M=21.3) scoring better than usual care (M=39.2).

Table 2. Used information materials

	Brochure group (n=13*)	**DA group (n=13*)**	**Usual care group (n=10)**
Brochures, n(%)			
All brochures	5(42)	3(27)	-
General brochure	10(83)	10(91)	1(10)
Cryopreservation of embryos	10(83)	8(73)	-
Cryopreservation of ovarian tissue	7(58)	4(36)	-
Cryopreservation of oocytes λ	6(50)	3(27)	-
Other	-	-	-
Use of the DA, n(%)	-	7 (54)	-
Textual information	-	7 (100)	-
VCE + textual information	-	6 (86)	-
Website + brochures	-	6 (86)	-
Counseling consultation n(%)			
Fertility/Gynaecology	11 (92)	12 (100)	6 (60)
Oncology	4 (33)	5 (42)	7 (70)

*Due to missing values, all percentages are calculated on a total of resp. 12 and 11

Table 3 Decision making processes and outcomes for the participants divided per randomization group

	Brochures (A)		**Brochures + DA (B)**		**Usual Care (C)**		***A vs B***	***A vs B vs C***		
	N=13 (after imputation)		N=13 (after imputation)		N=10					
	M (sd)	Mdn	M (sd)	Mdn	M (sd)	Mdn	p-value/ z-value/Cohen's d	p-value/ χ2-value	Post hoc	Cohens'd
Risk perception										
T0	6.7 (1.7)	7.3	8.2 (1.5)	8	n/a		P=.046/Z=-1.994/d=-.42			
T1	7.3 (1.8)	7.1	7.5 (1.8)	7.5	n/a		P=.705/Z=-.393/d=-.08			
T2	6.1 (2.9)	6.6	6.7 (2.5)	8	7.1 (2.0)	6.5	P=.852/Z=-.187/d=-.04	P=.752/ χ2=-.57		
Knowledge										
T0	5.7 (1.8)	5.7	5.5 (1.8)	5	n/a		P=.772/Z=-.289/d=-.06			
T1	6.9 (1.5)	6.7	7.0 (1.6)	7	n/a		P=.668/Z=-.576/d=-.12		B > C	-0,46
T2	6.6 (1.2)	6.6	7.1 (1.4)	7	4.8 (1.8)	5	P=.264/Z=-1.1448/d=-.24	P=.005/ χ2=10.42	A > C	-0,45
Total decisional conflict scale										
T1	15.9 (8.9)	17.8	21.7 (14.8)	23.4	n/a		P=.256/Z=-1.137/d=-.24			
T2	14.2 (10.6)	14.1	23.7 (17.9)	28.1	31.3 (12.9)	29.7	P=.115/Z=-1.585/d=-.34	P=.025/ χ2=7.37	A < C	
Values clarity										
T1	14.3 (15.4)	8.3	24.1 (16.5)	25	n/a		P=.105/Z=-1.625/d=-.32			
T2	15.3 (13.5)	16.6	29.5 (27.2)	25	35(14.6)	29.2	P=.147 /Z=-1.47/d=-.25	P=.034/ χ2=6.85	A < C	-0.45
Decision making Support										
T1	16.9 (16.0)	15.7	22.2 (15.8)	25	n/a		P=. 465/Z=-0.736/d=-.14		A < C	-0.55
T2	12.6 (13.4)	8.3	21.3 (14.7)	25	39.2(16.7)	37.5	P=.145 /Z=-1.468/d=-.25	P=.002/ χ2=12.23	B < C	-0,39
Effective decision making										
T1	30.3 (20.8)	33.3	25.2 (22.8)	25	n/a		P=.531 /Z=-.629/d=-.12			
T2	21.3 (18.8)	25	29.3 (28.8)	25	35.8 (9.6)	37.5	P=.616/Z=-.504/d=-.08	P=.18/ χ2=3.43		

(Table 3 continued)

	Brochures (A)		**Brochures + DA (B)**		**Usual Care (C)**		***A vs B***	***A vs B vs C***		
	M (sd)	Mdn	M (sd)	Mdn	M (sd)	Mdn	p-value/ z-value/Cohen's d	p-value/ χ2-value	Post hoc	Cohens'd
Decision making uncertainty										
T1	16.9 (16.3)	16.6	23.8 (21.2)	25	n/a		P=.307/Z=-1.022/d=-.20			
T2	11.9 (10.0)	13.5	20.8 (13.8)	25	30 (23.3)	20.8	P=.07 /Z=-1.792/d=-.30	P=.07/ χ2=5.25	A < C	-0.34
Decisional regret										
T1	13.9 (11.3)	10.6	18.6 (16.3)	15	n/a		P=.438/Z=-.783/d=.016			
T2	17.6 (11.2)	18.6	24.7 (20.6)	22.5	29 (20.9)	30	P=.499/Z=-.068/d=.014	P=.423/ χ2=1.72		
Anticipated regret (T0)										
No FP*	1.85 (1.2)	2	2.23 (.93)	2	n/a		P=.461/Z=-.738/d=-.15			
FP**	.15 (.38)	0	.23 (.44)	0	n/a		P=.626/Z=-.488/d=-.10			
Preparation for DM										
T1	75.5 (14.1)	75	69.7 (22.2)	73.1	n/a		P=.408/Z=-.864/d=-.18			
T2	81.4 (12.0)	80.6	68.8 (24.9)	71.0	60.8(23.8)	75	P=.124 /Z=-1.561/d=-.33	P=.096/ χ2=4.76		
Reproductive concerns										
T0	13.1 (7.3)	11	13.4 (7.9)	15	n/a		P=.918/Z=-.103/d=-.02			
T1	12.3 (7.1)	12.5	11.1 (4.8)	12.8	n/a		P=.799/Z=-.263/d=-.05			
T2	10.7 (4.9)	9	13.4 (6.4)	15	14.6 (5.3)	17	P=.180/Z=-1.347/d=-.28	P=.215/ χ2=3.09		
Anxiety (HADS)										
T0	10.2 (5.8)	11.7	12.5 (5.1)	12.8	n/a		P=.439/Z=-.774/d=-.16			
T1	6.3 (3.0)	6.8	7.7 (3.1)	7.4	n/a		P=.376/Z=-.091/d=-.02			
T2	6.1 (3.3)	6	9.5 (2.9)	9.6	6.4 (4.2)	6	P=.018/Z=-2.3906/d=-.49	P=.031/χ2=7.15	B > C	-0.36

*Minimum-maximum scores: risk perception 1-10, knowledge 0-10, total DCS 0-100, decisional regret 0-100, anticipated regret 0-5, preparation for decision making 0-100, reproductive concerns 0-40, quality of life 0-100, anxiety 0-21, depression 0-21. n/a= not applicable. Interpretation of cohens'd: negligible effect (>= -0.15 and <.15), small effect (>=.15 and <.40), medium effect (>=.40 and <.75), large effect (>=.75 and <1.10). FP=fertility preservation.*anticipated regret from not undergoing FP, ** anticipated regret from undergoing FP.*

Discussion

Women in our sample experienced relatively low levels of decisional conflict, with indication of slightly less effective decision making at T1 and higher levels of decisional conflict at T2 in women who received the DA in addition to brochures, compared to women who received brochures only (Cohen's d=.34). Mean levels of decisional conflict in the DA group were only low to moderate [19]. Perhaps these women felt there was not be much to be decided: over 20% of the women in our study mentioned they did not experience a choice in this decision. Moreover, the preferred FP option was often determined by a woman's possibilities in combination with the highest possible success rates [28]. The difference between the arms is in contrast to what we expected based on other DA evaluations. For example, a review by Stacey et al (2012) found a medium beneficial effect (Cohen's d=.43) of more detailed compared to simpler DAs with regard to decisional conflict in several screening and treatment decisions [29]. However, the decision about FP is a different type of decision when compared to screening- or treatment decisions. Future fertility is important for many women [28], and the decision about FP has to be made in a difficult (and short) time frame with competing demands from other medical decisions related to surviving the cancer [28;30;31]. Explicit confrontation through a DA may therefore increase decisional conflict in case of FP. However, Peate et al (2013)[32] compared a fertility related DA (a C5 booklet with information and values clarification exercises) to usual care, and found less decisional conflict in the DA group (Cohen's d=.52). This could indicate that the different formats of their and our DA (web-based or on paper) may have an impact [32]. Further, the design and content of our DA may have already suggested a difficult decision to the women (in an implicitly normative way [33]). Indeed, we only found significant differences in decisional conflict (effective DM) at T1, and not in the longer term (T2). Furthermore, all FP options are mentioned in the DA, which will not be optional for all patients. For some patients the availability of information about irrelevant options might be confusing, while others want to see as much information as possible. A similar phenomenon has been found before in a study in abdominal aneurysm patients [34], in which a DA with (more) information about treatment options resulted in fewer patients who were able to decide[33;34]. Additionally, a slight increase in decisional conflict is not necessarily disadvantageous [35;36]. This may for example also indicate that women are strongly involved in the decision [36].

Studies have found a role for personality in the preferred amount of information; i.e. having a blunting information seeking style was related to (less) DA-use (Garvelink et al submitted) [37;38] and neurotic and conscientious personalities were related to more uncertainty and less perceived DM support. These different information needs suggest the need for tailored information. It is possible that some women may have more benefit from DAs than others, but in our small sample size we were not able to evaluate this. Moreover, in this study the randomisation dictated which information patients should use, but it is possible that patients' would have chosen for or benefitted from other information had they been able to choose their own information source. The recruiting clinicians indicated that indeed some patients did not want to participate, because of the possibility that they would be randomized to the brochures. Additionally, a majority of women in this study mentioned that they considered the information of the fertility expert to be most relevant in DM[39]. Therefore, besides additional written information, referral to a fertility expert for counselling about FP is still of utmost importance. Moreover, the aim of our DA and brochures was to *prepare* women for a counselling consultation with a gynaecologist or fertility specialist. Information provision about FP has been found to be important throughout the process of DM, during and after treatment [4], which can be facilitated with these brochures and DA as they are available at all times. In clinical practice, patients should be able to choose between available informational sources and choose when the informational sources are used (prior to, during, or after the consultation).

The benefit of additional information is clear, since both information sources led to a significant increase in knowledge between baseline and follow-up (Cohen's d=0.61), comparable to the increase in knowledge that was reported by Peate et al (2012)[32]. Unlike other studies ([29;32]) the knowledge scores in our study did not differ between groups. However, the information in the brochures and DA was highly overlapping, and the majority of women in both randomisation groups read the brochures. Moreover, compared to usual care, we did found higher knowledge scores in women who received either brochures or the DA [32].

Some important limitations must be taken into consideration in interpreting these results. Our sample size is very low. Fewer patients than anticipated were eligible for the study (a majority of newly diagnosed patients had complete families or no desire for children), and the combination of the difficult timing in which patients had to be invited, the increasing number of studies for breast cancer patients, and the burden of a cancer diagnosis made recruiters sometimes hesitant to invite patients, or made patients unwilling to participate. Due to the small sample size, results are based on non-parametric tests only, and we had not enough power to control for possible confounders. Therefore existing baseline differences between groups should be kept in mind in interpreting the results. Additionally, we did not adjust for medical centre or department through which patients were invited, although it could have made a difference whether somebody is invited via their oncology department (early in the trajectory), or via their gynaecology department (shortly before, or even after counselling).

It should be noted though, that despite small sample sizes we were able to show some important significant differences between the groups. The low number of participants as well as the overlapping information in, and use of, the brochures and DA, made us decide to add an extra observational control group of 10 women who did not receive information. No important differences with regard to socio-demographical characteristics were found between these women and the randomized women, but caution should be adopted in interpreting results of comparisons, since these women were not randomized.

In conclusion, the results of this study indicate a beneficial effect with regard to knowledge and decisional support of receiving either brochures or a DA in addition to brochures, compared to usual care. Brochures were also beneficial with regard to reducing decisional conflict compared to usual care, but explicitly clarifying ones values with the DA seemed to introduce slightly more decisional conflict than reading brochures.

Practice implications

It is of utmost importance that patients are offered timely information about FP in addition to counselling. The DA as well as brochures improved knowledge and had no disadvantageous effects, and can thus be used to inform future patients. However, since use of the DA slightly increased decisional conflict, additional assistance in DM (during counselling consultations) should be available.

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Chapter 8

Summary and General Discussion

Summary

Chapter 2: *Women's experiences with information provision and deciding about fertility preservation in the Netherlands: 'satisfaction in general, but unmet needs'.*

In this qualitative needs assessment, 33 interviews were conducted with patients who had received a counselling consultation and made a decision about fertility preservation (FP) in the past. Women reported being generally satisfied with all aspects of information provision and decision-making about FP, but more in-depth answers brought to light that the information was not always timely, the information was not always correct, communication between hospitals or members of different specialties was poor and women had the feeling that assertiveness was necessary to receive all relevant information. Suggestions were made to develop informational materials (brochures, websites) for patients and checklists for clinicians.

Chapter 3: *Development of a decision aid about fertility preservation for women with breast cancer in the Netherlands.*

This chapter sequentially reported on all stages of the development of a decision aid (DA) about FP, involving patients, clinicians, and healthy women. The DA was developed according to the International Patient Decision Aid Standards (IPDAS) criteria for evaluation of recommended content and development processes for DAs. Content of the DA was determined by a multidisciplinary team of clinicians, researchers, website developers and text writers. The initiative to develop a DA was welcomed by patients and clinicians, and the proposed DA was deemed acceptable. With input from patients and clinicians, some adaptations were made to the draft DA in order to improve understanding, navigation or presentation. The DA was then understandable for both less and more highly educated women, as both groups had significantly improved knowledge about FP after viewing the DA. Results led to a final DA to be used in patient populations with newly diagnosed breast cancer.

Chapter 4: *A Delphi consensus study among patients and clinicians on the procedure of informing young breast cancer patients about Fertility Preservation.*

In this study, patients, clinicians and nurses were gathered in an expert panel (a Delphi panel, after the Greek Oracle) to reach consensus on the use of a DA about FP to inform patients and on the best procedures to implement and use the DA in oncologic practice (when, by whom, and for which patients). All participants thought information provision about FP was important. Agreement was reached that all eligible patients should be provided with general information about FP (irrelevant by whom) soon after diagnosis, and receive more detailed information from a fertility specialist at a later moment. Further, the procedure should be tailored to the individual and the situational context as much as possible. Potential end-users were motivated to use the DA in practice.

Chapter 5: *Values clarification in a decision aid about fertility preservation: does it add to information provision?*

This chapter reports on two experiments with two different samples of healthy participants who were asked to make a hypothetical decision about FP. The first assessed the effect of a DA with and without values clarification exercise (VCE). The second was an expansion of the first, to assess whether personality characteristics and information-seeking styles influenced DA use and effectiveness. Use of the DAs increased knowledge, especially for women who used the DA more thoroughly, highly conscientious women and women with a more monitoring information-seeking style. Information-seeking style affected DA use (high blunters viewed fewer pages) but not VCE use. Personality traits had some effect on aspects of decisional conflict (neurotic women felt more uncertain and less supported in decision-making; conscientious women, on the contrary, felt more certain). There were no indications that (use of) the VCE was beneficial for knowledge or decisional conflict.

Chapter 6: *Psychometric properties of the Reproductive Concerns Scale in three populations of women.*

This chapter describes the psychometric properties of a Dutch version of the Reproductive Concerns Scale in women with breast cancer, women with fertility problems and healthy women. Results showed that the scale was well able to differentiate between different groups of women (known groups construct validity), was related to theoretically related constructs (construct validity), measured reproductive concerns on a coherent scale (reliability) and was stable over a period of two weeks (re-test reliability). All psychometric properties were comparable in breast cancer patients and women with fertility problems, indicating generalizability and justifying its use as outcome measure for research purposes.

Chapter 7: *Additional value of decision aids in complex clinical situations: Effectiveness of a decision aid about Fertility Preservation for breast cancer patients.*

This chapter describes the effects of the DA in addition to brochures, compared to brochures only, on decision-making about FP in newly diagnosed breast cancer patients. Additionally, results were compared with those in women who received usual care (no additional written information). Both informational sources (brochures and DA) led to increased knowledge. There was a trend towards somewhat increased decisional conflict in the DA group when compared to brochures, but decisional conflict seemed even higher in the usual care group. This indicates a beneficial effect of receiving any additional information with regard to knowledge, but increased decisional conflict after using the DA with explicit values clarification exercise.

General discussion

The main purpose of this thesis was to study the needs of breast cancer patients with regard to information provision about fertility preservation (FP), and to assess whether these would be fulfilled by a web-based decision aid (DA) about FP. We have developed a web-based DA with input from various stakeholders, and assessed whether use of the DA and one aspect of the DA (i.e. a values clarification exercise; VCE) would lead to more knowledge and better decision-making outcomes (assessed in healthy women and patients). Additionally we have assessed for which women the DA could be most effective (assessed in healthy women).

Based on the results of the studies in this thesis, as summarized before, there are two important themes that need further discussion: first, the actual value of a DA above and beyond educational brochures in case of FP, and second, the value of values clarification exercises to facilitate decision-making in general. Before these themes are further discussed, some important limitations are discussed, which are important to consider in interpreting the results of this thesis. Subsequently, recommendations are made with regard to further research and clinical practice.

Methodological considerations (chapters 2–7)

In addition to the strengths and limitations that have already been addressed in the separate chapters, there are some important strengths and limitations of the studies in this thesis that we would like to mention here in detail.

Two strengths are the application of different research designs to answer different research questions (qualitative interviews, a Delphi panel, a cross-sectional study and RCTs) and the inclusion of various types of participants (patients who had made a decision about FP in the past, newly diagnosed patients, participants without cancer and clinicians). The application of different research designs allowed us to rigorously study our proposed aims with the most suitable research methods. Qualitative studies are known to be a good design to explore a field of which not much is known yet (ideal for a needs assessment; *chapter 2*), while more quantitative studies are a good design to quantify effects (pilot and validation studies, effect evaluations). The Delphi panel (*chapter 4*), which combined qualitative and quantitative methods, has been proven a good method to reach agreement among different kinds of experts [1;2]. Within quantitative designs we differentiated between retrospective designs (cross-sectional) allowing us to assess predictors for reproductive concerns (*chapter 6*) and prospective designs to evaluate effectiveness of our DA in RCTs (*chapter 5, chapter 7*). The variety of participants is a strength, since it increases the generalizability of results, but also a weakness, since the DA was originally developed for patients; it is therefore possible that results would have been different if newly diagnosed patients had been included in all studies (for example with regard to measures related to decision-making – hypothetical and actual decisions are not the same (*chapter 5*)). Reasons for not only studying needs and effects in newly diagnosed patients were either practical – i.e. sample sizes can be larger with healthy controls or ex-patients than with newly diagnosed patients (*chapters 2–6*) and ex-patients were thought to add more to the development of new materials because of their experience with information provision and deciding about FP (*chapter 2-4*) – or ethical (when patients are not thought to benefit from a study it is unethical to include them; *chapter 5*). In many cases one can include healthy subjects to study specific aspects of interventions in controlled experiments (*chapter 5*), as long as actual effect evaluations are conducted in actual patients for whom the intervention was developed originally (*chapter 7*).

There were some major limitations as well. In the development of the DA about FP, we involved stakeholders as much as possible (*chapter 2–4*). This improved the quality of the information and likely contributed to (future) implementation of the information provision, but it also led us to compromise the research design (in *chapter 7*). Especially in research on information provision for patients, conflicts of interest might exist between researchers and clinicians. Researchers aim to conduct rigorous research, with conclusions about the effectiveness of newly developed information as an endpoint, whereas clinical stakeholders just want to use the available materials to inform their patients as quickly as possible. Therefore, even though for years clinicians have offered only limited verbal information about FP to their patients, it seemed from a clinical point of view ethically unsound to withhold information materials about FP that are considered better than usual care from a subsample of patients (i.e. women randomized to the control arm). Hence, in addition to the DA we developed educational brochures about FP for the control group and broadly distributed them to hospitals throughout the country. The paper brochures and web-based DA contained the same information about FP options and similar information about cancer treatments and their impact on fertility, but the DA additionally contained background information about normal fertility and an explicit values clarification exercise. Further, brochures were linear, but in the DA patients could choose their navigation method and decide for themselves what proportion of the information to read. Although this compromise made clinicians more willing to participate in the trial, from a research perspective it had some disadvantages. For example, by offering both arms information that is thought to be good (brochures) or better (DA), we compromised the power of our study. Effect sizes were expected to be very small, with the consequence that large participant numbers were required to detect an effect. Offering good information to both study arms in *chapter 7* also led to unexpected results. For example, it resulted in the situation that women in both arms had read the brochures. This may have influenced their DA use and it prevented us from specifically studying the efficacy of the DA compared to brochures, but then it also facilitated the implementation of both informational sources (brochures and DA). Luckily, by addition of an observational control group to the RCT consisting of women who received usual care, we were also able to evaluate some effects of both developed information materials.

Lastly, a major limitation – which was a problem in all quantitative studies in which we aimed to include (breast cancer) patients (*chapter 6–7*) – was the difficulty recruiting young women with breast cancer that fulfilled the inclusion criteria for our studies. A majority of newly diagnosed patients had complete families or no desire for children, and the combination of the difficult time during which patients had to be invited, the increasing number of studies involving breast cancer patients and the burden of a cancer diagnosis made recruiters sometimes hesitant to invite patients, or made patients unwilling to participate.

The sense or non-sense of a DA about fertility preservation

Especially in the case of preference-sensitive medical decisions it is important that patients are aware of all treatment options and their benefits and risks, so that patients can form preferences and, together with the clinician, decide what the best treatment option is – i.e. shared decision-making (SDM). DAs have been developed for many such decisions and have been found to be effective with regard to increasing knowledge on the subject and reducing decisional conflict, leading to more realistic expectations with regard to the treatment and a higher percentage of patients who are able to make a decision [3;4]. Hence, for the preference-sensitive decision of whether or not to pursue FP, we also developed a DA.

Results of this thesis show that the web-based DA with VCE about FP was a good means to *inform* patients about FP. Both in actual patients (*chapter 7*) and in healthy participants (*chapter 3, chapter 5*), a medium to large increase in knowledge was found from using the DA. However, other developed informational sources (DA without

VCE; brochures, which contained similar information about FP but less background information; and no VCE) seemed just as good for knowledge increase (*chapter 5, chapter 7*). Moreover, from the addition of a historical control group who received no (written) information besides a counselling consultation, it became clear that in fact any additional information was beneficial with regard to knowledge increase, compared to receiving only a counselling consultation.

The DA was developed not only as an informational source but also as support in decision-making, so we expected that patients who received the DA would be better able to decide about FP than those who only received brochures about FP, since other studies have reported such effects of DAs [4;5]. For example, pooled results of the review by Stacey et al (2012) indicated that in several screenings and treatment decisions, explicit DAs were more likely to achieve informed, values-based decisions than other DAs [4], and that more detailed DAs led to less decisional conflict compared to simpler DAs [4]. Additionally, a previously developed DA about FP (a C5 booklet with information and values clarification exercises) had beneficial effects with regard to decisional conflict and regret (Cohen's d=.52) compared to usual care (a general guide on early breast cancer development not specifically about FP) [5]. When we compared our DA about FP to usual care, our results were similar to those of Peate et al. (2012), but compared to brochures (our original design), decisional conflict slightly *in*creased after use of the DA (*chapter 7*). Moreover, in our study the effects of brochures only and of DA in addition to brochures were equal with regard to value congruence and percentage of women who were able to decide (*chapter 7*), but women who received brochures reported more effective decision-making than women in the DA group (at T1, *chapter 7*). Secondary analyses in a group of patients who received no additional information compared to patients who received either brochures or the DA revealed that both informational sources increased the sense of being supported in decision-making, but that brochures additionally led to more clarity about values.

But why would a DA not work in the case of FP, when it has proven to be the tool of choice in other preference-sensitive decisions [4;6;7]? Explanations might be sought in (1) characteristics of the decision about FP, (2) characteristics of the DA (layout, content, addition of VCEs) or (3) characteristics of the DA users (personality, information-seeking style, literacy). We will discuss these possibilities one by one in more detail.

First, it is possible that a DA has less benefit in the decision of whether or not to pursue FP because this decision is of a different type compared to other treatment decisions for which DAs have been found effective [4]. It might even be questioned to what extent there is a decision to be made in the case of FP. When women have a future desire for children and consider preserving their fertility, the FP option they choose seems merely determined by the extent to which a child is desired in combination with the highest possible success rates (*chapter 1, chapter 7*) and is often dictated by the situation (available time, risk of metastasis) and patient characteristics (age, parity, having a partner or not [8]). In other decisions for which DAs have been found to be effective, the possible treatment options are perhaps less dependent on patient and situational characteristics. Additionally, decision-making (and FP treatment if chosen) has to take place in the short and emotional period between diagnosis of (breast) cancer and start of the oncologic treatment. Since many oncologists emphasize the urgent need for oncologic treatment rather than the option to pursue FP [9], patients may experience (too) much time pressure in decision-making about FP. Hence, women may not always perceive the decision to undergo FP as an actual decision and may therefore not benefit from DAs that "help them decide".

Another factor that may explain why DAs are not always effective may be the design and content of DAs (with VCEs), in that they may suggest a difficult decision to patients (in an implicitly normative way [10]) and thus increase the decisional conflict of users instead of decreasing it. Stiggelbout et al (2008) found a similar result in a study in patients with an abdominal aneurysm; the DA in their study resulted in fewer patients that were able to decide, and different preferences and choices regarding treatment [10;11]. It is possible that the design and the mentioning of all available FP options in our DA is confusing for some patients, since it suggests that they can choose (between all options), which is not always the case. Also, not all patients may need or want all possible information in order to make up their minds. In our population this seems not to be the case, however (*chapter 7*), since a majority of the patients viewed both the DA and brochures.

Besides informational content, our DA consisted of an explicit VCE. In the development of this VCE, important quality criteria and consideration of other research was incorporated to create a theoretically sound tool (*chapter 3*) [12-14]. However, the possible beneficial effect of a VCE in the stressful and short time that is available for decision-making about FP is not clear for every patient [15] (*chapter 7*), nor could it be proven in healthy women (*chapter 5*). In the latter group, use of the VCE led to more values clarity, more decision-making support and more effective decision-making, but only compared to non-use for women who were able to use the VCE (*first experiment, chapter 5*). There was no difference between women who used the VCE and those who did not use it because they were not able to (women who were randomized to a DA with information only). This indicates that in subgroups, the VCE was beneficial. To assess psychological characteristics of these subgroups, a second experiment was conducted with the same two randomization groups (information only versus information plus VCE) in addition to a third condition (information plus VCE with active referral to the VCE). We assessed not only the effectiveness of the DAs, but also the personality characteristics of the respondents. This experiment revealed several personality characteristics that were related to DA use and its effectiveness but was not able to confirm the beneficial effects of using the VCE that we had found before (neither with nor without referral to it), indicating that it might not have been the VCE or DA alone that caused the earlier effects, but possibly personality or characteristics related to women's use of health-related information (*second experiment, chapter 5*).

Third, as already suggested in the previous paragraph, it is possible that DAs are beneficial with regard to decision-making, but not for every patient – hence pleading against the use of a one-size-fits-all approach [16]. Other studies found possible roles for neuroticism, conscientiousness and monitoring and blunting in seeking medical information [17-19]. In healthy participants we have found that women with blunting information-seeking styles viewed fewer informational pages and spent less time on the total DA (*chapter 5*) [18;19]. Additionally, more neurotic women felt less supported and more uncertain in decision-making, whereas conscientious women felt more certain in decision-making (*chapter 5*)[17]. However it is unclear whether these feelings of uncertainty and support are merely traits of these women, or are actually related to use of the DA. Although the effect sizes of the associations with neuroticism were small (r=.18), it could be an indication of a possible role for personality in the effectiveness of a DA, and an interesting starting point for future research. It is also possible that a woman's personality has a greater influence on her decisional conflict than a DA does and thus modifies the effects of the DA on decisional conflict (*chapter 5*) [17;18]. Unfortunately our sample size was too small to stratify by personality (*chapter 7*), or to assess effect modification by personality. Moreover, it is known that especially neurotic women are at increased risk of reacting with feelings of depression to a negative event (such as cancer) [20]. In our RCT with patients (*chapter 7*), patients in the DA group had higher baseline depressive feelings than those in the brochure group (*data not shown*) and felt less certain in decision-making. It is possible that these women were more neurotic and therefore less certain in decision-making, but not due to the DA. Additionally, patients' literacy may have an important role in the effectiveness of DAs. Sub analyses in the review by Stacey et al (2012) found that DAs were mostly effective in low literate patients [4]. Of the patients in *chapter 7,* a majority were high literate (*data not shown*), which may have contributed to the limited beneficial effects of our DA.

The value of values clarification methods to facilitate decision-making <u>in general</u>?

From the studies in this thesis it appeared that the added value of a VCE in the DA about FP was not clear. The literature about many other DAs with values clarification methods (VCM) is also ambivalent with regard to the effectiveness of VCM [3;6;7;21-24]: some conclude VCM are beneficial, others find no beneficial or no significant effects of VCM. Additionally, effectiveness of VCM seems to differ in different study populations (i.e. patient or healthy populations).

A VCE may suggest a deliberative decision-making process, while there is no consensus as to whether or not medical decisions should be made deliberately, by intuition, or both [23;25-27]. In theory, deliberation (with VCM) and analytical reasoning may not always be beneficial for decision-making [23], since deliberation may overshadow important intuitive feelings that are more difficult to formulate but may be just as important in decision-making [23]. Intuition may play a more prominent role in medical decision-making than is accounted for in many DAs with VCE [23]. A combination of deliberation and intuition has been suggested to be beneficial for values clarification [23], possibly with the addition of specific encouragement for patients to become informed and learn about each option before they make a decision (delayed decision-making) to facilitate an unbiased process of preference construction [23]. Additionally, in designing VCM one could target potential stages of processing in decision-making: representation of the options, pre-selection of possible options, integration and evaluation of information about the options, selection of a final option and implementation of the decision (post-choice) [25].

Recently, an entire issue of the journal *BMC Medical Informatics and Decision-Making* was devoted to updating the evidence regarding development of DAs, with attention paid to VCM as well [28;29]. In this volume, some caution was added to the criterion that stated the need for addition of VCM as obliged part of DAs in the previous version of the IPDAS criteria. This criterion was attenuated due to the small number of evaluations of VCM, and heterogeneity of outcome measures and effects of VCM [13;29;30].

The ambivalent effects of the VCE in the different studies in this thesis, in addition to the inconsistent results in the literature, again emphasize that the black box of VCM is still not resolved. We do not know what the effective or ineffective parts of VCM are and how we should best apply these in future DAs, if at all.

Further research

Development and maintenance of DAs requires much time and resources (financial support, intellectual input). To justify these investments, it is important to assess the effectiveness of using DAs. We should not just develop DAs for all preference-sensitive decisions without first knowing whether, when and how they are useful [31]. However, in conducting future studies on the effectiveness of DAs, some important considerations should be taken into account. For example, future studies on the efficacy of DAs should be performed comparing the DA with actual usual care, not comparing good with better, like we did when comparing the DA to educational brochures (*chapter 7*). Therefore, we need to focus on research designs other than regular RCTs. Possible study designs might use a waiting list control group that will receive the intervention later, or a stepped wedge design [32-34]. Unfortunately, the waiting list solution is only possible for decisions in which there is sufficient time to decide, which was not the case in the decision about FP, and stepped wedge was not possible due to the large number of medical centres, clinicians and departments and limited time to complete the study. But Peate et al (2012) compared their DA about FP with usual care in a non-randomized approach, similar to stepped wedge, which seemed to work well [5]. With this study design, the needs of clinical practice are met – since no information is withheld from patients – without compromising the rigour of research. When studies are merely designed as implementation studies, *efficacy* of the materials cannot be studied. However, it is possible to assess *effectiveness* of the information materials and make a start with implementation in the participating medical centres. For further implementation, we might need to engage other parties, for example health insurance companies, to cover the expenses of promoting and distributing the materials. After all, they might also benefit from better informed patients and more shared decision-making (SDM) between patients and clinicians, since it may lead to more efficient and higher quality care [4;35].

If future experiments confirm the role of personality and information-seeking style in DA use, it might be important to stratify patients per personality trait in DA provision. Individual patients may have different reasons for seeking information and different informational needs and preferences [36-40], which additionally may change over time [41;42]. This can be seen in the different information-seeking behaviours of patients and healthy women in using a DA about FP (*chapter 5, chapter 7*) [5;15]. These research findings, opinions of clinicians and psychological (health) theories emphasize the importance of tailoring information to patients (needs) in general [43-46], as well as for FP (*chapter 4-7*). However, more research is needed on how personality effects DA use and effectiveness, and how tailoring could best be done. Additionally, we need to conduct more large-scale studies with healthy participants to identify the exact roles of different personality styles on information-seeking and decision-making.

VCM are considered to be an important component of DAs. However, the best method for values clarification is still not clear. Therefore it is important that we continue to search for the best VCM [30;47]. Since clarification of values occurs within the entire process of decision-making (from the initial diagnosis and mentioning of the treatment options to the moment that an actual decision is made) [48], VCM should not only be part of decision-making tools, but values clarification should be part of the clinical encounter as well. In determining which kind of VCM is best for a decision, VCM should reflect existing decision-making theories [25;30], and experimental studies should be conducted on aspects of VCM both inside and outside the clinical encounter.

The information and VCM in DAs ought to prepare patients for a consultation with a clinician and subsequent shared decision-making (e.g. by informing them and clarifying their values). An overarching purpose of DAs is thus to facilitate SDM between patient and clinician. Since the DA in this study informed patients but did not necessarily improve decision-making processes or outcomes for all patients, future research should focus on additional strategies for implementing SDM, instead of only focusing on the use of DAs as a possible facilitator of SDM. This DA might *facilitate* SDM by informing patients, but actual SDM is still something that takes place in the clinical encounter between patient and clinician.

Clinical implications

We may conclude from our studies that both brochures and the DA about FP seemed useful for clarifying FP options and made patients feel supported in decision-making, thus indicating a role for both as informational sources. Not enough women used the DA and VCE to attach strong conclusions to their effectiveness. However, in the future, brochures might become old-fashioned, and all relevant medical information should (at least “also”) be accessible via the internet in order to reach all patients. Since it is known that many breast cancer patients use the internet to fulfil other information needs (e.g. with regard to their primary treatment) [49;50], it seems a logic location for patient information regarding FP. One can place a large amount of information on the web, which is easy to update, and patients can access it at any time and from anywhere. Hence, despite indications of a slight increase in decisional conflict from the DA compared to the brochures in this thesis, online information will likely be the future for informing patients about FP options, thus justifying implementation of both materials as informational resources [51]. Moreover, since different patients seem to have different information needs and information-seeking styles it is important to offer them a choice between all available information sources, or to tailor the information. However, caution should be adopted in tailoring the information based on clinicians’ *perceptions* of what patients want or need [52], instead of actual *assessment* of these needs.

Unfortunately, availability of (online) DAs is not enough to achieve their routine use [16]. We know from other studies that if no attention is paid to implementation strategies, many (effective) DAs are not used in practice after the research period is over, because clinicians no longer refer to them [53]. Implementation models emphasize the need for thorough assessment of current procedures and how an intervention fits in, including the acceptability of users and situational context [54;55]. Hence, in order to facilitate implementation of the DA and brochures in clinical care, we conducted a pre-implementation study. Aims of this study were to create awareness of the DA, to increase health care professionals' and patients' motivation to use it and to assess the best procedure of implementing it in clinical practice, thereby taking into account barriers and facilitators (*chapter 4*). Involving stakeholders in the development and implementation of an intervention is an important step in the actual implementation of an intervention [56]. To facilitate *national* implementation of the DA and create awareness of the DA throughout the country, we included medical centres in all regions of the Netherlands, many clinicians and many clinical departments in the RCT (*chapter 7*). Additionally, we used an effectiveness design (instead of efficacy) to assess the effect of the DA (*chapter 7*), which facilitates implementation by embedding the intervention (handing out the DA or brochures) in regular clinical practice. Unfortunately, due to the low number of eligible patients that could be included in the trial (*chapter 7*), offering the DA has probably not yet become a routine. Hence, in the long run, time has yet to prove whether our implementation strategies were sufficient to sustain referral to the DA and brochures as informational sources in clinical practice.

(Future) developments in the field of information provision about FP

Breast cancer patients are only one category of cancer patients that might benefit from improved information about FP. This thesis focused on information provision to breast cancer patients only, but information provision has to be improved for other types of cancer as well! Therefore we are already in the process of developing a generic website (www.kankerenkinderwens.nl) in order to adapt the (information on the) DA for breast cancer patients to a broad range of cancers whose treatment compromises fertility, and thereby also to different kinds of patients (men and children in addition to women).

Not only patients, but also clinicians have mentioned that they would like more knowledge and information sources about FP (*chapter 4*) [57]. This is important for them to be able to better support patients in decision-making. In order to inform clinicians, as well as to have patient information available in another format, we are now in the process of developing a generic educational application ("app") about FP for both patients (males, females and children with various types of cancer) and clinicians. This tool can be used in the counselling consultation as well as at home, and is another step towards improving information provision about FP.

With the availability of different informational sources we can tailor the information provision, as much as possible, to individual patients' preferences. By developing information for clinicians as well, we can make sure that all clinicians have the necessary information to be able to inform all their patients about FP, and have materials to hand out for patients.

General conclusion

The main conclusion of this thesis is that improved information provision was deemed necessary and that the DA about FP developed for this end is acceptable to patients, nurses and clinicians and has beneficial effects with regard to knowledge. Although we cannot say much about effectiveness of the DA given our small sample sizes, it seemed that with regard to decision-making, the DA slightly increased decisional conflict. The method of choice to clarify patients' values is still not clear.

In order to form values and preferences and make (shared) decisions in the consultation with the clinician, patients must be informed first. The DA and brochures can therefore best be used as informational source. Since information-seeking needs and effects of DAs might differ for women with different personalities and given personal- and situational characteristics (partner status, age, disease stage), it is important to tailor the information provision as well as the procedure (timing) to patient needs as much as possible. Effects of DA use on the consultation should still be studied, as well as the effectiveness of the VCE in a larger population.

With regard to the procedure of informing patients, it is important that clinicians have sufficient knowledge about FP and include information provision about FP as a standard agenda item in consultations with young women with breast cancer.

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Nederlandse samenvatting

Door betere overlevingskansen na borstkanker wordt de kwaliteit van leven na behandeling steeds belangrijker voor patiënten. Onvruchtbaarheid, of zorgen over de vruchtbaarheid als gevolg van de behandeling van kanker, kunnen de kwaliteit van leven negatief beïnvloeden. Daarom is er steeds meer interesse in procedures om de vruchtbaarheid te sparen voorafgaand aan de behandeling van kanker (fertiliteitspreservatie; FP). In Nederland probeert men op dit moment de vruchtbaarheid te sparen door het invriezen van embryo's, eierstokweefsel of eicellen. Helaas is de informatievoorziening over FP voor patiënten nog niet altijd voldoende. Dit proefschrift richt zich daarom op het evalueren van de informatiebehoefte van patiënten en het ontwikkelen en evalueren van een keuzehulp over FP en aspecten daarvan (zoals een oefening voor het verhelderen van waarden), voor borstkanker patiënten in Nederland.

Algemene introductie

In *Hoofdstuk 1* wordt de complexiteit van het beslissen over FP voor jonge vrouwen met borstkanker uiteengezet. De diagnose borstkanker heeft al een behoorlijke impact op een patiënt, maar voor veel jonge vrouwen komen daar de gevolgen van de behandeling op de vruchtbaarheid nog eens bovenop. Van het ene op het andere moment is men patiënt en moeten er allerlei beslissingen worden genomen over borstsparende behandeling of amputatie, borstreconstructie, pruiken, gevolgen voor werk en privé, mogelijke genetische aspecten, én of men de vruchtbaarheid wil proberen te sparen voorafgaand aan de oncologische behandeling. In een emotioneel turbulente en zeer korte periode wordt er verwacht dat een beslissing kan worden genomen ten aanzien van FP en wordt men geacht te weten a) of men een kinderwens heeft voor de toekomst, b) met wie men deze kinderwens eventueel heeft, c) of men de vruchtbaarheid wil proberen te sparen, en d) zo ja, op welke manier. Omdat de FP opties vanuit medisch perspectief gelijkwaardig zijn, hangt de beste beslissing vooral af van waarden of preferenties van de patiënt (i.e. de beslissing is preferentiegevoelig). Daarom is het van belang dat de waarden van de patiënt worden meegenomen in de beslissing over FP, en dat patiënten actief meebeslissen met hun arts. Hiervoor is van belang dat een patiënt over kwalitatief goede informatie beschikt en in staat is haar eigen waarden en voorkeuren te overzien en deze te communiceren naar de arts. Een instrument dat hier mogelijk bij kan helpen is een keuzehulp. Keuzehulpen kunnen bijvoorbeeld folders, boekjes, Cd-roms of websites zijn, die informatie bevatten over het medische probleem, mogelijke behandelopties (inclusief niets doen), risico's en onzekerheden en een gebalanceerd overzicht van de voor- en nadelen van de mogelijke behandelopties. In het verbeteren van de informatievoorziening over FP kan een online keuzehulp mogelijk uitkomst bieden.

Deel I: Ontwikkeling van een keuzehulp over fertiliteitspreservatie

Het eerste deel van dit proefschrift (*hoofdstuk 2, 3, 4*) bestaat uit studies met betrekking tot de ontwikkeling van een keuzehulp over FP. Eerst hebben wij in kaart gebracht waar patiënten het meest behoefte aan hebben met betrekking tot informatievoorziening over FP (*hoofdstuk 2*), vervolgens hebben wij een keuzehulp ontwikkeld (*hoofdstuk 3*) en hebben wij onderzocht hoe de procedure van informeren van patiënten met deze keuzehulp vorm moet hebben in de klinische praktijk, en hoe het veld ertegenover staat (*hoofdstuk 4*).

Hoofdstuk 2 beschrijft de resultaten van een studie naar de behoeften met betrekking tot de (procedure van) informatievoorziening over FP, van (borst)kankerpatiënten die een beslissing over FP moesten nemen in de jaren dat er nog geen extra informatievoorziening was. Hoewel patiënten over het algemeen aangaven tevreden te zijn met de informatie die ze gekregen hadden, was deze niet altijd op tijd, klopte de informatie niet altijd en was de communicatie tussen ziekenhuizen en artsen onderling vaak slecht. Patiënten hadden het gevoel assertief te moeten zijn om alle relevante informatie te krijgen. Een aanbeveling die werd gedaan om de informatievoorziening voor toekomstige patiënten te verbeteren was bijvoorbeeld om informatiematerialen te ontwikkelen die patiënten zelf thuis konden lezen. En zo geschiede. We besloten een online keuzehulp te ontwikkelen die patiënten vanaf elke locatie, op elk gewenst tijdstip zouden kunnen gebruiken.

Hoofdstuk 3 beschrijft de ontwikkeling van deze online keuzehulp met alle daarbij behorende stappen (fasen). De *eerste fase* was de ontwikkeling van de keuzehulp zelf. De keuzehulp is ontwikkeld volgens de International Patient Decision Aid Standards (IPDAS) criteria voor evaluatie van ontwikkeling van keuzehulpen en bestaat enerzijds uit tekstuele informatie (aangevuld met illustraties) en anderzijds uit een expliciete waarden elicitatie oefening. De tekstuele informatie is geschreven door een multidisciplinair team van clinici, onderzoekers, website ontwikkelaars en tekstschrijvers. De waarden elicitatie oefening is ontwikkeld in overeenstemming met literatuur en bevindingen van anderen. In de *tweede fase*, toen een concept versie van de keuzehulp klaar was, is deze voorgelegd aan patiënten die eerder voor de beslissing hadden gestaan om wel of geen FP behandeling te ondergaan. Men verwelkomde het initiatief en waardeerde de keuzehulp zelf. De tekst werd grotendeels als helder en zinvol ervaren, hoewel de hoeveelheid door sommigen als te veel en door anderen als te weinig werd ervaren. Door middel van duidelijke kopjes en verwijzingen naar andere bronnen hebben we geprobeerd voor iedereen de juiste hoeveelheid informatie te geven. De waarden elicitatie oefening vond men enigszins verwarrend, dus met behulp van aanwijzingen van patiënten is deze aangepast. In de *derde fase* hebben we deze aangepaste versie vervolgens voorgelegd aan lager en hoger opgeleide gezonde vrouwen om te toetsen in hoeverre de kennis over FP toenam na het bekijken van de keuzehulp. Beide groepen hadden inderdaad significant meer kennis na het zien van de keuzehulp. Een laatste stap was, als deel van de Delphi studie uit *Hoofdstuk 4*, te kijken of een groep van patiënten, artsen en verpleegkundigen het eens kon worden over het antwoord op de vraag of de keuzehulp in zijn huidige vorm acceptabel was als informatiebron voor jonge vrouwen met borstkanker (met betrekking tot de inhoud, vormgeving en lay-out). Omdat dit het geval bleek kon de keuzehulp vanaf dat moment in zijn huidige vorm worden uitgereikt aan nieuw gediagnosticeerde borstkanker patiënten die voor de keuze staan om wel of geen FP behandeling te ondergaan.

Hoofdstuk 4 beschrijft een pre-implementatie studie, waarin met behulp van een zogeheten Delphi expert panel werd geprobeerd consensus te bereiken over de procedure waarmee de keuzehulp ingezet kon worden om patiënten te informeren (wanneer wordt de keuzehulp gebruikt, door wie wordt deze uitgereikt en aan welke patiënten?). Een dergelijke studie is belangrijk om barrières en faciliterende factoren voor de implementatie van een interventie (in dit geval de keuzehulp) te achterhalen en de optimale procedure te bepalen om de implementatie zo soepel mogelijk te laten verlopen, maar ook om eindgebruikers al tijdens de ontwikkeling te motiveren om een interventie te gaan gebruiken. Naar aanleiding van resultaten van studies in andere landen verwachtten wij dat men terughoudend zou zijn met het aanbieden van informatie aan alle patiënten die in aanmerking kunnen komen voor FP (ongeacht leeftijd, geslacht, of men een partner heeft, seksuele geaardheid, ziektestadium) maar dit bleek niet het geval. Men was het er over eens dat alle patiënten, kort na hun diagnose ten minste algemene informatie zouden moeten krijgen over FP (onbelangrijk door wie). Op een later moment kunnen zij van een fertiliteitsexpert desgewenst meer gedetailleerde informatie krijgen over de mogelijkheden. Deze procedure moest zo veel mogelijk worden afgestemd op de individuele en situationele context van de patiënt, omdat deze sterk kan verschillen tussen patiënten. Maar, informatievoorziening over FP vond men hoe dan ook belangrijk, en men was gemotiveerd om de keuzehulp hiervoor te gaan gebruiken.

Deel II: Effectiviteit van de keuzehulp

Met het tot stand komen van de keuzehulp, de positieve effecten van de keuzehulp op kennis en de acceptatie door het veld werd het van belang om te onderzoeken wat de meerwaarde van de waarden elicitatie oefening (values clarification exercise; VCE) is in de keuzehulp, en of de keuzehulp ook effectief is met betrekking tot kennis en belissingsambivalentie in patiënten die echt voor de beslissing staan om wel of geen FP te ondergaan. Het tweede deel van dit proefschrift (*hoofdstuk 5, 6, 7*) bestaat daarom uit experimenten met gezonde jonge vrouwen (*hoofdstuk 5*) en met jonge borstkanker patiënten (*hoofdstuk 7*), en een observationele studie met gezonde vrouwen en patiënten (*hoofdstuk 6*).

Hoofdstuk 5 beschrijft twee experimenten die zijn uitgevoerd met gezonde jonge vrouwen wie gevraagd werd een hypothetische beslissing over FP te nemen. Met het eerste experiment wilden wij onderzoeken wat het effect van de VCE in de keuzehulp was op kennis over FP en besluitvormingsambivalentie. Dit deden wij door een groep vrouwelijke studenten te randomiseren voor a) een keuzehulp met alleen informatie of b) een keuzehulp met informatie én met VCE. De tekstuele informatie in de twee versies van de keuzehulp was hetzelfde. De studenten kregen een script te lezen waarmee zij zich moesten proberen in te leven in de situatie dat zij de diagnose borstkanker zouden krijgen en daarvoor chemotherapie moesten ondergaan met mogelijk negatieve gevolgen voor hun vruchtbaarheid. De arts vertelt hen vervolgens over FP mogelijkheden voorafgaand aan de behandeling en verwijst ze door naar de keuzehulp om hier meer over te lezen en een beslissing te nemen. Deelnemers kregen op dat moment een link naar een van de twee typen keuzehulpen en hen werd gevraagd om een (hypothetische) beslissing te nemen. Uit de studie bleek dat de deelnemers in beide groepen na het zien van de keuzehulp meer kennis hadden over FP ten opzichte van ervoor. De toename van kennis verschilde niet tussen beide groepen. Slechts een minderheid van de deelnemers in de groep met een keuzehulp mét VCE bekeek de VCE, maar de deelnemers in deze groep die de VCE gebruikten hadden minder beslissingsambivalentie dan de deelnemers die geen gebruik maakten van de VCE (deze deelnemers bekeken alleen de pagina's met tekst). Echter, interessant was dat er geen verschillen in beslissingsambivalentie waren tussen deelnemers die de VCE gebruikten en deelnemers die de VCE niet gebruikten omdat dit niet mogelijk was (de groep die een keuzehulp met alleen informatie kreeg). Mogelijk waren er bepaalde (persoonlijkheids)kenmerken of informatie zoekstijlen van de deelnemers die ervoor zorgden dat men wel of geen gebruik maakte van de VCE en in welke mate, en die (mede) bepalend waren voor de effectiviteit van de VCE. Om deze hypothese te toetsen voerden wij een tweede experiment uit waarin we naast keuzehulp- en VCE-gebruik, ook persoonlijkheidskenmerken en stijl van informatie zoeken van de deelnemers onderzochten. Wederom randomiseerden wij gezonde proefpersonen tussen a) een keuzehulp met alleen informatie en b) een keuzehulp met informatie en een VCE, maar we voegden ook een derde groep toe c) die een keuzehulp met informatie en een VCE kreeg en actief werd verzocht de VCE te gebruiken. Uit dit tweede experiment bleek dat verwijzing naar de VCE zorgde voor meer VCE gebruik, maar dat geen van de persoonlijkheidskenmerken samenhing met VCE gebruik. Wel vonden wij wat betreft keuzehulpgebruik in het algemeen een associatie tussen een meer “blunter” type (informatie ontwijkend, angstig voor grote hoeveelheden informatie), het bekijken van minder pagina’s en het minder lang bezig zijn met de keuzehulp. Wat betreft uitkomsten gerelateerd aan beslissingsambivalentie vonden wij dat neurotischere vrouwen zich onzekerder en minder gesteund voelden in het beslissen en dat consciëntieuzere vrouwen zich zekerder voelden bij het beslissen. Hoewel de associaties zwak waren, suggereren de resultaten van deze twee studies dat er mogelijk wel een rol is voor persoonlijkheidskenmerken in het gebruik van keuzehulpen en het effect daarvan op besluitvormingsambivalentie. Dit is een interessant aanknopingspunt voor vervolg onderzoek.

Hoofdstuk 6 beschrijft de validatie van de Voortplanting Bezorgdheid Schaal (VBS), een meetinstrument (vragenlijst) dat meet in welke mate patiënten bezorgd zijn over hun vruchtbaarheid. Deze vragenlijst was ontwikkeld als Engelstalige vragenlijst en is vertaald naar het Nederlands waarna de psychometrische eigenschappen van deze Nederlandse versie in drie groepen Nederlandse vrouwen konden worden onderzocht. Deelnemers waren borstkanker patiënten, vrouwen met vruchtbaarheidsproblemen en gezonde vrouwen; allen in de vruchtbare leeftijd (18-40 jaar oud). De factorstructuur van de vragenlijst in een Nederlands populatie bestond uit 1 factor waarop 11 van de 14 items uit de vragenlijst laadden, met goede betrouwbaarheid (Cronbach’s alfa= *.87*). De totale score op deze 11 VBS items geeft de mate weer waarin iemand zich zorgen maakt over de vruchtbaarheid. Met deze VBS totaalscore kon goed onderscheid worden gemaakt tussen de drie groepen vrouwen (‘known groups’ construct validiteit); vrouwen met vruchtbaarheidsproblemen maakten zich het meest zorgen, gevolgd door borstkanker patiënten, en gezonde vrouwen het minst. Verder waren zorgen over de vruchtbaarheid positief gerelateerd aan vergelijkbare constructen zoals angst, depressie, en hulpeloosheid met betrekking tot het vruchtbaarheidsprobleem en negatief gecorreleerd aan acceptatie van het vruchtbaarheidsprobleem (construct validiteit). Als laatste, kon een tweede meting aantonen dat de mate van zorgen die de vrouwen ervaarden stabiel was op korte termijn (test-hertest betrouwbaarheid). Wij concludeerden, dat de Nederlandse VBS een valide en betrouwbare vragenlijst is om zorgen te meten in een Nederlandse populatie van borstkanker patiënten of vrouwen met vruchtbaarheidsproblemen en daarom gebruikt kan worden voor wetenschappelijk onderzoek. In ons geval betekende dit dat de vragenlijst kon worden gebruikt als een van de uitkomstmaten in de effect evaluatie van de keuzehulp met borstkankerpatiënten (*Hoofdstuk 7*).

Hoofdstuk 7 beschrijft het effect van de keuzehulp (in combinatie met folders) over FP in een populatie van nieuw gediagnosticeerde borstkanker patiënten. Hoewel meer dan 26 Medische Centra patiënten wierven voor deze studie, hebben we slechts 26 patiënten kunnen randomiseren in anderhalf jaar tijd. Dertien patiënten werden gerandomiseerd in de keuzehulp groep, en 13 in de foldergroep. Omdat de folders tevens vrij beschikbaar waren in de centra en op internet, konden patiënten in de keuzehulp groep van beide informatiebronnen gebruik maken. Daarom is tevens een groep van 10 patiënten benaderd die behandeld waren voor borstkanker in de periode dat nog geen schriftelijke informatie voorhanden was en die dus alleen mondelinge informatie gekregen hadden over FP. Met name dankzij deze laatste groep konden we enkele interessante conclusies trekken. In een vergelijking tussen vrouwen die óf folders kregen óf een keuzehulp (en folders) bleek dat beide groepen patiënten meer kennis hadden na het zien van de informatie, maar dat men in de keuzehulpgroep enigszins meer besluitvormingsambivalentie had.

Vergeleken met vrouwen die alleen mondelinge informatie kregen hadden beide groepen echter meer kennis en het gevoel meer gesteund te zijn in de beslissing. Deze resultaten suggereren dat beide informatiebronnen effectief zijn met betrekking tot het informeren van patiënten, maar dat de keuzehulp mogelijk tot iets meer beslissingsambivalentie leidt dan alleen informatiefolders.

Algemene discussie

Uit de studies die zijn uitgevoerd ten behoeve van dit proefschrift, bleek de noodzaak om de informatievoorziening over FP te verbeteren (*hoofdstuk 2*), de acceptatie van de daarvoor ontwikkelde keuzehulp met VCE onder patiënten en clinici (*hoofdstuk 3, hoofdstuk 4*), en het effect van de keuzehulp met betrekking tot kennis toename van de gebruikers (*hoofdstuk 3, hoofdstuk 5, hoofdstuk 7*). Echter, wanneer de keuzehulp werd vergeleken met informatiefolders over FP, bleken beiden te zorgen voor kennistoename en voor de perceptie gesteund te zijn in het beslissen. Daarnaast bleek de keuzehulp te zorgen voor meer beslissingsambivalentie dan de folders alleen (*hoofdstuk 7*). De effecten van de VCE waren minder duidelijk; deze wisselden tussen de verschillende studiepopulaties (*hoofdstuk 5, hoofdstuk 7*). Mogelijk hangt het effect van de VCE samen met persoonlijkheidskenmerken of informatie zoekstijlen (*hoofdstuk 5*).

Op basis van de hierboven genoemde resultaten komen twee thema's naar voren die verdere discussie behoeven. Allereerst kunnen we ons afvragen wat de toegevoegde waarde van een keuzehulp (in aanvulling op folders) is bij beslissingen over FP, omdat de effecten van de keuzehulp op kennis en beslissingsambivalentie niet beter waren dan van gewone informatie folders (zie: *de zin en onzin van een keuzehulp over FP*). Ten tweede kan ter discussie worden gesteld wat in het algemeen de waarde is van VCEs om te helpen bij het beslissen, gezien zowel de hierboven beschreven ambivalente resultaten met betrekking tot effectiviteit van de VCE in een keuzehulp over FP, als ook ambivalente resultaten in andere onderzoeken (zie: *de waarden van waarden elicitatie methoden*).

De zin en onzin van een keuzehulp over fertiliteitspreservatie

Hoewel onderzoek heeft aangetoond dat keuzehulpen voor veel preferentie-gevoelige beslissingen effectief kunnen zijn bij het helpen beslissen, lijkt dit voor de beslissing over FP misschien niet op te gaan. Immers, besluitvormingsambivalentie was hoger in patiënten die een keuzehulp gebruikten dan patiënten die alleen folders gebruikten. Hoewel enigszins verhoogde besluitvormingsambivalentie ook kan betekenen dat patiënten zich de beslissing aantrekken (wat logisch is) en er actief mee bezig zijn (wat klopt in een keuzehulp met expliciete waarden elicitatie oefening) neigen we er toch naar deze bevinding te interpreteren als zijnde nadelig. In dat geval rijst de vraag waarom een keuzehulp niet zou werken bij de beslissing om wel of geen FP behandeling te ondergaan, waar dit wel het geval is bij beslissingen om wel of geen borstsparende operatie te ondergaan, of wel of niet te screenen voor allerlei vormen van kanker? Verklaringen hiervoor kunnen we zoeken in 1) aspecten van de beslissing over FP, 2) aspecten van deze keuzehulp (layout, content, de VCE), of in 3) aspecten van de keuzehulp-gebruikers (persoonlijkheid, informatie zoekgedrag, vaardigheid in het omgaan met medische informatie). Ten eerste is er voor sommige patiënten helemaal geen keuze te maken over FP, maar hangt de "keuze" vooral af van de situatie (hoeveel tijd er is voor aanvang van de oncologische behandeling, risico op uitzaaiïngen) en patiënt karakteristieken (leeftijd, of zij een partner hebben) die samenhangen met welke vormen van FP mogelijk zijn. Een keuzehulp biedt dan wellicht weinig uitkomst bij het helpen beslissen. Ten tweede zijn er karakteristieken van de keuzehulp die enerzijds al suggereren dat er een moeilijke beslissing genomen moet worden (lay out, content, aanwezigheid VCE) en anderzijds ook nog eens verwarring kunnen veroorzaken omdat ze suggereren dat alle opties mogelijk zijn, terwijl dat voor veel patiënten niet het geval is (zie punt 1). Hoewel patiënten in de studies in dit proefschrift veel behoefte leken te hebben aan informatie over de FP opties, kan het zijn dat niet alle patiënten (afhankelijk van persoonlijkheid) behoefte hebben aan alle informatie om te beslissen, en dat anderen juist anders gaan beslissen of twijfelen als zij (te) veel informatie krijgen. Het hebben van een keus is goed, maar te veel keus of teveel opties om uit te kiezen is niet altijd wenselijk, aldus de “keuze paradox” (Barry Schwarz, The paradox of choice, why more is less; 2004). Dit heeft ook weer te maken met verschillen in informatiebehoefte en -zoekgedrag van patiënten, een derde verklaring waardoor een keuzehulp minder effectief zou kunnen zijn. Omdat niet alle patiënten identieke informatiebehoeften hebben en zij verschillend te werk gaan bij het zoeken naar informatie en het nemen van een beslissing is het mogelijk dat er niet één ideale informatiebron is voor alle patiënten, maar dat we informatie moeten afstemmen op de behoeften van patiënten. Ook de vaardigheid van patiënten in het omgaan met medische informatie kan meewegen in de effectiviteit van een keuzehulp. Gedacht wordt, dat mensen die minder vaardig zijn, meer baat hebben bij een keuzehulp. In de door ons uitgevoerde effect evaluatie met patiënten, waren de deelnemers relatief hoog opgeleid, waardoor de keuzehulp mogelijk minder effect had. Echter, meer (grootschalig) onderzoek is nodig naar de invloed van persoonlijkheid, informatie zoekstijl en vaardigheid in het omgaan met medische informatie op keuzehulpgebruik en effectiviteit.

De waarde van waarden elicitatie methoden

In dit proefschrift kon de waarde van een expliciete additieve waarden elicitatie oefening niet met zekerheid worden vastgesteld. Ook andere onderzoeken tonen ambivalente bevindingen aangaande waarden elicitatie methoden (values clarification methods; VCM). Men is er nog niet over uit hoe we waarden het best kunnen verhelderen en in hoeverre VCM daar aan bijdragen. In de literatuur wordt de discussie gevoerd of waarden verheldering een bewust proces moet zijn of meer door intuïtie gestuurd moet worden, of beiden. Een VCE zoals in de keuzehulp over FP suggereert een bewust proces, wat mogelijk belangrijke intuïtieve gevoelens negeert. Mogelijk moeten we zoeken naar een combinatie van beide processen. Op dit moment zijn er wel criteria waar het ontwerp van VCM aan moet voldoen, maar is niet helder wat de werkzame elementen in VCM zijn en in welke situaties deze werken. Op dit gebied is daarom nog veel onderzoek nodig. Het mysterie rond de werkzaamheid van VCM is nog altijd niet opgelost.

Conclusie

Uit de resultaten van dit proefschrift kunnen we concluderen dat het verbeteren van de informatievoorziening over FP als belangrijk werd ervaren door patiënten en clinici en dat de ontwikkelde informatiebronnen gewaardeerd werden. De keuzehulp leidde zowel in gezonde deelnemers als (nieuw gediagnosticeerde) borstkanker patiënten tot meer kennis over FP. Over de effectiviteit van de keuzehulp met betrekking tot beslissingsambivalentie is op basis van het kleine aantal deelnemers nog weinig te zeggen, maar de data suggereerde enigszins verhoogde beslissingsambivalentie bij patiënten die de keuzehulp kregen vergeleken met patiënten die alleen folders kregen. De beste methode om waarden van patiënten te verhelderen is nog altijd onduidelijk. Echter, omdat een geïnformeerde patiënt de eerste stap is in de richting van het verhelderen van waarden en van gezamenlijke besluitvorming tussen arts en patiënt, kunnen zowel de keuzehulp als informatiefolders gebruikt worden als informatiebron. Er moet dan nog wel worden onderzocht wat het effect van de informatie op het consult en de besluitvorming daarbinnen is en wat het effect van de VCE is in een grotere populatie.

Met betrekking tot de procedure van de informatievoorziening naar patiënten is het belangrijk dat clinici meer kennis hebben over de mogelijkheden van FP en het onderwerp steevast aan de orde stellen bij jonge patiënten. Omdat informatie zoekgedrag en informatiebehoefte kunnen verschillen tussen patiënten met verschillende persoonlijkheids- en situationele kenmerken (of zij een partner hebben, leeftijd, ziekte stadium) is het belangrijk om zowel de informatie als de timing zoveel mogelijk af te stemmen op de patiënt.

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Publications

Curriculum Vitae

Mirjam Marjolein Garvelink werd op 27 Oktober 1986 geboren in Zoeterwoude-dorp. In 2005 behaalde zij haar VWO-diploma aan het Vlietland College te Leiden en startte zij haar studie Gezondheidswetenschappen aan de Vrije Universiteit in Amsterdam. Tijdens haar studie verrichte zij onderzoeksstages bij de medische keuring van de Koninklijke Marine in Amsterdam en bij de afdeling Klinische Genetica van het VU Medisch Centrum. In 2008 behaalde zij haar Bachelor Gezondheidswetenschappen, in 2009 haar Master of Health Sciences in de richting Preventie en Volksgezondheid, met de keuzevakken Besliskunde en Genetica. Twee maanden later startte zij haar promotieonderzoek bij de afdelingen Gynaecologie en Medische Besliskunde van het Leids Universitair Medisch Centrum. De resultaten van dit onderzoek staan beschreven in dit proefschrift.

Tijdens haar onderzoek heeft zij verschillende nationale en internationale presentaties en posterpresentaties gegeven op congressen in en buiten Europa. In Nederland heeft zij scholing gegeven aan mammacare verpleegkundigen over fertiliteitspreservatie en besliskunde en werkgroepen van geneeskundestudenten begeleid over risicocommunicatie en besluitvorming. Parallel aan haar onderzoek heeft zij een epidemiologie-traject gevolgd, waarmee zij haar registratie voor epidemioloog A heeft kunnen behalen. Tevens heeft zij van 2010-2011 in het bestuur gezeten van het Leids Promovendi Overleg (LEO). Sinds 2012 is zij inhoudelijk betrokken bij de ontwikkeling van een educatieve applicatie (app) over fertiliteitspreservatie voor vrouwen, mannen en kinderen met kanker.

Op dit moment is zij ook betrokken bij de ontwikkeling van een keuzehulp voor Benigne Prostaat Hyperplasie, in samenwerking met de afdeling Urologie van het St. Elisabeth Ziekenhuis te Tilburg. Daarnaast heeft zij een adviserende rol bij de implementatie en pilottesten van een “Diagnose Consult” (“time out”) in de oncologische zorg in Nederland, een initiatief van BeBright dat artsen en patiënten meer tijd geeft om een geschikte behandeling te vinden na een diagnose van kanker.

In Juli 2014 zal zij starten met een postdoctoraal fellowship onder supervisie van Prof. France Légaré, de Canada Research Chair in Implementation of Shared Decision Making in Primary Care, aan de Université de Laval, Quebec, Canada.

Publications

- Garvelink MM; ter Kuile MM; Fischer MJ; Louwé LA; Hilders CGJM; Kroep JR; Stiggelbout AM. Development of a decision aid about fertility preservation for women with breast cancer in the Netherlands. *J Psychosomatic Obstet Gyn*, 2013;34(4):170-8.
- Garvelink MM; Kuile MM ter; Bakker RM; Geense WJ ; Jenninga E (†); Louwé LA; Hilders CGJM ; Stiggelbout AM. Women's experiences with information provision and deciding about fertility preservation: "satisfaction in general, but unmet needs". *Health Expectations*, in press 2013.
- Engelhard EG; Garvelink MM; de Haes HJCM; van der Hoeven JJM; Smets EM; Pieterse AH; Stiggelbout AM. Predicting and communicating the risk of recurrence and death in women with early-1 stage breast cancer: a systematic review of risk prediction models. *J Clinical Oncology*, 2014;32(3):238-50.
- Garvelink MM; ter Kuile MM; Hilders CGJM; Stiggelbout AM; Louwé LA.[Fertility preservation before chemotherapy] Fertiliteitspreservatie voor chemotherapie. *NedTijdschr Oncol* 2013; 10: 97-104.
- Garvelink, MM; Kuile, MM ter; Louwé, LA ; Hilders, CGJM; Stiggelbout, AM . A Delphi Consensus study among patients and clinicians in the Netherlands on the procedure of informing young women about Fertility Preservation. *Acta Oncol* 2012; 51(8): 1062-69.
- Garvelink MM; ter Kuile MM; Louwé LA; Fischer MJ; Hilders CGJM ; Stiggelbout AM. Effect evaluation of a Decision Aid for Fertility Preservation in Women with Breast Cancer; a Randomized Controlled Trial in the Netherlands (KEEP studie). *Ned Tijdschr Oncol 2012;9:283-5.*
- Dommering CJ; Garvelink MM; Moll AC; van Dijk J; Imhof SM; Meijers-Heijboer H, et al. Reproductive behavior of individuals with increased risk of having a child with retinoblastoma. *Clin Genet* 2012;81(3):216-23.

Submitted

- Garvelink MM; ter Kuile MM; Louwé LA; Hilders CGJM; Stiggelbout AM. Additional value of decision aids in complex clinical situations. Effectiveness of a decision aid about Fertility Preservation.
- Garvelink MM; ter Kuile MM; Louwé LA; Hilders CGJM; Stiggelbout AM. Psychometric properties of the Reproductive Concerns Scale in three populations of women.
- Garvelink MM; ter Kuile MM; Stiggelbout AM; de Vries M. Values Clarification in a decision aid about fertility preservation: does it add to information provision? Two randomized experiments with healthy participants.

Oral presentations at conferences

- Garvelink, MM; ter Kuile, MM; Louwé, LA; Hilders, GJM; Stiggelbout, AM. Pilot study of a decision aid about fertility preservation for breast cancer patients. International society for Fertility Preservation (ISFP), 7-9 November 2013, Valencia, Spain.

- Garvelink, MM; ter Kuile, MM; Stiggelbout, AM; de Vries, M. Values Clarification in a decision aid about fertility preservation: does it add to information? International Shared Decision Making conference (ISDM), June 2013, Lima, Peru.
- Garvelink, MM. [Fertility preservation and decision making] Mammacare conference, 04-02-2013, Ede, the Netherlands.
- Garvelink, MM; ter Kuile, MM; Stiggelbout, AM. The association between reproductive concerns and psychological functioning of women with Breast Cancer, women with fertility problems and healthy women. EORTC conference October 2012, Brussels, Belgium.
- Garvelink, MM. Fertility Preservation, the patient's view. National fertility preservation conference 15-12-2012, Oegstgeest, the Netherlands
- Garvelink, MM. The importance of information provision and decision making support in deciding about fertility preservation, Netherlands Network Fertility preservation (NNF)-scientific meeting, 09-11-2012 Radboud University, Nijmegen, the Netherlands.

Dankwoord

Gratitude is my attitude (C.G.J.M. Hilders, TedXWomen, Amsterdam, 2011). Natuurlijk is dit *mijn* proefschrift, maar ik heb het niet alleen gedaan. Daarom wil ik de volgende mensen bedanken voor hun bijdrage, bewust of onbewust, aan dit proefschrift.

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