

**TOWARDS IMPLEMENTATION
OF HIGH-QUALITY
FEMALE ONCOFERTILITY CARE**



MICHELLE VAN DEN BERG

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For reasons of consistency within this thesis, some terms have been standardized throughout the text. As a consequence, the text may differ from the articles that have been published.

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Promotor

Prof. dr. D.D.M. Braat

Copromotoren

Dr. R.P.M.G. Hermens

Dr. C.C.M. Beerendonk

Manuscriptcommissie

Prof. dr. H.J. Bloemendal (voorzitter)

Prof. dr. M. Goddijn (Amsterdam UMC)

Prof. dr. G.D.E.M. van der Weijden (Universiteit Maastricht)

Paranimfen

G.C. van den Berg

L.M. Janssen

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1

GENERAL INTRODUCTION

INTRODUCTION

In this thesis, we focus on research regarding the implementation of high-quality oncofertility care for female cancer patients. Current clinical practice guidelines recommend discussing the potential loss of fertility with all female cancer patients and, if desired, offering a referral to and counselling by a reproductive gynaecologist before the start of cancer treatment. However, it is not known to what extent healthcare professionals adhere to these guidelines. Therefore, key recommendations in female oncofertility care, adherence to these recommendations, and barriers impeding oncological healthcare professionals from adhering to these recommendations are evaluated in this thesis. The development of strategies to improve guideline adherence is included as well.

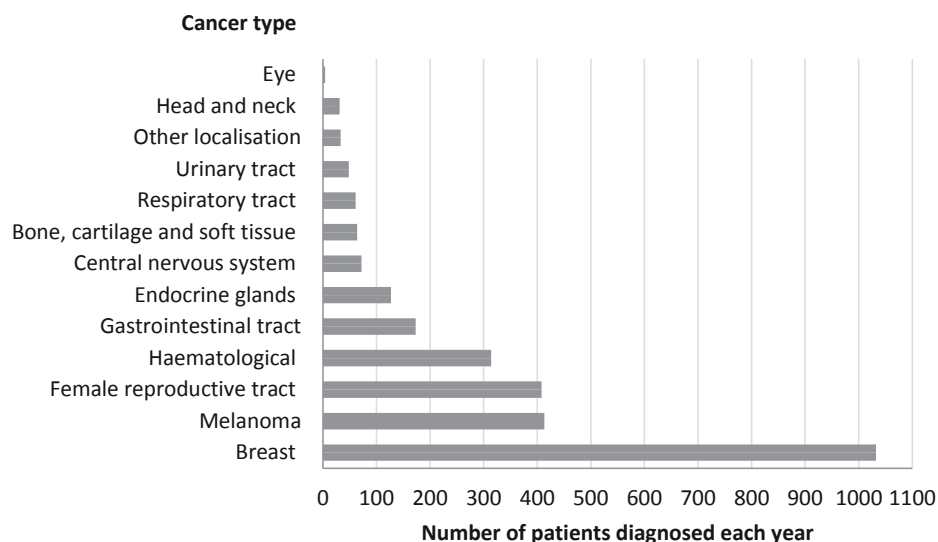
This chapter will start with information on the incidence of cancer in female adolescent and young adult patients, cancer treatments and (in)fertility, and current options to preserve fertility. Subsequently, guidelines in female oncofertility care are described, just as their implementation. Last, we outline the aims and content of this thesis.

Cancer in female adolescent and young adult patients

The incidence of cancer in adolescent and young adult females has been rising since the Dutch cancer registry started documenting cancer incidences (1). In the Netherlands, 2700-2800 adolescent and young adult females (18-40 years) are diagnosed with cancer each year. All types of cancer occur in adolescent and young adults, with incidences varying among cancer types. As shown in Figure 1, the most common cancer type in female adolescent and young adult cancer patients is breast cancer, followed by melanoma, female reproductive tract cancer and haematological cancer, with gastrointestinal tract cancer completing the top five. In addition, differences in incidences are also seen among different ages. For example, breast cancer incidence rapidly increases with age, while haematological cancer incidence is relatively stable at all ages.

Cancer treatments and (in)fertility

Over the past decades, improvements in the quality of cancer treatment have resulted in higher rates of cancer survival in young female patients (2, 3). Therefore, the importance of addressing the late side effects of cancer treatments and long-term quality of life issues has increased (4). One of the most undesirable side effects of cancer treatments in female adolescent and young adult cancer patients is the potential loss of fertility.

Figure 1. Incidence of cancer types in female adolescent and young adult cancer patients in 2020

Fertility is clinically defined as the capacity to establish a clinical pregnancy (5). Cancer treatments like chemotherapy, radiation therapy, and gonadal surgery are gonadotoxic and can have a negative effect on fertility (6). Both chemotherapy and radiotherapy on the pelvis lead to a decrease in the number of primordial follicles. When the reduction in the primordial follicle pool is near complete, the patient becomes infertile shortly after treatment. When there is only a partial loss of primordial follicles, the patient is still fertile, however her reproductive lifespan could be reduced with infertility occurring in several years or even decades after completing treatment (7, 8).

The effect of chemotherapy and radiotherapy on fertility is dependent upon several factors: the type of chemotherapy, size and location of the radiation field, dose, patient's age and her pre-treatment fertility (9). For example, alkylating chemotherapeutics are associated with a higher risk of infertility than non-alkylating agents; an irradiation dose of 2 Gray results in a loss of more than 50% of the primordial follicle pool in the ovary; and a higher patient's age will result in a higher risk of infertility due to natural age-related fertility decline (10, 11).

Radiotherapy could not only damage fertility, but also uterine function by inducing vascular damage and loss of distensibility of the uterus. The extent of damage is dependent on the location and dose of irradiation. Pregnancies and deliveries are reported at a dose of < 40 Gray, however patients have a higher risk of miscarriages, premature delivery, and low birth weight babies (12).

Cancer treatments requiring gonadal surgery, most commonly in female reproductive tract cancers, can have a direct effect on fertility and uterine function when ovaries, uterus and/or cervix are removed (13). In contrast to hormonal therapy, which has an indirect effect, as this is prescribed for 5 to 10 years and patients face a natural age-related fertility decline. With regard to relative novel cancer treatments (targeted therapy and immunotherapy), little is known about their effect on fertility (14).

Fertility preservation options

To secure the possibility to conceive children for female adolescent and young adult cancer patients after surviving cancer, the following fertility preservation options are currently available: cryopreservation of oocytes and embryos, cryopreservation of ovarian tissue, and ovarian transposition. Some other options are only available for specific cancer types, for example use of GnRH agonists (ovarian suppression) in breast cancer, and fertility sparing surgery in female reproductive tract cancer. Each fertility preservation option has advantages and disadvantages. In addition, not all fertility preservation options are appropriate for all patients. Dependent on a patient's age, relationship status, cancer type, cancer treatment, prognosis, and time before the start of the cancer treatment, some options are more appropriate than others. Table 1 provides an overview of available fertility preservation options.

Guidelines in female oncofertility care

How oncofertility care for female cancer patients should be delivered, hence what high-quality oncofertility care is, is described in several evidence-based (inter)national clinical practice guidelines (9, 14-17). The Dutch multidisciplinary oncofertility guideline was developed and disseminated on the Dutch national oncology website and on the national guideline database in 2016, and was updated in 2020/2021 (14). Important domains in these guidelines are information provision, referral, fertility preservation counselling, and decision-making. All guidelines recommend discussing the potential loss of fertility with all female cancer patients and, if desired, offering a referral to and counselling by a reproductive gynaecologist. Furthermore, decision support and information about fertility issues related to cancer treatment should be provided, irrespective of a female cancer patient's reproductive age, parity, and disease type or severity (9, 14)

Table 1. Overview of available fertility preservation options

	Applicable in following cancer treatments	Appropriate for following patients	Main disadvantages
Cryopreservation of oocytes	Chemotherapy and radiotherapy	Adolescent and young adult patients When there is time before starting cancer treatment Patients who are medically fit for hormonal stimulation	Hormonal stimulation is required
Cryopreservation of embryos	Chemotherapy and radiotherapy	Patients who have a stable relationship with a male partner When there is time before starting cancer treatment Patients who are medically fit for hormonal stimulation	Hormonal stimulation is required When relationship ends, embryos cannot be used anymore
Cryopreservation of ovarian tissue	Chemotherapy and radiotherapy	Patients aged ≤ 35 years with a high risk of infertility Patients who are medically fit to undergo surgery	Risk of reintroducing metastases when tissue is transplanted
Ovarian transposition	Radiotherapy	Patients who receive pelvic irradiation Patients who are medically fit to undergo surgery	Possible ovarian metastases do not receive irradiation Risk that transposition is ineffective
Ovarian suppression	Chemotherapy	Patients with breast cancer	Symptoms of menopause
Fertility sparing surgery	Gonadal surgery	Patients with early stage female reproductive tract cancer	Possibly less safe than standard surgery

In order to make a decision whether or not to undergo a fertility preservation treatment, it is important to receive adequate fertility preservation counselling. Female adolescent and young adult cancer patients expressed a need to be informed about the effects of cancer treatment on their fertility and the fertility preservation options available (18-20). They also highlighted the need to obtain this information shortly after the cancer diagnosis and to receive fertility preservation counselling by a reproductive gynaecologist to be able to make a well-informed decision (19, 21).

Even if information on fertility risks and options is provided, decision-making regarding future fertility is very difficult and complex (22). Some patients even report the decision

the most difficult decision ever made, and almost as distressing as the battle with cancer itself (23-25). The decision has to be made in a very short time frame in a period with great emotional distress in which patients focus on surviving cancer and not on their future fertility. As a consequence, patients experience decisional conflict regarding this decision. Decisional conflict increases if patients are not referred for fertility preservation counselling, if patients did not obtain enough information on all fertility preservation options, and if patients did not feel supported during decision-making (26-29). Unfortunately, studies have shown that not all patients are informed on infertility risks and fertility preservation options and patients have reported unmet information and support needs (29-37). This suboptimal oncofertility care affects female cancer patients' quality of life negatively, increases long-term regret and increases concerns regarding fertility (24, 38-41). Therefore, it is important that female cancer patients are well-informed and supported in fertility preservation decision-making (19, 42, 43). At this moment, it is not known to what extent Dutch healthcare professionals adhere to recommendations in the guidelines.

A way to improve information provision and support within the oncofertility process may be the assignment of patient navigators (44-46). Patient navigators fulfil the role of patient advocates for cancer patients; they provide additional information about medical procedures, help patients schedule appointments, and navigate and support patients through the process (47, 48). Initial results in oncology care indicate that the use of these patients navigators improves satisfaction in female adolescent and young adult cancer patients during their process (44-46). However, these patient navigators are currently not available at the fertility department where patients receive their fertility preservation consultation and treatment.

Another way to support female adolescent and young adult cancer patients in this complex decision-making and to decrease their decisional conflict, may be the provision of a decision aid. A recent study reviewed and evaluated nine fertility preservation decision aids (49). The decision aids significantly increased fertility preservation knowledge and decreased decisional conflict. Furthermore, they were found to be helpful, contained relevant information, and patients reported a high level of satisfaction with their use. Only three of these nine DAs are currently available for female cancer patients; one for breast cancer patients, in English, and two not specific to any cancer type, in Portuguese and in German (18, 50, 51). However, tailoring information to a patient's individual situation has also shown to be very important to be able to make high-quality decisions (52, 53). Decision aids that personalize information are not available yet.

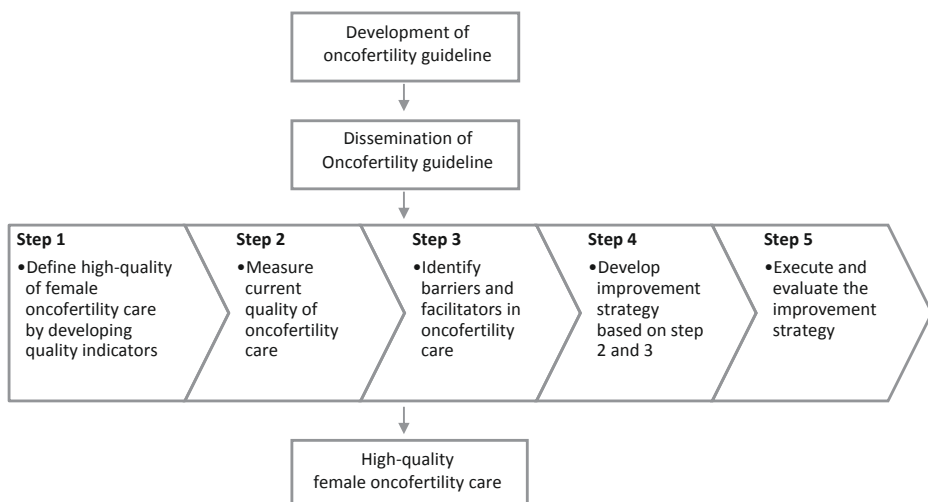
Unfortunately, development and dissemination of guidelines does not guarantee their implementation in daily clinical practice (54, 55). Studies have shown that this is also the case for guidelines in female oncofertility care, with not all patients receiving information about infertility risks and fertility preservation options, and not all patients, if desired, being referred for fertility preservation counselling (30-37). This suboptimal guideline adherence leads to practice variation and subsequently to a suboptimal quality of oncofertility care (56). Suboptimal quality of female oncofertility care contributes to higher levels of reproductive concerns, long-term regret and a lower quality of life in female cancer survivors (38, 40, 41, 57). Therefore, it is important to improve guideline adherence to provide a better quality of life in female cancer survivors.

At this moment, it is not known what the exact definition of high-quality oncofertility care is, to what extent high-quality oncofertility care is implemented, and which barriers impede this implementation. This thesis focuses on these gaps in knowledge.

Implementation of high-quality female oncofertility care

Improving guideline adherence and guideline implementation is very complex. Grol and Wensing developed a model to implement change in clinical practice (58). This model consists of several steps that should be followed to improve the quality of care. This model, adapted to the implementation of the female oncofertility care guideline, is shown in Figure 2.

Figure 2. Model to implement change in female oncofertility care



The first step is to define high-quality of care. Defining high-quality of care could be done by developing quality indicators that are based on evidence-based guidelines. Quality indicators are defined as 'measurable elements of practice performance for which there is evidence or consensus that it can be used to assess the quality, and hence change in the quality of care provided' (59). These quality indicators can detect potential problems in the current care, which then can be investigated, corrected and monitored (60). Their development would be a valuable step towards implementing oncofertility care as these indicators are currently not available.

The second step in improving guideline adherence is to systematically measure current quality of care with the developed quality indicators. Although studies have shown that guideline adherence is suboptimal, most studies did not assess the quality of care systematically (30-34, 37, 61). They reported the number of fertility discussions and referrals based on self-reported practices by healthcare providers or medical record documentation. Both methods have limitations. Regarding self-report: healthcare providers might overestimate their performance and thus a self-report bias should be taken into account (62). Regarding medical record documentation: disparity between discussions and documentation exists varying from 4% to 23% (63, 64).

Within the third step, barriers and facilitators in delivering high-quality care should be identified among healthcare professionals and patients. Reported barriers in international literature impeding oncological healthcare providers from discussing infertility risks and fertility preservation options are as follows: a lack of time, knowledge, or resources; a need for immediate cancer therapy; perceived poor success rates of fertility preservation options; poor patient prognosis; and patient characteristics (e.g. higher age and parity) (32, 53, 65-67). However, most of these studies have been performed in countries where financial aspects also play a key role in professionals' decisions to inform and refer a patient for fertility preservation counselling (32, 68, 69). In the Netherlands, cancer care and fertility preservation options are reimbursed by standard health care insurance or paid for by funds of academic hospitals. So, information about barriers and improvement suggestions in a setting where financial aspects do not play a role is still lacking.

Based on the results from step 2 and 3, a tailored improvement strategy can be developed in step 4. In the last step, the improvement strategy can be disseminated and implemented into daily practice where after a thorough evaluation should be conducted. At this moment, some improvement strategies have already been implemented and studied, although without a thorough analysis of all aspects of current quality of female oncofertility care. Therefore, their efficacy is unclear (44, 70, 71).

Aim and outline of this thesis

The main aim of this thesis is to study the implementation of high-quality oncofertility care for female adolescent and young adult cancer patients. Furthermore, special attention is paid to the evidence based development of tools to support patients in their oncofertility decision-making process. Within this thesis, the following research questions are addressed:

1. Which key recommendations, extracted from evidence-based guidelines, are most important to measure high-quality female oncofertility care, according to a multidisciplinary expert panel? (Chapter 2)
2. What is the current quality of female oncofertility care in the Netherlands measured with quality indicators, defined by key recommendations for high-quality oncofertility care? (Chapter 3)
3. Which determinants influence the current adherence to high-quality female oncofertility care? (Chapter 3)
4. To what extent is quality of female oncofertility care, measured with quality indicators, associated with quality of life, decisional conflict, decision regret, and reproductive concerns in female cancer survivors? (Chapter 4)
5. Which determinants influence quality of life, decisional conflict, decision regret, and reproductive concerns in female cancer survivors? (Chapter 4)
6. What are healthcare professionals' barriers and strategies for improving female oncofertility care? (Chapter 5)
7. What are patients' and professionals' experiences with the improvement strategy of implementing fertility navigators in female oncofertility care? (Chapter 6)
8. How can an online fertility preservation decision aid tailored to cancer type and treatments be systematically developed, and what are female cancer patients' experiences with its use? (Chapter 7)

Outline

In **Chapter 2**, we select key recommendations for high-quality female oncofertility care based on international clinical practice guidelines with a multidisciplinary expert panel. These key recommendations are transcribed into quality indicators and used as a tool to measure current adherence to high-quality female oncofertility care in the Netherlands in **Chapter 3**. Determinants of adherence are also studied in this chapter. Within **Chapter 4** we gain further insight into the association between current quality of female oncofertility care and quality of life, decisional conflict, decision regret, and reproductive concerns in female cancer survivors by means of a survey study. Furthermore, it is investigated which determinants influence quality of life, decisional conflict, decision regret, and reproductive concerns in this chapter.

Chapter 5 presents a qualitative study in which healthcare professionals are interviewed about barriers impeding them from adhering to the oncofertility guideline and about suggestions to improve oncofertility care. Thereafter, the results of an expert panel meeting with healthcare professionals and cancer survivors with the aim to select improvement strategies to overcome identified barriers and to improve oncofertility care are described. Two of the selected improvement strategies are further studied. The first selected improvement strategy is the implementation of fertility navigators in female oncofertility care to support female cancer patients in their oncofertility process. In **Chapter 6**, female cancer patients' and healthcare professionals' experiences with these fertility navigators (employed to support female cancer patients in their oncofertility process) are described. The second selected improvement strategy, the development and testing of a tailored online fertility preservation decision aid is described in **Chapter 7**. Aim of this decision aid is to inform and support female cancer patients in their decision-making process regarding future fertility. This thesis concludes with a general discussion in **Chapter 8**. A reflection on the results from the previous chapters is described and implications for future practice and research are made.

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2

KEY RECOMMENDATIONS FOR HIGH-QUALITY FEMALE ONCOFERTILITY CARE BASED ON INTERNATIONAL CLINICAL PRACTICE GUIDELINES

Ö. Baysal, M. van den Berg, F. Beldman, D.D.M. Braat,
W.L.D.M. Nelen, R.P.M.G. Hermens, C.C.M. Beerendonk

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ABSTRACT

Research question

Which guideline-based key recommendations can be selected for high quality female oncofertility care?

Design

The Delphi method was used to select a set of key recommendations for female oncofertility care. First, recommendations from (inter)national clinical practice guidelines were selected in four domains: risk communication, referral, counselling, and decision-making. Thereafter, they were scored, per domain, on their importance for high quality oncofertility care by a multidisciplinary, oncofertility expert panel, consisting of patients, referrers and counsellors, in two Delphi rounds. Finally, the selected key recommendations were presented for approval in a third round. Differences in perspectives between subgroups of the expert panel were analysed.

Results

A panel of 86 experts was asked to select key recommendations for high quality oncofertility care. Eleven key recommendations were selected. Key recommendations in the domains risk communication and referral focused on information provision and offering referral to a reproductive specialist to female cancer patients. Regarding the counselling domain, key recommendations focused on all aspects of counselling including different methods, safety, pros and cons. In the decision-making domain, key recommendations focused on shared decision-making and supporting the decision with written information. The final set of key recommendations was approved by 91% of the experts. Differences in perspectives were found between subgroups. In particular, patients found recommendations regarding decision-making and information provision more important.

Conclusion

A set of eleven key recommendations for high quality female oncofertility care was selected by a multidisciplinary expert panel. The involvement of patients', referrers' and counsellors' perspectives led to this valid, acceptable and credible set of key recommendations.

INTRODUCTION

The number of young adult cancer survivors is rising due to a rise in the incidence of malignant diseases combined with better survival rates due to more aggressive treatments (1, 2). However, one of the long term side effects of these more aggressive therapies in female patients is premature ovarian insufficiency leading to infertility (3). The possibility of treatment-related infertility can be the cause of concerns, worries and even depressive symptoms in young adult cancer survivors (4-6). To secure their possibility to conceive a biological child after gonadotoxic treatment, fertility preservation methods such as cryopreservation of embryo's, oocytes or ovarian tissue are available (3).

Fertility preservation counselling before starting cancer treatment increases quality of life after surviving cancer (7, 8). When fertility preservation counselling is unavailable or it does not meet informational needs, decisional conflict and regret regarding the patient's decision about fertility preservation occurs (7, 9). Therefore, internationally available clinical practice guidelines (CPGs) on oncofertility not only recommend timely referral of patients for fertility preservation counselling, but also provide tools to discuss the subject with patients (3, 10). Nevertheless, guideline adherence seems low, since studies not only found low fertility preservation counselling referral rates but also referral disparities (4, 11-13). Not adhering to evidence based guidelines leads to practice variation and subsequently to a suboptimal quality of care and quality of life in survivors (14). However, currently there is no tool available to evaluate the quality of female oncofertility care. Quality indicators for oncofertility care could be very helpful (15). A quality indicator is 'a measurable element of practice performance for which there is evidence or consensus that it can be used to assess the quality of care' (15). These quality indicators are able to detect potential problems in the current care, which then can be investigated, corrected and monitored (16). Previous studies encourage the involvement of both healthcare professionals and patients in selecting quality indicators, since they have different views regarding the best quality of care (17-19).

Therefore, the first aim of this study is to select a set of guideline-based key recommendations in order to translate these into quality indicators as an important first step to improve quality of female oncofertility care. The second aim is to identify differences in perspectives between patients and healthcare professionals regarding female oncofertility care.

MATERIALS AND METHODS

Design and participants

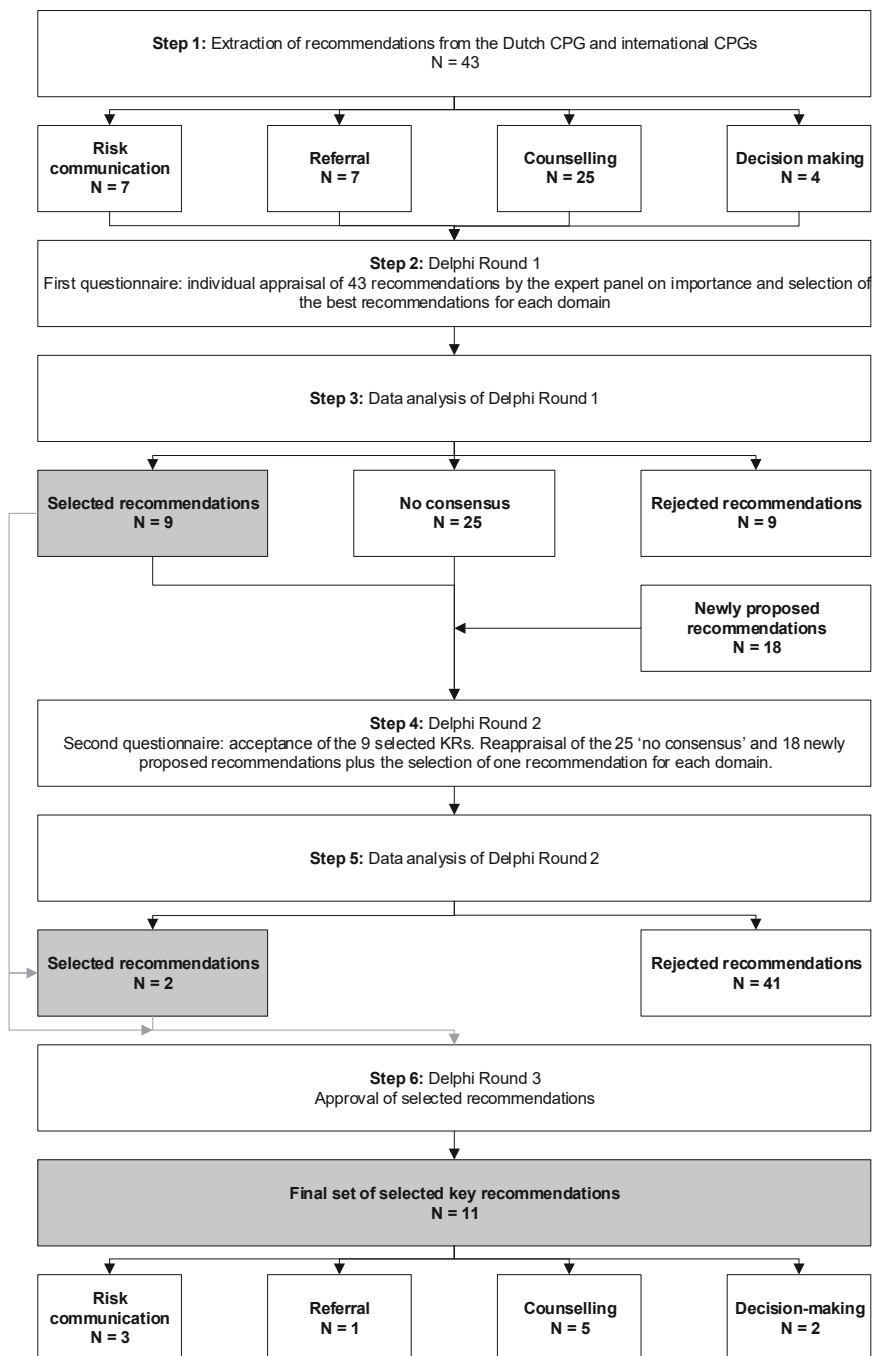
To select a set of key recommendations for female oncofertility care, the Delphi method was used (15, 20). The procedure consisted of three online questionnaires' rounds, in which a multidisciplinary, national panel of 86 oncofertility experts were asked to participate (15, 21). The expert panel consisted of three groups: (1) the 'referrers'; oncological healthcare providers treating women of reproductive age diagnosed with the three most commonly occurring malignancies (breast, haematological and gynaecological cancers); (2) the 'counsellors'; professionals (reproductive gynaecologists or residents with special interest in reproductive medicine) who have experience with fertility preservation counselling; and (3) adult female cancer survivors, recruited through Dutch patient associations. The online questionnaires were sent by SurveyMonkey® between March and June 2016. Approval for this study by an ethics committee was not required, in line with Dutch guidelines. Written consent was obtained from all participants.

Procedure for key recommendation selection

The key recommendation selection procedure was divided into six steps as shown in Figure 1: (1) inclusion of recommendations from CPGs; (2) first Delphi round in which the expert panel individually scored the recommendations; (3) analysis of the first round; (4) second Delphi round in which the expert panel could accept the selected key recommendations and score the 'no consensus' recommendations from the first Delphi round; (5) analysis of the second round; and (6) approval of the final set of selected key recommendations. The entire procedure was anonymous, and the experts were not aware of each other's selections.

Step 1: Inclusion of recommendations

It is important to select those recommendations that are crucial in a patient's care pathway to be able to assess the quality of female oncofertility care. Therefore, first recommendations from six international CPGs and the Dutch CPG were extracted without making any adjustments to the formulation of the recommendation (10, 22-27). These six international CPGs were appraised as high quality in a previous study from our research group by an international fertility preservation expert panel (28). In this study, an extended literature search was conducted to identify all international CPGs concerning female fertility preservation after which all CPGs were scored using the AGREE-II instrument (29). A 'high' methodological quality was defined as scoring 60% or more of the available points for 'Rigour of development' in the AGREE-II instrument.

Figure 1. Systematic Delphi method for the selection of key recommendations in female oncofertility care.

Thereafter, all extracted recommendations were reviewed individually by the authors to assess whether they met the inclusion criteria for expert panel assessment (Table 1). The recommendations on which no consensus was achieved after individual reviewing, were discussed in consultation with the research group. The remaining recommendations were checked for duplicates. In case of duplicates, the formulation of the Dutch recommendation was used. All included recommendations were divided into four domains, representing the fertility preservation pathway patients go through in chronological order (Figure 2): (1) Risk communication by the oncological healthcare provider, (2) Referral to a reproductive specialist for fertility preservation counselling and collaboration between oncological healthcare provider and reproductive specialist, (3) Fertility preservation counselling by a reproductive specialist, and (4) Decision-making by the patient. The ‘Counselling’ domain was divided into three sub-domains: methods of fertility preservation, preconditions of fertility preservation and discussion points in counselling meetings. These domains were consciously chosen, so that recommendations in the time frame from the moment of cancer diagnosis up until the decision whether a patient wants to undergo a fertility preservation treatment are included.

Table 1. In- and exclusion criteria for recommendations

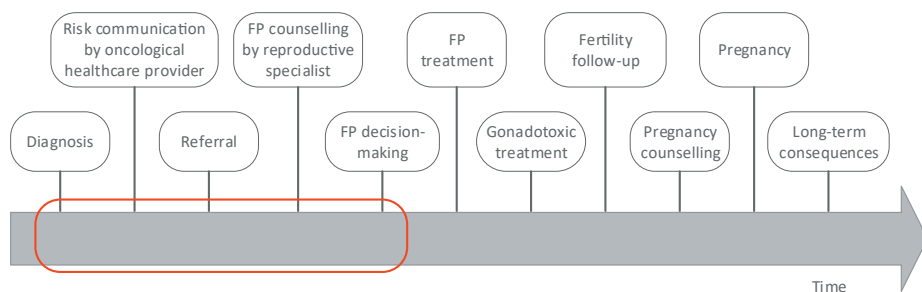
Inclusion criteria for recommendations to be selected	Exclusion criteria for recommendations to be rejected
Concerns fertility preservation care in adult women scheduled to undergo gonadotoxic treatment	Concerns fertility preservation care in men or children
Not specific for one cancer type	Concerns tumour specific counselling information
Applies to the care path selected for this study as shown in Figure 2	Refers to other parts of the care path than selected for this study as shown in Figure 2
	Concerns technical information on fertility preservation methods

Step 2: First Delphi round

The online questionnaire with the included recommendations, as written in the CPGs, was sent to the expert panel. The members were asked for their background characteristics and to rate each recommendation on its importance for assessing quality of female oncofertility care on a Likert scale of one (extremely unimportant) to nine (extremely important) (15, 20). Additionally, they were asked, per domain, to rank which recommendations they considered most important for assessing quality of female oncofertility care in order to differentiate between recommendations with a

high-Likert score (30). Finally, they were asked to add recommendations which, in their opinion, were missing in each domain.

Figure 2. Theoretic female oncofertility care pathway with the focus of this study indicated by the box



Step 3: Analysis of first Delphi round

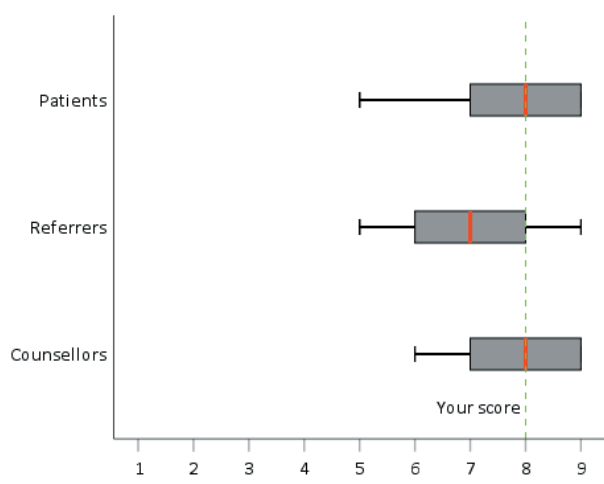
The results of the first Delphi round were analysed according to the predefined consensus criteria, which were based on the criteria previously described by Campbell et al. and the ranking method (16, 17, 19, 30, 31). The recommendations were considered valid and were selected if (1) the median Likert score was ≥ 8 , (2) there was panel agreement: 80% of the panel scored the recommendation in the highest tertile (7-9), and (3) the recommendation scored at least 40% of the maximum ranking score. Recommendations were rejected if the median Likert score was in the lowest tertile (1-3) and if 80% of the panel scored that recommendation in the lowest tertile or when the recommendation met none of the selection criteria (31). Recommendations that did not fall into either the 'selected' or 'rejected' groups were termed 'no consensus'. These 'no consensus' recommendations and the newly proposed recommendations that met inclusion criteria were presented again to the expert panel in the second Delphi round. Kruskal-Wallis and Mann-Whitney U tests were performed to identify potential differences in scoring behaviour between the three subgroups within the expert panel. Additionally, in order to analyse the added value of each subgroup, we excluded each subgroup one by one from the analysis and the change in either selection or rejection of each KR was considered. All data were analysed anonymously using SPSS Statistics (IBM corporation, version 25.0 for Windows).

Step 4: Second Delphi round

The second questionnaire was sent to all responders from the first round. First, the participants were informed about the selected recommendations from the first round. Second, the recommendations on which no consensus was reached, were presented again, and personalized feedback was given in the form of box-and-whiskers plots for

the three subgroups (example shown in Figure 3). Participants were instructed to review the results of the previous round and to score the 'no consensus recommendations' again. After review of each (sub-)domain, participants had the possibility to select one recommendation from the 'no consensus' group they would like to add to the selection of recommendations for each domain.

Figure 3. Example of box-and-whiskers plot of a recommendation presented to an expert in the second Delphi round



For each 'no consensus' recommendation, a personalized box-and-whiskers plot was presented to the expert in the second Delphi round. The expert was instructed to review the results of the previous round and to score the 'no consensus' recommendation again.

The dotted line represents the score given by the expert him or herself.

The box represents the 25th to 75th percentile of the subgroup score and the line represents the median score of the subgroup given to each recommendation.

Step 5: Analysis of second Delphi round

The results of the second Delphi round were analysed according to the same predefined consensus criteria as described in Step 3. All recommendations meeting these three criteria were selected for the final set of key recommendations. All other recommendations were rejected (31). As in the first round, additional analyses were performed to identify differences in perspectives between the three subgroups.

Step 6: Approval of the final set of key recommendations

The set of selected key recommendations was sent to all participants who were initially invited to participate in the first Delphi round. They were asked for their approval of the final selected set of key recommendations.

RESULTS

The results of the different steps are shown in Figure 1. In total, 43 recommendations were included for expert panel assessment (an overview of the recommendations is presented in Supplementary Table 1). The online questionnaire with the 43 included recommendations was sent to 86 experts (step 2). A total of 57 experts returned their questionnaires (66%). Response rates per group and characteristics of the expert panel are shown in Table 2.

Step 2 and 3: first Delphi round and analysis

Nine recommendations were selected as key recommendations, no consensus was achieved on 25 recommendations and nine recommendations were rejected. The experts suggested 47 new recommendations of which 17 met the inclusion criteria, and these were added to the second questionnaire (step 4). Analyses revealed significant differences in the scoring of 21 out of 43 recommendations between the three subgroups (Table 3). Of these recommendations, where a significant difference was seen between the subgroups, patients scored all recommendations in the decision-making domain and some of the recommendations on information provision higher. Counsellors scored recommendations in the referral and counselling domain higher and referrers scored higher on recommendations which recommend giving patients the opportunity to partake in counselling when cancer-related factors are taken into account. Eight of these 21 recommendations were selected as key recommendations (Table 3). Analyses of the added value of the subgroups showed that patients added two of those eight selected key recommendations (1.3 and 3C.1) and counsellors, just as patients, added key recommendation 1.3 and, additionally, added key recommendation 3B.11 (Table 3).

Step 4, 5 and 6: second Delphi round, analysis and approval of final set of Key recommendations in third Delphi round

The second Delphi round questionnaire was sent to the 57 first-round responders; the response rate was 79%. In step 5, all selected ($n = 9$) recommendations from round one were accepted and two recommendations (one from the newly added recommendations and one from the 'no consensus' recommendations) were added to the selection of key recommendations. Analyses showed scoring differences between the subgroups in 10 recommendations (Table 3). Again, patients scored recommendations in the decision-making domain higher. Both counsellors and patients scored recommendations in the subdomain methods of fertility preservation higher compared with referrers, and referrers scored the recommendation 'discussion about fertility preservation should be documented in the medical record' higher. None of these recommendations were selected as key recommendation. Analyses of the added value of the subgroups showed

that counsellors rejected one recommendation (3B.2) and referrers added another recommendation (4.4) (Table 3).

In total, 11 recommendations were selected as key recommendations: three on risk communication, one on referral, five on counselling and two on decision-making (Table 4). In step 6, the selection of key recommendations was presented via an online questionnaire to the total expert panel and was approved by 91% of the responders (response rate 62%).

Table 2. Expert panel background characteristics

	Referrers N=18		Counsellors N=24		Patients N=15	
Mean age in years (SD)	49.3	(8.2)	45.8	(9.1)	43.7	(10.9)
Gender (% female)	61%		63%		100%	
Occupation (n, %)						
Surgical oncologist	3/18	(17%)				
Haematologist	4/18	(22%)				
Gynaecologist	7/18	(39%)	17/24	(71%)		
Medical oncologist	4/18	(22%)				
Fertility doctor			1/24	(4%)		
Resident obstetrics and gynaecology			5/24	(21%)		
Fertility preservation researcher			1/24	(4%)		
Experience in the field, years (n, %)						
< 5	1/18	(6%)	1/24	(4%)		
5-9	7/18	(39%)	9/24	(38%)		
10-19	5/18	(28%)	8/24	(33%)		
20-29	2/18	(11%)	2/24	(8%)		
> 29	3/18	(17%)	4/24	(17%)		
Number of young female cancer patients professional treats yearly, mean (SD)	31.8	(19.6)	17.2	(11.3)		
Education level of patients (n, %)						
Secondary					1/15	(7%)
Vocational					1/15	(7%)
Higher professional					6/15	(40%)
University					7/15	(47%)
Mean age at time of diagnosis in years (SD)					35.7	(9.7)
Diagnosis (n, %)						
Breast cancer					8/15	(53%)
Haematological malignancy					2/15	(13%)
Gynaecological malignancy					5/15	(33%)
Response rate (n, %)						
First Delphi round	18/37	(49%)	24/31	(77%)	15/18	(83%)
Second Delphi round	13/18	(72%)	20/24	(83%)	12/15	(80%)
Third Delphi round	15/37	(41%)	24/31	(77%)	14/18	(78%)
Approval of the selection of key recommendations (%)	13/15	(87%)	22/24	(92%)	13/14	(93%)

Table 3. Differences in scoring behaviour between the three groups within the expert panel

	1 st Delphi round			2 nd Delphi round		
	Significantly higher importance score (p)	Significantly higher ranking score (p)	Conclusion of Delphi round 1	Analyses on added value of subgroups	Significantly higher importance score (p)	Significantly higher ranking score (p)
Domain 1. Risk communication						
3. The oncological healthcare provider should inform patients about the consequences [of the treatment] for their fertility when they have a wish to conceive, and when their ovaries, uterus and/or hypothalamus/pituitary gland are in the irradiation area (pelvic, skull, craniospinal irradiation or total body irradiation).		Patients (0.001) and Counsellors (0.001)	Selected	Patients and counsellors added KR		
5. It is the opinion of the workgroup that continuing oral contraceptives facilitates a swift start of ovarian hyper stimulation.	Counsellors (0.022)		Rejected			
8. The oncological healthcare provider should refer the patient to information about infertility, if desired.					Patients (0.005)	Rejected
Domain 2. Referral						
2. It is the opinion of the workgroup that the oncological healthcare provider should provide the opportunity [to patients] to partake in fertility preservation counselling with an expert gynaecologist early in the oncological process, if desired.		Referrers (0.021)	No consensus			

Table 3. (Continued)

1 st Delphi round			2 nd Delphi round					
	Significantly higher importance score (p)	Significantly higher ranking score (p)	Conclusion of Delphi round 1	Analyses on added value of subgroups	Significantly higher importance score (p)	Significantly higher ranking score (p)	Conclusion of Delphi round 2	Analyses on added value of subgroups
3. It is the opinion of the workgroup that the opportunity of counselling with a gynaecologist, with expertise in fertility preservation, should be offered to all women of reproductive age with cancer, who are scheduled to undergo a potential gonadotoxic treatment.	Counsellors (0.048)	Patients (0.001) and Counsellors (<0.001)	Selected					
4. The safety of the woman should be guaranteed by –prior to the execution of a fertility preservation treatment – executing an individualized selection and risk analysis within an expert multidisciplinary team. The composition of this team should be specified in a local protocol and should, at least, consist of the primary oncological healthcare provider and the treating gynaecologist.	Patients (0.048) and counsellors (0.012)		No consensus					
5. When deciding to offer fertility preservation to people diagnosed with cancer, take into account the following factors: diagnosis/ treatment plan/expected outcome of subsequent fertility treatment/prognosis of the cancer treatment/viability of stored/post-thawed material.		Referrers (0.029)	No consensus					

Table 3. (Continued)

	1 st Delphi round			2 nd Delphi round		
	Significantly higher importance score (p)	Significantly higher ranking score (p)	Conclusion of Delphi round 1	Analyses on added value of subgroups importance score (p)	Significantly higher ranking score (p)	Conclusion of Delphi round 2
Domain 3A. Counselling, methods of FP						
1. It is advised to offer IVF with cryopreservation of all embryos to women who are at risk of becoming infertile due to chemo- or radiotherapy, as an effective and safe method, when time and circumstances allow for it.		Patients (<0.001) and referrers (<0.001)	Selected			
2. It is the opinion of the workgroup that vitrification of oocytes can be offered to women who are at risk of becoming infertile as a result of chemotherapy or radiotherapy, when time and circumstances allow for it.	Patients (0.001) and counsellors (0.001)	Patients (<0.001) and counsellors (0.005)	No consensus	Patients (0.002) and counsellors (0.002)	Counsellors (0.035)	Rejected
3. Ovarian tissue cryopreservation is an investigational technique as it is and may be considered for young women at high risk of ovarian failure, or for whom other options may not be suitable.				Patients (0.017) and counsellors (0.004)		Rejected
4. It is the opinion of the workgroup that hormonal stimulation for emergency IVF or oocyte vitrification could be started at any moment in the menstrual cycle to prevent unnecessary oncological treatment delay with close collaboration between gynaecologist and oncological healthcare provider.				Patients (0.023) and counsellors (0.001)		Rejected

Table 3. (Continued)

1 st Delphi round			2 nd Delphi round					
	Significantly higher importance score (p)	Significantly higher ranking score (p)	Conclusion of Delphi round 1	Analyses on added value of subgroups	Significantly higher importance score (p)	Significantly higher ranking score (p)	Conclusion of Delphi round 2	Analyses on added value of subgroups
8. It is the opinion of the workgroup that oocyte vitrification, embryo cryopreservation and ovarian transposition are, at this moment, the preferred fertility preservation methods over the innovative/experimental method of ovarian tissue cryopreservation. However, ovarian tissue cryopreservation can be offered to women at high risk of premature ovarian failure, possibly combined with other [fertility preservation] options.		Referrers (0.004) and counsellors (0.001)	No consensus					
9. When deciding to offer fertility preservation to people diagnosed with cancer, take into account the following factors: diagnosis/ treatment plan/expected outcome of subsequent fertility treatment/prognosis of the cancer treatment/viability of stored/post-thawed material.		Referrers (<0.001)	No consensus					
Domain 3B. Counselling, preconditions of FP								
1. The safety of the woman should be guaranteed by –prior to the execution of a fertility preservation treatment– executing an individualized selection and risk analysis within an expert multidisciplinary team. The composition of this team should be specified in a local protocol and should, at least, consist of the primary oncological healthcare provider and the treating gynaecologist.		Referrers (0.018)	Selected					
2. The discussions concerning FP should be documented in the medical record.					Referrers (0.017)	Referrers (0.035)	Rejected	Counsellors rejected KR

Table 3. (Continued)

	1 st Delphi round			2 nd Delphi round				
	Significantly higher importance score (p)	Significantly higher ranking score (p)	Conclusion of Delphi round 1	Analyses on added value of subgroups	Significantly higher importance score (p)	Significantly higher ranking score (p)	Conclusion of Delphi round 2	Analyses on added value of subgroups
3. Women should be informed about the decreased success rates of oocyte vitrification at the age of 36 and above.	Patients (0.005)		No consensus					
4. It is advised not to perform autotransplantation of thawed ovarian tissue in leukaemia patients.	Counsellors (0.003)	Counsellors (0.031)	No consensus		Counsellors (0.001)		Rejected	
7. It is the opinion of the workgroup that there is no maximum storage time for oocytes, embryos and ovarian tissue.					Counsellors (0.001)		Rejected	
9. Because oocyte and ovarian tissue cryopreservation are still considered to be 'innovative/experimental', their application should include additional safeguards. This includes a process of careful decision making (oral and written information; written consent, counselling) and strict (and as unified as possible) reporting of treatment and follow-up.		Patients (0.002)	No consensus					
11. Embryo or oocyte cryopreservation should be discussed with all young women about to undergo potentially sterilizing chemotherapy or pelvic radiation and estimated as medically fit for the procedure/are expected to be able to tolerate the treatment regimen/have sufficient time before the commencement of their cancer treatment and/or are informed of the potential risks of cancer progression.		Counsellors (0.000)	Selected	Counsellors added KR				

Table 3. (Continued)

	1 st Delphi round			2 nd Delphi round		
	Significantly higher importance score (p)	Significantly higher ranking score (p)	Conclusion of Delphi round 1	Analyses on added value of subgroups	Significantly higher importance score (p)	Significantly higher ranking score (p)
Domain 3C. Counselling, discussion points in FP counselling						
1. Prior to performing emergency IVF, the patient should be well-informed about all aspects of the treatment.	Patients (0.026)	Patients (0.008)	Selected	Patients added KR		
3. The workgroup advises to emphasize that there are many drawbacks to gestational surrogacy when counselling women at high risk of losing their uterine- and ovarian function.					Counsellors (0.007)	Rejected
4. It is recommended to consult table 2.2* to determine the gonadotoxicity of various oncological treatments.	Counsellors (0.010)		No consensus			
5. It is the opinion of the workgroup that the gynaecologist should address the following aspects in fertility preservation counselling: a. The chance to preserve ovarian and/or uterine function and the chance of spontaneous pregnancy after cancer treatment. b. The chance to preserve ovarian and/or uterine function and the chance of pregnancy when using different fertility preservation methods and expectations for the future.		Counsellors (0.020)	Selected			

Table 3. (Continued)

	1 st Delphi round				2 nd Delphi round			
	Significantly higher importance score (p)	Significantly higher ranking score (p)	Conclusion of Delphi round 1	Analyses on added value of subgroups	Significantly higher importance score (p)	Significantly higher ranking score (p)	Conclusion of Delphi round 2	Analyses on added value of subgroups
c. The risks of fertility preservation procedures: delay of cancer treatment, surgery (laparoscopy, laparotomy), risk of reintroducing the tumour (metastases) after autotransplantation of cryopreserved ovarian tissue, premature menopause after cancer treatment and unilateral/partial oophorectomy.								
d. The conditions to undergo fertility treatment after cancer treatment (number of years a patient should be relapse-free after curative, posthumous reproduction etc.). The contracts should also be discussed.								
e. Alternatives, such as oocyte donation, gestational surrogacy or adoption.								
f. Necessary tests prior to a fertility preservation treatment, such as standard screening for viral pathogens and STDs.								
g. Hormonal screening through blood testing.								
h. Possibilities to treat endocrine consequences due to the loss of ovarian function.								

Table 3. (Continued)

1 st Delphi round			2 nd Delphi round					
	Significantly higher importance score (p)	Significantly higher ranking score (p)	Conclusion of Delphi round 1	Analyses on added value of subgroups	Significantly higher importance score (p)	Significantly higher ranking score (p)	Conclusion of Delphi round 2	Analyses on added value of subgroups
Domain 4. Decision-making								
1. The decision concerning protecting future fertility should be a shared decision [with patient and care providers].	Patients (0.018)		Selected					
3. It is the opinion of the workgroup that a decision aid could be offered to patients, to support the fertility preservation decision-making process.	Patients (0.008)		No consensus		Patients (0.002) and counsellors (0.021)		Rejected	
4. It is the opinion of the workgroup that fertility preservation counselling should be supported with written and/or digital information.	Patients (0.007)		No consensus					Referrers added KR
7. When considering embryo cryopreservation, adequate attention should be paid to the autonomy and decision of the partner as well, possibly with referral to a social worker or psychologist.					Patients (0.022)		Rejected	

Significantly higher importance score: the Mann Whitney U test revealed this group gave a significantly ($p \leq 0.05$) higher importance score to the recommendation in comparison to the other groups

Significantly higher ranking score: the Mann Whitney U test revealed this group gave a significantly ($p \leq 0.05$) higher ranking score to the recommendation in comparison to the other groups

$p =$ the Monte Carlo estimate of significance; differences were deemed significant at $p \leq 0.05$

Analyses on added value of subgroups: to analyse the added value of each subgroup, we excluded the subgroup one by one from the analysis and the change in either selection or rejection of each KR was considered.

Abbreviations: FP: fertility preservation, IVF: in vitro fertilization, STDs: sexually transmitted diseases

* Refers to table 2.2 in Dutch guideline (NVOG, 2016).

Final set of key recommendations

The three key recommendations in the domain risk communication mainly focused on information provision by the oncological healthcare provider on infertility risks early in the oncological process and consulting an expert colleague when the oncologist has insufficient knowledge. The key recommendation in the referral domain included offering referral to a reproductive specialist to all female cancer patients who are scheduled to undergo a potential gonadotoxic treatment. In the counselling domain, the key recommendation in the subdomain methods of fertility preservation focused on offering IVF with embryo cryopreservation to all female cancer patients if time and circumstances allow for it. The key recommendations in the subdomain preconditions focused on the role of a multidisciplinary team in guaranteeing safety of fertility preservation, and the key recommendations in the subdomain discussion points focused on all aspects that should be discussed in counselling. The domain decision-making consisted of two key recommendations focusing on making a shared decision and supporting the decision with written and/or digital information.

Table 4. Final set of key recommendations

Recommendation

Domain 1: Risk communication

It is the opinion of the workgroup that the oncological healthcare provider should at least discuss the risk of infertility with the patient, early in the oncological process.

The oncological healthcare provider should inform patients about the consequences [of the treatment] for their fertility when they have a wish to conceive, and when their ovaries, uterus and/or hypothalamus/pituitary gland are in the irradiation area (pelvic, skull, craniospinal irradiation or total body irradiation).

When the oncological healthcare provider has insufficient knowledge about fertility preservation, he/she should consult an expert colleague.

Domain 2: Referral

It is the opinion of the workgroup that the opportunity of counselling with a gynaecologist, with expertise in fertility preservation, should be offered to all women of reproductive age with cancer, who are scheduled to undergo a potential gonadotoxic treatment.

Domain 3A: Counselling, methods of fertility preservation

It is advised to offer IVF with cryopreservation of all embryos to women who are at risk of becoming infertile due to chemo- or radiotherapy, as an effective and safe method, when time and circumstances allow for it.

Domain 3B: Counselling, preconditions of fertility preservation

The safety of the woman should be guaranteed by –prior to the execution of a fertility preservation treatment– executing an individualized selection and risk analysis within an expert multidisciplinary team. The composition of this team should be specified in a local protocol and should, at least, consist of the primary oncological healthcare provider and the treating gynaecologist.

Table 4. (Continued)

Recommendation

Embryo or oocyte cryopreservation should be discussed with all young women about to undergo potentially sterilizing chemotherapy or pelvic radiation and estimated as medically fit for the procedure, are expected to be able to tolerate the treatment regimen, have sufficient time before the commencement of their cancer treatment and, are informed of the potential risks of hormonal treatment including the risks of cancer progression.

Domain 3C: Counselling, discussion points in fertility preservation counselling

Prior to performing emergency IVF, the patient should be well-informed about all aspects of the treatment.

It is the opinion of the workgroup that the gynaecologist should address the following aspects in fertility preservation counselling:

- a. The chance to preserve ovarian and/or uterine function and the chance of spontaneous pregnancy after cancer treatment.
 - b. The chance to preserve ovarian and/or uterine function and the chance of pregnancy when using different fertility preservation methods and expectations for the future.
 - c. The risks of fertility preservation procedures: delay of cancer treatment, surgery (laparoscopy, laparotomy), risk of reintroducing the tumour (metastases) after autotransplantation of cryopreserved ovarian tissue, premature menopause after cancer treatment and unilateral/partial oophorectomy.
 - d. The conditions to undergo fertility treatment after cancer treatment (number of years a patient should be relapse-free after curation, posthumous reproduction etc.). The contracts should also be discussed.
 - e. Alternatives, such as oocyte donation, gestational surrogacy or adoption.
 - f. Necessary tests prior to a fertility preservation treatment, such as standard screening for viral pathogens and STDs.
 - g. Hormonal screening through blood testing.
 - h. Possibilities to treat endocrine consequences due to the loss of ovarian function.
-

Domain 4: Decision-making

The decision concerning protecting future fertility should be a shared decision [with patient and care providers].

It is the opinion of the workgroup that fertility preservation counselling should be supported with written and/or digital information.

DISCUSSION

In this study, an oncofertility expert panel selected a set of 11 CPG-based key recommendations for high-quality female oncofertility care by using a Delphi procedure. The 11 key recommendations covered the fertility preservation pathway patients go through in chronological order with an accent on counselling. Key recommendations in risk communication and referral focused on information provision and offering referral to a reproductive specialist to female cancer patients by the oncological healthcare provider. Key recommendations on counselling focused on all aspects of counselling,

including different methods, safety, and pros and cons. Key recommendations in decision-making focused on making a shared decision and supporting the decision with written information. Differences in importance of recommendations were found between patients, referrers and counsellors. In particular, patients found recommendations on decision-making and information provision more important than referrers and counsellors. All subgroups have proven their added value in the expert panel. Each subgroup selected or rejected one or more key recommendations.

To the best of our knowledge, this is the first study to systematically select key recommendations for female oncofertility care based on (inter)national CPGs with the intent of future quality indicator development. A recently published opinion article described five key recommendations in female oncofertility care (32). Their expert group formulated key recommendations in a 1-day expert consensus meeting with allied healthcare professionals from several European countries. Their recommendations concerning the fertility preservation pathway before cancer treatment are exactly in line with our key recommendations (32). In addition to their recommendations, we selected more key recommendations concerning fertility preservation counselling, particularly on different methods, pros and cons. Furthermore, in contrast to the opinion article, we invited a larger group of experts, including patients, selected recommendations from high quality CPGs (scoring >60% on rigour of development in the AGREE-II instrument), and used a systematic Delphi method to select key recommendations as is recommended by Campbell et al. (15).

One other study reported to have measured four quality indicators for oncofertility: 'was the patient provided with written and verbal information regarding fertility preservation options', 'was the patient referred to a fertility specialist', 'did the patient undergo fertility preservation', and 'if yes—what preservation method' (33). The development of these quality indicators, however, was not described and, in contrast to our study, they did not cover the counselling and decision-making domain of the fertility preservation pathway. Our selected key recommendations make it possible to evaluate exactly on which levels current care is lacking and improvement is needed. Another recent study in this field developed an international oncofertility competency framework (34). This study provided statements on how oncofertility care should be organized, with focus on healthcare professionals' competencies and preconditions for organization of care. Furthermore, a structure for the training of healthcare professionals and implementation of care was proposed. In the present study, we have placed the patient at the centre and have selected recommendations in the healthcare pathway for patients, as a first step in improving oncofertility care. In the next step, we will measure the quality of care to identify where improvement is needed. To improve

oncofertility care, we can make use of the tools provided by the framework, such as training of healthcare professionals and implementation of decision aids (34).

Of note, our study is one of the few in which a combined panel of healthcare professionals (multidisciplinary, involving both referrers and counsellors) and patients is involved in the selection procedure. Previous studies have shown the added value of patients in assessing the importance of key recommendations and quality indicators because healthcare professionals might only have insight into their respective parts of the care pathway and patients have insight into the entire pathway (17, 18). Our study underlines these findings: the set of key recommendations would have been different if healthcare professionals alone were involved in the selection procedure. Patients were responsible for the selection of two key recommendations, one in the risk communication domain and one in the counselling domain. These key recommendations advise the oncological healthcare provider to inform patients about the consequences of irradiation therapy on their fertility and the counsellors to fully inform patients about all fertility preservation options and all aspects of emergency IVF treatment. Moreover, patients found recommendations on decision-making more important than healthcare professionals. These results are in line with previous studies reporting that patients want to be fully informed about infertility risks and available fertility preservation options and supported in their decision and healthcare professionals might underestimate these needs (9, 17, 19, 35, 36). Furthermore, it is interesting that documentation of oncofertility discussions in the medical record was not selected as a key recommendation for high-quality oncofertility care in our study. This recommendation was rejected in the second Delphi round by counsellors (Table 3, recommendation 3B.2). An explanation might be that counsellors assumed that documentation was already part of standard care, and therefore gave a lower importance score and ranking score. Documentation, however, is important for quality control and should, therefore, always take place (37).

An important message arising from our study is that, although the key recommendations were selected in a Dutch setting, they might also serve as key recommendations for oncofertility care in other countries as recommendations from six high-quality international CPGs were also included. Furthermore, compared with other studies we invited a large number of participants (N=86) to join our expert panel and our expert panel was diverse, consisting of professionals from different disciplines, as well as patients (19, 21, 31). This heterogeneity ensured that the main stakeholders from all steps in the care pathway were included, helps reduce the selection bias and increases the face validity, acceptability and credibility of the set of key recommendations and of the future quality indicators (21).

Some limitations, however, should be considered in the interpretation of the study results. Although the overall response rates were high for the three rounds, we found differences in response rates between the three subgroups, with especially the referrers having a lower response rate. An explanation might be that oncological healthcare providers do not feel as responsible for oncofertility care as counsellors do (38). They might find themselves not able to inform patients about infertility risks or fertility preservation options (39). Another explanation might be the time constraints or the complexity of the Delphi procedure. The fact that the opinions of the expert panel were obtained purely through online questionnaires and not through a consensus meeting, might have led to the lack of subtleties provided by a face-to-face discussion (21). Opinions were reconsidered through feedback in the second Delphi round (21). Although it may seem logical to have a face-to-face discussion and argumentation to reach consensus, we chose to do so by an online questionnaire. The advantage of using online questionnaires was ease of participation, across different parts of the Netherlands, at a time of the participant's choosing rather than attending a meeting at a set time and place. Furthermore, participants cannot be influenced by the, sometimes very strong opinion of other expert panel members (21). This may explain the high number of participants and response rates in our study, compared with similar studies that included a face-to-face consensus meeting (17, 30). Finally, our key recommendation selection criteria were more strict than most Delphi studies (21). A median Likert score of 7 or over is demanded, as higher scoring potential key recommendations (with panel agreement) are more inclined to be reproduced by a different panel of the same experts' composition (16, 17, 31). The 80% panel agreement ensured that we only selected those recommendations that the whole expert panel deemed to be of great importance for the quality of oncofertility care (15). Moreover, the high panel agreement increased the acceptability for the set of selected key recommendations.

The next step in improving female oncofertility care is to translate the key recommendations into quality indicators and submit them to a practice test. Thereafter, the feasible quality indicators can be used as a tool to identify problems and monitor actual quality of female oncofertility care. In future, the final set of quality indicators should be available for all hospitals to measure and monitor actual female oncofertility care and potential barriers to guideline adherence. To further improve female oncofertility care, a multifaceted improvement strategy tailored to guideline specific barriers should be developed and implemented (14, 34). The quality indicator set could then be used to evaluate whether the improvement strategy has a positive effect on quality of care and guideline adherence. At present, some improvement strategies have already been implemented and studied, although without a thorough analysis of all aspects of current quality of female oncofertility care. Therefore, their efficacy

is unclear (33, 40, 41). To evaluate improvement strategies systematically, our quality indicator set could be used in future studies.

CONCLUSION

In conclusion, in this study 11 key recommendations in female oncofertility care were systematically selected covering the fertility preservation pathway patients go through. By involving the perspectives of the patients, referrers and counsellors, the final set of CPG-based key recommendations is considered well balanced, valid, and has high acceptability. After transcribing these key recommendations into quality indicators and conducting a practice test, the feasible quality indicators are well suited as a measuring tool for identifying problems and improving the quality of female oncofertility care in the Netherlands and internationally.

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J.W. Aarts; MD, PhD, Resident Obstetrics and Gynaecology, F. Amant; MD, PhD, Gynaecological oncologist, C.C.M. Beerendonk; MD, PhD, Gynaecologist, R.L.M. Bekkers; MD, PhD, Gynaecological oncologist, S.H. Benneheij; MD, Gynaecologist, T. Bonestroo; MD, Resident Obstetrics and Gynaecology, A.M.E. Bos; MD, PhD, Gynaecologist, D.D.M. Braat; MD, PhD, Gynaecologist, M. Brandes; MD, PhD, Resident Obstetrics and Gynaecology, G. Brus; Patient representative, B.J. Cohlen; MD, PhD, Gynaecologist, R.D. De Beer; Patient representative, J.P. De Bruin; MD, PhD, Gynaecologist, C.D. De Kroon; MD, PhD, Gynaecological oncologist, J. De Wolf; Patient representative, M. Goddijn; MD, PhD, Gynaecologist, O. Hamdine; MD, PhD, Fertility doctor, C.J.C.M. Hamilton; MD, PhD, Gynaecologist, I. Heistek - Vos; Patient representative, S.E.J. Kaal; MD, Medical oncologist, C. Koolen; Patient representative, R.F.P.M. Kruitwagen; MD, PhD, Gynaecological oncologist, C.A.R. Lok; MD, PhD, Gynaecological oncologist, L.A. Louwé; MD, PhD, Gynaecologist, B.B. Mengerink; MD, Resident Obstetrics and Gynaecology, C.W. Menke - Van der Houven van Oordt; MD, PhD, Medical oncologist S.M. Mourad; MD, PhD, Resident Obstetrics and Gynaecology, A.W. Nap; MD, PhD, Gynaecologist, S. Nijhof-Blauw; Patient representative, H.S.A. Oldenburg; MD, PhD, Breast surgeon, M.H.M. Oonk; MD, PhD, Gynaecological oncologist, J.A.M. Oskam; Patient representative, J. Pit; Patient representative, ir. M.A.F. Potters; Patient representative, L. Roos - Wouters; Patient representative, I. Runneboom; Patient representative, R. Schats; MD, PhD, Gynaecologist, E. Scheenjes; MD, PhD, Gynaecologist, M.S. Schlooz - Vries; MD, Breast surgeon, H.C. Schouten; MD, PhD, Haematologist, D. Smedts; MD, Gynaecological oncologist, J.M.J. Smeenk; MD, PhD, Gynaecologist, M.L. Smidt; MD, PhD, Breast surgeon, G.S. Sonke; MD, PhD, Medical oncologist, W.B.C. Stevens; MD, Haematologist, M. Van den Berg; MD, Gynaecologist, M. van den Berg; MD, FP researcher, S. Van den Oever - Buitendijk; Patient representative Hematon, C.E.I.M. Van Dierendonck – Ferwerda; Patient representative Hematon, C.F. Van Heteren; MD, PhD, Gynaecologist, G.W. Van Imhoff; MD, PhD, Haematologist, E.J.P. Van Santbrink; MD, PhD, Gynaecologist, M. Van Wolfswinkel; Patient representative, R.H.M. Verheijen; MD, PhD, Gynaecological oncologist, M. Witte; Patient representative, P.O. Witteveen; MD, PhD, Medical oncologist, M.J. Wondergem; MD, PhD, Haematologist.

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Supplementary Table 1. All recommendations presented to the panel in this Delphi study

Domain	Nr	Recommendation	Source	Result 1 st round	Result 2 nd round
1: risk communication	1	It is the opinion of the workgroup that the oncological healthcare provider should at least discuss the risk of infertility with the patient, early in the oncological process.	Dutch guideline	Selected	NA
	2	It is recommended that Table 2.2 ^a should be consulted to determine the gonadotoxicity of various oncological treatments.	Dutch guideline	No consensus	Rejected
	3	The oncological healthcare provider should inform patients about the consequences of the treatment for their fertility when they wish to conceive, and when their ovaries, uterus, hypothalamus and pituitary gland, or all, are in the irradiation area (pelvic, skull, craniospinal irradiation or total body irradiation).	Dutch guideline	Selected	NA
	4	It is the opinion of the workgroup that all women who are about to undergo a potential gonadotoxic treatment should be informed about the possibility of peer support.	Dutch guideline	Rejected	NA
	5	It is the opinion of the workgroup that continuing oral contraceptives facilitates a swift start of ovarian stimulation.	Dutch guideline	Rejected	NA
	6	It is the opinion of the workgroup that, for an individual patient, measuring anti-Müllerian hormone before a potential gonadotoxic cancer treatment has no practical added value to the determination of the level of gonadotoxicity of chemotherapeutics.	Dutch guideline	Rejected	NA
	7	It is the opinion of the workgroup that oral contraceptives should not be prescribed to prevent ovarian failure during chemotherapy.	Dutch guideline	Rejected	NA
	8	The oncological healthcare provider should refer the patient to information about infertility, if desired.	Panel	NA	Rejected
	9	When the oncological healthcare provider has insufficient knowledge about fertility preservation, they should consult an expert colleague.	Panel	NA	Selected

Supplementary Table 1. (Continued)

Domain	Nr	Recommendation	Source	Result 1 st round	Result 2 nd round
2: referral	1	The oncological healthcare provider should refer a patient to an expert gynaecologist before starting radiotherapy for fertility preservation counselling and possible fertility preservation treatment, if desired.	Dutch guideline	No consensus	Rejected
	2	It is the opinion of the workgroup that the oncological healthcare provider should provide patients the opportunity to partake in fertility preservation counselling with an expert gynaecologist early in the oncological process, if desired.	Dutch guideline	No consensus	Rejected
	3	It is the opinion of the workgroup that the opportunity of counselling with a gynaecologist, with expertise in fertility preservation, should be offered to all women of reproductive age with cancer, who are scheduled to undergo a potential gonadotoxic treatment.	Dutch guideline	Selected	NA
	4	Before undergoing fertility preservation treatment, the safety of the woman should be guaranteed by carrying out an individualized selection and risk analysis within an expert multidisciplinary team. The composition of this team should be specified in a local protocol and should, at least, consist of the primary oncological healthcare provider and the treating gynaecologist.	Dutch guideline	No consensus	Rejected
	5	When deciding to offer fertility preservation to people diagnosed with cancer, take into account the following factors: diagnosis, treatment plan, expected outcome of subsequent fertility treatment, prognosis of the cancer treatment, and viability of stored or post-thawed material.	NICE-RCOG	No consensus	Rejected
	6	It is the opinion of the workgroup that the indication for fertility preservation can only be made in close consultation with the oncological healthcare provider, patient and gynaecologist involved. The risk of premature ovarian insufficiency and prognosis, as estimated by the oncological healthcare provider, should be taken into account when making this decision.	Dutch guideline	No consensus	Rejected
	7	It is advised to make the decision on ovarian transposition within a multidisciplinary team, taking into account other fertility preservation options and the risk of ovarian metastases.	Dutch guideline	No consensus	Rejected

Supplementary Table 1. (Continued)

Domain	Nr	Recommendation	Source	Result 1 st round	Result 2 nd round
2: referral	8	Referral for counselling with an expert gynaecologist should be achievable at short notice.	Panel	NA	Rejected
	9	Oncological healthcare providers in non-academic hospitals should work closely together with an expert gynaecologist and be able to refer early in the oncological process.	Panel	NA	Rejected
	10	Oncological healthcare providers in non-academic hospitals should be aware of the fertility preservation options.	Panel	NA	Rejected
	11	When deciding to offer fertility preservation to women diagnosed with cancer, the personal context of the patient, i.e. social, psychological, wishes and preferences, should be taken into account.	Panel	NA	Rejected
	12	If desired, the partner of the patient should also be involved in the decision-making process.	Panel	NA	Rejected
3A: counselling, methods of fertility preservation	1	It is advised to offer IVF with cryopreservation of all embryos to women who are at risk of becoming infertile as a result of chemotherapy or radiotherapy, as an effective and safe method, when time and circumstances allow for it.	Dutch guideline	Selected	NA
	2	It is the opinion of the workgroup that vitrification of oocytes can be offered to women who are at risk of becoming infertile as a result of chemotherapy or radiotherapy, when time and circumstances allow for it.	Dutch guideline	No consensus	Rejected
	3	Ovarian tissue cryopreservation is an investigational technique as it is and may be considered for young women at high risk of ovarian failure, or for whom other options may not be suitable.	COSA	No consensus	Rejected
	4	It is the opinion of the workgroup that hormonal stimulation for emergency IVF or oocyte vitrification could be started at any moment in the menstrual cycle to prevent unnecessary oncological treatment delay with close collaboration between gynaecologist and oncological healthcare provider.	Dutch guideline	No consensus	Rejected
	5	It is the opinion of the workgroup that, for the individual patient, measuring anti-Müllerian hormone before potential gonadotoxic cancer treatment has no practical added value to the determination of the level of gonadotoxicity of chemotherapeutics.	Dutch guideline	Rejected	NA

Supplementary Table 1. (Continued)

Domain	Nr	Recommendation	Source	Result 1 st round	Result 2 nd round
3A: counselling, methods of fertility preservation	6	It is the opinion of the workgroup that oral contraceptives should not be prescribed to prevent ovarian failure during chemotherapy.	Dutch guideline	Rejected	NA
	7	In the context of fertility preservation, gonadotrophin releasing hormone agonists should not routinely be prescribed to women with cancer who wish to conceive.	Dutch guideline	Rejected	NA
	8	It is the opinion of the workgroup that oocyte vitrification, embryo cryopreservation and ovarian transposition are, at this moment, the preferred fertility preservation methods over the innovative and experimental method of ovarian tissue cryopreservation. Ovarian tissue cryopreservation, however, can be offered to women at high risk of premature ovarian failure, possibly combined with other (fertility preservation) options.	Dutch guideline	No consensus	Rejected
	9	When deciding to offer fertility preservation to people diagnosed with cancer, take into account the following factors: diagnosis, treatment plan, expected outcome of subsequent fertility treatment, prognosis of the cancer treatment, and viability of stored and post-thawed material.	NICE-RCOG	No consensus	Rejected
	10	During counselling, the practicability of the fertility treatment should also be considered.	Panel	NA	Rejected
3B: counselling, preconditions of fertility preservation	1	Before undergoing fertility preservation treatment, the safety of the woman should be guaranteed by carrying out an individualized selection and risk analysis within an expert multidisciplinary team. The composition of this team should be specified in a local protocol and should, at least, consist of the primary oncological healthcare provider and the treating gynaecologist.	Dutch guideline	Selected	NA
	2	The discussions concerning fertility preservation should be documented in the medical record.	ASCO	No consensus	Rejected
	3	Women should be informed about the decreased success rates of oocyte vitrification at the age of 36 years and over.	Dutch guideline	No consensus	Rejected
	4	It is advised not to carry out autotransplantation of thawed ovarian tissue in patients with leukaemia.	Dutch guideline	No consensus	Rejected
	5	It is the opinion of the workgroup that, at this moment, there are no indications of adverse effects of autotransplantation of thawed ovarian tissue for the following pregnancy, the child, or both.	Dutch guideline	Rejected	NA

Supplementary Table 1. (Continued)

Domain	Nr	Recommendation	Source	Result 1 st round	Result 2 nd round
3B: counselling, preconditions of fertility preservation	6	The fact that a fertility preservation treatment is carried out does not necessarily mean that the frozen material can be used in a gestational surrogate.	Dutch guideline	No consensus	Rejected
	7	It is the opinion of the workgroup that there is no maximum storage time for oocytes, embryos and ovarian tissue.	Dutch guideline	No consensus	Rejected
	8	Oocyte cryopreservation should be carried out in centres with the necessary expertise. Oocyte harvesting for the purpose of oocyte or embryo cryopreservation can be started on a schedule independent of the cycle day.	ASCO	No consensus	Rejected
	9	Because oocyte and ovarian tissue cryopreservation are still considered to be 'innovative and experimental', their application should include additional safeguards. This includes a process of careful decision making (oral and written information; written consent; counselling) and strict (and as unified as possible) reporting of treatment and follow-up.	Dutch guideline	No consensus	Rejected
	10	Ovarian transposition (oophoropexy) can be offered when pelvic irradiation is carried out as cancer treatment. Because of the risk of remigration of the ovaries, this procedure (oophoropexy) should be carried out as close to the time of radiation treatment as possible.	ASCO	No consensus	Rejected
	11	Embryo or oocyte cryopreservation should be discussed with all young women about to undergo potentially sterilizing chemotherapy or pelvic radiation and estimated as medically fit for the procedure, are expected to be able to tolerate the treatment regimen, have sufficient time before the commencement of their cancer treatment, and are informed of the potential risks of hormonal treatment, including the risks of cancer progression.	COSA	Selected	NA

Supplementary Table 1. (Continued)

Domain	Nr	Recommendation	Source	Result 1 st round	Result 2 nd round
3C: counselling: discussion points in fertility preservation counselling	1	Before undergoing emergency IVF, the patient should be well-informed about all aspects of the treatment.	Dutch guideline	Selected	NA
	2	It is the opinion of the workgroup that all women, who are about to undergo a potential gonadotoxic treatment, should be informed about the possibility of peer support.	Dutch guideline	Rejected	NA
	3	The workgroup advises emphasis of the many drawbacks to gestational surrogacy when counselling women at high risk of losing their uterine and ovarian function.	Dutch guideline	No consensus	Rejected
	4	It is recommended that Table 2.2 ^a is consulted to determine the gonadotoxicity of various oncological treatments.	Dutch guideline	No consensus	Rejected
	5	It is the opinion of the workgroup that the gynaecologist should address the following aspects in fertility preservation counselling: a. The chance of preserving ovarian function, uterine function, or both, and the chance of spontaneous pregnancy after cancer treatment. b. The chance of preserving ovarian function, uterine function, or both, and the chance of pregnancy when using different fertility preservation methods and expectations for the future. c. The risks of fertility preservation procedures: delay of cancer treatment, surgery (laparoscopy, laparotomy), risk of reintroducing the tumour (metastases) after autotransplantation of cryopreserved ovarian tissue, premature menopause after cancer treatment and unilateral or partial oophorectomy. d. The conditions needed to undergo fertility treatment after cancer treatment (number of years a patient should be relapse-free after curation, posthumous reproduction etc.). The contracts should also be discussed. e. Alternatives, such as oocyte donation, gestational surrogacy or adoption. f. Necessary tests before a fertility preservation treatment, such as standard screening for viral pathogens and sexually transmitted diseases. g. Hormonal screening through blood testing. h. Possibilities to treat endocrine consequences owing to loss of ovarian function.	Dutch guideline	Selected	NA
	6	During counselling, the gynaecologist should emphasize that the final decision on the offered fertility preservation options lies with the patient.	Panel	NA	Rejected

Supplementary Table 1. (Continued)

Domain	Nr	Recommendation	Source	Result 1 st round	Result 2 nd round
4: decision-making	7	During counselling, the risk of passing on hereditary conditions should be discussed.	Panel	NA	Rejected
	8	The patient should bring an involved person (partner or supporter) to the counselling.	Panel	NA	Rejected
	1	The decision concerning protecting future fertility should be a shared decision (with patient and care providers).	Dutch guideline	Selected	NA
	2	It is the opinion of the workgroup that it is advisable to refer all women who, despite being counselled by a gynaecologist, cannot make a decision, to a specialized psychologist or social worker.	Dutch guideline	No consensus	Rejected
	3	It is the opinion of the workgroup that a decision aid could be offered to patients, to support the fertility preservation decision-making process.	Dutch guideline	No consensus	Rejected
	4	It is the opinion of the workgroup that fertility preservation counselling should be supported with written information, digital information, or both.	Dutch guideline	No consensus	Selected
	5	When a patient is referred to a psychologist, logistics for referral should be good, allowing the patient to have an appointment at very short notice.	Panel	NA	Rejected
	6	The patient should have at least 1–2 days to make her decision.	Panel	NA	Rejected
	7	When considering embryo cryopreservation, adequate attention should be paid to the autonomy and decision of the partner as well, possibly with referral to a social worker or psychologist.	Panel	NA	Rejected
	8	It is the opinion of the workgroup that it is advisable to refer all women who, despite being counselled by a gynaecologist, cannot make a decision, to spiritual care.	Panel	NA	Rejected
	9	If desired, the partner of the patient should also be involved in the decision-making process.	Panel	NA	Rejected
	10	It is the opinion of the workgroup that it is advisable to refer all women who, despite being counselled by a gynaecologist, cannot make a decision, to their general practitioner.	Panel	NA	Rejected

^a Refers to Table 2.2 in Dutch guideline (NVOG, 2016).

ASCO, American Society of Clinical Oncology; COSA, Clinical Oncology Society of Australia; NA, not applicable; NICE, National Institute for Health and Care Excellence; RCOG, Royal College of Obstetricians and Gynaecologists.



3

QUALITY OF INTEGRATED FEMALE ONCOFERTILITY CARE IS SUBOPTIMAL: A PATIENT-REPORTED MEASUREMENT

M. van den Berg, S.E.J. Kaal*, T.N. Schuurman*, D.D.M. Braat, C.M.P.W. Mandigers,
J. Tol, J.M. Tromp, M.J.D.L. van der Vorst, C.C.M. Beerendonk, R.P.M.G. Hermens

* joint second authors

Submitted

ABSTRACT

Background

Clinical practice guidelines recommend to inform female adolescent and young adults cancer patients about their infertility risks due to cancer treatment. Unfortunately it seems that guideline adherence is suboptimal and varies greatly. In order to improve quality of integrated female oncofertility care, a systematic assessment of current practice is necessary, just as an assessment of determinants that influence guideline adherence. However, at this moment, quality of care has not been systematically assessed, and has not been measured by consulting female cancer patients.

Patients and methods

A multicentre cross-sectional study was conducted to systematically measure quality of integrated female oncofertility care. Female cancer patients, diagnosed in 2016/2017, were included from six hospitals across the Netherlands, and were asked to fill in a survey in which a set of systematically developed quality indicators (N=11) was processed. These indicators represented all domains in oncofertility care; risk communication, referral, counselling and decision-making. Indicator scores were calculated and determinants were assessed by multilevel multivariate analyses.

Results

A total of 121 out of 344 (35%) female cancer patients participated. 8 out the 11 indicators scored below 90% adherence. Of all patients, 72,7% was informed about their infertility risks by their oncological healthcare provider, 51,2% was offered a referral to a gynaecologist, with 18,8% all aspects were discussed in fertility preservation counselling, and 35,5% received written and/or digital information. Four determinants (patient's age, strength of wish to conceive, time before cancer treatment, and type of healthcare provider) were found to significantly influence the scores of three indicators on referral and (support of) shared decision-making.

Conclusions

Current quality of integrated female oncofertility care is far from optimal. Therefore, improvement is needed. To achieve this, improvement strategies that are tailored to the identified determinants and to guideline-specific barriers should be developed.

INTRODUCTION

The potential loss of fertility due to gonadotoxic cancer treatments is one of the most important concerns in female adolescent and young adult (AYA) cancer patients (1-3). Therefore, they are interested in receiving information about infertility risks and fertility preservation (FP) options (4-6). Current clinical guidelines recommend oncological healthcare professionals to provide information on infertility risks and FP options, and, if desired, to offer a referral to and counselling by a fertility specialist (7-9). Providing information to female AYA cancer patients affects quality of life positively, reduces long-term regret and reduces concerns regarding fertility (1, 10, 11). Despite these guidelines and positive effects, studies have shown that the proportion of patients provided with information on their infertility risks and FP options is suboptimal and varies greatly from 26% to 95% (12-17). The referral process to a fertility specialist also shows variation in practice, only 9,8% to 67% is referred (13, 15, 16, 18).

These low rates indicate a suboptimal adherence to female oncofertility guidelines and suggest a suboptimal quality of care. In order to improve quality of integrated female oncofertility care, a systematic assessment of current practice is necessary, just as an assessment of determinants that influence guideline adherence (19). Regarding the systematic assessment of current practice, most studies did not assess the quality of care systematically. They reported the number of FP discussions and referrals based on self-reported practices by healthcare providers or medical record documentation. Both methods have limitations. Regarding self-report: healthcare providers might overestimate their performance and thus a self-report bias should be taken into account (20). Regarding medical record documentation: disparity between discussions and documentation exists varying from 4% to 23% (21, 22). Therefore, it would be better to measure quality of integrated care by consulting actual female cancer patients, because it is more important to know what patients remember than what is documented in incomplete medical records. Furthermore, studies have shown that patients can accurately report on their cancer diagnosis, treatment and characteristics (22, 23).

To systematically assess the current quality of female oncofertility care, quality indicators (QIs) can be used. QIs are measurable elements of practice performance for which there is evidence or consensus that it can be used to assess quality, and hence change the quality of care provided (24). In our previous study, key recommendations for high quality integrated female oncofertility care were selected by means of a Delphi procedure with a multidisciplinary national expert panel (25). After translating these key recommendations into QIs, these are well suited to systematically assess the quality of integrated oncofertility care. Regarding determinants that influence guideline

adherence, these can be found on patient, professional and hospital level. Insight into these determinants can explain the variation in care and should be taken into account when developing tailored improvement strategies to improve quality of care, since quality of care does not improve by itself.

In our current study, the first aim was therefore to systematically assess the quality of integrated female oncofertility care by a patient-reported measurement of QIs. The second aim was to measure which determinants were associated with this quality of care to be able to develop tailored improvement strategies to improve quality of integrated female oncofertility care.

METHODS

Design and setting

This multicentre cross-sectional study was conducted by means of a survey to female AYA cancer patients in six hospitals; three academic hospitals, and three (large) non-academic hospitals. In the Netherlands, patients receive multidisciplinary oncological care and can be referred for FP counselling by any medical specialist involved. FP counselling is performed by reproductive gynaecologists. In the Netherlands, patients have no financial reasons to refrain from FP counselling or undergoing FP treatment, because it is covered by basic health insurance or by the hospital cryobanks themselves. This study was approved by the Medical Ethics Committee of Arnhem-Nijmegen (NL61570.091.17).

Study population

Female AYA cancer patients (18 up to and including 40 years) who were diagnosed in 2016 or 2017, and received a (potential) gonadotoxic treatment were eligible to participate. The Netherlands Cancer Registry was used by the Netherlands Comprehensive Cancer Organization (IKNL) to identify potentially eligible patients in each participating hospital. After identification, the patient's primary oncological healthcare provider was asked to assess the following exclusion criteria: patient was deceased, severely diseased, had severe psychological problems, had undergone a hysterectomy and/or oophorectomy prior to the start of her cancer treatment, did not receive follow-up care in the participating hospital, or did not understand the Dutch language.

Survey development

The survey was developed within our research team. The survey consisted of baseline and clinical characteristics (patient's age, partner relationship, diagnosis and cancer treatment, strength of wish to conceive) and questions that represented the QIs (see below). After reaching consensus with the research team, the survey was pilot-tested in five female cancer survivors and four non-cancer patients after which small adjustments were made.

Quality indicators

In our previous research we used a systematic Delphi procedure to select key recommendations for high quality integrated female oncofertility care with a multidisciplinary oncofertility expert panel including female cancer survivors (25). These key recommendations were first extracted from high quality international clinical guidelines on this subject and then selected and approved by the expert panel by means of three consensus rounds (25, 26). This resulted in 11 key recommendations. Subsequently, the research team transcribed the key recommendations into 11 QIs (defining numerators and denominators). An example of the transcription from key recommendation to a QI is shown in Figure 1. The questions that were developed to measure this QI were: "Did your oncological healthcare provider discuss the risk of infertility due to the cancer treatment with you?" and 'When did the oncological caregiver discuss the risk of infertility with you?'. A total of 40 questions were developed to measure the 11 indicators. The questions measured quality of female oncofertility care for female AYA cancer patients focusing on risk communication, referral, counselling and decision-making. All QIs are shown in Table 1.

Figure 1. Example of quality indicator as a tool to measure quality of care

Key recommendation: It is the opinion of the workgroup that the oncological healthcare provider should at least discuss the risk of infertility with the patient, early in the oncological process.		
Numerator Number of patients in an oncological process who receive a gonadotoxic treatment with whom at least the risk of infertility is discussed by their oncological healthcare provider early in the oncological process (i.e. within 2 weeks)	x 100%	Quality indicator Percentage of patients in an oncological process who receive a gonadotoxic treatment with whom at least the risk of infertility is discussed by their oncological healthcare provider early in the oncological process (i.e. within 2 weeks)
Denominator Total number of patients in an oncological process who receive a gonadotoxic treatment.		

Table 1. Quality indicators distributed over the domains in female oncofertility care

Domain	Quality indicators
Risk Communication	Percentage of patients in an oncological process who receive a gonadotoxic treatment...
	QI1 with whom at least the risk of infertility is discussed by their oncological healthcare provider early in the oncological process (i.e. within 2 weeks).
	QI2 with whom the consequences (of the treatment) for their fertility are discussed when they have a wish to conceive, and when their ovaries, uterus, hypothalamus, pituitary gland (or all) are in the irradiation area (pelvic, skull, craniospinal irradiation or total body irradiation).
	QI3 of whom the oncological healthcare provider consulted an expert colleague when he/she had insufficient knowledge about fertility preservation.
Referral	QI4 Percentage of patients in an oncological process who receive a gonadotoxic treatment to whom the opportunity of counselling with a gynaecologist with expertise in fertility preservation is offered.
Counselling	Percentage of patients in an oncological process who receive a gonadotoxic treatment...
	QI5 for whom an individualized selection and risk analysis has been executed within an expert multidisciplinary team (i.e. primary oncological healthcare provider and treating gynaecologist).
	QI6 (who are estimated as medically fit for the procedure, are expected to be able to tolerate the treatment regimen, have sufficient time before the commencement of their cancer treatment and, are informed of the potential risks of hormonal treatment including the risks of cancer progression), with whom oocyte and embryo cryopreservation has been discussed during fertility preservation counselling.
	QI7 to whom embryo cryopreservation is offered as an effective and safe method, when time and circumstances allow for it.
	QI8 who have had fertility preservation counselling with a gynaecologist in which all aspects (a – h) have been discussed. a. The chance to preserve ovarian, uterine function, or both, and the chance of spontaneous pregnancy after cancer treatment. b. The chance to preserve ovarian, uterine function, or both, and the chance of pregnancy when using different fertility preservation methods, and expectations for the future. c. The risks of fertility preservation procedures: delay of cancer treatment, surgery (laparoscopy, laparotomy), risk of reintroducing the tumour (metastases) after autotransplantation of cryopreserved ovarian tissue, premature menopause after cancer treatment and unilateral and partial oophorectomy. d. The conditions to undergo fertility treatment after cancer treatment, (number of years a patient should be relapse-free after curation, posthumous reproduction, etc.). The contracts should also be discussed. e. Alternatives, such as oocyte donation, gestational surrogacy or adoption.

Table 1. (Continued)

Domain	Quality indicators
	f. Necessary tests before a fertility preservation treatment, such as standard screening for viral pathogens and sexually transmitted diseases. g. Hormonal screening through blood testing. h. Possibilities to treat endocrine consequences owing to the loss of ovarian function.
	QI9 who have been well-informed about all aspects of the treatment prior to performing emergency IVF.
Decision-making	Percentage of patients in an oncological process who receive a gonadotoxic treatment...
	QI10 with whom a shared decision has been made concerning protecting future fertility (together with oncological healthcare provider and gynaecologist).
	QI11 who have had fertility preservation counselling which was supported with written, digital information, or both.

Data collection

Eligible patients received an invitation letter from their primary oncological healthcare provider to participate. After obtaining informed consent, a paper version of the survey was sent by mail in 2020/2021. In total, 344 patients were invited to participate. If no informed consent or completed survey was received within three weeks, one reminder was sent.

Data analysis

QI adherence scores were calculated per indicator. Herewith, current practice was expressed as the percentage of patients who received care as recommended in the QI. In addition, hospital variation was calculated. To evaluate which determinants were associated with the quality of integrated female oncofertility care, we first studied the univariate relation between indicator scores (dependent variables) and determinants (independent variables) that could influence the indicator score. Determinants were extracted from literature and included age, relationship status, parity, strength of wish to conceive, type of cancer, type of cancer treatment, time before start of cancer treatment, type of healthcare provider, and type of hospital (12, 15, 16, 18, 27, 28). We used a generalized linear mixed model which accounts for the nested structure of data, because individual patients (patient level=1) are nested within hospitals (hospital level=2). For determinants with $p < 0.20$ in univariate analyses, we performed multivariate logistic regression. Collinearity between determinants was also tested. If a correlation (>0.6) was detected, the most relevant variable with respect to content was included in the multivariate analyses. Odds ratios described the association between indicator scores and determinants. Indicator scores were recalculated for each indicator

and for each part of the associated determinant. For example, an indicator could be recalculated for all patients aged 18-29 years, and for all patients aged 30-41 years.

RESULTS

Study population

In total, 566 patients were identified by IKNL of whom 344 met the inclusion criteria. Figure 2 shows reasons for exclusion. A total of 121 out of 344 (35%) surveys was returned. Mean patient age at diagnosis was 34 years, 60,3% was diagnosed with breast cancer, and 37,2% had undergone FP treatment (Table 2).

Table 2. Baseline characteristics

Characteristic	Number	%
Response rate total and per hospital	121/344	35
Academic hospital		
- Hospital A	24/56	42,9
- Hospital B	15/55	27,3
- Hospital C	50/147	34
Large non-academic hospital		
- Hospital D	11/26	42,3
- Hospital E	11/33	33,3
- Hospital F	10/27	37
Mean age at diagnosis	34,0 years (range 18-41, SD 5,1)	
Type of cancer		
- Bladder cancer	1	0,8
- Brain tumour	2	1,7
- Breast cancer	73	60,3
- Cervical cancer	14	11,6
- Colorectal cancer	5	4,1
- Head and neck cancer	1	0,8
- Leukaemia	3	2,5
- Lung cancer	1	0,8
- Lymphoma	15	12,4
- Osteosarcoma	2	1,7
- Ovarian cancer	2	1,7
- Soft tissue sarcoma	2	1,7

Table 2. (Continued)

Characteristic	Number	%
Cancer treatment		
- Breast surgery	72	59,5
- Chemotherapy	112	92,6
- Hormone therapy	45	37,2
- Immunotherapy	20	16,5
- Irradiation therapy	80	66,1
- Breast	56	70
- Skull/Craniospinal	8	10
- Pelvic	10	12,5
- Total body	6	7,5
- Uterine or ovarian surgery	11	9,1
Relationship status		
- Yes, more than 2 years	90	74,4
- Yes, less than 2 years	20	16,5
- No, single	11	9,1
Parity		
- Nulliparous	50	41,3
- Parous	71	58,7
- Para 1	29	40,8
- Para 2	29	40,8
- Para 3	12	17
- Para 4	1	1,4
Strength of wish to conceive at diagnosis (mean, scale 1-10)	5,8 (range 1-10, SD 3,5, median 5)	
- Nulliparous	7,0 (range 1-10, SD 2,9, median 7,5)	
- Parous	4,9 (range 1-10, SD 3,6, median 5)	
Number of patients who had undergone fertility preservation treatment (3 patients had 2 treatments)	45 / 121	37,2
- Oocyte cryopreservation	24	53,3
- Embryo cryopreservation	11	24,4
- Ovarian tissue cryopreservation	3	6,7
- Trachelectomy or unilateral ovariectomy	9	20
- GnRH agonists	1	2,2

Figure 2. Flowchart: eligibility and response

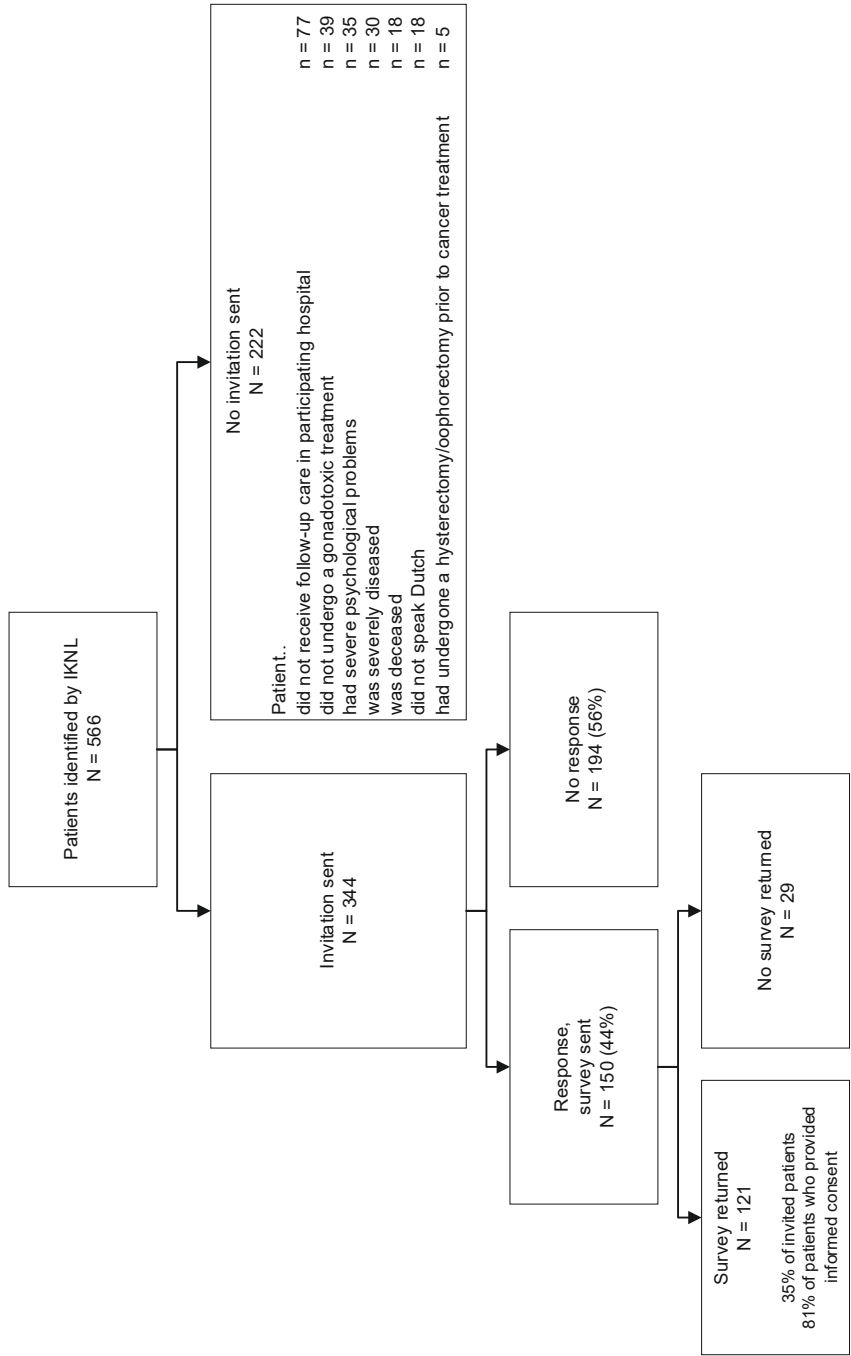


Table 3. Results of quality indicators, variation per hospital and determinants

Quality indicator	Total score Nominator / denominator	%	Variation per hospital %	Missing data %	Determinants (multivariate analyses)
Q11 - Risk of infertility discussed within 2 weeks after diagnosis - At diagnosis - Within 1 week - Within 2 weeks - After 2 weeks - Not discussed	88/121 29 35 24 27 6	72,7	46,7 – 83,3	0	None
Q12 – Risk of infertility discussed when pelvic, skull, craniospinal or total body irradiation takes place	23/24	95,8	85,7 – 100	0	None
Q13 - Oncological healthcare provider consulted expert colleague when he/she had insufficient knowledge about fertility preservation - Insufficient knowledge - Consulted expert colleague	7/16 22/120 7/16	43,8	25 – 100	27,3	None
Q14 - Opportunity of counselling with a gynaecologist is offered	62/121	51,2	40 – 70,8	0	Patient's age; Strength of wish to conceive
Q15 - Individualized selection and risk analysis has been executed within an expert multidisciplinary team prior to fertility preservation treatment - Selection and risk analysis - Multidisciplinary team	19/21 28/35 19/21	90,5	0-100	53,3	None
Q16 - Oocyte and embryo cryopreservation has been discussed with eligible patients - Medically fit - Tolerate FP treatment - Sufficient time - Risks hormone treatment	22/22 33/36 36/38 37/39 22/22	100	100	47,5	None

Table 3. (Continued)

Quality indicator	Total score Nominator / denominator	%	Variation per hospital %	Missing data %	Determinants (multivariate analyses)
Q17 - Embryo cryopreservation is offered as an effective and safe method, when time and circumstances allow for it	34/39	87,2	75 – 100	2,6	None
Q18 - All aspects (a – h) have been discussed in fertility preservation counselling	6/32	18,8	0 – 40	47,5	None
- a. Chance preserve fertility after cancer	28/37				
- b. Chance preserve fertility after FP	20/31				
- c. Risks FP treatment	7/26				
- d. Conditions to have FP treatment	16/34				
- e. Alternative family building options	14/41				
- f. Necessary tests before FP treatment	27/37				
- g. Hormonal screening	6/32				
- h. Possibilities to treat endocrine consequences	12/37				
Q19 - Well-informed about all aspects of the treatment prior to performing emergency IVF	27/33	81,8	60 – 100	5,7	None
Q110 - Shared decision has been made concerning protecting future fertility	44/60	73,3	42,9 – 100	0	Type of healthcare provider
Q111 - Decision was supported with written and/or digital information	43/121	35,5	6,7 – 50	0	Strength of wish to conceive; Time before start of cancer treatment

FP: Fertility preservation

Current quality of female oncofertility care and variation

Guideline adherence, measured with the 11 QIs, is presented in Table 3. Overall, 8 out of 11 QIs scored below 90% adherence. Regarding the different domains, for the domain risk communication a score of 72,7% was reported for 'discussing the risk of infertility within 2 weeks after diagnosis' (QI1). The indicator with the lowest score in this domain was 'consulting an expert colleague when an oncological healthcare provider has insufficient knowledge' (QI3, 43,8%); the indicator with the highest score was 'to discuss infertility risks when a patient receives gonadotoxic radiation therapy' (QI2, 95,8%). In the referral domain, the indicator 'offering FP counselling with a gynaecologist to a patient' scored 51,2% (QI4). Indicators in the counselling domain showed a range from 18,8-100%, with 'discussing all aspects in FP counselling' (QI9) as lowest score, and 'discussing oocyte and embryo cryopreservation with eligible patients' (QI6) as highest score. In the domain of decision-making, a score of 73,3% was reported for 'making a shared decision' (QI10), and a score of 35,5% for 'supporting the decision with written and/or digital information' (QI11).

In all four domains, QI scores varied greatly among the six participating hospitals (Table 3). In 10 out of 11 QIs >20% variation was observed among hospitals.

Determinants

Results from univariate analyses are shown in Supplementary Table 1; for determinants with $p < 0,20$ multivariate analyses were performed. Multivariate analyses showed that 3 determinants at patient level (patient's age, strength of wish to conceive, and time before start of cancer treatment) and 1 determinant at professional level (type of healthcare provider) influenced the scores of 3 indicators significantly (Table 4). Patients who were younger (<30 years), or with a higher wish to conceive (score 6-10) showed a greater adherence to the indicator 'offering FP counselling with a gynaecologist' (QI4). Treatment by a medical oncologist was associated with a lower score for 'making a shared decision' (QI10), and patients with a higher wish to conceive, or with more time before start of cancer treatment (>2 weeks) showed a higher score for 'receiving written and/or digital information' (QI11).

Table 4. Determinants in multilevel analyses and stratified indicator score

Quality indicator	Determinants	N	Multivariate analysis Odds Ratio (95% CI), p-value	Stratified indicator score %
QI4 - Opportunity of counselling with a gynaecologist is offered	Patient's age			
	- 18-29 years	24	4,03 (1,34-12,23), p0,015	79,2%
	- 30-41 years	97	Ref	44,3%
	Strength of wish to conceive			
	- 1-5	61	Ref	36,1%
	- 6-10	60	3,18 (1,46-6,95), p0,004	66,7%
QI10 - Shared decision has been made concerning protecting future fertility	Type of healthcare provider			
	- Medical oncologist	21	Ref	52,4%
	- Other than medical oncologist	39	5,22 (1,29-21,12), p0,02	84,6%
QI11 - Decision was supported with written and/or digital information	Strength of wish to conceive			
	- 1-5	61	Ref	26,2%
	- 6-10	60	2,69 (1,20-6,05), p0,02	45%
	Time before start cancer treatment			
	- < 2 weeks	29	Ref	20,7%
	- > 2 weeks	92	3,03 (1,07-8,62) p0,04	40,2%

DISCUSSION

This study demonstrated that the quality of integrated female oncofertility care measured by a patient-reported measurement with a set of systematically developed QIs is far from optimal. Improvement potential (indicators with <90% adherence) was found for 8 out of the 11 QIs representing all domains in female oncofertility care; risk communication, referral, counselling and decision-making. In addition, a great variation in indicator scores (>20% for 10 out of 11 QIs) was seen among hospitals. Four determinants (patient's age, strength of wish to conceive, time before cancer treatment and type of healthcare provider) were found to significantly influence the scores of three indicators on referral and (support of) shared decision-making.

To the best of our knowledge, this is the first study in which the quality of integrated female oncofertility care was systematically assessed with a set of QIs, using a patient-reported measurement. In a previous study conducted in the Netherlands, oncological healthcare providers were asked via a survey how often they discuss fertility issues with female cancer patients and refer them for FP counselling. In total, 79% usually or always

discussed fertility issues, and 54% usually or always referred patients for FP counselling (15). These percentages are in line with our indicator scores on these items (Q11 72,7% and Q14 51,2%) meaning that still no improvement in quality of care has taken place. Comparing with patient survey studies in other countries without a systematic assessment, our indicator scores are lower. An Australian study reported a discussion rate about infertility risks of 88%, and referral rate of 59% (12), and an American survey study found a discussion rate of 74,5% (29). This could be explained by the study population, in those studies, patients were much younger (15 and 21 years respectively), which was a determinant we found to increase referral rates. Furthermore, in contrast to our study, these studies have addressed the rates of fertility discussions and referrals, but did not focus on FP counselling and decision-making. Previous studies have reported that patients want to be fully informed about all aspects of FP and supported in their decision (4, 30, 31). Unfortunately, we found low scores for the indicators that cover these items; about one fifth for discussing all aspects in FP counselling, one third for supporting the decision with written and/or digital information, and three quarters who have made a shared decision regarding FP. This underlines the fact that not only discussion and referral rates need improvement, but also FP counselling and FP decision-making. A way to improve FP counselling and decision-making could be the provision of a decision aid (32, 33). We developed a FP decision aid that is tailored to cancer type and associated cancer treatments (34). First results are promising, but future research should evaluate its effectiveness.

We found that a higher patient's age was associated with lower referral rates. This is in line with previous studies (35-37). This might be explained by the fact that healthcare providers think that patients who are older do not have a wish to conceive anymore, without asking for it. Furthermore, we found that a higher wish to conceive was associated with higher referral rates and receiving written and/or digital information. A possible explanation is that these patients might ask themselves for a referral. Both associations underline the importance of asking a patient for her needs and wishes regarding future fertility. Our determinants could be used to develop tailored improvement strategies to improve quality of integrated female oncofertility care. For example, oncology nurses can play an essential role in this, as they already play an important role in cancer care programs, and as patient advocates (38-40).

A strength of our study is that it is the first study that systematically assessed the quality of integrated female oncofertility care using QIs extracted from high-quality international clinical guidelines and using a patient-reported measurement. Furthermore, we included a diverse study population, i.e. female cancer survivors with all types of cancers and treatments, from all types of hospitals, of all reproductive ages,

with and without children or relationship, and with a variety in their strength of wish to conceive. This ensured that our results represent clinical practice and are generalizable to other countries.

However, despite the systematic assessment, some limitations should be considered in the interpretation of our results. Selection bias could have occurred because of our low response rate, although this is in line with other survey studies among AYA patients (41), and because each primary oncological healthcare provider had to give consent to invite a patient for participation. In case of exclusion, the reason for exclusion was shared, however this could not be checked by the research team because of regulations regarding data protection. This could have led to exclusion of patients that did not adhere to QIs, while they did match the inclusion criteria. We have tried to minimize this selection bias by explicitly asking each healthcare provider to stick to the in- and exclusion criteria, and in doubt, to discuss the case with the research team. Furthermore, in comparison to other studies, we found a high rate of patients who had FP treatment (37%) (11, 42). This may indicate that patients who have received FP care as recommended, were more likely to participate than patients who did not receive recommended care. This might have led to an overestimation of the quality of integrated female oncofertility care, and in fact, the quality is even lower. Furthermore, recall bias could have played a role as patients were asked to fill in questions three to four years after their diagnosis, treatment, and consultation. In addition, some QIs were hard to answer for patients. Some because they asked for very specific details of information given in consultations (QI6 and 8), others because they asked for things a patient might not know (QI3 and 5). For these QIs, relatively many data are missing, so for future it should be evaluated if these QIs could be measured in medical records or provided by healthcare providers.

In conclusion, our study showed a considerable difference between daily practice performance and care as described in evidence-based guidelines. Low guideline adherence is associated with lower, and therefore suboptimal, quality of care since guidelines assist in delivering the most optimal care. Suboptimal care increases concerns regarding fertility and long-term regret, affecting female cancer AYA patients' quality of life negatively (2, 10, 11). Therefore, improvement is needed. To achieve this, improvement strategies that are tailored to the identified determinants and to guideline-specific barriers should be developed, for example a decision aid (34, 43, 44). Our QI set could then be used to evaluate whether the improvement strategy has a positive effect on quality of integrated female oncofertility care in both the Netherlands and internationally.

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Supplementary Table 1. Determinants in univariate analyses

	Q11 - Risk of infertility is discussed within 2 weeks p-value	Q14 - Opportunity of counselling with a gynaecologist is offered p-value	Q110 - Shared decision has been made concerning protecting future fertility p-value	Q111 - Decision was supported with written and/or digital information p-value
Patient's age	0,812	0,006*	0,186*	0,239
Relationship status	0,489	0,444	0,476	0,941
Parity	0,110*	0,001*	0,560	0,237
Strength of wish to conceive	0,534	0,002*	0,082*	0,026*
Type of cancer	0,754	0,973	0,610	0,119*
Type of cancer treatment	0,076*	0,468	0,979	0,967
Time before start of cancer treatment	0,649	0,689	0,789	0,056*
Type of healthcare provider	0,740	0,336	0,015*	0,646
Type of hospital	0,768	0,891	0,255	0,780

* Multilevel analyses were performed for this determinant (p<0,20)



4

SUBOPTIMAL QUALITY OF INTEGRATED FEMALE ONCOFERTILITY CARE IS ASSOCIATED WITH A LOWERED QUALITY OF LIFE AND WITH MORE DECISIONAL CONFLICT AND REGRET IN FEMALE CANCER SURVIVORS

M. van den Berg, C.C.M. Beerendonk, S.E.J. Kaal, C.M.P.W. Mandigers,
T.N. Schuurman, J. Tol, J.M. Tromp, M.J.D.L. van der Vorst, D.D.M. Braat,
R.P.M.G. Hermens

Submitted

ABSTRACT

Purpose

Female adolescent and young adult cancer patients should be informed about their infertility risks due to cancer treatment. However, quality of female oncofertility care is far from optimal. It is not known whether this suboptimal quality of care is associated with patient-reported outcome measures (PROMs), particularly quality of life, decisional conflict, regret, reproductive concerns, and fertility preservation knowledge.

Patient and methods

A multicentre cross-sectional survey study was conducted to measure the association between quality of oncofertility care and PROMs in female cancer survivors from six hospitals across the Netherlands. Quality indicators were used to assess quality of care, and validated scales to assess PROMs. Quality indicator and PROM scores were calculated, and associations were analysed by T-tests and multilevel multivariate analyses.

Results

Female cancer survivors (N=121) received a suboptimal quality of care with 8 out of 11 quality indicators scoring <90% adherence. When survivors were informed about infertility risks, and were offered fertility preservation counselling, and received digital/written information (i.e. adherence to three quality indicators), their quality of life was highest, and levels of decisional conflict and regret were lowest. Physical quality of life, decision regret, reproductive concerns, and fertility preservation knowledge scores were significantly influenced by female cancer survivor's age, relationship status, strength of wish to conceive, and type of cancer.

Conclusion

Receiving high-quality integrated female oncofertility care is associated with an improved quality of life, and with less decisional conflict and regret in female cancer survivors. As quality of oncofertility care is suboptimal, strategies should be developed and tailored to the current gaps, and to guideline-specific barriers, to improve quality of care and, importantly, quality of life in female cancer survivors.

INTRODUCTION

The importance of addressing the late side effects of cancer treatments and long-term quality of life issues has increased since cancer survival rates in female adolescent and young adult (AYA) cancer patients have improved (1-3). Female AYA cancer patients would like to have a 'normal' life after surviving cancer in which fertility and the possibility to have children in the future are key components (4-6). Therefore, clinical guidelines recommend oncological healthcare professionals to provide information about infertility risks and fertility preservation (FP) options, and, if desired, to offer a referral to and counselling by a reproductive gynaecologist (7-9). Unfortunately, studies have shown that adherence to these guidelines is suboptimal, with not all patients being informed about infertility risks or offered FP counselling (10-13).

Previous studies have shown that female cancer survivors' quality of life is lower and decision regret is higher when they did not receive FP counselling (14-16). Furthermore, decisional conflict increases when survivors have unmet information needs or negative experiences with FP counselling, and decision regret is higher when they did not have a FP treatment (17-20). However, not only receiving FP counselling and having FP treatment, but more key elements are important in delivering high-quality female oncofertility care. These key elements are described in our previous study in which key recommendations were selected from international guidelines and transcribed into 11 quality indicators (QIs) (21, 22). QIs were distributed over four domains in integrated female oncofertility care, particularly, risk communication by the oncological healthcare provider, referral to a gynaecologist for FP counselling, FP counselling and (support of) shared decision-making on FP (21). Within this previous study it has been demonstrated that quality of integrated female oncofertility care measured with the above described QIs is far from optimal (13).

However, at this moment, it is not known whether adherence to oncofertility guidelines measured with QIs is associated with a better quality of life, less decisional conflict, regret, and reproductive concerns in female AYA cancer survivors. In a few studies in cancer care, but not yet in oncofertility care, it has been proven that adhering to guidelines was associated with a better health-related quality of life among cancer survivors (23-25). Furthermore, insight into determinants influence patient-reported outcomes as quality of life can explain the variation in outcomes and should be taken into account when developing tailored improvement strategies.

Within this current study, our first aim was therefore to measure the association between quality of integrated female oncofertility care measured with QIs and quality of

life, decisional conflict, decision regret, reproductive concerns, and fertility preservation knowledge in female AYA cancer survivors. Our second aim was to measure which determinants were associated with these patient-reported outcome measures to be able to develop tailored improvement strategies.

METHODS

Design and setting

This multicentre cross-sectional study was conducted by means of a survey to female AYA cancer survivors in six Dutch hospitals. In the Netherlands, patients receive multidisciplinary oncological care and can be referred for FP counselling by any healthcare provider involved. Patients have no financial reasons to refrain from FP counselling or FP treatment, because it is covered by basic health insurance or by the hospital cryobanks themselves. This study was approved by the Medical Ethics Committee of Arnhem-Nijmegen (NL61570.091.17).

Study population

Female AYA cancer survivors (18-40 years) who were diagnosed in 2016 or 2017, and received a (potential) gonadotoxic treatment were eligible to participate. The Netherlands Cancer Registry was used by the Netherlands Comprehensive Cancer Organization to identify potentially eligible survivors in each participating hospital. After identification, the survivor's primary oncological healthcare provider was asked to assess the following exclusion criteria: survivor was deceased, severely diseased, had severe psychological problems, had undergone a hysterectomy and/or oophorectomy before the start of cancer treatment, or did not receive follow-up care in the participating hospital.

Survey development

The survey was developed within our research team. It consisted of baseline and clinical characteristics, questions that represented the QIs, and questions that represented patient-reported outcome measures (PROMs), particularly quality of life, decisional conflict, decision regret, reproductive concerns, and FP knowledge.

Survey outcome measures

Quality indicators

A total of 40 questions was developed to measure the 11 QIs in female oncofertility care. This process has been described in our previous studies (13, 21). Supplementary Table 1 shows all QIs.

Quality of life

Quality of life was measured using the validated 12-item Short Form Health Survey (SF-12) (26). The 12 items represent physical as well as mental health. The summary physical and mental SF-12 scores were based on the scoring algorithms manual with higher scores representing a better quality of life and scores below 50 representing a lowered quality of life (27). One item was added by our research team to measure quality of life; a thermometer in which survivors had to score their current health status on a scale of 0-100.

Decisional conflict

Female cancer survivors' conflict with decision-making was measured using a Dutch translation of the validated Decisional Conflict Scale (28). This scale includes 16 items evaluating survivors' perspectives of how certain they felt about the decision whether they wanted to have FP counselling or FP treatment on a five-point Likert scale, ranging from 0 (totally disagree) to 4 (totally agree) (29). Item 15 ('I expect to stick with my decision') was removed due to the retrospective design of our study. Items were converted to a final score of 0-100 with higher scores representing higher levels of conflict. Scores below 25 are associated with an absence of decisional conflict, whereas scores exceeding 37,5 are associated with decision delay and feeling unsure (29).

Decision regret

Female cancer survivors' current regret regarding their past decision (decision to have FP counselling or to have FP treatment) was measured using the validated Decisional Regret Scale on a five-point Likert scale, ranging from 1 (totally disagree) to 5 (totally agree) (30). Sum scores ranged from 5 to 25, with higher scores representing greater regret (30).

Reproductive concerns

Reproductive concerns were measured using a Dutch translation of the validated Reproductive Concerns Scale consisting of 11 items scored on a five-point Likert scale ranging from 0 (not at all) to 4 (very much) (31). The items are statements about thoughts and feelings related to fertility, reproduction or having children. Total score ranged from 0-44, with higher scores representing more reproductive concerns. For healthy controls the mean score is 6,4 (31).

Fertility preservation knowledge

FP knowledge was measured using 12 statements which were retrieved from two questionnaires from previous studies (32,33). For example, one of the statements was: 'All cancer treatments result in infertility', answering categories were 'true', 'false'

or 'do not know'. A total FP knowledge score was calculated (range 0-12), with a higher score representing more knowledge.

Data collection

Eligible female cancer survivors received an invitation letter from their primary oncological healthcare provider to participate in 2020/2021. After obtaining informed consent, a paper version of the survey was sent by mail. In total, 344 survivors were invited to participate. If no informed consent or completed survey was received within three weeks, one reminder was sent.

Data analysis

QI adherence scores were calculated in our previous study (13). PROMs (quality of life, decisional conflict, decision regret, reproductive concerns, and FP knowledge) were analysed descriptively according to the published manuals. To evaluate which determinants were associated with PROMs, we first studied the univariate relation between PROMs (dependent variables) and determinants (independent variables) that could influence the PROM. Determinants were extracted from literature and included age, relationship status, parity, strength of wish to conceive, type of cancer, type of cancer treatment, time before start of cancer treatment, type of healthcare provider, and type of hospital (10, 11, 34). We used a generalized linear mixed model which accounts for the nested structure of data, because individual patients (patient level=1) are nested within hospitals (hospital level=2). For determinants with $p < 0.20$ in univariate analyses, we performed multivariate linear regression analyses. Collinearity between determinants was also tested. If a correlation (>0.6) was detected, the most relevant variable with respect to content was included in the multivariate analyses. Independent samples T-tests were used to evaluate whether QI adherence scores were associated with the PROMs. In order to achieve reliable results, associations were only calculated for those QIs with a minimum of 10 responses for adherence or non-adherence. Thereafter, multivariate analyses were performed to adjust for the effect of the determinants that were associated with the PROMs. Furthermore, QIs were combined for adherence to evaluate if (non)-adherence to a combination of QIs was also associated with the PROMs. Again, a minimum of 10 responses was needed for each degree of freedom in the model to develop a reliable multilevel model.

RESULTS

Study population

In total, 566 survivors were identified by IKNL of whom 344 met inclusion criteria. Main reasons for exclusion were: survivor did not receive follow-up care in participating hospital (N=77), had severe psychological problems (N=35), or was severely diseased (N=30). A total of 150 out of 344 survivors provided informed consent of whom 121 (35%) returned their survey. Mean female cancer survivor's age at diagnosis was 34 years, 51,2% had FP counselling, and 37,2% had FP treatment (Table 1).

Quality indicator scores

Guideline adherence, measured with the 11 QIs is presented in Table 2. Of all survivors, 72,7% was informed about her infertility risks, 51,2% was offered FP counselling with a gynaecologist, with 18,8% all aspects were discussed in FP counselling, and 35,5% received written/digital information.

Table 1. Baseline characteristics

Characteristic	Number	%
Response rate	121 / 344	35
Mean age at diagnosis	34,0 years (range 18-41, SD 5,1)	
Type of cancer		
- Bladder cancer	1	0,8
- Brain tumour	2	1,7
- Breast cancer	73	60,3
- Cervical cancer	14	11,6
- Colorectal cancer	5	4,1
- Head and neck cancer	1	0,8
- Leukaemia	3	2,5
- Lung cancer	1	0,8
- Lymphoma	15	12,4
- Osteosarcoma	2	1,7
- Ovarian cancer	2	1,7
- Soft tissue sarcoma	2	1,7
Cancer treatment		
- Breast surgery	72	59,5
- Chemotherapy	112	92,6
- Hormone therapy	45	37,2
- Immunotherapy	20	16,5
- Irradiation therapy	80	66,1
- Breast	56	70
- Skull/Craniospinal	8	10
- Pelvic	10	12,5
- Total body	6	7,5
- Uterine or ovarian surgery	11	9,1

Table 1. (Continued)

Characteristic	Number	%
Relationship status		
- Yes, in a relationship	110	90,9
- No, single	11	9,1
Parity		
- Nulliparous	50	41,3
- Parous	71	58,7
Strength of wish to conceive at diagnosis (mean, scale 1-10)	5,8 (range 1-10, SD 3,5, median 5)	
- Nulliparous	7,0 (range 1-10, SD 2,9, median 7,5)	
- Parous	4,9 (range 1-10, SD 3,6, median 5)	
Number of survivors who received fertility preservation counselling	62 / 121	51,2
Number of survivors who had fertility preservation treatment (3 survivors had 2 treatments)	45 / 121	37,2
- Oocyte cryopreservation	24	53,3
- Embryo cryopreservation	11	24,4
- Ovarian tissue cryopreservation	3	6,7
- Trachelectomy or unilateral ovariectomy	9	20
- GnRH agonists	1	2,2

Table 2. Quality indicator scores

Quality indicator	Total score Nominator / denominator	%
Q11- Risk of infertility discussed within 2 weeks after diagnosis		72,7
- Yes	88/121	
- No	33/121	
Q12 – Risk of infertility discussed when pelvic, skull, craniospinal or total body irradiation takes place		95,8
- Yes	23/24	
- No	1/24	
Q13 – Oncological healthcare provider consulted expert colleague when he/she had insufficient knowledge about fertility preservation		43,8
- Yes	7/16	
- No	9/16	
Q14 – Opportunity of counselling with a gynaecologist is offered		51,2
- Yes	62/121	
- No	59/121	

Table 2. (Continued)

Quality indicator	Total score Nominator / denominator	%
Q15 - Individualized selection and risk analysis has been executed within an expert multidisciplinary team prior to fertility preservation treatment		90,5
- Yes	19/21	
- No	2/21	
Q16 - Oocyte and embryo cryopreservation has been discussed with eligible patients		100
- Yes	22/22	
- No	0/22	
Q17 - Embryo cryopreservation is offered as an effective and safe method, when time and circumstances allow for it		87,2
- Yes	34/39	
- No	5/39	
Q18 - All aspects (a – h) have been discussed in fertility preservation counselling		18,8
- Yes	6/32	
- No	26/32	
Q19 - Well-informed about all aspects of the treatment prior to performing emergency IVF		81,8
- Yes	27/33	
- No	6/33	
Q110 - Shared decision has been made concerning protecting future fertility		73,3
- Yes	44/60	
- No	16/60	
Q111 - Decision was supported with written and/or digital information		35,5
- Yes	43/121	
- No	78/121	

Determinants associated with patient-reported outcome measures

Multivariate analyses showed that four determinants at patient level (female cancer survivor's age, relationship status, strength of wish to conceive, and type of cancer) influenced the scores of physical quality of life, decision regret, reproductive concerns, and FP knowledge significantly (Table 3). A higher wish to conceive was associated with a higher physical quality of life. Survivors who were single or who had another type of cancer than breast cancer had higher levels of decision regret. Furthermore, higher levels of reproductive concerns were associated with survivors who were younger, were single and had a higher wish to conceive.

Table 3. Mean scores of patient-reported outcome measures and their associated determinants in multilevel multivariate analyses

Patient-reported outcome measure	Mean score (range) (SD)	Determinants	N	Multilevel multivariate analysis Coefficient, (CI), p-value
Physical quality of life (scale 0-100)	48,47 (28,13-62,48) (8,84)	Strength of wish to conceive - 1-5 - 6-10	61 60	3,33 (0,20 - 6,47) p0,038 Ref
Mental quality of life (scale 0-100)	47,95 (21,08-60,94) (9,80)	None significant		
Current health status (scale 0-100)	74,98 (20-100) (12,81)	None significant		
Decisional conflict (scale 0-100)	31,22 (0-98,33) (19,73)	None significant		
Decision regret (scale 5-25)	8,82 (5-23) (4,33)	Relationship status		2,81 (0,15 - 5,48) p0,039
		- Single	10	
		- Partner	111	Ref
		Type of cancer		1,66 (-0,001 - 3,32) p0,05
Reproductive concerns (scale 0-44)	11,21 (0-44) (11,27)	- Breast cancer	73	Ref
		- Other than breast cancer	48	
		Female cancer survivor's age		5,88 (0,99 - 10,78) p0,019
		- 18-29	24	
		- 30-41	97	Ref
		Relationship status		8,06 (1,36 - 14,76) p0,019
		- Single	10	
		- Partner	111	Ref
		Strength of wish to conceive		9,49 (5,77 - 13,22) p0,000
		- 1-5	61	Ref
		- 6-10	60	
Fertility preservation knowledge (scale 0-12)	8,91 (1-12) (1,90)	Female cancer survivor's age		0,89 (0,03 - 1,76) p0,044
		- 18-29	24	
		- 30-41	97	Ref
		Strength of wish to conceive		0,89 (0,21 - 1,58) p0,011
		- 1-5	61	Ref
		- 6-10	60	

Patient-reported outcome measures and their association with guideline adherence

Results of the mean PROM scores of all female cancer survivors are shown in Table 3. Adherence to the QI and PROMs was calculated for four out of eleven QIs (Q11, 4, 10, 11), and three QIs could be combined for adherence (Q11, 4 and 11) (Table 4).

Quality of life

Physical and mental quality of life was slightly lower than in the average healthy

population (48,47 and 47,95 vs 50, Table 3). Table 4 shows that female cancer survivors who received FP counselling had significant higher levels of physical quality of life. In addition, even when only the opportunity of counselling was offered, higher levels of as well physical as mental quality of life were reported. Physical quality of life was lowest when survivors were not informed about infertility risks, were not offered counselling, and did not receive written/digital information, i.e. did not adhere to all three QIs (44,05 vs 51,05 for adherence). Regarding mental quality of life, greatest significant difference was seen between adherence and non-adherence to QI4 (FP counselling offered) and QI11 (received written/digital information) (49,96 vs 45,16). Female cancer survivors scored their current health status 74,98 on a scale of 0-100 (Table 3). This score significantly increased when they were offered or received FP counselling, or received written/digital information. Again, score was highest when there was adherence to all three QIs (80,92 vs 68,33 for non-adherence) (Table 4).

Decisional conflict

Decisional conflict was perceived by female cancer survivors, with a mean score of 31,22 (Table 3). As well as for all QIs separately, as for all combinations of QIs, levels of decisional conflict significantly increased when there was no adherence to the QI(s). When female cancer survivors were not informed about infertility risks, and were not offered counselling, and received no written/digital information, decisional conflict levels exceeded far above 37,5 (score of 48,22) which is associated with decision delay and feeling unsure (Table 4).

Decision regret

Decision regret levels significantly decreased when female cancer survivors received FP counselling (9,69 vs 8,11), had FP treatment (9,72 vs 7,49), or received written/digital information (9,73 vs 7,27). The highest level of decision regret was found when there was no adherence to all three QIs (10,73 vs 7,5 for adherence) (Table 4).

Reproductive concerns

Mean score of reproductive concerns was 11,21 on a scale of 0-44 (Table 3). For all QIs, levels of reproductive concerns did not differ significantly between adherence and non-adherence (Table 4).

Fertility preservation knowledge

Overall, female cancer survivors had a high FP knowledge score (Table 3). Survivors who received FP counselling, had FP treatment, or received written/digital information had significantly more FP knowledge. Again, FP knowledge was highest when there was adherence to all three QIs (Table 4).

Table 4. Patient-reported outcome measures and their association with fertility preservation counselling, treatment, and quality indicator adherence

Patient-reported outcome measure		Physical quality of life ¹ (scale 0-100) Mean score p-value		Mental quality of life (scale 0-100) Mean score p-value		Current health status (scale 0-100) Mean score p-value		Decisional conflict (scale 0-100) Mean score p-value		Decision regret ² (scale 5-25) Mean score p-value		Reproductive concerns ³ (scale 0-44) Mean score p-value		FP knowledge ⁴ (scale 0-12) Mean score p-value	
Received counselling (N=62)		51,06		49,33		79,06		26,47		8,11		14,67		9,69	
Did not receive counselling (N=59)		45,76		46,61		70,68		36,60		9,68		7,76		8,16	
<i>T-test (p-value)</i>		0,001		0,114		0,000		0,006		0,058		0,001		0,000	
<i>Multivariate analyses (p-value)</i>		0,007								0,011		0,524		0,002	
Had FP treatment (N=45)		50,36		50,05		77,58		22,54		7,49		13,29		9,92	
Did not have FP treatment (N=76)		47,36		47,36		73,43		36,92		9,72		10,09		8,39	
<i>T-test (p-value)</i>		0,071		0,070		0,085		0,000		0,007		0,159		0,000	
<i>Multivariate analyses (p-value)</i>		0,283								0,002		0,343		0,002	
Association with adherence to quality indicator															
Q11 - Infertility risks discussed															
Yes (N=88)		48,82		48,20		75,76		27,94		8,48		11,11		9,01	
No (N=33)		47,52		47,29		72,87		40,06		9,79		11,48		8,62	
<i>T-test (p-value)</i>		0,471		0,652		0,272		0,004		0,160		0,881		0,341	
<i>Multivariate analyses (p-value)</i>		0,531								0,143		0,590		0,513	
Q14 - Opportunity of counselling with gynaecologist is offered															
Yes (N=62)		51,18		49,98		78,92		26,83		8,61		12,81		9,36	
No (N=59)		45,62		45,82		70,83		36,37		9,08		9,54		8,47	
<i>T-test (p-value)</i>		0,000		0,019		0,000		0,011		0,573		0,132		0,012	
<i>Multivariate analyses (p-value)</i>		0,002								0,431		0,656		0,195	

Table 4. (Continued)

Patient-reported outcome measure		Physical quality of life ¹ (scale 0-100) Mean score		Mental quality of life (scale 0-100) Mean score		Current health status (scale 0-100) Mean score		Decisional conflict (scale 0-100) Mean score		Decision regret ² (scale 5-25) Mean score		Reproductive concerns ³ (scale 0-44) Mean score		FP knowledge ⁴ (scale 0-12) Mean score	
		p-value		p-value		p-value		p-value		p-value		p-value		p-value	
Q110 - Shared decision concerning FP has been made															
Yes (N=44)		51,06		50,35		78,38		23,37		7,86		15,54		9,76	
No (N=16)		50,29		46,45		80,19		34,79		9,00		13,38		9,73	
<i>T-test (p-value)</i>		0,736		0,169		0,553		0,022		0,310		0,550		0,949	
<i>Multivariate analyses (p-value)</i>		0,451								0,358		0,606		0,823	
Q111 - Decision was supported with written and/or digital information															
Yes (N=43)		50,23		49,64		78,23		24,22		7,27		10,94		9,70	
No (N=78)		47,50		47,02		73,18		35,63		9,73		11,35		8,47	
<i>T-test (p-value)</i>		0,104		0,161		0,037		0,003		0,003		0,860		0,001	
<i>Multivariate analyses (p-value)</i>		0,208						0,003		0,005		0,357		0,004	
Association with adherence to quality indicators combined															
Q11+Q14															
Adherence to both (N=49)		50,80		50,23		78,84		26,45		8,55		12,41		9,46	
Non-adherence to both (N=20)		44,20		46,16		68,75		49,12		10,56		9,35		8,50	
<i>T-test (p-value)</i>		0,002		0,111		0,003		0,000		0,073		0,334		0,036	
<i>Multivariate analyses (p-value)</i>		0,006								0,144		0,732		0,164	

Table 4. (Continued)

Patient-reported outcome measure		Physical quality of life ¹ (scale 0-100) Mean score p-value		Mental quality of life (scale 0-100) Mean score p-value		Current health status (scale 0-100) Mean score p-value		Decisional conflict (scale 0-100) Mean score p-value		Decision regret ² (scale 5-25) Mean score p-value		Reproductive concerns ³ (scale 0-44) Mean score p-value		FP knowledge ⁴ (scale 0-12) Mean score p-value	
Q11+Q111															
Adherence to both (N=35)		50,15		48,72		78,69		23,67		7,26		11,24		9,79	
Non-adherence to both (N=25)		46,53		45,25		71,80		44,92		10,59		12,10		8,41	
<i>T-test (p-value)</i>		0,104		0,206		0,062		0,000		0,003		0,800		0,002	
<i>Multivariate analyses (p-value)</i>		0,128								0,002		0,269		0,008	
Q14+Q111															
Adherence to both (N=32)		51,28		49,96		80,28		23,13		7,44		11,81		9,86	
Non-adherence to both (N=48)		45,26		45,16		70,50		38,83		9,63		9,77		8,28	
<i>T-test (p-value)</i>		0,004		0,039		0,002		0,001		0,023		0,484		0,001	
<i>Multivariate analyses (p-value)</i>		0,011								0,052		0,600		0,016	
Q11+Q14+Q111															
Adherence to all three (N=26)		51,05		48,98		80,92		24,55		7,5		12,62		9,96	
Non-adherence to all three (N=18)		44,05		45,49		68,33		48,22		10,73		8,93		8,44	
<i>T-test (p-value)</i>		0,006		0,287		0,005		0,000		0,005		0,356		0,004	
<i>Multivariate analyses (p-value)</i>		0,014								0,016		0,173		0,012	

FP: fertility preservation, Q1: quality indicator.

¹: multivariate analyses to adjust effect for strength of wish to conceive

²: multivariate analyses to adjust effect for relationship status and type of cancer

³: multivariate analyses to adjust effect for female cancer survivor's age, relationship status, and strength of wish to conceive

⁴: multivariate analyses to adjust effect for female cancer survivor's age and strength of wish to conceive

DISCUSSION

Receiving high-quality integrated female oncofertility care is associated with an improved quality of life, and with less decisional conflict and regret in female AYA cancer survivors measured with QIs. When there was adherence to three QIs (i.e. survivors were informed about infertility risks, and were offered FP counselling, and received digital/written information) female cancer survivor's quality of life was highest, and levels of decisional conflict and regret were lowest. In addition, four determinants (female cancer survivor's age, relationship status, strength of wish to conceive, and type of cancer) were found to significantly influence four PROM scores, particularly physical quality of life, decision regret, reproductive concerns, and FP knowledge.

To the best of our knowledge, this is the first study in which it was demonstrated that adhering to QIs, in integrated female oncofertility care is associated with an improved quality of life in female cancer survivors. In previous studies, an improved quality of life was seen in female cancer survivors who have received FP counselling or FP treatment (14-16). This was in line with our study. However, we also demonstrated that only offering FP counselling was also associated with an improved physical quality of life, and that adherence to more QIs was associated with the highest physical quality of life. Some other studies have shown that decisional conflict increases when female cancer survivors have unmet information needs (19, 20). We were able to confirm these results, as decisional conflict increased when infertility risks were not discussed, and when the decision was not supported with written/digital information. A way to meet information needs and to decrease decisional conflict is the provision of a FP decision aid (35). Our team developed a FP decision aid that is tailored to cancer type and associated cancer treatments, however its effect on decision conflict is still to be evaluated (36).

In contrast to a previous study, we did not find an association between receiving FP counselling and higher levels of reproductive concerns after adjusting for the effects of the associated determinants (female cancer survivor's age, partner relationship, and strength of wish to conceive) (37). Two determinants (age, partner relationship) were also found in the previous study, and adjustments for these effects took place. A possible explanation for the difference in outcome might be the higher number of survivors who received counselling (141 vs 62 in our study), and the fact that they used the reproductive concerns after cancer scale (vs reproductive concerns scale in our study) which measures some additional items.

All above mentioned studies focused on one or two elements in female oncofertility care, for example on receiving FP counselling, or having FP treatment, or receiving information. This is in contrast to our study in which we focused on all domains in

female oncofertility care, particularly on information provision, on offering referral for FP counselling, on FP counselling by a gynaecologist, and on FP decision-making. All these domains have shown to be important in delivering high-quality integrated female oncofertility care as these were selected as key by a multidisciplinary expert panel (21). Within our previous study we showed that the quality of female oncofertility care is far from optimal on all these domains and not only on receiving information or FP counselling (13).

It is often assumed that suboptimal guideline adherence, hence a suboptimal quality of care, is associated with a decreased quality of life in patients, measured with PROMs. However, only a few previous studies, not in female oncofertility care, were, just like us, able to prove this assumption. An American study evaluated adherence to guideline recommendations on cancer prevention among elderly female cancer survivors. They demonstrated that both physical and mental quality of life improved when adherence to the recommendations in the guideline was higher (25). Two recent studies confirmed these results; a Dutch study showed that adherence to these recommendations improved health-related quality of life among colorectal cancer survivors, and a Chinese study showed this association among breast cancer patients (23, 24). With our study, we added evidence to the assumption that a suboptimal quality of integrated care in oncofertility is associated with a lowered quality of life.

A strength of our study is that it is the first study that showed an association between quality of integrated female oncofertility care and quality of life, decisional conflict, and decision regret in female cancer survivors. Furthermore, in contrast to other studies, we analysed more PROMs in the same study population, and analysed their association with adherence to all domains that have proven to be important in delivering high-quality integrated female oncofertility care.

There are also a few limitations to our study. First, selection bias could have occurred as we have no insight into reasons for non-responding and we have a low response rate (35%), although this is in line with previous study among AYA cancer survivors (16, 38). Perceived oncofertility care and PROM results might be different for non-responders than those from responders, which might have biased the results. Second, because of the low response rate, we could not analyse the association with PROMs for all QIs, especially not for QIs in the FP counselling domain. Future research should focus on this aspect. Furthermore, we could not perform multivariate analyses for the association between QIs and decisional conflict as there were no significant influencing determinants. However, because of the highly significant associations between QI scores and decisional conflict in T-tests, we expect that it would still be significant if we were able to perform multivariate analyses. Last, recall bias could have played a role as patients were asked to fill in questions three to four years after

their diagnosis, treatment, and consultation. However, outcome measures like decision regret and reproductive concerns should be assessed when survivors are aware of the consequences of their decision which is the case in our study.

Several conclusions and implications for clinical practice can be drawn from our study. As we have shown that suboptimal quality of integrated female oncofertility care is associated with a suboptimal quality of life in female cancer survivors, efforts should be made to improve this quality. Since quality of care does not improve by itself, improvement strategies should be developed. These strategies should be tailored to the current gaps in oncofertility care, to guideline-specific barriers, and thereafter implemented (39). At this moment, some improvement strategies have already been implemented and studied. Described effects are positive, with more documentations on infertility risks, more access to FP counselling, and more satisfaction with received information being reported (40-43). However, a systematic evaluation of all aspects of integrated quality of female oncofertility care and PROMs is lacking in these studies. In future studies, our QI set could be internationally used to evaluate whether newly developed strategies have a positive effect on quality of integrated female oncofertility care, and, importantly, on quality of life in female cancer survivors.

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Supplementary Table 1. Quality indicators distributed over the domains in female oncofertility care

Domain	Quality indicators
Risk Communication	Percentage of patients in an oncological process who receive a gonadotoxic treatment...
	QI1 with whom at least the risk of infertility is discussed by their oncological healthcare provider early in the oncological process (i.e. within 2 weeks).
	QI2 with whom the consequences (of the treatment) for their fertility are discussed when they have a wish to conceive, and when their ovaries, uterus, hypothalamus, pituitary gland (or all) are in the irradiation area (pelvic, skull, craniospinal irradiation or total body irradiation).
	QI3 of whom the oncological healthcare provider consulted an expert colleague when he/she had insufficient knowledge about fertility preservation.
Referral	QI4 Percentage of patients in an oncological process who receive a gonadotoxic treatment to whom the opportunity of counselling with a gynaecologist with expertise in fertility preservation is offered.
Counselling	Percentage of patients in an oncological process who receive a gonadotoxic treatment...
	QI5 for whom an individualized selection and risk analysis has been executed within an expert multidisciplinary team (i.e. primary oncological healthcare provider and treating gynaecologist).
	QI6 (who are estimated as medically fit for the procedure, are expected to be able to tolerate the treatment regimen, have sufficient time before the commencement of their cancer treatment and, are informed of the potential risks of hormonal treatment including the risks of cancer progression), with whom oocyte and embryo cryopreservation has been discussed during fertility preservation counselling.
	QI7 to whom embryo cryopreservation is offered as an effective and safe method, when time and circumstances allow for it.
	QI8 who have had fertility preservation counselling with a gynaecologist in which all aspects (a – h) have been discussed. a. The chance to preserve ovarian, uterine function, or both, and the chance of spontaneous pregnancy after cancer treatment. b. The chance to preserve ovarian, uterine function, or both, and the chance of pregnancy when using different fertility preservation methods, and expectations for the future. c. The risks of fertility preservation procedures: delay of cancer treatment, surgery (laparoscopy, laparotomy), risk of reintroducing the tumour (metastases) after autotransplantation of cryopreserved ovarian tissue, premature menopause after cancer treatment and unilateral and partial oophorectomy. d. The conditions to undergo fertility treatment after cancer treatment, (number of years a patient should be relapse-free after curation, posthumous reproduction, etc.). The contracts should also be discussed. e. Alternatives, such as oocyte donation, gestational surrogacy or adoption.

Supplementary Table 1. (Continued)

Domain	Quality indicators
	f. Necessary tests before a fertility preservation treatment, such as standard screening for viral pathogens and sexually transmitted diseases. g. Hormonal screening through blood testing. h. Possibilities to treat endocrine consequences owing to the loss of ovarian function.
	QI9 who have been well-informed about all aspects of the treatment prior to performing emergency IVF.
Decision-making	Percentage of patients in an oncological process who receive a gonadotoxic treatment...
	QI10 with whom a shared decision has been made concerning protecting future fertility (together with oncological healthcare provider and gynaecologist)
	QI11 who have had fertility preservation counselling which was supported with written, digital information, or both.



5

PROFESSIONALS' BARRIERS IN FEMALE ONCOFERTILITY CARE AND STRATEGIES FOR IMPROVEMENT

M. van den Berg, Ö. Baysal, W.L.D.M. Nelen, D.D.M. Braat,
C.C.M. Beerendonk, R.P.M.G. Hermens

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ABSTRACT

Study question

What are healthcare professionals' barriers and strategies for improvement in female oncofertility care?

Summary answer

Professionals perceived barriers in knowledge, attitude and organization of oncofertility care and suggested strategies to improve oncofertility care.

What is known already

The potential loss of fertility is one of the most important undesirable side effects of cancer treatment in women of reproductive age. Unfortunately, despite guideline recommendations, not all patients are informed about their fertility risks and referred for fertility preservation counselling. Insight into barriers for discussing fertility preservation and appropriate referral is necessary before improvements can be made.

Study design, size, duration

The aim of this study was to identify barriers and gather improvement suggestions through semi-structured in-depth interviews conducted with 24 professionals working in oncofertility care. Subsequently, an expert panel meeting was held to reach consensus on a set of improvement strategies.

Participants/materials, setting, methods

Oncological professionals were recruited from the three Dutch expertise hospitals for female fertility preservation and their affiliated hospitals. The expert panel consisted of six healthcare professionals, five survivors and two researchers. In the Dutch setting, financial aspects do not play a role in oncofertility care.

Main results and the role of chance

Barriers were identified and categorized into the patient level (e.g. focus on surviving cancer), the professional level (e.g. lack of awareness, knowledge, time, and attitude), or the organizational level (e.g. unavailable written information, disagreement on who is responsible for discussing infertility risks). The expert panel reached consensus on essential elements for a multifaceted improvement programme: development of information materials (leaflets, online decision aid), education of professionals, a role for specialized oncology nurses in informing patients and patient navigators at the fertility department to facilitate referral and counselling, medical record reminders, standard consultations with a gynaecologist, and agreement on responsibility.

Limitations, reasons for caution

Selection bias could have occurred because it is likely that only professionals with interest in oncofertility care participated. However, this would mean that the barriers were underestimated.

Wider implications of the findings

This study forms the basis for the development of a multifaceted oncofertility programme, which is essential to increase adherence to the national clinical guideline.

INTRODUCTION

Over the past decades, the rates of cancer survivorship in young female patients have increased (1). Therefore, attention should be paid to the late side effects of cancer treatment and long-term quality of life issues (2). One of the most important undesirable side effects of cancer treatment in women of reproductive age is the potential loss of fertility. Some women even report the potential loss of fertility almost as distressing as the battle with cancer itself (3). When damage to reproductive organs is likely, oophoropexy, cryopreservation of embryos or oocytes are effective options available for women to preserve fertility prior to starting their cancer treatment; cryopreservation of ovarian tissue is still considered as experimental (4).

The optimal oncofertility care for young female cancer patients is described in several evidence-based national and international clinical practice guidelines (5-8). These guidelines recommend discussing the potential loss of fertility with all female cancer patients and, if desired, offering a referral to and counselling by a fertility specialist. Hereafter, a patient can decide whether she wants to undergo fertility preservation (FP) treatment. Information about fertility issues related to cancer treatment should be provided, irrespective of a female cancer patient's reproductive age, parity, and disease type or severity (8). Providing information, referral and counselling to these patients affects quality of life positively, reduces long-term regret, and reduces concerns regarding fertility (8-11).

Unfortunately, studies have shown that despite these evidence-based recommendations, the rates of patients who received information about their fertility risks and FP options still vary greatly, from 51% to 95% (11-15). The referral process to a fertility specialist also shows variation in practice: with 9.8%- 67% of these patients being referred (12, 16, 17). It is important to get insight into barriers for delivering optimal oncofertility care to reduce this variation in practice and improve oncofertility care and guideline adherence. Reported barriers in international literature impeding oncologists from discussing infertility risks and FP options are as follows: a lack of time, knowledge, or resources; a need for immediate cancer therapy; perceived poor success rates of FP options; poor patient prognosis; and patient characteristics (e.g. higher age and parity) (12, 18-22). However, most of these studies have been performed in countries where financial aspects also play a key role in professionals' decisions to inform and refer a patient for FP counselling (12, 23, 24). In the Netherlands, cancer care and FP options are reimbursed by standard health care insurance. The first aim of our study was therefore to assess barriers and improvement suggestions among healthcare professionals in female oncofertility care in a setting where financial aspects do not play a role.

Furthermore, whereas multiple studies have assessed barriers in providing optimal oncofertility care, none have included tailoring improvement strategies. Therefore, the second aim of our study was to identify essential elements for a tailored programme to overcome barriers and improve oncofertility care.

MATERIALS AND METHODS

Design

Our study consisted of two parts. First, semi-structured in-depth interviews were conducted with healthcare professionals to identify their barriers and improvement suggestions in female oncofertility care. Second, tailored improvement strategies were selected with a patient and healthcare professional experts to overcome the barriers, fitting it into a nationwide oncofertility programme.

Setting

In the Netherlands, cancer patients receive multidisciplinary oncological care and can be referred for specialized FP care by any medical specialist involved. Dutch breast cancer patients also need referral to a gynaecologist for FP counselling, because they are operated on by surgical oncologists. At three Dutch hospitals, all FP options, including ovarian tissue cryopreservation, are performed (expertise hospitals: Radboudumc Nijmegen, LUMC Leiden, Erasmus MC Rotterdam). All legal residents of the Netherlands are obliged by law to have basic health insurance, which covers FP counselling and all FP options, meaning that patients have no financial reasons to refrain from it.

Study population

Part 1: Identification of barriers and improvement suggestions

Professionals involved in Dutch female oncofertility care were eligible to participate in the study. They included medical, gynaecological and surgical oncologists, haematologists, specialized oncology nurses, and reproductive gynaecologists. They were recruited from the three Dutch expertise hospitals for female FP care (Radboudumc, LUMC, and ErasmusMC) and their approximately 20 affiliated hospitals. Professionals (N=43) were approached by the researcher (MB) by email to participate. Depending on professional's preference, interviews were conducted in person or via telephone. They were not offered compensation for their participation.

Part 2: Selection of improvement strategies

Both patients and professionals were eligible to participate in the expert panel meeting. Patients were recruited from the following patients' networks: Olijf (gynaecological

cancers), AYA (national adolescent and young adult) platform, and the patient advisory board of the research theme Women's Cancers at the Radboudumc. Professionals were recruited from the Radboudumc and its affiliated hospitals. In total, 22 experts were invited to participate.

Data collection and analysis

Part 1: Identification of barriers and improvement suggestions

Semi-structured, in-depth interviews were performed to identify professionals' barriers and improvement suggestions. Interviews were preferred over a survey, because we wanted to obtain in-depth and detailed information on barriers and improvement suggestions. The interview guide was based on key recommendations for high quality female oncofertility care, previously identified by our research team. These key recommendations were extracted and selected by a multidisciplinary expert panel from six national and international guidelines, then appraised as high-quality guidelines by our research team, complemented with the Dutch guideline using a Delphi consensus procedure (25). The key recommendations are distributed over the FP healthcare pathway for patients (risk communication, referral, counselling, and decision-making) and shown in Supplementary Table 1. Barriers and improvement suggestions regarding risk communication and referral were discussed in the interviews, while barriers regarding counselling and decision-making have been identified previously (26). Different levels, based on the framework developed by Flottorp et al. 2013, were used to explore barriers and improvement suggestions (27). This framework facilitates identification and assessment of potential barriers using seven levels: guideline-related factors, patients, professionals, professional interactions, incentives and resources, organization, and social, legal and political characteristics. The interview guide was adapted when new barriers or improvement suggestions were identified, and is shown in the Supplementary Table 2. All interviews were conducted by MB in 2016, and the number of interviews was determined by data saturation (the point at which no new information was mentioned). To confirm that no new information was mentioned, three additional interviews were conducted.

In order to analyse data, all interviews were recorded and transcribed verbatim. Transcripts were not returned to participants for comments. The texts were imported in qualitative research software Atlas.ti (version 7.1.5, Berlin) and coding was, again, guided by Flottorp's framework (27). The coding process consisted of four steps. All steps were performed independently by two researchers (MB and ÖB) to increase reliability and validity. First, all interview transcripts were read. Second, both researchers selected and labelled phrases in which potential barriers or improvement suggestions were described, using open encoding. These codes were then grouped into categories

and finally, these categories were assigned to the appropriate levels, as described by Flottorp. After each step, the results were compared, and any discrepancies were discussed until consensus was reached. If no consensus was reached, a third independent person (WN) was consulted. The inter-coder score was calculated by percent agreement, because it is unlikely that agreement would occur by chance (28). The two coders agreed on 717 out of the initial 778 codes (92% agreement) and discussed about 61 out of 778 codes (8% disagreement). All disagreements included codes that were initially missed and not coded by either one of the researchers. The inter-coder score of 92% is deemed acceptable (28).

Part 2: Selection of improvement strategies

In the second part of our study, an expert panel meeting was held in 2018 to select improvement strategies to overcome the identified barriers. Again, the framework of Flottorp was used (27). To select strategies, a prioritization of barriers was necessary, because barriers that have a large influence on the performance objective are likely to be important targets for an intervention. The expert panel meeting was led by the main researcher (MB) and started with the presentation of all barriers identified in the interviews, complemented with the barriers identified in previous research (26). All barriers are presented in Table 2. Thereafter, the expert panel was divided into three subgroups, each consisting of patients and professionals. Each subgroup separately discussed all barriers, added new barriers, and scored the impact of each barrier on a scale of one to three. The impact score represented to what extent the barrier hindered the adherence to the key recommendation (1: minor extent, 2: moderate extent, 3: major extent) (27). Thus, for three subgroups, the minimum score was three and the maximum score was nine. The scores of all subgroups were added together for each barrier, and a priority list was made. The top eight of identified barriers were considered most important because of the feasibility of implementing adherent improvement strategies for a total of eight barriers in a multifaceted improvement strategy (29, 30). These eight barriers and their associated improvement strategies were discussed with the entire expert panel as part of the development of a multifaceted programme, taking into account the improvement suggestions identified in part I. Finally, the selection of improvement strategies was based on the suggestions made by the professionals in the in-depth interviews, on the priority given by the expert panel, and on previous research (27, 31). Thus, both exploratory and theory-inspired methods were used to select interventions as is recommended in the review by Wensing (32).

Ethical approval

Approval for this study by an ethics committee was not required, in line with Dutch guidelines. The study was performed in accordance with the Declaration of Helsinki, and written consent was obtained from all participants.

RESULTS

Part 1: Identification of barriers and improvement suggestions

In total, 24 out of 43 individual professionals agreed to participate in the interviews. Reasons for declining participation were a lack of time (N=4), not experiencing problems in FP discussions (N=2) and not responding to the initial or follow-up invitations (N=13). The participants' characteristics are presented in Table 1.

Table 1. Participants' characteristics

Part of study	Characteristics	Value, N (%)
Part 1	Type of professional (N=24)	
	Medical oncologist	7 (29%)
	Surgical oncologist	7 (29%)
	Gynaecological oncologist	2 (8%)
	Haematologist	1 (4%)
	Specialized oncology nurse	1 (4%)
	Specialized breast cancer nurse	4 (17%)
	Reproductive gynaecologist	2 (8%)
	Gender	
	Male	3 (12%)
	Female	21 (88%)
	Type of hospital	
	Academic hospital	15 (63%)
	Non-academic hospital	9 (37%)
	Years of experience	
	0-5 years	3 (12%)
	5-9 years	11 (46%)
	10-19 years	5 (21%)
	20-29 years	5 (21%)
	Number of oncofertility patients professionals treat yearly	
	≤ 10 patients	2 (8%)
	11-20 patients	10 (42%)
	21-30 patients	5 (21%)
	> 30 patients	6 (25%)
	Unknown	1 (4%)

Table 1. (Continued)

Part of study	Characteristics	Value, N (%)
Part 2	Type of experts (N=13)	
	Researchers, quality of care	2 (15%)
	Professionals	6 (46%)
	Medical oncologist	2
	Gynaecological oncologist	1
	Specialized oncology nurse	1
	Specialized fertility nurse	2
	Survivors	5 (39%)
	Breast cancer	2
	Gynaecological cancer	2
	Soft tissue sarcoma	1
	Gender	
	Male	1 (8%)
	Female	12 (92%)

A total of 28 barriers and 18 improvement suggestions were identified in the interviews, categorized into the patient, professional, and care organization level. Table 2 shows all barriers and Table 3 shows all improvement suggestions. Both are ranked by the number of times they were mentioned (range, 1-23). Barriers and improvement suggestions mentioned most by the professionals are described in the text below. To provide a degree of quantification, we have used words to define rates of mentions: almost all, most, some, half and a third. Supplementary Table 3 shows illustrative quotes of some suggested barriers.

Patient level

Barriers

Most oncological professionals reported that they feel that patients do not place fertility high on their priority list because they are focused on surviving cancer. Furthermore, according to some professionals, patients are not motivated to preserve their fertility because they want to start their cancer treatment as soon as possible.

Improvement suggestions

Almost all professionals think an online individualized decision-aid on oncofertility and handing out information leaflets at the oncology department will improve oncofertility care. Furthermore, they think that it would help if patients themselves were aware of infertility risks when they receive gonadotoxic cancer treatments. Awareness could be created, for example, by a national campaign by the cancer society, or through more online information by disease-specific cancer associations.

Professional level

Barriers

Most professionals reported that they routinely discuss FP, but lack the knowledge of the FP options, methods and tools, particularly the options corresponding to different cancer types. In addition, most professionals reported to be less aware of discussing fertility in patients who are of a higher age, who have children, who don't have a (clear) wish to conceive or who have a poor cancer prognosis. Furthermore, half of the professionals reported lacking the time to discuss fertility, because they have to give a large amount of information regarding the cancer diagnosis in the first consultation with a new patient. Regarding professionals' attitude towards FP, the most frequent mentioned barrier was disagreement between surgical oncologists and medical oncologists on who is responsible for discussing infertility risks.

Improvement suggestions

Improving professionals' awareness of FP is an important suggestion. Most professionals think this could be achieved through education by gynaecologists with expertise in FP. Furthermore, most professionals reported that surgeons should refer breast cancer patients to a gynaecologist for FP counselling in order to leave more time for FP before cancer treatment. Another suggested improvement is to create awareness among oncological professionals on positive or negative ways of communication about infertility risks and FP options.

Organization level

Barriers

At the level of the organization, the barrier most frequently mentioned was the lack of available written FP information at their department. Furthermore, at a third of the hospitals, fertility issues are not routinely discussed at the weekly multidisciplinary team meetings (i.e. meetings where treatment plans for all newly diagnosed cancer patients are discussed).

Improvement suggestions

Almost all professionals mentioned that specialized oncology nurses should have a role in FP care, because nurses have more interest in the psychosocial aspect of the cancer diagnosis. It may, therefore, be logical to give them a role in the FP discussion. Furthermore, almost all professionals reported that fertility should be discussed at those weekly multidisciplinary team meetings, including appointing a primarily responsible physician at each hospital.

Table 2. Professionals' barriers in female oncofertility care

Phase of FP	Level	Barrier
Risk communication and referral	Patient	Fertility is not a priority for patients; they focus on surviving cancer*
		Patients are not motivated; they focus on immediate cancer treatment
		Patients are scared of IVF
		Patients do not come up with the fertility topic themselves
	Professional	Professionals lack knowledge <ul style="list-style-type: none"> - of FP options* - of infertility risks - regarding FP options in different cancer types Particularly professionals working in non-academic hospitals lack knowledge of FP
		Professionals lack awareness <ul style="list-style-type: none"> - of the decision aid* - of the FP guideline - in patients with an older age* - in patients with a higher parity - in patients with a poor prognosis - in patients without a (active) wish to conceive - in mentally disabled patients - in single patients Particularly surgical oncologists lack awareness of FP
		Professionals have a lack of time* <ul style="list-style-type: none"> - professionals have to provide too much information at diagnosis - professionals do not provide written information
		Professionals have a lack of agreement <ul style="list-style-type: none"> - surgical oncologists believe that medical oncologists are responsible for FP discussions - if there is no definitive treatment plan
		Professionals have a lack of self-efficacy <ul style="list-style-type: none"> - FP is a difficult topic for them to discuss
		Professionals have a lack of outcome expectancy <ul style="list-style-type: none"> - professionals think they scare women when they discuss FP
	Organization	Written information is not available*
		FP is not discussed at multidisciplinary meetings
		It is difficult to arrange an appointment with a gynaecologist for a patient
		Disagreement between departments on who is responsible for fertility discussions
		No nurses are available to support professionals

Table 2. (Continued)

Phase of FP	Level	Barrier
Counselling and decision-making	Patient	Patients do not feel supported
		Patients' preferences are not taken into account by gynaecologists
	Professional	Professionals have a lack of communication
		- patients do not have the opportunity to ask all questions
		Professionals provide incomplete information
		- not all applicable options are discussed
		- not all benefits and disadvantages of FP options are clearly explained
	Organization	Written information is not available
		Professionals lack time for counselling

*More than 50% of all professionals mentioned the barrier

FP: Fertility preservation, IVF: In vitro fertilization

Table 3. Professionals' improvement suggestions in female oncofertility care

Phase of FP	Level	Improvement suggestion
Risk communication and referral	Patient	Development and provision of patient information materials
		- Decision aid*
		- Leaflets*
		- Option grid
		Increase patients' awareness
	Professional	Professionals refer women for fertility preservation counselling who have doubts
		Education of professionals*
		- Educate professionals' way of communication
		Increase professionals' awareness*
		Surgical oncologists refer women for fertility preservation counselling*
		Feedback to professionals on their performance
	Organization	Role for specialized oncology nurses*
		Fertility is a standard item at multidisciplinary meetings*
		Easy referral process*
		Standard consultations with a gynaecologist for all female cancer patients of reproductive age*
		Reminders in medical record
		Agreement between healthcare departments on who is responsible for fertility discussions
		Fertility is mentioned in each cancer-specific protocol
Counselling and decision-making	Organization	Implementation of a patient navigator at the fertility department

*More than 50% of all professionals mentioned the improvement suggestion

FP: Fertility preservation

Part 2: Selection of improvement strategies

In total, 13 out of 22 experts agreed to participate in the expert panel meeting. The reason for declining participation was a lack of time. Participants' characteristics are shown in Table 1. Patients in the expert panel agreed with the identified barriers among professionals. Two additional barriers were identified by the patients in the expert panel: namely that prior to the cancer treatment only the medical perspective is discussed at multidisciplinary team meetings, without a mention of consequences for fertility and that no attention is paid to reproductive concerns after cancer treatment. Based on the scores of all subgroups for each barrier, a priority list was made. Table 4 shows the top eight barriers distributed over the FP healthcare pathway for patients, and the seven selected improvement strategies on which consensus was reached to overcome these barriers.

Table 4. Barriers and their impact score including the selected improvement strategies

Phase of FP	Impact score	Barrier	Adherent improvement strategies
Risk communication Referral	9	Lack of knowledge	1
	9	Lack of awareness	1, 2, 3
	9	Disagreement between departments on who is responsible for fertility discussions	4
	8	No written information available	5
	8	Fertility is not a priority for cancer patients	3, 5, 6
	7	Lack of time	6
Counselling Decision-making	7	Incomplete information in fertility preservation counselling	5,7
	7	Gynaecologist does not take patients' preferences into account	7
		No attention for reproductive concerns after cancer treatment*	6,7

Impact score: three subgroups scored to what extent the barrier hindered the adherence to a recommendation (1:minor extent, 2:moderate extent, 3:major extent). Minimum score 3, maximum score 9.

* Barrier newly added by the expert panel

Adherent improvement strategies that overcome barriers:

1. Education of professionals
2. Reminders in medical record
3. Standard consultation with gynaecologist for all female cancer patients of reproductive age
4. Agreement between healthcare departments on who is responsible for fertility discussions
5. Written and online information materials (leaflets, decision aid)
6. Role for specialized oncology nurses
7. Role for patient navigators at fertility department

DISCUSSION

This study reports the findings of a qualitative, in-depth assessment of perceived barriers and improvement suggestions among professionals working in oncofertility care. Barriers have been revealed by using the model of Flottorp, and have been categorized into the patient, professional and organizational level. On the patient level, a focus on surviving cancer instead of fertility, on the professional level, a lack of awareness and a lack of knowledge, and on the organizational level, a lack of available written information and disagreement on who is responsible for discussing fertility, were mentioned as main barriers for optimal oncofertility care. During the expert panel meeting, in which patients also took part, these barriers were confirmed and the barrier that no attention is paid to reproductive concerns after cancer treatment was added. The improvement strategies selected by the expert panel were as follows: development and availability of patient information materials (leaflets, decision aid), education of professionals, a role for specialized oncology nurses in discussing fertility issues, reminders in the medical record, standard consultations with a gynaecologist, agreement in each hospital on who is responsible to discuss infertility risks, and a role for patient navigators at the fertility department.

To the best of our knowledge, this is the first study to identify barriers and tailor improvement strategies to these barriers to deliver optimal oncofertility care. Previous studies have examined barriers or improvements separately, but not concurrently. The identified barriers were in line with earlier studies, in which a lack of professionals' knowledge and patients' characteristics (higher age, higher parity, and poor cancer prognosis) were also identified as barriers (12, 19, 21, 22). It is striking that despite the presence of national clinical guidelines and a national website on FP (www.nnf-info.nl), the main barriers among professionals were still a lack of awareness, and a lack of knowledge. A possible explanation is that professionals are unaware of these guidelines, because they are published in journals and websites that are mainly read by gynaecologists and not by professionals working in oncology care. Therefore, in an attempt to overcome this barrier, the most recent national FP guideline is also published on the Dutch national oncology website and on the national guideline database (7).

Another identified barrier was that professionals feel that women focus on surviving cancer and not on their risk of infertility. Earlier studies have also identified this, the need for immediate therapy either by the professional or by the patient (15, 19, 21). However, other studies reported that cancer survivors have more decisional conflict and regret, and a lower quality of life if they had not received specialized FP counselling (11, 33). An implication of this finding is that professionals should correctly prioritize

the fertility topic at the appropriate moment. Therefore, education of professionals is needed, in particular on oncofertility knowledge and communication skills. Moreover, specialized oncology nurses can play an important role in this. The effectiveness of nurses participating in oncofertility care has already been studied; nurses feel responsible for addressing fertility issues, patients are more satisfied, and more referrals for FP counselling take place (34-36).

One of the strengths of our study is the recruitment of a great diversity of professionals from the three Dutch expertise academic hospitals for female FP care and their affiliated non-academic hospitals. This provides a reflection of the perceived barriers and improvement suggestions throughout the Netherlands. Another strength is the in-depth insight into the barriers and improvement suggestions, in contrary to previous studies where only a quantitative assessment was performed. This provided us with more detailed information and more input to select improvement strategies.

This study also has some limitations. First, all professionals were asked for participation via email. It is likely that only professionals with interest in oncofertility care participated in this study. However, this would mean that we have underestimated the number of barriers and that even more barriers exist. To identify non-participants' barriers, we could have sent an online survey. However, 13 out of the 19 participants who declined participation did not respond to our e-mail invitations at all, so they would be very unlikely to respond to a survey. Furthermore, the question is whether it would have revealed additional barriers, because most barriers in our study were identified by exploring them in-depth. Second, patients were involved in the expert panel meeting, but not in the barrier identification. Results might have been different if individual interviews were performed with both professionals and patients. To reduce these possible differences, all patients received an overview of the identified barriers 2 weeks prior to the expert panel meeting, in order to have enough time to agree with the identified barriers and/or to add new barriers. Third, bias could have occurred in the interpretation of the interview transcripts. Therefore, all interview transcripts were independently coded by two researchers, and discrepancies were discussed. Fourth, most interviewed professionals worked at an academic hospital at which FP awareness might be higher due to short communication lines between oncology and fertility departments. However, this would also signify an underestimation of the barriers.

The establishment and dissemination of the national clinical female oncofertility care guideline is not sufficient to improve care. In order to improve adherence to the guideline, implementation activities are necessary. Our tailored improvement strategies form the basis for a multifaceted oncofertility programme, which is an important and essential implementation activity. In Canada and the United States of

America, dedicated cancer and fertility programmes were developed and evaluated for their effect on patient satisfaction, information provision, and referral. These studies show improvements in patient satisfaction, and more referrals (34, 36, 37). These outcomes are promising for the design of a nationwide oncofertility programme in the Netherlands, since FP care is reimbursed in our country and, patients and professionals have no financial reasons to refrain from referral for FP counselling.

Conclusion

In summary, this is the first study to identify barriers and tailor improvement strategies associated with these barriers, with the aim of delivering optimal oncofertility care. Professionals particularly perceived barriers in awareness, knowledge, attitude, and organization of female oncofertility care. To overcome these barriers, patients and professionals selected seven tailored improvement strategies, including development of patient information materials, education of professionals, roles for specialised oncology nurses, and agreement in each hospital on who is responsible for discussing infertility risks. This selection forms the basis for a multifaceted oncofertility programme, which is essential to increase adherence to the national clinical guideline on female oncofertility care to provide a better quality of life for female cancer survivors.

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Supplementary Table 1. Key recommendations in female oncofertility care distributed over the oncofertility care pathway

Key recommendation

Domain 1: Risk communication

It is the opinion of the workgroup that the oncological healthcare provider should at least discuss the risk of infertility with the patient, early in the oncological process.

The oncological healthcare provider should inform patients about the consequences [of the treatment] for their fertility when they have a wish to conceive, and when their ovaries, uterus and/or hypothalamus/pituitary gland are in the irradiation area (pelvic, skull, craniospinal irradiation or total body irradiation).

When the oncological healthcare provider has insufficient knowledge about fertility preservation, he/she should consult an expert colleague.

Domain 2: Referral

It is the opinion of the workgroup that the opportunity of counselling with a gynaecologist, with expertise in fertility preservation, should be offered to all women of reproductive age with cancer, who are scheduled to undergo a potential gonadotoxic treatment.

Domain 3A: Counselling, methods of fertility preservation

It is advised to offer IVF with cryopreservation of all embryos to women who are at risk of becoming infertile due to chemo- or radiotherapy, as an effective and safe method, when time and circumstances allow for it.

Domain 3B: Counselling, preconditions of fertility preservation

The safety of the woman should be guaranteed by –prior to the execution of a fertility preservation treatment– executing an individualized selection and risk analysis within an expert multidisciplinary team. The composition of this team should be specified in a local protocol and should, at least, consist of the primary oncological healthcare provider and the treating gynaecologist.

Embryo or oocyte cryopreservation should be discussed with all young women about to undergo potentially sterilizing chemotherapy or pelvic radiation and estimated as medically fit for the procedure, are expected to be able to tolerate the treatment regimen, have sufficient time before the commencement of their cancer treatment and, are informed of the potential risks of hormonal treatment including the risks of cancer progression.

Domain 3C: Counselling, discussion points in fertility preservation counselling

Prior to performing emergency IVF, the patient should be well-informed about all aspects of the treatment.

It is the opinion of the workgroup that the gynaecologist should address the following aspects in fertility preservation counselling:

- a. The chance to preserve ovarian and/or uterine function and the chance of spontaneous pregnancy after cancer treatment.
 - b. The chance to preserve ovarian and/or uterine function and the chance of pregnancy when using different fertility preservation methods and expectations for the future.
 - c. The risks of fertility preservation procedures: delay of cancer treatment, surgery (laparoscopy, laparotomy), risk of reintroducing the tumour (metastases) after autotransplantation of cryopreserved ovarian tissue, premature menopause after cancer treatment and unilateral/partial oophorectomy.
 - d. The conditions to undergo fertility treatment after cancer treatment (number of years a patient should be relapse-free after curative, posthumous reproduction etc.). The contracts should also be discussed.
 - e. Alternatives, such as oocyte donation, gestational surrogacy or adoption.
 - f. Necessary tests prior to a fertility preservation treatment, such as standard screening for viral pathogens and STDs.
 - g. Hormonal screening through blood testing.
 - h. Possibilities to treat endocrine consequences due to the loss of ovarian function.
-

Domain 4: Decision-making

The decision concerning protecting future fertility should be a shared decision [with patient and care providers].

It is the opinion of the workgroup that fertility preservation counselling should be supported with written and/or digital information.

Supplementary Table 2. Interview guide

Risk communication

- Could you tell me something about your consultations in which you diagnose young women with cancer?
- When do you provide information on infertility risks to young female cancer patients? Why? Do you provide information on infertility risks to all female cancer patients under age of 40?
- What are reasons for not providing information?

Guideline related

- » Disagreement with guideline?

Professional related

- » Lack of awareness? Dependent on age? Parity? Partner? Wish to conceive? Prognosis? Cancer type?
- » Lack of knowledge? On risk of infertility? On fertility preservation options?
- » Lack of time? Lack of agreement? Lack of communication? Attitude towards fertility preservation? Capacity to change behaviour? Need for immediate treatment?

Patient related

- » Patients' preferences? Patients focus on cancer(treatment)? Patients do not ask for infertility risks themselves? Patients attitude towards fertility preservation?

Professional interactions

- » Lack of knowledge in team? Poor communication?
- What are reasons for not providing information?

Incentives and resources related

- » Resources (un)available? Leaflets? Decision aid?
- » No other colleagues available for support?

Organizational related

- » Disagreement on who is responsible for fertility discussions?
- » Low priority for fertility preservation in organization?
- » Not discussed at multidisciplinary meetings?

Social, political and legal factors?

Referral

- Do you offer a referral to all female cancer patients to a fertility specialist? How often do you offer a referral? Why?
 - What are reasons for not offering a referral? (ask for factors described above)
-

Improvement suggestions

- Do you have suggestions on how risk communication and referral rates could be improved?
 - What do you need to improve this care?
 - What do you think the patient needs?
 - What do you think about the following improvement suggestions?
 - » Increase professionals' awareness? How?
 - ◇ Reminders in medical record?
 - ◇ Standardised checklists? For consultations and multidisciplinary meetings?
 - » Increase professionals' knowledge? How? Education of professionals?
 - ◇ Development of written information materials?
 - ◇ Development of individualised decision aid? What information should it contain? When should it be provided?
 - » Involvement of specialised oncology nurses?
 - » Agreement on who is responsible for discussing infertility risks? Surgeon? Medical oncologist?
 - » Standard consultation for all female cancer patients under age of 40?
 - » Use of patient navigators at the fertility department?
-

Supplementary Table 3. Illustrative quotes of barriers mentioned by professionals

Level	Quote
Patient	
Fertility is not a priority: they focus on surviving cancer	Because a majority of women, even though they are really young and have no children, only focus on their cancer. But in the end, they are really glad they received [fertility preservation] counselling.
Patients are not motivated: they focus on immediate cancer treatment	Women say, I want to have my cancer treatment as soon as possible. Well, we know when women choose oocyte preservation, there can be a small delay. Well we know it is okay to have that delay, medically spoken, but in a women's head there can be no delay.
Professional	
Lack of knowledge of FP options	Well, [I tell] before or after surgery, eggs will be raised, yes I keep it really basic, otherwise I should know more about it..Yes, only that there is something and that they will be referred and it will be picked up quickly.
Lack of knowledge of infertility risks	But actually, I have too little knowledge of it. Therefore, I don't tell percentages to the patient.
Lack of knowledge in different cancer types	In my opinion, we are more reserved to refer young women with a Ewing sarcoma or osteosarcoma to a fertility specialist compared to women with breast cancer, as breast cancer patients have, in general, better prognosis.
Lack of knowledge in non-academic hospitals	And that could also be the surgical oncologist in Lutjebroek [small non-academic hospital], and he or she should already mention something [about fertility risks].
Lack of awareness in patients with a higher age	Also, when a woman is older, it could be forgotten sometimes.
Lack of awareness in patients with a higher parity	I think that you do not, especially women at their end 30's who have children aged 8 or 9 years, ask for their wish to conceive.
Lack of awareness in surgical oncologists	Eh, well often, well let me say it this way, it occurs with some regularity that at the multidisciplinary meeting (MM), when at the MM is said; yes there is an indication for chemotherapy, could you [medical oncologist] call the patient. It occurs regularly that we have to ask and does that woman have a wish to conceive. And sometimes it is clear that she does not have it, but very regularly there are doubts and it still has to be asked.
Lack of awareness in patients with a poor prognosis	Yes I do not discuss it [risk of infertility] with women with a life expectancy of a few years.
Lack of awareness in patients without a (active) wish to conceive	Young women are confronted with questions they never thought off and that is another issue, women cannot over think that so quickly.
Lack of time	Look, when I am also discussing that [fertility preservation options], I will have to reserve 2 hours for a patient.

Supplementary Table 3. (Continued)

Level	Quote
Lack of time: professionals have to provide too much information at diagnosis	Look, you have to imagine that when a patient is seen [by a specialist], she leaves dizzy of all the information [she got].
Lack of self-efficacy: FP is a difficult topic to discuss	So, those are some issues that make it difficult for us; how can we tell all that information for God's sake.
Organization	
FP is not discussed at multidisciplinary meetings	It is not a matter of practice, I also do not think that that is necessary, but it is absolutely a fallacy to assume that it is like that [wish to conceive, was asked for] without really knowing it.
Disagreement between departments on who is responsible for fertility discussions	But the effect of chemotherapy, let medical oncologists include that in their system. I do not want to insult them but the entire world ties everything to surgeons and that may not be logical at all.



6

FERTILITY NAVIGATORS IN FEMALE ONCOFERTILITY CARE IN AN ACADEMIC MEDICAL CENTER: A QUALITATIVE EVALUATION

M. van den Berg, S. Nadesapillai, D.D.M. Braat,
R.P.M.G. Hermens, C.C.M. Beerendonk

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ABSTRACT

Purpose

To explore patients' and professionals' experiences with fertility navigators in female oncofertility care.

Methods

Semi-structured in-depth interviews were conducted with nine female cancer patients and six healthcare professionals to explore their experiences. They were recruited from an academic medical center (referral clinic for female fertility preservation care). Data were analysed using the concepts of grounded theory.

Results

Patients were satisfied about the supportive role of the fertility navigator in their fertility preservation process: fertility navigators added value as they became "familiar faces" and provided information, emotional support, personal care, and served as patients' primary contact person. The fertility navigators had a pleasant collaboration with professionals and supported professionals by taking over tasks. To improve the role of fertility navigators, it was suggested that they should always be present in fertility preservation counselling, and attention should be paid to their availability to improve continuity of care.

Conclusion

Fertility navigators provide personal care, improve satisfaction in patients in their oncofertility process, and support professionals. The overview of issues that need to be addressed when assigning fertility navigators in female oncofertility care combined with the improvement suggestions could be used by other centres when considering implementing fertility navigators.

INTRODUCTION

Improvements in the quality of cancer treatment have resulted in higher rates of cancer survival (1, 2). For this reason, the importance of addressing the late side effects of cancer treatment and long-term quality of life issues has increased (3, 4). A major quality of life issue for female adolescent and young adult (AYA) cancer patients is the potential loss of fertility. Depending on the type of cancer, fertility can be affected by gonadotoxic treatments like chemotherapy or radiotherapy, or as a consequence of gonadal damage caused by surgery (5). In order to secure future reproductive function, female AYA cancer patients can undergo a fertility preservation (FP) treatment before the start of their cancer treatment. Current FP options include cryopreservation of embryos, oocytes, ovarian tissue, and ovarian transposition (5).

Studies have shown that female AYA cancer patients would like to be informed about the effects of cancer treatment on their fertility and the FP options available (6-8). Patients also highlighted the need to obtain this information shortly after the cancer diagnosis and to discuss the FP options with a reproductive specialist to be able to make a well-informed decision in a situation with high time pressure (7-9). In addition to their information needs, patients indicated that attention should be paid to their emotional needs and personal concerns in FP decision-making (7, 10). Some patients even report the decision regarding FP the most difficult decision ever made, and almost as distressing as the battle with cancer itself (7, 11, 12). Unfortunately, patients still report unmet needs, when it comes to personalized care (6, 7, 13).

In cancer care, various navigation programs have been implemented to improve information provision and support within the treatment process (14-16). Support is provided by patient navigators (PNs), a role usually performed by nurses, social workers or health educators who are trained for this role (17, 18). PNs fulfil the role of patient advocates for cancer patients; they provide additional information about medical procedures, refer patients for FP counselling, help patients schedule appointments, coordinate communication among the medical team, and navigate and support patients through the process (14-16, 18, 19). In recent years, studies have been carried out using PNs in oncofertility care at the oncology department (20, 21). Initial results indicate that the use of these PNs improves satisfaction in female AYA cancer patients during their oncofertility process (20, 21). However, patients receive their FP consultation and treatment at the fertility department where the oncology PNs are not available. Regarding FP consultation and decision-making, patients also indicated a need to pay attention to their emotional needs and personal concerns (7).

To meet these needs, we assigned two fertility nurses at our academic medical center fertility department as fertility navigators (FNs) in female oncofertility care as a pilot in October 2016. Our aim is to explore patients' and healthcare professionals' experiences with these FNs. In addition, we will explore suggestions for improving FNs' role to ultimately improve female oncofertility care.

METHODS

In this qualitative study, semi-structured in-depth interviews were conducted with patients and healthcare professionals to explore their experiences with fertility navigators (FNs), and to explore their improvement suggestions. COREQ guidelines were used to report our research.

Setting and role of fertility navigators

At the Radboud university medical center (Radboudumc), a referral and expertise center for female FP care, FP counselling is performed by gynaecologists, specialised in reproductive medicine. They inform female AYA cancer patients about the risk of infertility due to cancer treatment and possible FP options.

In October 2016, two fertility nurses were assigned as FNs at the fertility department to support female AYA cancer patients. Before their assignment, the FNs were trained; first, they visited a patient navigator who worked in a hospital in Belgium to get familiar with the role. Thereafter, they attended numerous FP counselling consultations by the gynaecologist to gain experience. After 6 months, they completed this training and fulfilled their role. Their role as FN consisted of the following: the FNs had their first consultation with a patient if a patient chose to undergo a FP treatment after FP counselling with a gynaecologist. They provided instructions about hormonal injections, helped patients schedule appointments, performed ultrasound follow-ups, and attended the oocyte collection if possible. Throughout the process, patients could contact the FN if they had any questions or needed support. One week after the oocyte collection, FNs contacted patients by phone to evaluate their condition and answer any remaining questions.

Participants

Female AYA patients were eligible for participation if they had been diagnosed with cancer, aged 18–40, had undergone FP treatment before their cancer treatment and had at least one consultation with the FN. They were excluded if FP treatment took place because of a benign disease or recurrent cancer. Patients were randomly recruited in July 2018 by selecting every fifth person on the list of 65 patients cared for by FNs

between October 2016 and July 2018 at the Radboudumc. They were approached by a personalized letter from the researchers to participate. To reach data saturation (i.e., the point at which no new information was mentioned), a second round of recruitment was carried out in which every eighth person on the list was randomly selected. All healthcare professionals who perform FP counselling and had worked with the FNs (N=6) were eligible for participation and were invited by e-mail.

Data collection

To guide interviews, two topic lists were developed; one for patients and one for professionals (Supplementary Table 1). These were based on literature and discussions with the research team (6, 7, 17, 22-25). Patients' interviews started with explorative questions about their overall experience at the fertility department. This was followed by discussing various topics about FNs' role; e.g., support, approachability and guidance through the FP process. Interviews with professionals included questions about the support FNs provided to professionals and professionals' opinion of navigators' contribution to patient care. Both the interviews with patients and professionals ended with asking for suggestions to improve FNs' role. Two pilot interviews were conducted to refine the questions. The interviews were conducted between July and September 2018 by S.N., took place at the Radboudumc or by telephone, depending on patients' and professionals' preferences, and lasted approximately 30 min.

Data analysis

All interviews were audio recorded, transcribed verbatim, and analysed through grounded theory analysis using qualitative research software Atlas.ti (version 8.2, Berlin) (26). Patients' and professionals' data were anonymized and analysed separately. The transcripts were not returned to participants for comments or feedback. The coding process consisted of the following steps. Each step was performed independently by the two authors (M.B. and S.N.) to increase reliability and validity. First, all patients' and professionals' interviews were read. Second, both authors selected and labelled phrases describing experiences or improvement suggestions, using open encoding (i.e., using participants' own words). The descriptive codes that showed resemblance were combined and redefined into specific subthemes. These subthemes were then merged into broader themes by using axial coding. The broader themes formed the conceptual model for patients' experiences with FNs that was devised by using the grounded theory method. After each step, the results were compared, and any discrepancies were discussed until consensus was reached. In the coding process, obtained data were continuously compared with previous data as is described in the grounded theory method (26). In addition, each interview was analysed directly, so new topics could be added to the initial topic lists.

RESULTS

Patients’ experiences

In the first round of recruitment, 6 out of the 13 selected patients participated and in the second round, 3 out of the 6 selected patients. The last two patients were interviewed to confirm data saturation. Reasons for declining participation were a lack of time, and some patients did not want to look back on the emotional period. Participants’ characteristics are presented in Table 1. Their experiences with FNs were distributed over four main themes and ten subthemes. An overview of themes and subthemes is presented in Figure 1 and described in detail below. Illustrative quotes from the interviews are presented in Table 2.

Table 1. Demographic patients’ characteristics

Characteristics	Patients (N=9)
Mean age, years (range)	32 (20-40)
Level of education¹	
Low	0
Medium	4
High	5
Marital status during fertility preservation counselling	
Single	3
Partner, but not married	6
Married	0
Type of malignancy	
Breast cancer	7
Hodgkin's lymphoma	2
Chosen fertility preservation treatment	
Oocyte cryopreservation	6
Embryo cryopreservation	3
First contact with fertility navigator	
January – June 2017	4
July – December 2017	4
January – June 2018	1
Mean time between first contact with fertility navigator and time of interview in months (range)	13 (9-20)

¹: Low, primary school or lower vocational education; medium, secondary or intermediate vocational education; high, higher professional education or university.

Navigation through the FP process

Primary contact person

Most patients mentioned that the FN was their primary contact in the FP process. They knew that they could approach them if they had any questions which was pleasant. However, some patients were unaware that the FN was specifically assigned as their contact person.

FNs guided patients through FP process

All patients were satisfied with the FNs' guidance in their FP process. They mentioned that the FN was very supportive, for example in providing information and reassurance during treatment, was patient, and clear in communication. Furthermore, they indicated that the contact with the FN was pleasant because they were personal and showed empathy. Their personal care was reflected in speaking on first name terms, talking to patients in the waiting room while waiting for appointments, being well-informed about a patient's personal situation, and in paying attention to you as a person instead of regulations. Moreover, most patients mentioned that the FN took time for them, gave the feeling that they could ask anything, and kept an eye on their FP process.

Continuity of care

First contact: information provision

Most patients had their first contact with the FN after FP counselling with the gynaecologist. Patients were informed about hormonal injections and the course of the FP process. Some patients mentioned that practicing with the injections and the reassurance FNs gave while practicing were the most supportive activities.

Familiar face in the FP process

Most patients were pleased that the FN, someone familiar, performed ultrasound follow-ups in their process. In some cases, the FN was not available at the follow-up, and although patients understood that they were not always available, others would have preferred them to perform all follow-ups. Furthermore, patients valued the presence of the FN during their oocyte collection and the telephone contact in which they were asked about their condition.

Follow-up care after FP

Half of the patients had contact with their FN after the oocyte collection, and they thought that it matched with the personal care they had experienced. The majority mentioned that they would contact the FN again if they had any questions about fertility during or after their cancer treatment.

Provision of support

Patients could approach FN for mental support

None of the patients approached the FN for mental support. However, almost all patients mentioned that they would have approached the FN if they needed mental support because of the personal care that they had experienced. Two patients mentioned that they would have approached the oncology nurse instead of the FN because of the regular follow-ups in and the distance to the hospital where they were being treated for their cancer.

FNs provided information

All patients mentioned that the FN provided useful information about FP options, the course of the FP process, expected treatment outcomes, and hormonal injections. In addition, the amount of information was well-dosed given that this was a situation where they had to manage large amounts of information. Many patients noted that providing information about hormonal injections was one of the most supportive activities.

FNs provided logistic support

Most patients indicated that the FN helped them schedule FP appointments, taking into account any existing oncology appointments.

Approachability

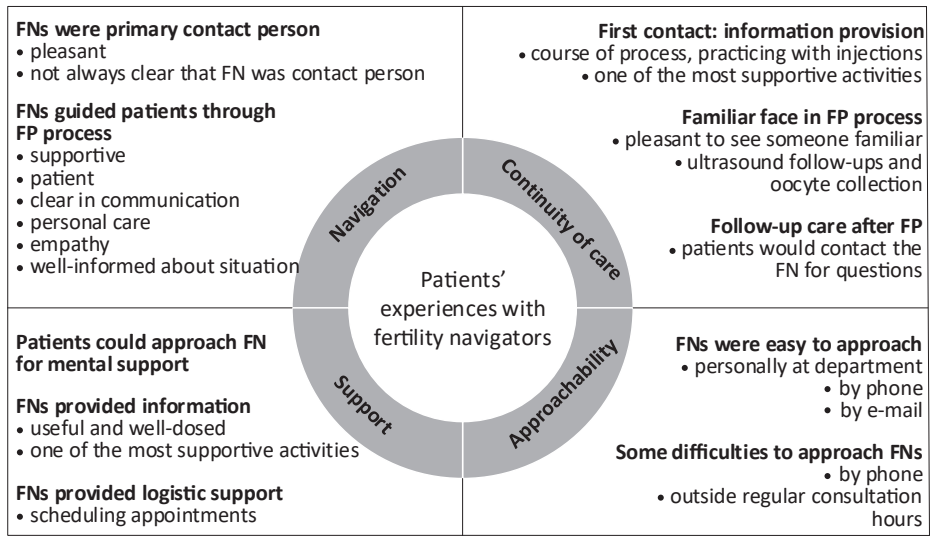
FNs were easy to approach

Almost all patients mentioned that the FN was easy to approach at the fertility department. The majority asked questions in their follow-up appointments or approached the FN personally at the department. Most patients mentioned that the FN also gave them a card with relevant contact details.

Some difficulties to approach FNs

Three out of four patients who contacted the FN by phone were connected directly, while one patient reported having difficulties reaching the FN. Eventually, she had to come to the fertility department to approach the FN personally. Another patient reported that it was difficult to call outside the regular consultation hours.

Figure 1. Overview of patients' experiences with fertility navigators



Healthcare professionals' experiences

In total, six professionals had collaborated with the FNs and participated in the interviews. One professional was gynaecologist in training and five were gynaecologists specialised in reproductive medicine. Professionals' own experiences with FNs were distributed over two main themes and five subthemes, described in detail below. Illustrative quotes from the interviews are presented in Table 2. Professionals confirmed the following patients' experiences: FN is a contact person for patients, navigates patients through the FP process, and provides information and mental support.

Support for professionals

Taking over tasks

Almost all doctors reported that the FN provided support by taking over tasks they performed themselves before the implementation of FNs. For example, taking the medical history and entering data in the medical record prior to FP counselling. As a result, the doctor had more time to provide information about FP in the consultation. After this consultation, FNs took over patient care and coordinated planning. One doctor said that she still had to do most tasks by herself, due to limited availability of the FNs.

Back-up

A few doctors were pleased that the FNs functioned as a back-up in a process with a lot of arrangements, like scheduling appointments.

Table 2. Illustrative quotes from patients' and professionals' experiences

Themes	Subthemes	Illustrative quotes from patients and professionals
Navigation	Primary contact person	<p>'It is just nice to have a primary contact, someone who understands what you are going through, whom you can ask questions to.' (Patient 9)</p> <p>'I know I have had a lot of contact with her [FN], so looking back, yes I guess she was my primary contact, but I cannot remember if that was specifically mentioned.' (Patient 1)</p>
	FNs guided patients through FP process	<p>'It is nice that someone picks you up and literally takes you through the process and, as a figure of speech, drops you off again at the oncology department after two weeks.' (Patient 4)</p> <p>'I really liked that they [FNs] were very personal, for example, they called me by my first name. And they were also really thoughtful, because when you enter this rollercoaster [FP process], it is really nice that they [FNs] not only focus on regulations, but also pay attention to you as a person.' (Patient 2)</p>
Continuity of care	First contact: information provision	<p>'I was still stressed, because I am really afraid of injections, but she really did her best to allay my fears.' (Patient 5)</p> <p>'She also made me inject myself, so I knew what it felt like. That was very pleasant, because, yes you have to inject yourself, and you have to know if you are doing it right.' (Patient 8)</p>
	Familiar face in FP process	<p>'In this process, your body is exposed to everyone, so it's pleasant that you don't have to repeat your story to someone new when you have to undergo another ultrasound or puncture.' (Patient 2)</p>
	Follow-up care after FP	<p>'I really liked that [telephone contact after FP treatment]. It felt like they [FNs] were still thinking about me and that was a nice feeling.' (Patient 5)</p> <p>'If I would have questions [after cancer treatment], I would approach the fertility navigator and only if she [FN] could not answer, I would approach the doctor, because she [FN] guided and supported me [through the FP process].' (Patient 5)</p>
Support	Patients could approach FN for mental support	<p>'Yes, and I definitely had the feeling that, if I was worried about something, I could approach her [FN].' (Patient 6)</p>
	FNs provided information	<p>'She [FN] provided a lot of information, for example about hormone injections, why those are necessary, what the expected outcome is, but also instructions about the preparation, how to inject yourself, yes she really prepared me for the [FP] process.' (Patient 2)</p>
	FNs provided logistic support	<p>'She [FN] really tried to make it easier for me by combining as much as possible [appointments], so I did not have to come [to the hospital] all the time.' (Patient 9)</p>

Table 2. (Continued)

Themes	Subthemes	Illustrative quotes from patients and professionals
Approach-ability	FNs were easy to approach	'I received a complete instruction on when to call which person and that went very smoothly. That [instruction] was always given very accurately.' (Patient 7)
	Some difficulties to approach FNs	'I could not call her [FN] directly, but I was also supposed to call the front desk [of the fertility department], so I had problems with reaching her [FN] once. I happen to live close by, so I went there [fertility department] myself.' (Patient 4)
Suggestions for improvement		'Well, I would have liked that one of them [FNs] always performed the ultrasound follow-ups. Because some nurses were not informed about my situation and they [nurses] said [during ultrasound]: Oh you really have a lot of follicles. And I thought, yes, but this is my only chance, and I did not feel like explaining that again.' (Patient 2)
Support for professionals	Taking over tasks	'Well, it is really pleasant that I can delegate a lot of tasks to them [FNs], so I can focus on the medical aspect of the [FP] counselling and they [FNs] take care of the practical aspects [of FP treatment].' (Professional 1)
	Back-up	'And what they [FNs] both do... they are well aware of what needs to be done and ask me sometimes: Oh, have you already done this, or did you arrange that?' (Professional 1)
Collaboration with FNs		'They [FNs] try to be very flexible to see [FP] patients, so they are also willing to see patients outside regular consultation hours.' (Professional 2)
	Contact person for other professionals	'For example, other IVF nurses, who have to give an instruction [about hormone injections] to a patient, approach them [FNs] with questions about schedules or medication'. (Professional 5)
	Approachability	'Most of the time I approach them [FNs] in person, I know I can also call them or send an e-mail, but I usually prefer personal contact to discuss what needs to be done.' (Professional 6)
	Availability	'Yes, the availability still deserves attention, certainly. It is just annoying when you don't know if you can count on them [FNs].' (Professional 2)
Suggestions for improvement		'I think a schedule should be made so one of them is always available as fertility navigator.' (Professional 3) 'I would prefer that they [FNs] are always present [in FP counselling], so they know exactly what was said, how the patient responded and what subtleties I have made. In addition, the patient also knows that she [FN] has heard it [counselling] and she [patient] can ask questions about the counselling [to the FN].' (Professional 6) 'I really think they [FNs] could expand their tasks alongside patient care, they could educate medical students and nurses and eventually [give presentations] on conferences and symposia.' (Professional 3)

Collaboration with FNs

In general, doctors reported to have a pleasant collaboration. FNs' qualities that contributed to a pleasant collaboration were: flexibility, dedication, and being well-informed about the entire FP process.

Contact person for other professionals

All doctors reported that the FNs were also their primary contact person. Doctors could specifically ask the FN to provide patients additional information after counselling, instead of spending time searching for one of the fertility nurses. Moreover, most doctors mentioned that other fertility nurses also approached the FN as contact person if they had noticed that a patient needed extra support or had questions.

Approachability

All doctors mentioned that FNs were easy to approach if they had questions. They preferred to approach them in person at the fertility department instead of by phone or e-mail.

Availability

All doctors indicated that FNs' availability requires further attention. Currently, both FNs work part-time, combining this role with their job as a fertility nurse. As a result, it may happen that both nurses are unavailable as FNs. This leads to a lack of continuity and flow of care in the process for patients, and doctors needed more time to arrange the FP process themselves.

Suggestions for improvement

Suggestions from patients and professionals to improve FNs' role are presented in Table 3. Patients mentioned that FNs' role should be highlighted more in the beginning of the process, and that they should always be present in FP counselling, ultrasound follow-up, and oocyte collection. Professionals suggested more improvements, in particular that FNs' availability and approachability should be improved, that FNs should have a consultation with a patient before FP counselling, and that they should be present in the counselling. Furthermore, their tasks could be expanded when no new FP patients are referred. Illustrative quotes are presented in Table 2.

Table 3. Patients' and professionals' improvement suggestions

Patients' suggestions	Professionals' suggestions
General improvements	General improvements
FNs' role should be highlighted more in the beginning of the FP process	FNs' availability should be improved <ul style="list-style-type: none"> - FNs should have more time as FNs beside their other tasks - Third nurse should be appointed as FN - FNs should be structurally available in regular FP consultation hours
FNs' approachability should be improved by expanding telephone consultation hours	FN's approachability should be improved by having their own pager and phone number
Improving FNs' role in the future	Improving FNs' role in the future
FNs should always be present in FP counselling	FNs should always have a consultation with the patient prior to FP counselling <ul style="list-style-type: none"> - To make patients aware of their role - FNs should take a large part of the medical history giving doctors more time to provide information in FP counselling
FNs should perform all ultrasound follow-ups	FNs should always be present in FP counselling but should not perform FP counselling themselves
FNs should be present during oocyte collection	FNs should have contact with other healthcare professionals, particularly oncological caregivers
FNs should be patients' primary contact person if they start with the IVF-process after recovery of cancer	FNs could support male cancer patients who will undergo semen cryopreservation FNs' tasks could be expanded when no new FP patients are referred, for example: <ul style="list-style-type: none"> - Taking care of planning regarding ovarian tissue cryopreservation - Completing data in registry retrospectively - Educating students and (oncology) nurses to create awareness about FP

FN: fertility navigator, FP: fertility preservation

DISCUSSION

This study explored patients' and healthcare professionals' experiences with FNs in female oncofertility care and explored suggestions to improve their role. Patients and professionals were satisfied about the supportive role of the FN. FNs navigated patients through the FP process, improved continuity of care, provided support to patients and professionals, were easy to approach, and collaborated pleasantly. Suggestions to improve their role concerned their presence and availability to further improve continuity of care.

To the best of our knowledge, ours is the first study that describes both patients' and healthcare professionals' experiences with FNs at the fertility department in female oncofertility care. Although the Oncofertility Consortium (Chicago, USA) implemented a similar program with a FN (27), they did not describe experiences with this program. Similarities between both programs are the following: the FN was the primary contact person for patients and professionals, navigated patients through the FP process, and provided personal care and information about the course of the process. A difference between the programs was that the FN in Chicago also performed FP counselling, while in our study, gynaecologists specialised in reproductive medicine performed the counselling. However, all professionals in our study mentioned that the gynaecologist should always perform FP counselling, as they have broader experience and knowledge in complex individual cases. Another difference is that the FN in Chicago was available 24 h a day for FP counselling (27); it may not be necessary to create a similar 24-h availability in our setting, because none of the patients tried to contact the FNs outside office hours.

In general, our themes and subthemes corresponded with results from previous studies describing patients' experiences with PNs at an oncology department (20-25). In these studies, the PN served as patients' primary contact person at the oncology department guiding them through the cancer treatment process and paying attention to their individual needs (20, 23-25). In addition, patients in our study were glad that the navigators were aware of their situation and provided personal care. Although previous studies reported that oncology PNs provided emotional support to female cancer patients, we were unable to confirm this in our study. None of our patients approached the FN in their process for mental support. However, patients indicated that they received mental support because the FNs provided personal care, and they would approach them if they would need mental support. Furthermore, as in previous studies, our patients reported that information provision was one of the most supportive activities of the FN (20, 21, 23-25).

A strength of our study is the use of semi-structured in-depth interviews that enabled patients and professionals to mention a variety of important aspects of FNs' role. In this way, the overall experiences of the two most important groups who had contact with FNs could be explored.

However, several limitations should be considered in the interpretation of our results. Responses might have been influenced by recall bias. Some patients were interviewed more than 1 year after their FP treatment and they indicated that they did not remember that the FN was specifically assigned to them. Furthermore, most interviewed patients were diagnosed with breast cancer. Patients with other types of cancer may have different experiences with FNs. However, the representation of breast cancer patients in our study can be explained by the relatively high incidence of breast cancer in women of reproductive age (28). In order to minimize possible bias during analysing interviews, M.B. and S.N. coded and analysed all transcriptions separately. Finally, it is uncertain to what extent the implementation of FNs in one single center (the Radboudumc), and their role in female oncofertility care is applicable in other countries, considering the differences in coordination of care and reimbursement.

In the future, more attention should be paid to highlight FNs' role to patients. Main points to take into consideration in improving their future role are their availability in office hours, their presence in FP counselling, and expanding their tasks alongside patient care. These improvement suggestions combined with our overview of issues that need to be addressed when assigning FNs at a fertility department can be used by other centres when considering implementing FNs.

In conclusion, this study explored patients' and healthcare professionals' experiences with FNs in female oncofertility care. They contributed to patient care by navigating patients through the FP process, and providing personal care and information about the process. FNs mainly supported professionals by taking over tasks resulting in more time for them to perform FP counselling. Improvement suggestions can be used to improve FNs' role at the fertility department to ultimately improve female oncofertility care.

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Supplementary Table 1. Topic lists for patients and professionals

Topic list for patients

General topics on fertility preservation (FP) process

- Description of course/process at fertility department?
- Experience at fertility department? Positive, negative?
- First contact person?

Specific topics on fertility navigator (FN)

- When was FN introduced? Right moment?
 - What did FN do for/with you throughout FP process?
 - » Guidance?
 - » Support? What? When?
 - » Most supportive activity?
 - Information provision?
 - » Which information?
 - » Amount?
 - Opportunity to ask questions?
 - Communication with FN?
 - Approachability?
 - When was the last contact with FN? Right moment?
 - » Opportunity to ask questions in future?
 - Explain role and value of FN in your process?
 - Improvement suggestions?
 - » Did you miss any form of guidance/support?
 - » Ideal role of FN in future?
-

Topic list for professionals

- What is, in your opinion, the role of FNs?
 - Any change noticed since introduction FNs? What?
 - Advantages of use of FNs? What? Why?
 - Disadvantages of use of FNs? What? Why?
 - Support?
 - » For you? How?
 - » For patients? How? Added value?
 - Collaboration?
 - » Approachability?
 - » Contact person?
 - Improvement suggestions?
 - » What could FN improve? Why? How?
 - » Ideal role of FN in future?
-



7

DEVELOPMENT AND TESTING OF A TAILORED ONLINE FERTILITY PRESERVATION DECISION AID FOR FEMALE CANCER PATIENTS

M. van den Berg, K. van der Meij, A.M.E. Bos, M.C.S. Boshuizen, D. Determann,
R.R.J.P. van Eekeren, C.A.R. Lok, E.E. Schaake, P.O. Witteveen, M.J. Wondergem,
D.D.M. Braat, C.C.M. Beerendonk, R.P.M.G. Hermens

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ABSTRACT

Background

Decision-making regarding future fertility can be very difficult for female cancer patients. To support patients in decision-making, fertility preservation decision aids are being developed. However, to make a well-informed decision, patients need personalized information tailored to their cancer type and treatment. Tailored decision aids are not available yet.

Methods

Our decision aid was systematically developed by a multidisciplinary steering group (N=21) in an iterative process of draft development, three rounds of alpha testing, and revisions. The drafts were based on current guidelines, literature, and patients' and professionals' needs.

Results

In total, 24 cancer-specific decision aids were developed. In alpha testing, cancer survivors and professionals considered the decision aid very helpful in decision-making, and scored an 8.5 (scale 1-10). In particular, the cancer-specific information and the tool for recognizing personal values was of great value. Revisions were made to increase readability, personalization, usability, and be more careful in giving any false hope.

Conclusions

A fertility preservation decision aid containing cancer-specific information is important in the daily care of female cancer patients and should be broadly available. The final version is highly appraised, valid, and usable in decision-making. After evaluating its effectiveness with newly diagnosed patients, the decision aid can be translated and adjusted according to (inter)national guidelines.

INTRODUCTION

Improved survival rates for cancer patients of reproductive age have increased the importance of addressing long-term side effects of cancer treatments (1, 2). Potential loss of fertility due to the gonadotoxicity of cancer treatments is an important long-term side effect for female cancer survivors of reproductive age (3, 4). Therefore, guidelines recommend that the risk of infertility and fertility preservation options should be considered before the start of the cancer treatment (5, 6). Current fertility preservation options include cryopreservation of oocytes, embryos, and ovarian tissue, ovarian transposition, ovarian suppression, and fertility sparing surgery.

Patients want to be informed about the effects of cancer treatment on their fertility and the available fertility preservation options via written and/or digital information in order to make a well-informed decision (7-9). However, studies have shown that in current care not all patients are informed on these risks and options, and patients have reported unmet information needs (10-13). Even if information on fertility risks and options is provided, decision-making regarding future fertility is very difficult and complex. The decision has to be made in a very short time frame in a period with great emotional distress in which patients and their partners focus on surviving cancer and not on their future fertility (9). In addition, not all fertility preservation options are appropriate for all patients. Dependent on patient's age, relationship status, cancer type, cancer treatment, prognosis and the amount of time before the start of the cancer treatment, some preservation options are more appropriate than others. As a consequence, patients experience decisional conflict regarding this decision. Decisional conflict increases if patients are not referred for fertility preservation counselling, if patients did not obtain enough information on all fertility preservation options, and if patients did not feel supported during decision-making (13-16). This suboptimal care in information provision and support increases concerns regarding fertility and long-term regret, affecting female cancer patients' quality of life negatively (3, 17-20).

Therefore, it is important that cancer patients are well-informed and supported in their decision regarding fertility preservation. Providing a decision aid (DA) may be a way to support female cancer patients in this complex decision-making process. DAs are described as evidence-based tools designed to support patients in making choices among healthcare options. They provide evidence-based information on the options, associated benefits and harms, and help patients to recognize their personal values in the decision-making process. DAs increase patients' knowledge and decrease their decisional conflict compared to usual care (21).

A recent study reviewed and evaluated nine fertility preservation DAs (22). These DAs significantly increased fertility preservation knowledge and decreased decisional conflict. Furthermore, they were found to be helpful, contained relevant information, and patients reported a high level of satisfaction with their use. Only three of these nine DAs are currently available for female cancer patients; one for breast cancer patients, and two not specific to any cancer type, in Portuguese and in German (23-25).

DAs that personalize information based on cancer type and treatment are not available yet. Therefore, the aim of this study was to develop and test an online fertility preservation DA tailored to cancer type and associated cancer treatments and infertility risks for female cancer patients of reproductive age.

METHODS

This section describes the process of development, alpha testing, and revisions of the DA.

Development process

The fertility preservation DA was systematically developed in 2019/2020 using the recommendations published by Coulter et al. (26) and in accordance with the international patient DA standards (IPDAS) criteria (27). The development process is shown in Figure 1. This process was performed by a project group (N=6) consisting of reproductive specialists, researchers with expertise in shared decision-making, and medical writers, and was guided by a multidisciplinary steering group. The steering group (N=15) consisted of healthcare professionals working in female oncofertility care throughout the Netherlands (embryologist, haematologist, medical oncologist, gynaecological oncologist, psychologist, oncological surgeon, radiotherapist, reproductive gynaecologist, specialised oncology nurse, and a specialised fertility nurse), and female cancer survivors and patient advocates (from the adolescent and young adult community, breast cancer, gynaecological and haematological cancer association). Members of the steering group were recruited from the national fertility preservation guideline working group who developed the Dutch guideline in 2016, and were mandated by their scientific association.

Scope and purpose

The scope and purpose of the DA was defined by the project group. The DA should be part of the implementation of the national fertility preservation guideline. A face-to-face meeting was held with the project and steering group to reach consensus on the scope, purpose, target audience and moment of providing the DA.

Content and format

Patients' needs and preferences

To explore patients' needs and preferences in a fertility preservation DA, in-depth interviews were conducted with female cancer survivors with various cancer diagnoses who had fertility preservation counselling and made a decision on fertility preservation treatment in the past. Nineteen survivors were invited to participate and were recruited from an academic medical center. A topic list guided the interviews, survivors were asked for their opinion about: the content of the DA (information about cancer, cancer treatment, fertility preservation options, pregnancy chances, risks, and alternative family building options), the format, ways to personalize the DA (general information or cancer-specific, associated infertility risks, all fertility preservation options or only the ones applicable), a value clarification exercise, time to spent, and the moment the DA should be provided.

Professionals' needs and preferences

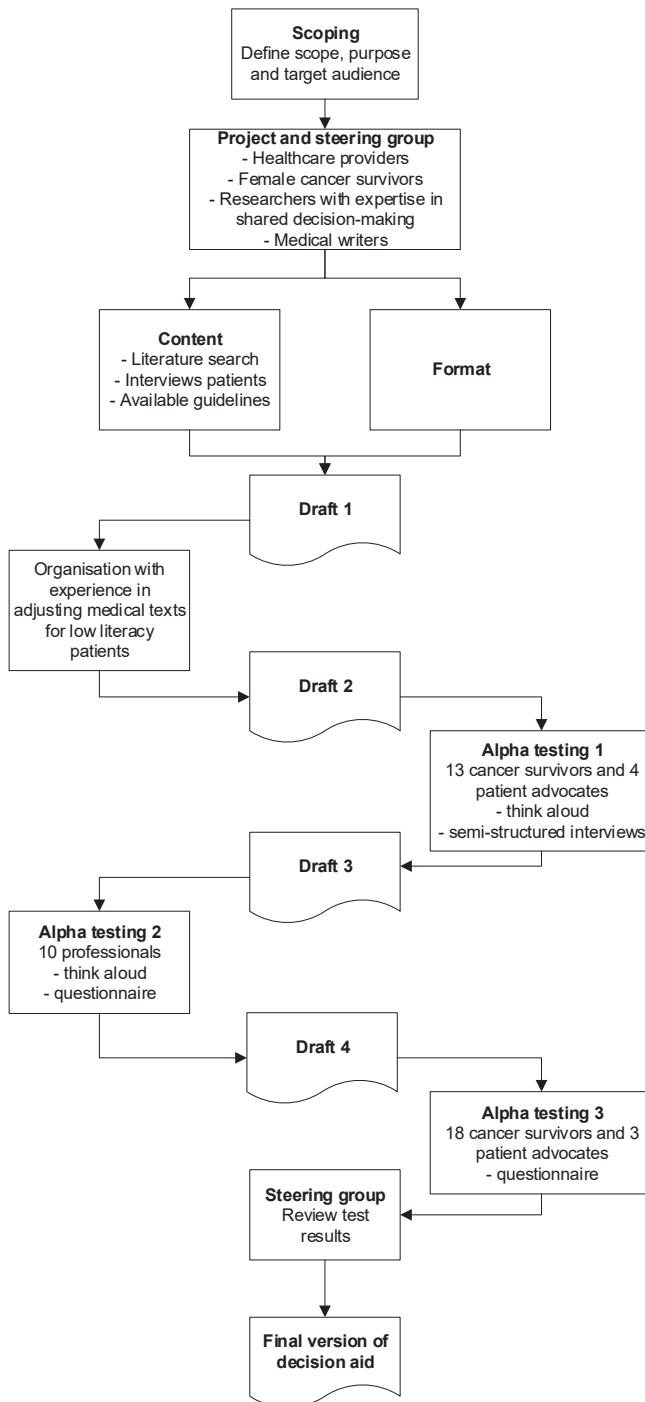
As part of our previous study, 24 oncological healthcare providers and reproductive specialists were interviewed about their barriers and improvement suggestions in female oncofertility care (9). Regarding barriers in information provision, professionals mentioned that there was a lack of written and digital information for patients. Furthermore, professionals mentioned that patients had a need for fertility preservation information tailored to their personal situation to be able to make a decision.

Content

Besides the interviews, a literature review was performed to provide information on current infertility risks and pregnancy chances of fertility preservation options. The following domains were important in fertility preservation decision-making according to professionals' interviews and the literature review (9): (1) infertility risks associated with cancer treatment; (2) burden and risks of fertility preservation treatment; (3) pregnancy chances associated with fertility preservation options; (4) consequences of the decision for future fertility; (5) patients' personal values in decision-making. The content of these domains was tailored according to patients' needs and preferences. The current national fertility preservation guideline formed the basis for the content of domain 1-4 (5). For the fifth domain, important items to clarify patients' values in decision-making were extracted from patients' interviews.

Format

An online, web-based, format was chosen by the project and steering group to be able to provide a DA that is tailored to a patient's cancer type.

Figure 1. Systematic development process of the fertility preservation decision aid.

Alpha testing and revision

After an iterative process of reviewing and revising the content with the project and steering group, the first draft was ready for evaluation by an organisation with experience in adjusting medical texts for low literacy patients (www.stichtingmakkelijklezen.nl). The second draft was evaluated with female cancer survivors who made a decision regarding fertility preservation in the past, and with patient advocates. They were recruited from an academic medical center and patient associations (from the adolescent and young adult community, breast cancer, and gynaecological cancer association). Although they were not the target audience, we invited them for a face-to-face interview because they have experience with fertility preservation decision-making and the consequences of this decision. The first part of the interview was unstructured according to the think aloud method (28). The second part of the interview was semi-structured, they were asked about the content, lay-out, readability, comprehensibility, usability, and acceptability of the DA (29-31). Based on the received feedback, a third draft was developed and alpha-tested with professionals working in oncofertility care, as suggested by Coulter et al. (26), recruited from the steering group. They were also invited for a face-to-face interview using the think aloud method, and were asked to fill in a questionnaire with questions about the content, clearness, usefulness, and to rate the DA. The questionnaire was based on literature and previous interviews (30, 31). Last, a revised fourth draft was quantitatively evaluated with female cancer survivors and patient advocates. They were, again, recruited from an academic medical center and from patient associations. After receiving consent to participate, a questionnaire, similar to the professionals' questionnaire, was sent. In addition to the quantitative evaluation, the quality of the fourth draft was tested against the 64 IPDAS criteria.

RESULTS

Development process

Scope and purpose

The scope and purpose of the DA was to support female cancer patients in their decision whether they want to undergo a fertility preservation treatment or not. The steering group agreed that the DA should be provided before fertility preservation counselling with a reproductive gynaecologist and is meant to be complementary to the counselling. Furthermore, the target audience was defined as female cancer patients of reproductive age (> 18 years) who have to undergo a gonadotoxic cancer treatment and who have to make a decision whether they want to undergo a fertility preservation treatment or not. No cancer types were excluded.

Content and format

Patients' needs and preferences

Nine out of nineteen female cancer survivors participated in the in-depth interview about their needs and preferences in a fertility preservation DA. Reasons for declining participation were a lack of time, and some patients did not want to look back on the emotional period. Their mean age was 32 years, they were diagnosed with breast cancer and with Hodgkin's lymphoma, and all had undergone a fertility preservation treatment.

Regarding the content, all patients mentioned that the DA should be developed per cancer type, so they do not have to read information that is not applicable to them. Furthermore, the most important topics to provide were the consequences of cancer treatment for fertility and the live birth rate per fertility preservation treatment. Patients expressed a need to know their personal risk of infertility in order to make a decision, meaning that the risk of infertility should be provided per cancer treatment. The burden, risks, pros and cons of each fertility preservation option should be extensively provided, in particular the risk of using hormones in hormone sensitive cancers and the impact of using hormones on physical and mental health. Regarding egg donation, adoption, foster care and surrogacy, most patients wanted the possibility to read information about these options, but it should also be possible to skip this information. They mentioned that this is important for the future, but not always at the moment of decision-making. In addition, some patients wanted to read about the steps to go through if you have a wish to conceive after surviving cancer, because that information is lacking at this moment. Another topic in the interviews was the way the DA should be personalized. All patients wanted a DA personalized to their cancer type, and the risk of infertility associated with all cancer treatments possible for their cancer type as it was not always clear what cancer treatment they would receive at the

moment of counselling. Regarding fertility preservation treatments, patients wanted to read about the following options: 'wait and see', oocyte, embryo and ovarian tissue cryopreservation, even if one of those options was not applicable to them. They did not want to have the feeling that options were deliberately withheld from them. However, it should be very clear for whom the treatment is applicable. All patients wanted to use the DA online, and wanted to spent around 30 minutes. Most patients would use the DA before counselling with a reproductive gynaecologist, however some patients mentioned they had been so overwhelmed by the cancer diagnosis that they would use the DA after counselling.

Content and format

Based on patients' and professionals' needs and preferences, the project and steering group decided to develop 24 cancer-specific DAs, one for each cancer type occurring in young females (Figure 2).

Figure 2. Overview of the 24 developed cancer-specific decision aids

<u>Breast</u>	<u>Gastrointestinal tract</u>
Breast cancer – hormone negative	Gallbladder cancer
Breast cancer – hormone positive	Pancreatic cancer
	Rectal cancer
	Stomach cancer
<u>Bone and articular cartilage</u>	
Sarcoma	
<u>Central nervous system</u>	<u>Hematology</u>
Brain, spinal cord cancer	Leukemia
	(non-)Hodgkin lymphoma
	Multiple myeloma
<u>Endocrine gland</u>	<u>Head and neck</u>
Thyroid cancer	Head and neck cancer
<u>Female reproductive tract</u>	<u>Respiratory tract</u>
Cervical cancer	Lung cancer
Endometrial cancer	
Ovarian cancer	
<u>Gastrointestinal tract</u>	<u>Skin</u>
Anal cancer	Melanoma
Colon and small intestine cancer	<u>Urinary tract</u>
Esophageal cancer	Kidney cancer
Liver cancer	Bladder cancer

All DAs were divided into five chapters according to a commonly used design in DAs (32); Information; Comparison of options; Important items; Your preference and values; and Closure.

The first chapter 'Information' begins with an introduction for whom the DA is applicable, the purpose, and the summary of the content. Thereafter, general information about wish to conceive and about cancer treatment and infertility is provided. In the next page, tailored information about cancer treatments and associated risk of infertility is provided, including consequences for uterine function, if applicable. After reading about infertility risks, the decision is displayed; 'wait and see' versus 'fertility preservation treatment' including all treatments. In the next pages, extensive information about the following topics is provided for all options; for whom the option is appropriate, explanation about treatment, live birth rate, safety, risks, pros, and cons. Furthermore, an image has been developed to explain each treatment. This chapter ends with information about the steps to go through when a patient has a wish to conceive after surviving cancer, including alternative family building options. In chapter 2, patients can compare all fertility preservation options including 'wait and see' in an interactive table. To personalize this table, patients can check and uncheck all options and all above mentioned topics. In chapter 3, patients are asked to answer basic questions about cancer and fertility to check if they understood the information. In the fourth chapter, patients are asked to fill in a value clarification exercise containing nine statements to recognize their personal values in decision-making. An example of a statement is shown in Supplementary Figure 1 and shows that patients could score the statement on a scale of 0 (neutral) to 5 (totally agree). Subsequently, patients could fill in if they leaned towards 'wait and see' or towards a fertility preservation treatment and how confident they were about their preference on a scale of 1 to 10. In the final chapter, patients are asked to fill in three questions to clarify if they had gained enough knowledge, learned about their values in this decision, and if they were prepared for the fertility preservation counselling consultation.

Alpha testing and revision

To increase readability, wording, sentences and tables were changed in the first draft. For example 'fertility preservation options' was changed into 'possibilities to have children in the future', enumerations were used to clarify complex sentences, and detailed information was removed from tables to increase readability. In addition, where possible, the text was shortened to keep patients' attention and to increase readability for patients with a low health literacy.

Alpha testing round 1

Consensus was reached on the adjustments with the steering group, and the second draft was ready for evaluation by using the think aloud method and a semi-structured interview. In total, 17 out of 24 female cancer survivors and patient advocates consented to participate. Their characteristics are shown in Table 1. Overall, they were satisfied with the content and lay-out and considered it very helpful in decision-making. In particular, the cancer-specific information and the tool for recognizing personal values was of great value. The information in the DA was comprehensible and the images were very illustrative. All cancer survivors would have liked to use the DA if this would have been available. However, they also had suggestions to improve the DA. Regarding the content, they suggested to add information about the process of accepting that a patient might never have children, to move information about alternative family building options from 'wait and see' to 'wish to conceive after surviving cancer', to emphasize that the DA does not replace oncofertility consultations, and to be careful in giving any false hope or wrong expectations. To increase usability, it was suggested to clarify navigation through the DA. Cancer survivors also suggested to personalize the DA more by choosing which fertility preservation options to read about instead of going through all options. Last, to increase readability, they suggested to make icon arrays and tables visible at a glance and to add colours. This led to major changes in the third draft.

Table 1. Characteristics of female cancer survivors and patient advocates in alpha testing round 1 and round 3

	Alpha testing round 1		Alpha testing round 3	
	Cancer survivors (N=13)	Patient advocates (N=4)	Cancer survivors (N=18)	Patient advocates (N=3)
Mean age in years (range)				
Current	35,3 (23-49)	52,7 (43-69)	34,8 (23-49)	56 (43-70)
At diagnosis	28,6 (19-35)		28,4 (19-35)	
Gender (% Female)	100%	75%	100%	67%
Education level (N, %)				
Secondary education	1/13 (7,7%)	0/4 (0%)		
Vocational education	2/13 (15,4%)	1/4 (25%)	3/18 (16,7%)	1/3 (33%)
Higher professional education	5/13 (38,5%)	2/4 (50%)	6/18 (33,3%)	1/3 (33%)
University degree	5/13 (38,5%)	1/4 (25%)	9/18 (50%)	1/3 (33%)
Diagnosis (N, %)				
Breast cancer	5/13 (38,5%)		7/18 (38,9%)	
Cervical cancer	4/13 (30,8%)		5/18 (27,8%)	
Endometrial cancer			1/18 (5,6%)	
Hodgkin's disease	2/13 (15,4%)		2/18 (11,1%)	
Ovarian cancer	1/13 (7,7%)		1/18 (5,6%)	
Soft tissue sarcoma	1/13 (7,7%)		1/18 (5,6%)	
Vulvar cancer			1/18 (5,6%)	

Table 1. (Continued)

	Alpha testing round 1		Alpha testing round 3	
	Cancer survivors (N=13)	Patient advocates (N=4)	Cancer survivors (N=18)	Patient advocates (N=3)
Advocate of (N, %)				
Breast cancer		2/4 (50%)		
Haematological malignancy		1/4 (25%)		2/3 (67%)
Gynaecological malignancy		1/4 (25%)		1/3 (33%)
Mean years of experience as advocate (range)		7,0 (3-9)		7,7 (5-10)
Cancer treatment (N, %)				
Surgery breast	5/13 (38,5%)		7/18 (38,9%)	
Surgery reproductive organs	4/13 (30,8%)		7/18 (38,9%)	
Chemotherapy	11/13 (84,6%)		14/18 (77,8%)	
Radiotherapy (reproductive organs)	3/13 (23,1%)		3/18 (16,7%)	
Radiotherapy (not on reproductive organs)	2/13 (15,4%)		4/18 (22,2%)	
Targeted therapy	1/13 (7,7%)		1/18 (5,6%)	
Endocrine therapy	2/13 (15,4%)		2/18 (11,1%)	
Relationship status at diagnosis (N, %)				
Single	4/13 (30,8)		5/18 (27,8%)	
In a relationship	5/13 (38,5%)		8/18 (44,4%)	
Married	4/13 (30,8%)		5/18 (27,8%)	
Parity at diagnosis				
Nulliparous	10/13 (76,9%)		15/18 (83,3%)	
Parous	3/13 (23,1%)		3/18 (16,7%)	
Strength of wish to conceive on a scale of 1-10 (mean, range)			7,1 (2-10)	
Fertility discussed (N, %)				
Yes	11/13 (84,6%)		15/18 (83,3%)	
No	2/13 (15,4%)		3/18 (16,7%)	
Fertility preservation counselling received (N, %)				
Yes, by reproductive gynaecologist	7/13 (53,8%)		10/18 (55,6%)	
Yes, by gynaecological oncologist	4/13 (30,8%)		2/18 (11,1%)	
No	2/13 (15,4%)		6/18 (33,3%)	
Fertility preservation treatment (N, %)				
Yes	10/13 (76,9%)		10/18 (55,6%)	
Oocyte cryopreservation	3/10		3/10	
Embryo cryopreservation	1/10		1/10	
Ovarian tissue cryopreservation	2/10		3/10	
Ovarian transposition	3/10		3/10	
Fertility sparing surgery	3/10		2/10	
Hormonal ovarian suppression	1/10		1/10	
Combined treatments	3/10		3/10	
No	3/13 (23,1%)		8/18 (44,4%)	
Pregnancy pursued (N, %)	1/13 (7,7%)		3/18 (16,7%)	
Stored material used (N, %)	0/13 (0%)		1/18 (5,6%)	

Alpha testing round 2

The third draft was face-to-face evaluated with a total of 10 professionals by using the think aloud method and a questionnaire. Their characteristics are shown in Table 2. In general, professionals were very satisfied with the content, format and lay-out of the DA. They had fewer suggestions to improve the DA than survivors had. They suggested to add a disclaimer to emphasize that the information is based on current guidelines, but is subject to change over time. In addition, they suggested to clarify which treatment (cancer or fertility preservation) is meant in various places throughout the DA, and to add that a patient should ask her oncological healthcare provider for advice if her cancer treatment is not mentioned in the DA. Specifically for the gynaecological DAs, it was suggested to alter the images of the fertility sparing treatments in cervical cancer and endometrial cancer to make them more clear. Results from the questionnaire are shown in Table 3. All professionals would recommend the use of the DA and scored it with an 8,5 (scale 1-10). All suggestions were included in the fourth draft.

Alpha testing round 3

The fourth draft was sent to 23 female cancer survivors and patient advocates of whom 21 responded (Table 1). Results from the questionnaire are shown in Table 3. Female cancer survivors spent an average of 24 minutes on the DA and all assessed the length as 'just right'. Furthermore, the DA was scored as balanced, clear, comprehensible, and 95% would find it very or moderate useful in decision-making if they would have to choose between a fertility preservation treatment or not. Confusing items were reported by 29%, this concerned word use for which suggestions were made, the usability of the comparison table, clearness of risks, and carefulness in giving any false hope to patients. All participants would recommend the DA to others and scored the DA with an 8,5 on a scale of 1-10. Based on the improvement suggestions, a final version of the DAs was drafted with the project and steering group.

Table 2. Professionals' characteristics in alpha testing round 2

	Professionals (N=10)
Mean age in years (range)	47,1 (36-65)
Gender (% Female)	90%
Type of professional (N, %)	
Gynaecological oncologist	1 (10%)
Haematologist	1 (10%)
Medical oncologist	1 (10%)
Oncological surgeon	1 (10%)
Radiotherapist	1 (10%)
Reproductive gynaecologist	2 (20%)
Specialised oncology nurse	1 (10%)
Specialised fertility nurse	2 (20%)
Type of hospital (N, %)	
Academic hospital	7 (70%)
Non-academic hospital	1 (10%)
Cancer center	2 (20%)
Years of experience as professional (N,%)	
0-5 years	1 (10%)
5-10 years	3 (30%)
10-15 years	3 (30%)
15-20 years	0
> 20 years	3 (30%)
Number of oncofertility patients professional treats yearly (N, %)	
0-10	0
10-20	2 (20%)
20-30	4 (40%)
30-40	2 (20%)
>40	2 (20%)

IPDAS criteria

The checklist of the IPDAS collaboration was used to assess the quality of our DA (27). A total of 45 out of 64 criteria on the checklist were applicable to our study based on the development of the DA. Criteria on the field-testing and effectiveness were not applicable as this has not been evaluated yet. The final version of the DA met 43 out of the 45 (96%) applicable IPDAS criteria (Supplementary Table 1). In the content domain, all 23 criteria were met. Regarding the development process domain 19 out of 21 criteria were met. We did not meet the criteria that the online DA allows patients to search for key words. Furthermore, the criteria that patients received feedback on personal entered information was not met, as patients did not have to enter personal information because the DA was already cancer-specific.

Table 3. Alpha testing among female cancer survivors, patient advocates and healthcare professionals

	Draft 3 Healthcare professionals (N=10)	Draft 4 Female cancer survivors and patient advocates (N=21)
Time spent in minutes (range)	30 (20-50)	24 (10-60)
Length		
Too long	0	0
Too short	0	0
Just right	10 (100%)	21 (100%)
Amount of information		
Too much	0	1 (4,8%)
Too little	0	1 (4,8%)
Just right	9 (90%)	19 (90,4%)
Missing	1 (10%)	
Information balanced?		
Yes	9 (90%)	21 (100%)
No, leaning towards wait and see	0	0
No, leaning towards fertility preservation	0	0
Missing	1 (10%)	
DA comprehensible in general?		
Very good	2 (20%)	11 (52,4%)
Good	8 (80%)	10 (47,6%)
Moderate	0	0
Bad	0	0
Risks comprehensible?		
Very good	5 (50%)	6 (28,5%)
Good	4 (40%)	14 (66,7%)
Moderate	0	1 (4,8%)
Bad	0	0
Missing	1 (10%)	
DA clear?		
Very good	4 (40%)	9 (42,9%)
Good	6 (60%)	12 (57,1%)
Moderate	0	0
Bad	0	0
Information appropriate for patients?		
Very good	8 (80%)	10 (47,6%)
Good	2 (20%)	8 (38,1%)
Moderate	0	2 (9,5%)
Bad	0	0
Missing		1 (4,8%)

Table 3. (Continued)

	Draft 3 Healthcare professionals (N=10)	Draft 4 Female cancer survivors and patient advocates (N=21)
Information order logical?		
Very good	4 (40%)	12 (57,1%)
Good	6 (60%)	9 (42,9%)
Moderate	0	0
Bad	0	0
Navigation through DA?		
Very good	6 (60%)	10 (47,6%)
Good	3 (30%)	9 (42,9%)
Moderate	1 (10%)	1 (4,8%)
Bad	0	0
Missing		1 (4,8%)
Credibility?		
Very	3 (30%)	13 (61,9%)
Moderate	7 (70%)	8 (38,1%)
A little	0	0
Not at all	0	0
Confusing items?		
Yes	4 (40%)	6 (28,5%)
No	6 (60%)	15 (71,5%)
Images helpful?		
Very	8 (80%)	15 (71,5%)
Moderate	1 (10%)	6 (28,5%)
A little	0	0
Not at all	0	0
Missing	1 (10%)	
Personal value clarification helpful?		
Made choice easier	7 (70%)	11 (52,4%)
Made choice harder	0	0
Does not influence choice	2 (20%)	9 (42,9%)
Missing	1 (10%)	1 (4,8%)
DA helpful in decision-making?		
Very	9 (90%)	12 (57,1%)
Moderate	1 (10%)	8 (38,1%)
A little	0	1 (4,8%)
Not at all	0	0
Average score on scale of 1-10 (range)?	8,5 (8-9)	8,5 (7-10)
Recommend use of DA? (%)	100%	100%

DISCUSSION

This paper described the systematic development process of 24 online fertility preservation DAs tailored to cancer type and associated treatments for female cancer patients by a multidisciplinary steering group. All DAs addressed risks, safety, pros and cons of 'wait and see', and of all applicable fertility preservation treatments (cryopreservation of oocytes, embryos, ovarian tissue, ovarian transposition, ovarian suppression, and fertility sparing surgery). The final versions were considered clear, appropriate, usable, and helpful in decision-making by female cancer survivors, patient advocates and their healthcare professionals. All female cancer survivors would have liked to use the DA if this would have been available, and would recommend it to newly diagnosed cancer patients. Furthermore, 43 out of 45 quality criteria for content and development process of the IPDAS checklist were met.

This is the first study to develop a fertility preservation DA tailored to cancer type and treatment. Previous studies have developed fertility preservation DAs either for one specific cancer type or not specific to any cancer type (22). These DAs proved to be effective in improving knowledge and reducing decisional conflict. In addition, patients experienced the DAs as helpful and were highly satisfied. However, tailoring information to a patient's individual situation has also shown to be very important to be able to make high-quality decisions. In a narrative review, a wide range of factors was found to impact the fertility preservation decision-making process, including a patient's personal situation and status, and a patient's dilemma of deciding to be in the survival mode or to prioritize fertility preservation treatment (33). Another qualitative study among breast cancer survivors explored patients' experiences with fertility preservation discussions and information (34). Patients reported a strong desire to have their individual preferences and personal situations addressed during fertility discussions, and therefore, predetermined fertility preservation information would not be appropriate. These studies emphasize the need of tailoring information to patient's specific values and preferences which can be done by providing our tailored DA.

Noteworthy, our study underlines the importance of involving patients in all stages during the development of the DA. Most studies describing the development of a fertility preservation DA, also involved patients in the development process, however not throughout all stages (35-38). Our DA would have been different if patients were not involved throughout all stages. In order to develop the first draft of our DA, female cancer survivors were members of our steering group, and we explored patients' needs and preferences in decision-making. This led to the development of DAs that were cancer-specific, and provided information about a patient's personal risk of infertility

and all available fertility preservation options. In the next stages of development, other female cancer survivors with various cancer types and patient advocates were asked to evaluate the DAs where after major changes were made to increase the usability and readability of the DA. So, although patients were involved in developing the first draft, the final versions of the DAs were still considerably different underlining the importance to involve patients throughout all steps of DA development.

A strength of our study is that it is one of the few studies in which three consecutive rounds of alpha testing and revision were conducted to optimize the DA. In other studies, alpha testing was conducted with a group of female cancer survivors, and, in some studies, with a group of healthcare professionals, either concurrently or consecutively (35-40). Coulter and colleagues recommend to alpha test the draft with patients and professionals in a iterative process, as we did, but do not recommend the number of participants (26). Our number of participants (female cancer survivors N=38, healthcare professionals N=10) in alpha testing was higher than in most studies (female cancer survivors N=10-20, and healthcare professionals N=7-17). This ensured we involved female cancer survivors with all types of cancers and cancer treatments, of all reproductive ages, and of whom some had undergone a fertility preservation treatment while others had not. Our study showed that this was of utmost importance in the development of the gynaecological cancer DAs, as major changes were made according to the feedback during alpha testing. In particular, patients suggested to be careful in giving any false hope, because fertility sparing surgery is only appropriate for certain stages and grades of cancer. Therefore, careful information provision and counselling should take place (41).

Some limitations, despite the systematic development according to international standards, should be considered in the interpretation of the results. Although we included a high number of female cancer survivors in alpha testing, the DAs were not tested with newly diagnosed cancer patients. Newly diagnosed patients might have different information and decision support needs. However, female cancer survivors were specifically asked to respond thinking back at the time of their diagnosis. An advantage of testing with female cancer survivors is that they were also aware of the consequences of their decision. This provided us with additional information that newly diagnosed patients probably could not have overseen. Furthermore, bias could have occurred because most female cancer survivors had a partner and a strong wish to conceive before decision-making. Patients who were single and who had doubts about their wish to conceive and refrained from a treatment may make their decision based on different information and values. In addition, most female cancer survivors were highly educated (50% having a university degree) which may bias the results regarding the comprehensibility and usability of the DA. However, an organisation

with experience in adjusting medical texts for low literacy patients was also involved in the development of the DA to minimize this bias. Last, although the information in the DAs was tailored and cancer-specific, it should only be used complementary to fertility preservation counselling. Oncological healthcare providers should still refer all patients to a reproductive specialist to discuss the information in the DA. After using the DA, reproductive specialists should take patient's values into consideration when making a shared decision regarding fertility preservation.

The next step in our development process is to field-test the DAs in 'real life' conditions with patients and professionals not involved in the development process (26). This will lead to the final version of the DA which is then ready for implementation into daily clinical practice. This implementation will be facilitated, because multiple key stakeholders, both healthcare providers and patient associations, were already involved in the development process (42). Thereafter, it should be evaluated if the DA reduces decisional conflict and decision regret regarding fertility preservation decision-making. In future, our final version of the fertility preservation DA can be translated and adjusted according to (inter)national guidelines to make it broadly available for female cancer patients.

In conclusion, a fertility preservation DA tailored to cancer type and associated cancer treatments was systematically developed for female cancer patients of reproductive age. The DA aims to support patients in well-informed fertility preservation decision-making based on their personal situations and preferences. The involvement of healthcare providers, female cancer survivors, and patient associations led to a final version of the DA that is highly appraised, valid, and usable in decision-making. After field-testing and evaluating the impact on decision-making in newly diagnosed patients, the DA will be available in the Netherlands, and eventually internationally, after translation and adjustment to international guidelines.

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Supplementary Figure 1. Example of a statement in the value clarification exercise**Supplementary Table 1.** International Patient Decision Aid Standards (IPDAS) Checklist

Criteria	Answer
Domain 1. Content: Does the patient decision aid...	
<i>Provide information about options in sufficient detail for decision-making?</i>	
1. Describe the health condition	Yes
2. List the options	Yes
3. List the option of doing nothing	Yes
4. Describe the natural course without options	Yes
5. Describe procedures	Yes
6. Describe positive features (benefits)	Yes
7. Describe negative features of options (harms / side effects / disadvantages)	Yes
8. Include changes of positive / negative outcomes	Yes
<i>Present probabilities of outcomes in an unbiased and understandable way?</i>	
9. Use event rates specifying the population and time period	Yes
10. Compare outcome probabilities using the same denominator, time period, scale	Yes
11. Describe uncertainty around probabilities	Yes
12. Use visual diagrams	Yes
13. Use multiple methods to view probabilities (words, numbers, diagrams)	Yes
14. Allows the patient to select a way of viewing probabilities (words, numbers, diagrams)	Yes
15. Allow patient to view probabilities based on their own situation (e.g. age)	Yes
16. Place probabilities in context of other events	Yes
17. Use both positive and negative frames (e.g. showing both survival and death rates)	Yes
<i>Include methods for clarifying and expressing patients' values?</i>	
18. Describe the procedures and outcomes to help patients imagine what it is like to experience their physical, emotional, social effects	Yes
19. Ask patients to consider which positive and negative features matter most	Yes
20. Suggest ways for patients to share what matters most with others	Yes
<i>Include structured guidance in deliberation and communication?</i>	
21. Provide steps to make a decision	Yes
22. Suggest ways to talk about the decision with a health professional	Yes
23. Include tools (worksheet, question list) to discuss options with others	Yes
Domain 2. Development process: does the patient decision aid...	

Supplementary Table 1. (Continued)

Criteria	Answer
<i>Present information in a balances manner?</i>	
24.Able to compare positive / negative features of options	Yes
25.Shows negative / positive features with equal detail (fonts, order, display of statistics)	Yes
<i>Have a systematic development process</i>	
26.Include developers' credentials / qualifications	Yes
27.Finds out what users (patients, practitioners) need to discuss options	Yes
28.Has peer review by patient / professional experts not involved in development and field testing	Yes
Domain 2. Development process: does the patient decision aid...	
<i>Have a systematic development process</i>	
29.Is field tested with users (patients facing the decision; practitioners presenting options)	Not yet
The field test with users (patients, practitioners) show the patient decision aid is:	
30.Acceptable	N/A
31.Balanced for undecided patients	N/A
32.Understood by those with limited reading skills	N/A
<i>Use up to date scientific evidence that is cited in a reference section or technical document?</i>	
33.Provides references to evidence used	Yes
34.Reports steps to find, appraise, summarise evidence	Yes
35.Report date of last update	Yes
36.Report how often patient decision aid is updated	Yes
37.Describe quality of scientific evidence (including lack of evidence)	Yes
38.Uses evidence from studies of patients similar to those of target audience	Yes
<i>Disclose conflicts of interest?</i>	
39.Report source of funding to develop and distribute the patient decision aid	Yes
40.Report whether authors or their affiliations stand to gain or lose by choices patients make after using the patient decision aid	Yes
<i>Use plain language?</i>	
41.Is written at a level that can be understood by the majority of patients in the target group	Yes
42.Is written at a grade 8 equivalent level or less according to readability score (SMOG or FRY)	Yes
43.Provides ways to help patients understand information other than reading (audio, video, in-person discussion)	Yes
<i>Meet additional criteria if the patient decision aid is internet based</i>	
44.Provide a step-by-step way to move through the web pages	Yes
45.Allow patients to search for key words	No
46.Provide feedback on personal health information that is entered into the patient decision aid	No
47.Provides security for personal health information entered into the decision aid	Yes
48.Make it easy for patients to return to the decision aid after linking to other web pages	Yes

Supplementary Table 1. (Continued)

Criteria	Answer
49.Permit printing as a single document	Yes
Domain 3. Effectiveness: does the patient decision aid ensure decision making is informed and values based?	
<i>Decision processes leading to decision quality. The patient decision aid helps patients.</i>	
50.Recognize a decision needs to be made	N/A
51.Know options and their features	N/A
52.Understand values that affect decision	N/A
53.Be clear about option features that matter most	N/A
54.Discuss values with their practitioner	N/A
55.Become involved in preferred ways	N/A
<i>Decision quality. The patient decision aid...</i>	
56.Improves the match between the chosen option and the features that matter most to the informed patient	N/A



8

GENERAL DISCUSSION

GENERAL DISCUSSION

With increasing cancer survival rates, it became clear that ‘cure is not enough’. Research should also focus on quality of life after surviving cancer, as cancer survivors can suffer from long-term consequences of their cancer treatment. Potential loss of fertility is one of the most undesirable long-term side effects for female adolescent and young adult cancer patients. With current available clinical practice guidelines, an attempt is made to increase female adolescent and young adult cancer patients’ quality of life by informing them about infertility risks and available fertility preservation options, and, if desired, to offer a referral to and counselling by a reproductive gynaecologist before the start of cancer treatment. This thesis focused on research regarding the implementation of high-quality oncofertility care for female adolescent and young adult cancer patients with the aim of improving female cancer survivors’ quality of life.

In this chapter, the main findings of this thesis are presented and discussed from the perspective of a female adolescent and young adult cancer patient, an oncological healthcare provider, a reproductive specialist, a policy maker, and a researcher. This chapter ends with a final conclusion.

MAIN FINDINGS

- High-quality female oncofertility care is defined by a set of eleven key recommendations which was selected by a multidisciplinary expert panel, consisting of female cancer survivors, oncological healthcare providers, and reproductive gynaecologists. Key recommendations were distributed over four domains in female oncofertility care; risk communication by the oncological healthcare provider, referral for fertility preservation counselling, fertility preservation counselling by a reproductive gynaecologist, and shared decision-making.
- Current quality of female oncofertility care assessed with a patient-reported measurement using our set of systematically developed quality indicators is far from optimal. Improvement potential was found for eight out of the eleven quality indicators representing all domains in female oncofertility care: of all patients, 72,7% was informed about her infertility risks by her oncological healthcare provider, 51,2% was offered a referral to a gynaecologist, with 18,8% all aspects were discussed in fertility preservation counselling, and 35,5% received written/digital information. Patient’s age, strength of wish to conceive, time before cancer treatment, and type of healthcare provider were found to significantly influence the scores of three indicators on referral and (support of) shared decision-making.

- Receiving high-quality female oncofertility care is associated with an improved quality of life, and with less decisional conflict and regret in female adolescent and young adult cancer survivors measured with quality indicators. Female cancer survivors' quality of life was highest when they were informed about infertility risks, and were offered fertility preservation counselling, and received written/digital information about fertility preservation. In addition, female cancer survivor's age, relationship status, strength of wish to conceive, and type of cancer were found to significantly influence scores of fertility preservation knowledge, decision regret, reproductive concerns, and quality of life.
- Healthcare providers perceived barriers in awareness, knowledge, attitude, and organization of care impeding them from delivering high-quality female oncofertility care. To overcome these barriers, an expert panel consisting of female cancer survivors and healthcare providers selected seven tailored improvement strategies, including development of information materials (decision aid), education of professionals, a role for specialised oncology nurses in discussing fertility issues, medical record reminders, standard consultations with a gynaecologist, agreement on responsibility, and roles for fertility navigators at the fertility department.
- The implementation of fertility navigators was positively experienced by female cancer patients. They navigated patients through their fertility preservation process and provided personal care. In addition, they supported reproductive gynaecologists by taking over tasks.
- A total of 24 online fertility preservation decision aids tailored to cancer type and associated cancer treatments was systematically developed for female adolescent and young adult cancer patients by a multidisciplinary steering group. The final versions were highly appraised, valid, and usable in decision-making by female cancer survivors, patient advocates and healthcare providers, and a total of 43 out of 45 IPDAS quality criteria for content and development process were met.

FEMALE ADOLESCENT AND YOUNG ADULT CANCER PATIENT'S PERSPECTIVE

As a young woman, I think most important after surviving cancer is to have a normal life again, of which having the possibility to conceive children is an important component. Although I know it is not always possible to prevent young women from becoming infertile, an attempt should be made to increase quality of life, to decrease decisional conflict, and to prevent decision regret in the future by providing high-quality oncofertility care. What is high-quality oncofertility care for me as a young woman?

Risk communication and referral

First, I believe that my oncological healthcare provider should inform me about the gonadotoxic effects of my cancer treatment and offer a referral for fertility preservation counselling. This is important because at the moment of my cancer diagnosis, I am so overwhelmed, I do not think about my life after cancer, but only focus on survival and starting cancer treatment as soon as possible (chapter 5) (1, 2). To prevent a lowered quality of life and long-term decision regret (chapter 4), I think it is important that oncological healthcare providers emphasize, early in the oncological process, that this is the moment to think about future fertility (chapter 2, 4 and 5).

Furthermore, whether to be informed about infertility risks and to be referred for fertility preservation counselling should not be decided by my oncological healthcare provider. My age, parity, relationship status, strength of wish to conceive, time before the start of my cancer treatment, or type of oncological healthcare provider should not influence my oncological healthcare provider in providing information or offering a referral (chapter 3 and 5). I believe that all women should be informed and referred irrespective of these characteristics. I want to make my own well-informed decision whether to have fertility preservation counselling or have a fertility preservation treatment or not, of course in consultation with my oncological healthcare provider.

Discussion and future perspectives

In order to achieve this, education of oncological healthcare providers is needed, in particular on oncofertility knowledge and communication skills (chapter 5). Previous studies emphasize this need, as they have shown that healthcare providers reported negative feelings about provision of fertility preservation care: they consider this communication difficult, and sometimes even as a burden, they feel uncomfortable, lack confidence, feel embarrassed, and unprepared (3-5). Professionals who believe discussing infertility risks is their responsibility are twice as likely to discuss it (6). Furthermore, professionals who attend an educational session about fertility preservation are more likely to consider a patient's desire for fertility when planning her treatment than those who do not attend (7).

Moreover, specialised oncology nurses can play an important role in improving information provision and referral (chapter 5). The effectiveness of nurses participating in oncofertility care has already been studied; nurses feel responsible for addressing fertility issues, patients are more satisfied, and more referrals for fertility preservation counselling take place (8-10). A web-based educational program (ENRICH) was developed in America to assist oncology nurses with timely and relevant information regarding reproductive health issues to adolescent and young adult cancer patients and survivors. Evaluation of this program shows that it is successful in increasing

knowledge, communication skills, and frequency of discussion of reproductive health (11, 12). Because it is a web-based program, it might be interesting to adopt this in the Netherlands, rather than developing such a programme ourselves.

Another strategy to overcome this barrier might be that patients themselves are aware of infertility risks due to gonadotoxic treatments. So-called patient-directed strategies have been studied and might be effective (13, 14). One study in oncofertility care found a nine-fold increase in the number of phone calls and consultations with a reproductive gynaecologist when a brochure about fertility is distributed in patient waiting areas of oncology departments (15). Other studies showed that referrals are more likely if the patient initiates the discussion about fertility preservation (5, 16, 17). This was also mentioned by healthcare providers in our study as facilitator to inform or refer patients (chapter 5). However, it should be further evaluated if patient-directed strategies could be effective in female oncofertility care as patients focus on survival at time of cancer diagnosis and not on future fertility.

Fertility preservation counselling and decision-making

Then, when I (female adolescent and young adult cancer patient) am referred for fertility preservation counselling, I would like to be prepared for this consultation. I believe this consultation will be more constructive and more tailored to my individual situation when I am aware of fertility preservation options that are applicable to me, and specific issues that are important to me (chapter 7) (1, 18). Ideally, my oncological healthcare provider would offer me a tailored online fertility preservation decision aid. When I use this as preparation for the consultation, more attention will be paid to my individual situation and preferences, and I will have the feeling that I am an equal partner in the consultation (18-20).

Last, when I am at the fertility department for either fertility preservation counselling or fertility preservation treatment, it would be very pleasant when I have my own contact person. Someone who guides me through the process, who provides personal care, who is aware of my situation, and to whom I can ask all my questions (chapter 6).

Discussion and future perspectives

Whether a tailored decision aid improves the quality of fertility preservation counselling and whether it is helpful in making a shared decision should be further studied. Previous developed decision aids, either for one specific cancer type or not specific to any cancer type, improved knowledge and reduced decisional conflict and regret regarding fertility preservation decision-making (21). Whether this is also the case for the developed decision aid in this thesis should also be evaluated.

Regarding having a contact person at the fertility department, the role of fertility navigators was studied in this thesis. Patients were very satisfied with their guidance and support: however, some improvements should still be made to optimize their role. First, as it was not clear for all patients that the fertility navigator was specifically assigned as their contact person, this should be highlighted in the beginning of their visit at the fertility department. Furthermore, fertility navigators should always be available in office hours and should always be present in fertility preservation counselling and during treatment. In the future, fertility navigators can play an important role in educating oncological healthcare professionals and specialised oncology nurses.

For me as a young woman, the above described represents high-quality oncofertility care, contributing to a better quality of life after surviving my cancer.

ONCOLOGICAL HEALTHCARE PROVIDER'S PERSPECTIVE

Risk communication and referral

As an oncological healthcare provider, I want to provide my patients with the best care possible. Therefore, I would like to inform female adolescent and young adult cancer patients accurately about their diagnosis and their treatment options to ensure that their survival chances are as high as possible. Within this first consultation, I must tell large amounts of information, and patients are often intensely sad and devastated by their diagnosis, so they cannot remember everything I tell them (chapter 5). This is one of the reasons that discussing the side effects of cancer treatments, like infertility risks, is difficult in this first consultation, even though I think it is really important for female adolescent and young adult patients (22-24). Other reasons that make it difficult for me are my lack of awareness and knowledge of infertility risks, fertility preservation options, and the fertility preservation guidelines (chapter 5). Despite these reasons, I believe it is important to provide information regarding infertility risks and offer a referral for fertility preservation counselling to all female adolescent and young adult cancer patients who receive a gonadotoxic treatment (25-27).

Furthermore, I would like to provide my patients with written and/or digital information regarding fertility preservation so they can decide whether they want to be referred for fertility preservation counselling (22, 28). To the best of my knowledge, these are not available at our department, or I do not know where to find them. In addition, I noticed that patients have a need for fertility preservation information tailored to their personal situation instead of predetermined information (chapter 5).

Discussion and future perspectives

Unfortunately, not all patients are informed (72,7%) and offered a referral (51,2%) (chapter 3), with also a wide variation in practice in international literature (17, 29-34). Determinants for not providing information or a referral have been observed. Female cancer patients who are older, who have children or who have a lower wish to conceive are less often referred for fertility preservation counselling (chapter 3). In addition, type of cancer, type of cancer treatment, and type of healthcare provider have also shown to influence discussion and referral rates (1, 31-35). In addition, within our study a great variation in informing patients (46,7 – 83,3%) and offering referral (40 – 70,8%) was seen among hospitals. These determinants and variation among hospitals illustrate disparity in access to oncofertility care for female cancer patients.

It is striking that despite good intentions and willingness of oncological healthcare providers and existing guidelines, the quality of female oncofertility care is still suboptimal in the Netherlands, and abroad, contributing to a lowered quality of life in female cancer survivors (chapter 4). Within chapter 5, a multidisciplinary expert panel, also consisting of oncological healthcare providers, selected improvement strategies to overcome perceived barriers. Regarding the main barriers, lack of awareness and knowledge, it was proposed to educate healthcare providers, to embed reminders in the medical record, and to implement standard consultations for female adolescent and young adult cancer patients.

In addition to the previous described ways to educate healthcare providers, audit and feedback and educational outreach visits could be effective since these have been evaluated to be effective in changing practice behaviour (36, 37). The audit and feedback could consist of a feedback report of the quality-of-care measurement from chapter 3. This will give oncological healthcare providers insight in their care performance and the related care experiences from their patients in relation to the performance of all participating hospitals (chapter 4). During the visit, a tailored improvement strategy and local implementation plan could be discussed. We expect that this will lead to an improved awareness and knowledge among oncological healthcare providers and an improved quality of female oncofertility care. Moreover, it could be possible that oncological healthcare providers were unaware of fertility preservation guidelines, because they were published in journals and websites that are mainly read by gynaecologists and not by healthcare providers working in oncology care. Therefore, in an attempt to overcome this barrier, the most recent national fertility preservation guideline was also published on the national guideline database (25).

Medical record reminders have been studied and found to have a potential beneficial effect on practice behaviours in preventive care, however its effectiveness in

oncofertility care is still unknown (38, 39). The same applies to standard consultations with a gynaecologist for all female cancer patients, this could be effective, however, oncological healthcare providers should still be aware of this.

Regarding the provision of written and/or digital information, the developed fertility preservation decision aid described in this thesis is tailored to cancer type and cancer treatments and could serve as the information an oncological healthcare provider could give to patients. The decision aid should be implemented into routine care for female cancer patients (chapter 7). Therefore, it is important that all oncological healthcare providers are aware of the existence of this decision aid. Some attempts have already been made. The decision aid is already available on websites of healthcare insurances, and in future it will be available on patient associations' websites which we already involved in development, on patient platforms like Kanker.nl, and on websites of scientific healthcare associations.

For me as an oncological healthcare provider, the above described will help me in providing the best oncofertility care possible for female adolescent and young adult cancer patients, leading to an improved quality of life in female cancer survivors.

REPRODUCTIVE SPECIALIST'S PERSPECTIVE

Fertility preservation counselling and decision-making

As a reproductive specialist, I would like to counsel female adolescent and young adult cancer patients about all fertility preservation options that are available and appropriate for them. Moreover, I would like to address their individual preferences and personal situations during this consultation as patients have emphasized that this is extremely important to them (chapter 5 and 7) (1, 18). This means that I have to provide a lot of information about infertility risks, fertility preservation options and treatments, including live birth rates, safety, risks, pros, and cons. In addition, I want to tailor this information to a patient's individual situation that I am not yet aware of at the time of consultation. It is challenging to achieve this all-in-one consultation.

Furthermore, I want to ensure that my patients are involved in decision-making and make a shared decision. I can imagine that patients who do not feel involved and supported in their decision-making have more difficulties with making the decision (22, 40-42). Especially, because it is a very complex decision that has to be made in a very short time frame in a period with great emotional distress (43).

Discussion and future perspectives

This thesis illustrates that there is room for improvement in quality indicators in the fertility preservation counselling domain. Especially in the indicators that state that all aspects should be discussed in fertility preservation counselling (18,8%), and that patients should be well-informed about all aspects of the treatment prior to performing emergency IVF (81,8%) (chapter 3). Other studies have also reported these unmet information needs in fertility preservation counselling which leads to higher levels of decisional conflict (chapter 5) (41, 44). In addition, improvement potential was also seen in the decision-making domain with not all patients receiving written and/or digital information (35,5%), and making a shared decision after fertility preservation counselling (73,3%) (chapter 3). Not receiving information or making a shared decision was associated with higher levels of decisional conflict, and higher levels of decision regret (chapter 4) (40, 44).

A way to meet information needs, to facilitate shared decision-making, and to decrease decisional conflict and regret might be the provision of a fertility preservation decision aid (chapter 7) (21, 45). As mentioned before, we were the first to develop a decision aid tailored to cancer types and cancer treatments. Within the decision aid, a tool was developed that helps patients recognize their personal values in making this decision whether to have a fertility preservation treatment. When patients fill in this tool before they have the fertility preservation counselling consultation, a reproductive gynaecologist can tailor the provided information to a patient's individual situation. Moreover, a reproductive gynaecologist will have more time to address patient's preferences and to provide decision support because a patient has already read information about infertility risks, applicable fertility preservation options including burden, live birth rates, and pros and cons before the consultation. It is still to be evaluated in future studies whether our fertility preservation decision aid leads to lower levels of decisional conflict and regret and leads to more shared decision-making.

Another way to improve fertility preservation counselling and decision-making may be the assignment of fertility navigators at a fertility department (chapter 6) (46). Next to the before mentioned positive effects on patient care, they also supported reproductive gynaecologists. The fertility navigators took over tasks and served as a back-up for reproductive gynaecologists resulting in more time for them to perform fertility preservation counselling. Whether this also leads to a higher quality of fertility preservation counselling should be further studied. Moreover, in future fertility navigators' tasks could be expanded, for example by being the primary contact person for oncological healthcare providers when they have questions regarding fertility preservation, and by educating oncology nurses and students about

fertility preservation. Future studies should evaluate if this will result in more time for reproductive specialists to inform and support patients in fertility preservation counselling and decision-making.

For me as a reproductive specialist, the above described will help me in providing high-quality fertility preservation counselling and improved shared decision-making, leading to an improved quality of life in female cancer survivors.

POLICY MAKER'S PERSPECTIVE

As a policy maker, I would like to create a balance between delivering high-quality oncofertility care and the costs of oncofertility care. Due to the results described in this thesis, I am well aware of the positive effects on quality of life and long-term regret when high-quality female oncofertility care is delivered. In addition, I know that high-quality care does not mean that all patients should have a fertility preservation treatment. In the Netherlands, all fertility preservation options are provided without costs for patients, however, ovarian tissue cryopreservation is not covered by healthcare insurances and are paid for by hospital cryobanks themselves.

I also know from international literature that a lot of patients who have cryopreserved their oocytes or embryos do not return to attempt for a pregnancy, with percentages ranging between 7,2 - 33% (47-50). This means that costs for these treatments are high for society while some cancer survivors do not make use of the stored material. However, only a very small group of patients decide to have a fertility preservation treatment, and these costs are not in proportion to the far higher costs of oncological care.

Furthermore, in order to reduce costs, I think it is important to collaborate with (inter) national initiatives to either develop new strategies or adopt strategies that already have been developed to improve oncofertility care (51).

Discussion and future perspectives

Currently, it is not known what the return rates are in the Netherlands and why some female cancer survivors do not return. In addition, the potential beneficial psychological effects for female cancer survivors of knowing that they always have the possibility to attempt for a pregnancy is also unknown at this moment. Therefore, it is important that data are collected in a national registry, and future research should focus on cost-benefit analyses. In these cost-benefit studies, the costs associated with psychological distress of suboptimal quality of female oncofertility care, and dealing with unwanted infertility in female cancer survivors, and the costs associated with alternative family building options (oocyte donation, surrogacy, and adoption) should also be analysed.

Regarding the collaboration with (inter)national initiatives, some successful training programmes have already been developed and could be adopted instead of developed by each hospital or country themselves (52). The Oncofertility Consortium is a good example of collaborating and bundling all initiatives, and the Radboud university medical center is already a collaborating global partner (53-55).

For me as a policy maker, the above-described aspects could contribute to a good balance between delivering high-quality female oncofertility care and the costs of this care.

RESEARCHER'S PERSPECTIVE

As a researcher, I would realize that this thesis forms a solid basis and provides tools for implementing high-quality female oncofertility care, but also that there is still a lot of work to be done. Efforts should be made to improve and implement high-quality female oncofertility care. At this moment, some improvement strategies have already been implemented and studied. Described effects are positive, with more documentations on infertility risks, more access to fertility preservation counselling, and more satisfaction with received information being reported (56-59). However, a systematic evaluation of all aspects of quality of female oncofertility care and patient-reported outcome measures is lacking in these studies, and therefore their efficacy is unclear.

Methodological considerations

As a researcher, I am quite satisfied with the methodology used in the studies in this thesis. Qualitative as well as quantitative studies were conducted, patients were involved in the design and execution of all studies, and applicable checklists and guidelines were used to conduct the studies. However, there is room for improvement. Especially for the studies in chapter 3 and 4. A multicentre cross-sectional survey study was conducted in six hospitals across the Netherlands in which female cancer survivors were asked to fill in the survey three to four years after their cancer diagnosis, treatment, and consultation. Because of the retrospective design and the participation of (only) six hospitals, recall bias and selection bias could have played a role which could have influenced the study results. A prospective design could eliminate these forms of bias. To conduct such a prospective study, all female adolescent and young adult cancer patients who receive a (potential) gonadotoxic treatment should be registered into a national database by oncological healthcare providers. Then, patients can fill in the survey directly after receiving oncofertility care leading to more reliable results. By setting up this database, the quality of female oncofertility care can be monitored continuously. In addition, as it will be a national

database, quality of female oncofertility care can be assessed in all hospitals (academic and non-academic) throughout the Netherlands.

Future perspectives

In this thesis it became clear that quality of female oncofertility care is far from optimal and leads to a lowered quality of life in female cancer survivors. Barriers for this suboptimal quality have been revealed, and improvement strategies tailored to these gaps in oncofertility care and barriers have been selected. This set of tailored improvement strategies should form the basis for a multifaceted oncofertility programme.

In Table 1, a multifaceted oncofertility programme is proposed in order to implement high-quality female oncofertility care. The strategies in the programme have been discussed in the sections above. To succeed, it is of great importance to involve all relevant stakeholders in the development, and dissemination, and to facilitate the implementation of this programme (60). Within this thesis, a lot of relevant stakeholders were already involved, with female cancer survivors being of utmost importance in our studies. Furthermore, oncological healthcare providers, and reproductive specialists from hospitals across the Netherlands, the AYA Care Network, patient’s associations (Breast Cancer association ‘BVN’, Gynaecological Cancer association ‘Olijf’, and Haematological Cancer association ‘Hematon’), scientific associations (of gynaecology ‘NVOG’, of medical oncology ‘NVMO’, and of embryology ‘KLEM’), patient information platform (Kanker.nl), and the Netherlands Comprehensive Cancer Organization (IKNL) were also involved in one or more studies of this thesis.

Table 1. A multifaceted oncofertility programme to improve quality of female oncofertility care

Risk communication Referral	Fertility preservation counselling Decision-making
Education of oncological healthcare providers	Fertility preservation decision aid
Role for specialised oncology nurses	Fertility navigators
Fertility preservation decision aid	
Reminders in medical record	
Standard consultations with gynaecologist	
Agreements on responsibility	

This oncofertility programme should be implemented into clinical practice. A cluster randomized trial, including a stepped wedge design with time intervals could be used to evaluate the programme (61). Great advantage of a stepped wedge design is that in

the end all participating hospitals are exposed to the oncofertility programme, which increases their willingness to actively participate. The effectiveness of this oncofertility programme could be measured with our set of quality indicators. Thereafter, a process evaluation should take place to evaluate which elements of the oncofertility programme are particularly responsible for the effectiveness (62). In addition, a cost-benefit analysis should also be focus of future research to ensure that policy makers and healthcare insurances are also convinced of the positive effects of such an oncofertility program.

For me as a researcher in female oncofertility care, my ultimate goal is that each female adolescent and young adult cancer patient is well-informed about her infertility risks enabling her to make a shared decision whether she wants to have a fertility preservation treatment or not. This will contribute to an improved quality of life for female cancer survivors.

FINAL CONCLUSION

This thesis focused on research regarding the implementation of high-quality oncofertility care for female cancer patients. It became clear that quality of female oncofertility care measured with systematically developed quality indicators, is far from optimal and is associated with a lowered quality of life in female cancer survivors. Reasons for this suboptimal quality of care have been elucidated, and improvement strategies tailored to these gaps in oncofertility care and barriers have been selected. Although, there is still work to be done, this thesis forms a solid basis, involved relevant stakeholders, and provides tools to implement high-quality female oncofertility care leading to an improved quality of life in female cancer survivors.

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9

SUMMARY | SAMENVATTING

SUMMARY

This thesis focused on the implementation of high-quality oncofertility care for female adolescent and young adult cancer patients. As we described in **Chapter 1**, female adolescent and young adult cancer patients are at risk of losing their fertility due to gonadotoxic cancer treatments like chemotherapy, radiation therapy, and gonadal surgery. To secure the possibility to conceive children after surviving cancer, fertility preservation options as cryopreservation of oocytes, embryos, ovarian tissue, ovarian transposition, ovarian suppression, and fertility sparing surgery are available. In order to have the possibility to conceive children in the future, guidelines recommend discussing the potential loss of fertility with all female cancer patients and, if desired, offering a referral to and counselling by a reproductive gynaecologist. However, it seems that not all patients are informed and referred for counselling, which could contribute to a lower quality of life and long-term regret in female cancer survivors. To improve female cancer survivors' quality of life, it is important to improve guideline adherence and guideline implementation. A model to implement change in clinical practice, to improve guideline adherence, and to improve quality of female oncofertility care, was followed in this thesis.

In **Chapter 2**, we defined high-quality of female oncofertility care as first step of the model by selecting a set of key recommendations. The Delphi method was used to select this set of key recommendations for high-quality female oncofertility care by a multidisciplinary oncofertility expert panel (N=86), consisting of patients, referrers, and counsellors. First, recommendations from six international clinical practice guidelines and the Dutch clinical guideline were extracted, and divided into four domains; risk communication by the oncological healthcare provider, referral to a reproductive gynaecologist, fertility preservation counselling, and decision-making on fertility preservation. Thereafter, key recommendations were scored, per domain, on their importance for high-quality oncofertility care by the expert panel. A total of eleven key recommendations was selected. Key recommendations in the domains risk communication and referral focused on information provision and offering referral to a reproductive gynaecologist to female cancer patients. Regarding the counselling domain, key recommendations focused on all aspects of counselling including different methods, safety, pros and cons. In the decision-making domain, key recommendations focused on shared decision-making and supporting the decision with written and/or digital information. Finally, the set of eleven key recommendations was approved by 91% of the experts. Differences in perspectives about importance of recommendations were found between subgroups. In particular, patients found recommendations

regarding decision-making and information provision more important than referrers and counsellors.

As second step of the model, the set of eleven key recommendations for high-quality female oncofertility care was transcribed into quality indicators in order to measure current quality of care systematically in **Chapter 3**. We conducted a multicentre cross-sectional study among female cancer survivors, diagnosed in 2016/2017, from six hospitals across the Netherlands, to measure quality of care systematically. Survivors were asked to fill in a survey in which the set of quality indicators was processed. Determinants that were associated with oncofertility care were also evaluated. In total, 121 out of 344 (35%) female cancer survivors participated in the study, their mean age at diagnosis was 34 years, 60,3% was diagnosed with breast cancer, and 37,2% had a fertility preservation treatment. Overall, 8 out of 11 quality indicators scored below 90% adherence representing all domains in female oncofertility care. Of all patients, 72,7% was informed about their infertility risks by their oncological healthcare provider, 51,2% was offered a referral to a gynaecologist, with 18,8% all aspects were discussed in fertility preservation counselling, and 35,5% received written and/or digital information. In addition, a great variation in indicator scores (>20% for 10 out of 11 quality indicators) was seen among hospitals. Four determinants (patient's age, strength of wish to conceive, time before cancer treatment, and type of healthcare provider) were found to significantly influence the scores of three indicators on referral and (support of) shared decision-making. We concluded that current quality of female oncofertility care is far from optimal and improvement is needed.

In **Chapter 4**, we evaluated whether this suboptimal quality of female oncofertility care was associated with patient-reported outcome measures, particularly with quality of life, decisional conflict, regret, reproductive concerns, and fertility preservation knowledge. A multicentre cross-sectional survey study was conducted among female cancer survivors from six hospitals across the Netherlands. Validated scales were used to assess the patient-reported outcome measures, and determinants associated with these outcomes were evaluated. Overall, physical and mental quality of life was slightly lower than in the average healthy population, and decisional conflict was perceived by female cancer survivors. Female cancer survivor's quality of life was highest, and levels of decisional conflict and regret were lowest when there was adherence to three quality indicators (i.e. survivors were informed about infertility risks, and were offered FP counselling, and received written and/or digital information). Levels of reproductive concerns did not differ significantly between adherence and non-adherence to the quality indicators. In addition, four determinants (female cancer survivor's age, relationship status, strength of wish to conceive, and type of cancer) were found to

significantly influence the scores of physical quality of life, decision regret, reproductive concerns, and fertility preservation knowledge. These results led to the conclusion that receiving high-quality female oncofertility care was associated with an improved quality of life, and with less decisional conflict and regret in female cancer survivors.

As we have shown that quality of oncofertility care is suboptimal, strategies should be developed and tailored to the current gaps in oncofertility care, and to guideline-specific barriers, to improve quality of female oncofertility care, and, importantly, quality of life in female cancer survivors. To identify barriers impeding oncological healthcare providers from delivering high-quality female oncofertility care, and improvement suggestions, we conducted a qualitative study in **Chapter 5** as third step of the model to implement change in clinical practice. Subsequently, an expert panel meeting with healthcare providers, female cancer survivors, and researchers was held to reach consensus on a set of improvement strategies as fourth step of the model. A total of 28 barriers was identified and categorized into the patient level (e.g. patients focus on surviving cancer), the professional level (e.g. lack of awareness, knowledge, time, and attitude), or the organizational level (e.g. unavailable written information, disagreement on who is responsible for discussing infertility risks). The expert panel reached consensus on essential elements for an improvement programme: development of information materials (leaflets, online decision aid), education of professionals, a role for specialised oncology nurses in informing patients, medical record reminders, standard consultations with a gynaecologist for all female cancer patients of reproductive age, agreement in each hospital on who is responsible to discuss infertility risks, and a role for fertility navigators at the fertility department to facilitate fertility preservation counselling.

This selection of improvement strategies forms the basis for an oncofertility programme which is essential to improve female oncofertility care. Two strategies were developed and further studied in this thesis as part of the fifth, and last step of the model. The first selected improvement strategy was the implementation of fertility navigators to support female cancer patients in their oncofertility process. In **Chapter 6**, patients' and healthcare providers' experiences with fertility navigators at the fertility department were explored by means of semi-structured in-depth interviews (N=15), and analysed using the concepts of grounded theory. Patients were satisfied about the supportive role of the fertility navigator in their oncofertility process: fertility navigators added value as they became "familiar faces", served as patients' primary contact person, and provided information, emotional support, and personal care. The fertility navigators had a pleasant collaboration with healthcare providers and supported healthcare providers by taking over tasks. To improve the role of fertility navigators in future, it was suggested

that they should always be present in fertility preservation counselling, and attention should be paid to their availability to improve continuity of care. In conclusion, fertility navigators improve satisfaction in patients in their oncofertility process, and support healthcare providers, contributing to an improved quality of female oncofertility care.

The second selected improvement strategy, the development and testing of a tailored online fertility preservation decision aid is described in **Chapter 7**. Our decision aid was systematically developed using the recommendations by Coulter et al, and in accordance with the international patient decision aid standards. This process was performed by a multidisciplinary steering group (N=21) consisting of oncological and reproductive healthcare providers, female cancer survivors, and patient advocates, in an iterative process of draft development, three rounds of alpha testing, and revisions. The drafts were based on current guidelines and literature, and patients' and healthcare providers' needs explored by in-depth interviews. In total, 24 online fertility preservation decision aids tailored to cancer type and associated treatments for female cancer patients were developed. All decision aids addressed risks, safety, pros and cons of 'wait and see', and of all applicable fertility preservation treatments (cryopreservation of oocytes, embryos, ovarian tissue, ovarian transposition, ovarian suppression, and fertility sparing surgery). The final versions were considered clear, appropriate, usable, and helpful in decision-making by female cancer survivors, patient advocates and their healthcare providers. All female cancer survivors would have liked to use the decision aid if this would have been available, and would recommend it to newly diagnosed cancer patients. In particular, the cancer-specific information and the tool for recognizing personal values was of great value. Revisions were made to increase readability, personalization, usability, and be more careful in giving any false hope. Furthermore, 43 out of 45 quality criteria for content and development process of the international patient decision aid standards checklist were met. We concluded that our tailored fertility preservation decision aid is important in supporting patients in well-informed fertility preservation decision-making based on their personal situations and preferences. After field-testing and evaluating the impact on decision-making in newly diagnosed patients, the decision aid should be broadly available.

At last, the content of this thesis is discussed from the perspective of a female adolescent and young adult cancer patient, an oncological healthcare provider, a reproductive specialist, a policy maker, and a researcher in **Chapter 8**. A multifaceted oncofertility programme is proposed in order to implement high-quality female oncofertility care with the ultimate goal to improve quality of life in female cancer survivors.

SAMENVATTING

Dit proefschrift gaat over de implementatie van oncofertiliteitszorg van hoge kwaliteit voor adolescente en jongvolwassen vrouwen met kanker. Zoals we in **Hoofdstuk 1** hebben beschreven, hebben adolescente en jongvolwassen vrouwen met kanker een risico om hun vruchtbaarheid te verliezen door kankerbehandelingen die schadelijk zijn voor de vruchtbaarheid, zoals chemotherapie, bestraling en een operatie aan de voortplantingsorganen. Om de mogelijkheid om nog kinderen te kunnen krijgen veilig te stellen na het overleven van de kanker, zijn er mogelijkheden tot fertiliteitspreservatie beschikbaar zoals het invriezen van eicellen, embryo's, of eierstokweefsel, het verplaatsen van de eierstok(ken), het onderdrukken van de eierstokken en een operatie waarbij de eierstok en/of baarmoeder gespaard wordt. Om de mogelijkheid te behouden om kinderen te krijgen in de toekomst, bevelen richtlijnen aan om het mogelijke verlies van de vruchtbaarheid met iedere vrouw met kanker te bespreken en indien gewenst, de mogelijkheid aan te bieden voor verwijzing naar een gynaecoloog voor counseling. Het lijkt er echter op dat niet alle patiënten geïnformeerd worden en verwezen worden voor counseling wat kan bijdragen aan een lagere kwaliteit van leven en langdurige spijt bij vrouwen die hun kanker hebben overleefd. Om de kwaliteit van leven van vrouwen die hun kanker hebben overleefd te verbeteren, is het belangrijk om de naleving en de implementatie van de richtlijn te verbeteren. In dit proefschrift is een model gevolgd om verandering in de klinische praktijk te implementeren, om naleving van de richtlijn te verbeteren en om de kwaliteit van oncofertiliteitszorg voor vrouwen te verbeteren.

In **Hoofdstuk 2** hebben we, als eerste stap van het model, gedefinieerd wat oncofertiliteitszorg van hoge kwaliteit is. Met behulp van de Delphi methode werd een set van belangrijke aanbevelingen voor oncofertiliteitszorg van hoge kwaliteit geselecteerd door een multidisciplinair expert panel bestaande uit patiënten, verwijzers en counselors. Hiertoe werden eerst aanbevelingen vanuit zes internationale evidence based richtlijnen en de Nederlandse richtlijn geëxtraheerd en ingedeeld in vier domeinen; risicocommunicatie door de oncologisch zorgverlener, verwijzing naar een gynaecoloog, fertiliteitspreservatie counseling en het maken van een keuze over fertiliteitspreservatie. Vervolgens werden de aanbevelingen, per domein, gescoord op het belang voor oncofertiliteitszorg van hoge kwaliteit door het expert panel. In totaal werden elf aanbevelingen voor oncofertiliteitszorg van hoge kwaliteit geselecteerd. De geselecteerde aanbevelingen in de domeinen "risicocommunicatie en verwijzing" zijn gericht op het geven van informatie en het aanbieden van een verwijzing naar een gynaecoloog aan vrouwen met kanker. In het domein "fertiliteitspreservatie counseling" zijn de geselecteerde aanbevelingen gericht op alle aspecten van de counseling,

inclusief het bespreken van de verschillende behandelingen, de veiligheid en de voor- en nadelen van de behandelingen. In het domein “het maken van een keuze over fertiliteitspreservatie”, zijn de geselecteerde aanbevelingen gericht op het maken van een gezamenlijke keuze en het ondersteunen van de keuze met schriftelijke en/of digitale informatie. De definitieve set van elf aanbevelingen werd goedgekeurd door 91% van de experts. Tussen de verschillende subgroepen van experts bleken de meningen over het belang van de aanbevelingen te verschillen. Met name patiënten vonden de aanbevelingen over het maken van een keuze en het geven van informatie belangrijker dan verwijzers en counselors.

Als tweede stap in het model werd deze set van elf geselecteerde aanbevelingen voor oncofertiliteitszorg van hoge kwaliteit omschreven naar kwaliteitsindicatoren om de huidige kwaliteit van zorg systematisch te kunnen meten in **Hoofdstuk 3**. We hebben een multicenter cross-sectioneel onderzoek uitgevoerd in zes ziekenhuizen in Nederland onder vrouwen, die gediagnosticeerd waren in 2016/2017 en die hun kanker hebben overleefd, om de kwaliteit van zorg systematisch te meten. Vrouwen werd gevraagd om een vragenlijst in te vullen waarin de set van kwaliteitsindicatoren was verwerkt. Determinanten die geassocieerd waren met de oncofertiliteitszorg werden ook geëvalueerd. In totaal hebben 121 van de 344 (35%) vrouwen deelgenomen aan het onderzoek. Hun gemiddelde leeftijd ten tijde van de diagnose was 34 jaar, 60,3% had borstkanker en 37,2% had een fertiliteitspreservatie behandeling ondergaan. Acht van de elf kwaliteitsindicatoren scoorden onder de 90% naleving en deze omvatten alle domeinen in de oncofertiliteitszorg. Van alle patiënten was 72,7% geïnformeerd over hun risico op onvruchtbaarheid door de oncologisch zorgverlener, werd aan 51,2% een verwijzing naar een gynaecoloog aangeboden, werd met 18,8% alle aspecten van fertiliteitspreservatie counseling besproken en had 35,5% schriftelijke en/of digitale informatie ontvangen. Daarnaast werd een grote variatie in indicator scores gezien tussen ziekenhuizen (namelijk >20% variatie voor tien van de elf kwaliteitsindicatoren). Vier determinanten (leeftijd van de patiënt, de grootte van de kinderwens, de tijd voor de start van de kankerbehandeling en het type zorgverlener) hadden een significante invloed op de score van drie kwaliteitsindicatoren op het domein van verwijzing en (ondersteuning van) gezamenlijke besluitvorming. Wij concludeerden dat de huidige kwaliteit van oncofertiliteitszorg voor vrouwen verre van optimaal is en dat er verbetering nodig is.

In **Hoofdstuk 4** hebben we geëvalueerd of deze suboptimale oncofertiliteitszorg geassocieerd was met patiënt-gerapporteerde uitkomstmaten, zoals met kwaliteit van leven, de mate van moeite met het maken van een keuze (decisional conflict), het hebben van spijt over een gemaakte keuze (decision regret), zorgen over de vruchtbaarheid

en kennis over fertiliteitspreservatie. Een multicenter cross-sectioneel vragenlijst onderzoek werd uitgevoerd in zes ziekenhuizen in Nederland onder vrouwen die hun kanker hebben overleefd. Gevalideerde vragenlijsten werden gebruikt om patiënt-gerapporteerde uitkomstmaten te meten en determinanten die geassocieerd zijn met deze uitkomstmaten werden geëvalueerd. In het algemeen was de fysieke en mentale kwaliteit van leven iets lager dan in de gemiddelde gezonde populatie en werd decisional conflict ervaren door vrouwen. De kwaliteit van leven van vrouwen was het hoogst en de mate van decisional conflict en regret was het laagst als drie kwaliteitsindicatoren werden nageleefd (dat wil zeggen, als vrouwen werden geïnformeerd over het risico op onvruchtbaarheid en als fertiliteitspreservatie counseling werd aangeboden en als schriftelijke en/of digitale informatie werd gegeven). De mate van zorgen over de vruchtbaarheid verschilde niet significant tussen naleving en niet-naleving van de kwaliteitsindicatoren. Daarnaast werden vier determinanten gevonden (leeftijd van de vrouw, het al dan niet hebben van een relatie, grootte van de kindwens en de soort kanker) die de scores van de fysieke kwaliteit van leven, decision regret, zorgen over de vruchtbaarheid en kennis over fertiliteitspreservatie significant beïnvloedden. Deze resultaten leidden tot de conclusie dat het ontvangen van oncofertiliteitszorg van hoge kwaliteit leidt tot een betere kwaliteit van leven en tot minder decisional conflict en regret onder vrouwen die hun kanker hebben overleefd.

Aangezien we hebben aangetoond dat de kwaliteit van oncofertiliteitszorg suboptimaal is, moeten strategieën worden ontwikkeld om de kwaliteit van de oncofertiliteitszorg voor vrouwen en, belangrijker nog, de kwaliteit van leven van vrouwen die hun kanker hebben overleefd, te verbeteren. Deze strategieën dienen afgestemd te worden op de huidige hiaten in de oncofertiliteitszorg en op richtlijnspecifieke knelpunten. Om knelpunten die oncologisch zorgverleners ervan weerhouden om oncofertiliteitszorg van hoge kwaliteit te leveren en suggesties voor verbetering te identificeren hebben we een kwalitatieve studie uitgevoerd **in Hoofdstuk 5** als derde stap in het model om verandering in de klinische praktijk te implementeren. Vervolgens werd een expert panel bijeenkomst gehouden met zorgverleners, met vrouwen die hun kanker hebben overleefd en met onderzoekers, om consensus te bereiken over een set van verbeterstrategieën als vierde stap van het model. In totaal werden 28 knelpunten geïdentificeerd en ingedeeld op patiëntniveau (bijvoorbeeld patiënt focust zich op het overleven van haar kanker), op zorgverlener niveau (bijvoorbeeld gebrek aan bewustzijn, kennis, tijd en houding), of op organisatieniveau (bijvoorbeeld schriftelijke informatie is niet beschikbaar, onenigheid over wie verantwoordelijk is voor het bespreken van het risico op onvruchtbaarheid). Het expert panel heeft consensus bereikt over elementen die essentieel zijn in een verbeterprogramma: het ontwikkelen van informatiemateriaal (folder, een online keuzehulp), het geven van educatie aan zorgverleners, een rol

voor gespecialiseerd oncologie verpleegkundigen in het informeren van patiënten, herinneringen in het medisch dossier, standaard consult met een gynaecoloog voor alle vrouwen met kanker in de vruchtbare leeftijd, overeenstemming in ieder ziekenhuis wie verantwoordelijk is om het risico op onvruchtbaarheid te bespreken en een rol voor fertiliteitsnavigatoren (gespecialiseerde verpleegkundigen) op de fertiliteitsafdeling om de fertiliteitspreservatie counseling te verbeteren.

Deze selectie van verbeterstrategieën vormt de basis van een oncofertiliteitsprogramma dat essentieel is om de oncofertiliteitszorg te verbeteren. Twee strategieën werden ontwikkeld en verder onderzocht in dit proefschrift als deel van de vijfde en tevens laatste stap van het model. De eerst geselecteerde verbeterstrategie was de implementatie van fertiliteitsnavigatoren om vrouwen met kanker te ondersteunen in hun oncofertiliteitsproces. In **Hoofdstuk 6** werden de ervaringen van patiënten en zorgverleners met de fertiliteitsnavigatoren op de fertiliteitsafdeling verkend door middel van semi-gestructureerde diepte-interviews (N=15) en geanalyseerd met behulp van de concepten van 'grounded theory'. Patiënten waren tevreden over de ondersteunende rol van de fertiliteitsnavigators in hun oncofertiliteitsproces: fertiliteitsnavigatoren waren van toegevoegde waarde omdat ze "bekende gezichten" werden, de primaire contactpersoon waren, en informatie, emotionele steun en persoonlijke zorg gaven. De fertiliteitsnavigatoren hadden een prettige samenwerking met zorgverleners en ondersteunden zorgverleners door hun taken over te nemen. Om de rol van de fertiliteitsnavigatoren in de toekomst te verbeteren werd gesuggereerd dat zij altijd aanwezig moeten zijn bij fertiliteitspreservatie counseling en dat er aandacht moet zijn voor hun beschikbaarheid om de continuïteit van zorg te waarborgen. Concluderend verbeteren fertiliteitsnavigatoren de tevredenheid van patiënten over hun oncofertiliteitsproces en ondersteunen ze zorgverleners, wat bijdraagt aan een betere kwaliteit van oncofertiliteitszorg.

De tweede geselecteerde verbeterstrategie, het ontwikkelen en uittesten van een op maat gemaakte online keuzehulp over fertiliteitspreservatie is beschreven in **Hoofdstuk 7**. Onze keuzehulp werd systematisch ontwikkeld aan de hand van de aanbevelingen van Coulter et al en in overeenstemming met de internationale standaarden voor patiëntkeuzehulpen. Dit proces werd uitgevoerd door een multidisciplinaire stuurgroep (N=21) bestaande uit oncologisch zorgverleners, zorgverleners vanuit de voortplantingsgeneeskunde, vrouwen die hun kanker hebben overleefd en patiënt-vertegenwoordigers in een iteratief proces van conceptontwikkeling, drie rondes van alfa testen en revisies. De concepten waren gebaseerd op de huidige richtlijnen en literatuur en op de behoeften van patiënten en zorgverleners welke werden geïnventariseerd door middel van diepte-interviews. In totaal werden 24 online

keuzehulpen over fertiliteitspreservatie ontwikkeld voor vrouwen met kanker en op maat gemaakt voor de verschillende soorten kanker en kankerbehandelingen. Alle keuzehulpen gingen in op de risico's, de veiligheid, de voor- en nadelen van afwachten en van alle fertiliteitspreservatie behandelingen die van toepassing waren (het invriezen van eicellen, embryo's, of eierstokweefsel, het verplaatsen van de eierstok(ken), het onderdrukken van de eierstokken en een operatie waarbij de eierstok en/of baarmoeder gespaard wordt). De definitieve versies werden door vrouwen die hun kanker hebben overleefd, door patiëntvertegenwoordigers en hun zorgverleners als duidelijk, geschikt, bruikbaar en behulpzaam geacht bij het maken van een keuze. Alle vrouwen zouden graag gebruik hebben gemaakt van de keuzehulp als deze beschikbaar was geweest, en zouden het aanraden aan nieuw gediagnosticeerde vrouwen met kanker. Vooral de kankerspecifieke informatie en het hulpmiddel om persoonlijke waarden te herkennen was van grote meerwaarde. Revisies zijn gemaakt om de leesbaarheid, personalisatie en bruikbaarheid te vergroten en om voorzigtiger te zijn met het geven van valse hoop. Bovendien werd voldaan aan 43 van de 45 kwaliteitscriteria voor inhoud en ontwikkelingsproces van de internationale checklist voor standaarden voor patiëntkeuzehulpen. Wij concludeerden dat onze op maat gemaakte keuzehulp over fertiliteitspreservatie belangrijk is om patiënten te ondersteunen bij het nemen van goed geïnformeerde beslissingen over fertiliteitspreservatie op basis van hun persoonlijke situaties en voorkeuren. De keuzehulp zou voor iedereen beschikbaar moeten zijn na het uittesten in de praktijk en na evaluatie van de impact op de besluitvorming bij nieuw gediagnosticeerde patiënten.

Tot slot wordt in **Hoofdstuk 8** de inhoud van dit proefschrift bediscussieerd vanuit het perspectief van een adolescente en jongvolwassen vrouw met kanker, een oncologisch zorgverlener, een gynaecoloog, een beleidsmaker en een onderzoeker. Er wordt een oncofertiliteitsprogramma voorgesteld om oncofertiliteitszorg van hoge kwaliteit voor vrouwen te implementeren met als ultieme doel de kwaliteit van leven van vrouwen die hun kanker hebben overleefd te verbeteren.



APPENDIX



RESEARCH DATA MANAGEMENT

PHD PORTFOLIO

BIBLIOGRAPHY

CURRICULUM VITAE

DANKWOORD

RESEARCH DATA MANAGEMENT

This thesis is based on the results of human studies which were conducted in accordance with the principles of the Declaration of Helsinki, the Medical Research involving Human Subjects Act (WMO), and the Guideline voor Good Clinical Practice.

For Chapter 2 and 5, ethical approval was not required, in line with Dutch guidelines. Ethical approval for the studies conducted in Chapter 3 and 4 was obtained by the Medical Research Ethics Committee of Arnhem-Nijmegen as they were WMO-obligatory (CMO reference number; NL61570.091.17, date of approval; 16 April 2018). In addition, six local ethical committees for patient-related research also approved the study (AmsterdamUMC location AMC, Antoni van Leeuwenhoek Hospital, Canisius-Wilhelmina Hospital, Jeroen Bosch Hospital, Radboud university medical center, and Rijnstate Hospital). For the studies conducted in Chapter 6 and 7, the local ethical committee of the Radboudumc provided approval (Chapter 6, reference number; 2018-4348, date of approval; 2 May 2018, Chapter 7, reference number; 2018-4996, date of approval; 30 January 2019).

This research project is stored in the Digital Research Environment (DRE) of the Radboudumc, a cloud based, globally available research environment where data is stored and organized securely, in the workspace named Inform-1. All study participants (patients, patient advocates, and healthcare providers) provided written informed consent to participate in all of our studies. The hard copies of the informed consent files and of the surveys were stored in the department archive of the Radboudumc.

The privacy of the study participants is warranted by use of encrypted and unique individual subject codes. Members of the research team, the Data and Safety Monitoring Board, and the Health Care Inspectorate are the only persons who have access to the key of the code. This key of the code was stored separately from the study data, also in DRE. Coded data from the surveys were entered into SPSS (version 25.0) for analysis purposes.

The data will be saved for 15 years after termination of the study (2 October 2021). Using these patient data in future research is only possible after renewed permission by the patient as recorded in the informed consent. The datasets analysed during these studies are available from the corresponding author on reasonable request.

PHD PORTFOLIO



Name PhD candidate: M. van den Berg	PhD period: 01-09-2015 31-07-2020
Department: Obstetrics and Gynaecology	Promotor: Prof. dr. D.D.M. Braat
Graduate School: Radboud Institute for Health Sciences	Co-promotors: Dr. C.C.M. Beerendonk Dr. R.P.M.G. Hermens

Training activities	Year(s)	ECTS
<i>a) Courses & workshops</i>		
Radboudumc introduction day	2015	0.4
RIHS Introduction course for PhD candidates	2015	0.75
BROK course	2017	1.5
Digital Research Environment (DRE) course	2017	0.1
Scientific Writing for PhD candidates	2018	3.0
ESHRE pregress course, 3x (Barcelona, Vienna, Online)	2018-2020	1.5
Radboudumc Scientific Integrity	2019	1.0
Presentation Skills	2019	1.0
Statistics for PhD candidates using SPSS	2019	2.0
<i>b) Seminars & Lectures</i>		
Oncofertility Virtual Grand Rounds (online)	2017-2020	1.0
Refereeravond: Kwaliteit van leven na gynaecologische kanker (Arnhem)	2017	0.1
ESHRE Campus Course 'The future fertility of women cancer survivors': oral presentation and chair of diverse sessions (Tbilisi, Georgia)	2018	2.0
PhD Lunchmeetings Theme Women's Cancers (Nijmegen)	2017-2020	0.75
<i>c) Symposia & Congresses</i>		
NVOG Pijlerdag: oral presentation (Utrecht)	2017	0.5
National AYA "Jong en Kanker" Congress (Utrecht)	2018	0.25
ESHRE annual Meeting: poster presentation (Barcelona)	2018	1.0
Resident Refereeravond (Nijmegen): oral presentation	2018-2020	0.5
RIHS PhD retreat: oral presentation (Den Bosch)	2019	1.0
ESHRE annual Meeting: 2x poster presentation (Vienna)	2019	1.0
ISPSG Conference (Den Haag)	2019	0.25
ISFP Conference: poster presentation (New York)	2019	2.0
ESHRE annual Meeting: oral presentation (Online)	2020	1.0

d) Other

Writing grants for KWF (2x), Radboud Oncology Fund, Paul Speth Fund	2015-2019	3.0
Journal clubs/Scientific Meetings Reproductive Medicine	2017-2020	2.0
Peer reviewing medical papers related to fertility preservation	2017-2020	0.5
Meetings patient advisory board of theme Women's Cancers: presentation	2017-2019	0.2
Research evenings PhD students: oral presentations	2018-2019	0.2
Oral presentation to Soroptimistenclub Batenburg to thank for donation	2020	0.1
Oral presentation for Radboud Oncology Committee about decision aid	2020	0.1

e) Lecturing

Lecture for medical students on guideline implementation	2020	0.4
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f) Supervision of internships

Supervision of 3 Bachelor students	2017	3.0
Supervision of 1 Master student for research internship	2018	4.0

Total		36.1
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Radboud University



Radboudumc
university medical center

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M. van den Berg, C.C.M. Beerendonk, S.E.J. Kaal, C.M.P.W. Mandigers, T.N. Schuurman, J. Tol, J.M. Tromp, M.J.D.L. van der Vorst, D.D.M. Braat , R.P.M.G. Hermens. *Suboptimal quality of integrated female oncofertility care is associated with a lowered quality of life, and with more decisional conflict and regret in female cancer survivors*. Submitted

M. van den Berg, S.E.J. Kaal*, T.N. Schuurman*, D.D.M. Braat, C.M.P.W. Mandigers, J. Tol, J.M. Tromp, M.J.D.L. van der Vorst, C.C.M. Beerendonk, R.P.M.G. Hermens. *Quality of integrated female oncofertility care is suboptimal: a patient-reported measurement*. Submitted. *Joint second authorship.

Oral presentations

Van richtlijn naar goede kwaliteitsindicatoren voor fertiliteitspreservatie. Zijn we op de goede weg? NVOG Pijlerdag Fertiliteitspreservatie en Endometriose, 2017, Utrecht, the Netherlands. Awarded for best oral presentation.

Patient's preferences and decision making in fertility preservation. European Society of Human Reproduction and Embryology (ESHRE) Campus Course, 2018, Tbilisi, Georgia. Oral presentation and chair of diverse sessions.

Ontwikkeling van een keuzehulp voor jonge vrouwen met kanker en een kinderwens. Resident Research 'Refereeravond', June 2020, Nijmegen, the Netherlands.

Development and testing of a tailored online fertility preservation decision aid for female cancer patients. European Society of Human Reproduction and Embryology (ESHRE) annual Online Meeting, July 2020.

Poster presentations

Professionals' barriers in female oncofertility care and strategies for improvement. European Society of Human Reproduction and Embryology (ESHRE) annual Meeting, July 2018, Barcelona, Spain.

Key recommendations for high-quality female oncofertility care based on clinical practice guidelines. European Society of Human Reproduction and Embryology (ESHRE) annual Meeting, June 2019, Vienna, Austria.

Fertility navigators in female oncofertility care in an academic medical centre: a qualitative evaluation. European Society of Human Reproduction and Embryology (ESHRE) annual Meeting, June 2019, Vienna, Austria.

Professionals' barriers in female oncofertility care and strategies for improvement. International society for fertility preservation, November 2019, New York, United States of America.

CURRICULUM VITAE

Michelle van den Berg werd op 27 januari 1990 thuis geboren als oudste in een gezin van twee kinderen en groeide op in Dodewaard en Andelst. Na het cum laude behalen van haar gymnasium diploma aan het Stedelijk Gymnasium in Nijmegen, kon zij direct starten met de opleiding Geneeskunde aan de Radboud Universiteit te Nijmegen.

Tijdens haar coschap Gynaecologie en Verloskunde in Ziekenhuis Gelderse Vallei te Ede (2013) ontdekte zij haar passie voor het vak. Vanaf dat moment startte zij, als student, met wetenschappelijk onderzoek binnen de gynaecologie onder begeleiding van dr. Nelen. Haar interesse voor zowel de kliniek als de wetenschap werd bevestigd tijdens haar seniorcoschap in het Rijnstate Ziekenhuis te Arnhem en haar wetenschappelijke stage in het Radboudumc (2014).

Na haar afstuderen eind 2014, startte zij haar wetenschappelijke carrière met een project over de implementatie van een online beslishulp over prenatale testen, onder supervisie van Dr. M. Bekker en Prof. Dr. J. van Vugt in het Radboudumc. Vervolgens mocht zij aan haar eigen promotietraject beginnen onder begeleiding van prof. dr. Braat, dr. Nelen en dr. Beerendonk in september 2015. Tijdens het traject nam dr. Hermens het 'copromotor' stokje van dr. Nelen over. De eerste drie jaar combineerde zij dit met klinisch werk op de afdeling Gynaecologie van het Radboudumc, waarna zij nog twee jaar fulltime aan haar promotieonderzoek heeft gewerkt. Hierna is zij gaan werken als arts-assistent op de afdeling Obstetrie en Gynaecologie in het Catharina Ziekenhuis te Eindhoven en heeft ze haar proefschrift afgerond.

Michelle is sinds 2010 samen met Christopher en zij wonen in Lent. Eind 2021 werd hun liefde bekroond met de geboorte van hun dochter Fenna. In 2022 zal Michelle gaan starten met de opleiding tot gynaecoloog binnen het cluster Nijmegen.

DANKWOORD

Dit promotietraject was er niet geweest zonder de hulp en de steun van velen. Graag wil ik iedereen bedanken die heeft bijgedragen aan het tot stand komen van dit proefschrift. Een aantal personen wil ik hierbij in het bijzonder bedanken.

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Dr. C.C.M. Beerendonk, beste Ina, jouw klinische blik is bij iedere studie van hele grote meerwaarde geweest. Ik ben je dankbaar dat je mij, vanuit jouw Principal Clinicianschap, de mogelijkheid hebt gegeven om fulltime aan dit proefschrift te werken. Jouw passie en inzet om de oncofertiliteitszorg, zowel klinisch als wetenschappelijk, te optimaliseren bewonder ik enorm. En wat een ervaring was het om samen op congres in New York te zijn! Ontzettend bedankt voor alles.

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Leden van de manuscriptcommissie, geachte prof. dr. H.J. Bloemendal, prof. dr. M. Goddijn, prof. dr. G.D.E.M. van der Weijden, hartelijk dank voor jullie beoordeling van het manuscript. Alle leden van de corona wil ik graag bedanken voor het invullen van hun taak als opponent bij mijn verdediging.

Graag bedank ik het Radboud Oncologie Fonds, het Paul Speth Fonds en Ferring B.V. voor hun financiële ondersteuning van dit project.

Daarnaast was de samenwerking met zorgverleners in de oncologie en gynaecologie vanuit het Radboudumc en vanuit andere ziekenhuizen essentieel voor dit proefschrift. Bedankt voor het includeren van patiënten, het bereid zijn tot het geven van diepte-interviews en het meedenken in hoe we de zorg voor deze groep patiënten kunnen verbeteren. In het bijzonder wil ik de leden van de richtlijn werkgroep Fertiliteitsbehoud bij vrouwen met kanker bedanken voor hun medewerking aan het ontwikkelen van onze keuzehulp. Nu op naar de landelijke implementatie!

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Graag wil ik de gynaecologen, assistenten, verloskundigen en verpleegkundigen uit het Catharina Ziekenhuis en het Radboudumc bedanken voor de enorm leerzame en leuke tijd in de kliniek. Door jullie is mijn enthousiasme voor het vak alleen maar

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En natuurlijk mijn liefste paranimfen. Wat ben ik blij dat jullie vandaag hier naast mij staan!

Liefste Laura, wie had nu kunnen denken in de eerste klas van de middelbare school dat we uiteindelijk bijna hetzelfde traject zijn gaan volgen! Van middelbare school tot aan studie geneeskunde tot aan een promotietraject. Het is zo fijn om jou als vriendin te hebben. Op jou kan ik terugvallen tijdens de minder fijne momenten, maar vooral ook genieten van de leuke momenten, zoals onze feestjes en etentjes samen en onze reizen naar St. Petersburg, Rome, Antwerpen, Argelès-sur-Mer, Riga, Londen en Valencia. Ondanks dat we elkaar nu wat minder zien, hebben we altijd aan een half woord genoeg om elkaar te begrijpen. Bedankt voor wie je bent!

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