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Practice, attitude and knowledge of Dutch paediatric oncologists regarding female fertility

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ABSTRACT

Background: Chemotherapy and radiotherapy for childhood cancer can result in a decreased reproductive function. It is therefore important that paediatric oncologists discuss the possible impact of treatment on female fertility and available fertility preservation options with their patients. However, it is unknown what Dutch paediatric oncologists know about of the effect of cancer treatment on female fertility, whether or not they address this issue in clinical practice, what their attitudes are towards addressing fertility after cancer treatment and fertility preservation options, and to what extent they require additional information resources.

Methods: In this nationwide quantitative cross-sectional study a survey was sent to all registered paediatric oncologists in the Netherlands (n=64).

Results: Thirty-seven paediatric oncologists participated (participation rate 58%). Fertility issues were discussed with patients and/or parents by 97%. Of the paediatric oncologists, 54-76% were aware of possibilities for fertility preservation; however only <25% reported a moderate or high confidence in their knowledge of these techniques. Paediatric oncologists stated that they had little resources to counsel their patients and 92% found educational resources not completely sufficient.

Conclusion: Paediatric oncologists are well aware of the effect that cancer treatment may have on female fertility and their responsibility to counsel their patients and/or the parents on this issue. They do not (yet) possess the knowledge to sufficiently counsel these patients and, if needed, do not frequently refer them to a fertility specialist.

KEYWORDS

Infertility, fertility preservation, paediatric oncology, late effects, cancer survivorship

INTRODUCTION

In Western countries, childhood cancer mortality rates declined by more than 50% between 1975 and 2006 as a result of more effective treatments identified and implemented during this period.[1] However, the anti-cancer treatments given to achieve these lower mortality rates may adversely affect reproductive function. In women, the pool of primordial follicles in the ovaries is fixed, and chemotherapy and radiotherapy can substantially deplete this oocyte pool. This may lead to ovarian dysfunction, infertility and premature menopause. Late effects of cancer treatment on fertility outcomes in childhood cancer survivors have been evaluated in a number of studies. Studies based on questionnaire data showed that female childhood cancer survivors had a higher risk of premature menopause[2-5] and were more likely to experience adverse pregnancy outcomes than their siblings due to the chemotherapy and radiotherapy these survivors received.[6-9] Recently, several studies have been conducted that measure ovarian reserve by means of antimullerian hormone (AMH) or ultrasound measurements[10-13], showing that the ovarian reserve is indeed depleted after certain forms of chemotherapy and pelvic radiotherapy.

A nationwide cohort study on reproductive function of female childhood survivors is currently being conducted in

the Netherlands (the DCOG LATER-VEVO study). Results of this study will provide insight into the effects of cancer treatment on the reproductive system of female childhood cancer survivors in the Netherlands and their risk of premature menopause. The effects of treatment in general will be assessed, as well as the effects of different treatment modalities, doses of drugs, radiation sites and doses, and age at time of treatment. The data gathered in this project will provide important information to girls with cancer (and their parents) about the possible adverse effects of treatment on the reproductive function. However, while conducting the nationwide study, it seemed that in Dutch paediatric oncologists knowledge about fertility issues and fertility preservation was often limited. Studies in adult oncological care indicate that knowledge about fertility issues and fertility preservation among physicians is often lacking.[14-20] In a recent study performed in Saudi Arabia, oncologists are found to have a positive attitude towards fertility preservation; however, knowledge regarding the possibilities and the success rates is poor, with up to 46% of the respondents not being familiar with any female fertility preservation options.[19] In the USA and in Canada, approximately half of the oncologists rarely referred their patients to an infertility specialist[17,20], whereas in Saudi Arabia, more than 85% did not refer[19].

Only three studies are available that have quantitatively assessed the knowledge and attitudes towards discussing female fertility issues among paediatric oncologists, two of which were performed in the USA and one in the UK.[21-23] Possibly, the lack in knowledge is due to the limited possibilities that are available in the prevention or therapy of premature menopause for female childhood cancer patients, especially when the patient is prepubertal.

Available established fertility preservation options consist of cryopreservation of embryos, vitrification of oocytes and ovarian transposition. Experimental techniques include cryopreservation of ovarian tissue, and cryopreservation of the whole ovary including vascular anastomoses. *Table 1* provides a short overview of the available techniques and their limitations in female childhood cancer patients.[24-26] To assess the current practice, the attitudes, and the knowledge of Dutch paediatric oncologists involved in oncological care regarding fertility and fertility preservation options in female childhood cancer patients, the PAK study was performed.

MATERIALS AND METHODS

The PAK study was designed as a nationwide quantitative cross-sectional study. Approval for the study was obtained and a waiver of informed consent was received from the Medical Ethics Committee of the VU University Medical Center.

Study population

The study population consisted of paediatric oncologists registered with the Dutch Childhood Oncology Group (DCOG, n=64). Paediatric oncologists were retrospectively excluded in case of retirement, or if they had treated less than five girls, aged 0-18 years, in the past year. The rationale to exclude these subjects was to ensure recent and adequate amount of experience with treating female paediatric patients.

Table 1. *Procedures and limitations of fertility preservation techniques*

Technique	Procedure	Limitations
Established techniques		
Cryopreservation of embryos	Hormonal stimulation of the ovary with exogenous FSH. Ultrasound-guided transvaginal oocyte pick-up. Fertilisation of the oocyte with the sperm in vitro. Primary freezing of the embryos. Embryo transfer after cancer treatment and follow-up is complete	• Not applicable to prepubertal girls • Male partner or sperm donor is obligate • May delay anti-cancer treatment
Vitrification of oocytes	Hormonal stimulation of the ovary with exogenous FSH. Ultrasound-guided transvaginal oocyte pick-up. Rapid freezing (vitrification) of the oocytes. Fertilisation and embryo transfer after cancer treatment and follow-up is complete	• Not applicable to prepubertal girls • May delay anti-cancer treatment
Ovarian transposition	Laparoscopic procedure to remove ovaries from the radiation field	• Effect of chemotherapy remains • Scatter radiation
Experimental techniques		
Cryopreservation of ovarian tissue	Laparoscopic or laparotomic procedure to retrieve strips of ovarian cortex. Strips are vitrified. Reimplantation of the strips (heterotopically or orthotopically) after cancer treatment and follow-up is complete	• Success rate unknown • Risk of reseeding malignancy
Transplantation of the whole ovary	Transplantation of the whole ovary with vascular anastomoses	• Success rate unknown • No pregnancies reported with this method

Data collection

Contact information of the paediatric oncologists was provided by the DCOG. The DCOG is a collaboration between paediatric oncologists and other involved experts working in the seven paediatric oncology and stem cell transplant centres in the Netherlands. Each paediatric oncologist was sent a study information package by post. This package contained a hardcopy of the survey, a cover letter and a pre-stamped and addressed return envelope, together with log-in details for filling out the online version of the survey, if preferred. In addition, the paediatric oncologists were asked to fill out a refusal form if they decided not to participate. This form included several questions regarding characteristics of the paediatric oncologist as well as a question regarding the reason for not wanting to participate in the study. After three to six weeks, paediatric oncologists who had not yet responded were sent a reminder letter by post together with another copy of the study information package. If no response was received within three months, a reminder was sent by email. This email included a hyperlink, which could directly be followed in order to fill out the survey or the refusal form online. If the paediatric oncologist also did not respond to the reminder by email, the paediatric oncologist was considered a non-responder. Participants were not reimbursed for completed surveys.

Survey development

The survey was adapted from the survey used by Duffy *et al.*[16] and was translated from English to Dutch by two independent medical translators. The two forward translations were carefully compared and a reconciled version was then back translated. The original survey was based on qualitative studies with oncologists and recommendations from a national advisory panel of experts in survivorship and reproductive technologies were incorporated.[16] It was slightly modified and some questions were deleted altogether, to account for differences in patient group (young age) and the fact that parents are often involved in decision-making regarding medical issues of their children. In general, questions regarded girls aged 0-18 years with cancer. For some questions, a discrimination was made between pre- and post-pubertal girls. The survey covered issues related to female fertility and fertility preservation in cancer treatment and included the following sections: (1) physician characteristics; (2) current practice; (3) availability and need for information or training; (4) knowledge; and (5) attitude. Five-point Likert scales were used in questions with regard to the paediatric oncologist's attitude and the confidence in their knowledge of fertility and fertility preservation in girls with cancer. We decided not to directly test knowledge. It was assumed that this might create a sense of an 'exam', which might lead to non-participation. However, in this way, it was not possible to report on the objective knowledge of paediatric oncologists as was done by Goodwin *et al.*[22]

Statistical analysis

The data were checked for normal distribution. Descriptive statistics were performed on all variables. IBM SPSS Statistics, version 20.0.0 for Windows was used for all analyses.

RESULTS

Response rate and paediatric oncologists' characteristics

In total, 64 paediatric oncologists were sent a study invitation, of whom 39 (61%) were deemed eligible.

Figure 1. *Flow chart depicting an accrual and participation rates*

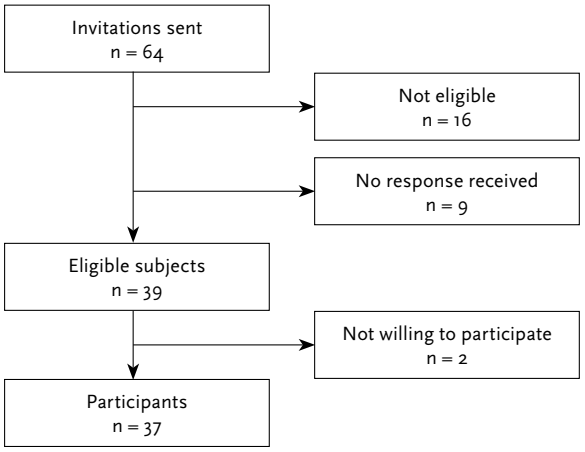

Table 2. *Characteristics of the participating paediatric oncologists (n=37)*

	Participants (n=37) N (%)
Sex	
Male	18 (48.6)
Female	19 (51.4)
Age	
30-39 years	9 (24.3)
40-49 years	18 (48.6)
50-59 years	9 (24.3)
>60 years	1 (2.7)
Years of experience	
Median	12
Range	1-30

Fourteen (22%) persons were not eligible, because they had treated less than five girls in the past year, and an additional two (4%) claimed not to be eligible but did not provide a reason for this. There were nine non-responders (14%), of whom five were female and four were male. Because of the anonymous design of the study, we were not able to evaluate whether there were differences in attitude between the participants and the non-responders. Finally, of 39 eligible subjects, 37 (58%) agreed to participate. The reasons for not participating were insufficient time (n=1) and being invited for surveys too frequently (n=1) (*figure 1*). Of the participants approximately half were male. Seventy-two per cent were between 40 and 60 years old. The median number of years in practice was 12 years (*table 2*).

Practice

Eleven paediatric oncologists (30%) treated 5-10 children aged 0-12 years annually, whereas another 30% treated 10-20 children, aged 0-12 years. Eight oncologists treated more than 20 children aged 0-12 years annually. Seven indicated that they were not sure how many children they treat. In the age group 12-18 years, 18 oncologists treated 5-10 children, seven treated 10-20 children and three treated more than 20 children annually. In this age group, nine oncologists indicated that they did not know how many children they treated. Seventy-five per cent of the paediatric oncologists reported to usually or always discuss fertility issues before the onset of treatment with prepubertal girls or their parents and 89% discussed the issue with postpubertal girls. Almost all paediatric oncologists (97%) discussed the issue with the parents if the patient was a prepubertal girl and 32% discussed it with the girl herself. In case the girl was postpubertal, 84% of the paediatric oncologists discussed the issue with the parents and 97% with the girl herself. More than three-quarters (77%) of the paediatric oncologists indicated to spend between 5-15 minutes on fertility issues, whereas 20% spent more than 15 minutes. Approximately half of the paediatric oncologists (46%) often referred their female patients to a fertility specialist, whereas 38% sometimes referred, 3% always referred and 11% never referred.

Perceived availability of fertility preservation options in own centre

All paediatric oncologists were asked which fertility preservation options were available in their own centre. As the survey was anonymous, it was not possible to substantiate the answers in the centres concerned. Therefore, when the paediatric oncologists affirmed that the requested technique was available in their centre or when they stated that it was not available, the answer was labelled 'aware of availability'. Those paediatric oncologists who responded who they did not know whether that technique was available in their centre were labelled 'unaware of availability'. Most paediatric oncologists were aware of the possibilities for cryopreservation of ovarian tissue, for ovarian transposition and for embryo cryopreservation (76%, 68%, and 65%, respectively). However, it appeared that only 54% were aware of the presence of the options for oocyte cryopreservation (*table 3*).

Table 3. *Perceived availability of fertility preservation options in own centre (n=37)*

	N (%)
Cryopreservation of ovarian tissue	
Aware of availability	28 (75.7)
Not aware of availability	8 (21.6)
Transposition of the ovaries	
Aware of availability	25 (67.6)
Not aware of availability	12 (32.4)
Cryopreservation of embryos	
Aware of availability	23 (62.2)
Not aware of availability	13 (35.1)
Cryopreservation of oocytes	
Aware of availability	19 (51.4)
Not aware of availability	17 (45.9)
Transplantation of the ovary	
Aware of availability	8 (21.6)
Not aware of availability	28 (75.7)
Percentages may not add up to 100% due to missing values.	

Information resources for female patients

It was asked which information resources for female patients were available in each centre about fertility and fertility preservation after cancer treatment. Thirty-five per cent of paediatric oncologists stated that a printed brochure was available, and 14% reported that they had a list with references to resources with regard to fertility and fertility preservation at their disposal. Forty-one per cent reported specialised nurses or social workers trained to inform female patients about fertility issues to be available. One-third of the paediatric oncologists (30%) reported to have a fertility specialist available to refer the female patient to. Sixteen per cent of the paediatric oncologists reported there were no resources at all available for female patients.

Information and education resources for paediatric oncologists

Paediatric oncologists themselves were most likely to use the scientific literature in order to stay updated on the subject of fertility preservation (68%). Other resources

used were national guidelines (35%), consult with fertility specialist (19%) or scientific meetings (5%). Three per cent of the paediatric oncologists stated that the information available on fertility preservation was not at all sufficient, while 89% found the available information to be rather or largely sufficient. Eight per cent reported the available information to be completely sufficient.

Knowledge

Overall, paediatric oncologists had a moderate or high confidence (score 4 or 5 on Likert scale) in their own knowledge of the effects of chemotherapy and radiotherapy on fertility (81% and 78% for chemotherapy and radiotherapy, respectively). However, few paediatric oncologists had a moderate or high confidence in their knowledge of ovarian transposition (24%), IVF protocols for the cryopreservation of embryos (19%) and oocytes (5%), and ovarian tissue cryopreservation (14%). Confidence in knowledge regarding health risks for the mother or foetus during pregnancy associated with various cancer treatments was rated moderate to high in 24% (mother) to 49% (foetus) of the paediatric oncologists (*table 4*).

Attitude

Respondents were asked to which extent they felt it is their responsibility to discuss fertility issues with their female patients. Ninety-seven per cent reported to find it largely to entirely their responsibility to discuss infertility with the girl or parent, whereas 75% perceived it was largely or entirely their responsibility to discuss fertility preservation. In addition, paediatric oncologists were asked whether they would accept a decrease in disease-free survival in order to increase the chance of preserving fertility. Not only their *own* opinion on this matter was questioned, but also their judgment regarding the proportion of decrease in survival that *girls and/or parents* would be willing to accept. Remarkably, many paediatric oncologists (70%) did not answer these two questions. Those paediatric oncologists

Table 4. *Proportion of paediatric oncologists reporting moderate or high confidence in knowledge of fertility issues and options for preservation (n=37)*

Item	N (%)
The risk of infertility associated with the specific chemotherapy agents that you prescribe most often	30 (81.1)
The risk of infertility associated with abdominal and pelvic irradiation	29 (78.4)
Health risks to the foetus associated with the mother having received various cancer treatments	18 (48.6)
Health risks to the mother associated with pregnancy after various cancer treatments	9 (24.3)
Surgical techniques to protect the ovary from radiation damage	9 (24.3)
Performing current protocols for IVF cycles before cancer treatment in order to freeze embryos	7 (18.9)
Cryopreserving ovarian tissue containing primordial follicles for later auto transplantation after cancer treatment	5 (13.5)
Use of GnRH agonists prior to treatment	3 (8.1)
Cryopreserving unfertilised oocytes for future fertilisation and implantation after cancer treatment	2 (5.4)
Radical trachelectomy	0

Percentages may not add up to 100% due to missing values.

Table 5. *Barriers posed to discussing fertility and fertility preservation in women with cancer (n=37)*

Item	N (%)
Patient characteristics	
Has a poor prognosis for long-term survival	9 (24.3)
Appears distressed or overwhelmed about her cancer diagnosis and/or treatment	1 (2.7)
Has aggressive disease and needs rapid initiation of cancer treatment	0
Is under age 16	0
Healthcare system barriers	
Insufficient time to discuss fertility issues with patients	33 (89.2)
Lack of knowledge about fertility preservation options	12 (32.4)
Lack of availability of fertility specialists in your geographic area	4 (10.8)
Physicians' attitude barriers	
Talking about fertility after cancer gives women false hope that they will have a normal lifespan	0
Bringing up infertility is upsetting to patients	0
Bringing up infertility could make some patients decide to forego lifesaving treatments	0
Medical considerations	
Lack of data on the effectiveness of fertility preservation options in women with cancer	8 (21.6)
Chemotherapy prior to conception could increase the risk of birth defects in offspring	7 (18.9)
Discussing options for fertility preservation could delay cancer treatment	3 (8.1)
A woman treated for cancer could have health complications during a subsequent pregnancy	2 (5.4)
The hormones used in many types of fertility preservation could stimulate the growth of cancer	2 (5.4)
A pregnancy, even after successful cancer treatment, could promote cancer recurrence	0

Reported proportions represent scores 4 or 5 on the Likert scale. Percentages may not add up to 100% due to missing values.

who did answer the question (n=11) accepted at most a 1-5% decrease in disease-free survival, and they judged that parents or patients would accept the same amount.

Perceived barriers

Paediatric oncologists were asked whether in daily clinical practice they experience certain barriers that make it less likely for them to discuss fertility or fertility preservation. The barriers reported (*table* 5) were mainly related to the healthcare system, physicians' attitude, medical considerations and patient characteristics that made it less likely to discuss fertility (preservation options). Many paediatric oncologists (89%) stated that insufficient time is an important barrier to discuss fertility issues with the patients or their parents. In addition, one-third of the paediatric oncologists found their lack of knowledge about fertility preservation options a barrier. Approximately 1 in 5 paediatric oncologists reported that the lack of scientific data on the effectiveness of fertility preservation options in women with cancer influenced their willingness to discuss fertility and fertility preservation. A poor prognosis for long-term survival was mentioned by 24% of the paediatric oncologists as a reason not to discuss fertility issues. Other factors, for example, whether the patient has an aggressive disease and needs rapid initiation of cancer treatment, whether the patient is under the age of 16, or whether the patient appears distressed or overwhelmed about her cancer diagnosis and/or treatment, did not seem to influence the paediatric oncologist's willingness to discuss fertility and fertility preservation options (*table* 5).

DISCUSSION

This is the first study assessing the practice, knowledge and attitudes towards female fertility and cancer in paediatric oncologists in the Netherlands and continental Europe. Compared with response rates from other nationwide surveys conducted among paediatric oncologists in the UK and the USA, our response rate was higher (15%[23]) or similar (68%[21]). Our high response rate might be due to the fact that there are only a limited number of paediatric oncologists in the Netherlands and since they are all acquainted, possibly, social desirability played a role in the willingness to complete the questionnaire. When interpreting the results of our study, some limitations should be considered. Although the response rate was high, self-selection bias might have been introduced. Paediatric oncologists who were more interested in the subjects of (in)fertility and fertility preservation options were possibly more likely to discuss fertility issues with their female patients and consequently might have been more likely to participate in this study. Further, within the questions regarding barriers to discuss fertility or referral options no distinction was made between pre- and post-pubertal girls. It is likely, and has been demonstrated by Kohler *et al.*, that pubertal status influences the paediatric oncologist's attitude and practice regarding fertility and fertility preservation.[23] Moreover, it is plausible that the paediatric oncologist's knowledge is less extensive in prepubertal girls, because few possibilities for fertility preservation exist in this patient group and these are mostly experimental. We decided not to directly test knowledge. It was assumed that this might create a sense of an 'exam', which might lead to non-participation. However, in this way, it was not possible to report on the objective knowledge of paediatric oncologists as was done by Goodwin *et al.*[22] When evaluating the answers given as well as the remarks made by the participants, it seemed that some questions in the survey were considered difficult to answer or could be interpreted in various ways. For some questions, this makes it difficult to draw unambiguous conclusions.

In accordance with previous literature[21,23], our results show that paediatric oncologists frequently discuss fertility issues, but referral rates remain relatively low. The reason for this might be that the options for fertility preservation (especially in prepubertal girls) are scarce. To date the procedure of ovarian tissue cryopreservation is still experimental, but it should be realised that it might take several years to decades before these young girls will request transplantation. It is likely that the techniques that are at this moment experimental will at that time be regarded as usual care and, moreover, success rates might be much higher. Although 75% of paediatric oncologists in the PAK study were aware of the possibilities for ovarian tissue cryopreservation, only 13.5% claimed that they were confident in their knowledge regarding this technique. Other studies found similar proportions of awareness.[22,23] These results indicate that there is a lack of knowledge among paediatric oncologists regarding fertility preservation options and that there is a need for additional education. Further education for paediatric oncologists should preferably be structured in protocols or guidelines, in order to standardise fertility preservation care as much as possible in the different centres. In addition, printed brochures on the effect of cancer treatment on fertility as well as fertility preservation options (established as well as experimental) should be available for all paediatric oncologists to hand out to their patients. Good counselling and if possible, adequate action to preserve fertility will add to the future quality of life of female childhood cancer survivors.

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