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Fertility preservation in pediatric and adolescent cancer patients in Switzerland: A qualitative cross-sectional survey

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ABSTRACT

Fertility preservation (FP) is an important topic of discussion in the field of oncology, particularly in pediatric oncology. Despite the awareness of severe impact of infertility on quality of life and different guidelines available in this area, the options in FP are not routinely discussed with the pediatric cancer patients and their parents. To the best of our knowledge, this is the first survey report concerned to FP counseling and procedures in pediatric and adolescent cancer patients in Switzerland. This survey was conducted from June 2014 to October 2014 on the counseling and procedures performed between 2009 and 2013; the questionnaire was completed by one of the professional from hematology/oncology centers in Switzerland. Currently, only four out of nine centers have a program for FP. In 2013, 45/301 (15%) patients received FP counseling and 36/301 (12%) underwent an FP procedure. The most commonly performed procedures from 2009 to 2013 were administration of gonadotropin releasing hormone agonist (3%) and cryopreservation of ovarian tissue in females (3%) and cryopreservation of sperms in males (6%); the most frequently cited reason for the absence of FP counseling was lack of time (55%). Therefore, this survey should help to develop and harmonize practices with respect to FP counseling and procedures in Switzerland, and to establish FP as a standard of care during cancer treatment.

1. Introduction

Fertility preservation (FP) has become an important topic of discussion in the field of oncology, particularly in pediatric oncology. This increasing importance is due to the progress in cancer research leading to the long-term survival of children and adolescents and advances in reproductive medicine, along with the significant impact of infertility on quality of life in cancer survivors. In developed European countries, the current 5-year overall survival rate for childhood cancer is approximately 80% [1]. This progress is largely due to the use of multimodal therapies and improvement in supportive care strategies. In Switzerland, approximately 230 new cases of childhood cancer (children and adolescents) have been diagnosed during 2013–2014 (www.Kinderkrebsregister.ch). All of these patients undergo treatment in one of the nine specialized centers belonging to *Schweizerische Pädiatrische Onkologie Gruppe (SPOG)*. According to the statistics, approximately 180 patients are expected to survive cancer each year.

However, cancer treatment can be harmful particularly to the gonads, leading to the impairment of pubertal development and/or causing infertility. Infertility may result in psychosocial distress, anxiety, depression, and low self-esteem thereby affecting quality of life in cancer survivors [2]. Therefore, fertility impairment during cancer treatment has been acknowledged by several groups worldwide, thus prompting different guidelines to be published over recent years concerned to FP counseling and procedures [3–6]. Despite these recommendations, data show that FP is considered or offered only in 40% of the eligible patients [7].

Herein, we present the results of our survey investigating FP counseling and procedures performed on pediatric and adolescent

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cancer patients registered for cancer treatment in Switzerland. To the best of our knowledge, this is the first survey report on FP counseling and procedures in Switzerland. The aim of this survey was to evaluate the different practices in FP performed on children and adolescents, and to identify unmet needs in this field.

2. Methods and statistics

All nine Swiss pediatric hematology/oncology centers were contacted to participate in this survey, which was conducted from June 2014 to October 2014. "Five of the 9 centers were university hospitals, performing allogeneic or autologous HSCT. In these centers a network of oncologists, pediatricians, gynecologists, and endocrinologists was present. Four of them had SOPs for FP which were predominately similar. The 4 remaining centers were tertiary hospitals where mostly the pediatrician and the gynecologist only performed the consultation. A questionnaire was sent by mail and e-mail to the head of each of the nine pediatric hematology/oncology departments in Switzerland. The questionnaire, which was filled by one physician from each center, consisted of 24 items divided into the following four sections: [1] the principal characteristics of the center, [2] the availability of FP counseling and/or a standard operating procedure (SOP) in FP counseling including the time point at which counseling is offered and the person/team responsible for it, [3] the FP procedures offered to maintain fertility, and [4] the physician's own view of FP. Questions seeking opinions on the relevance of FP, coverage of costs, and suggestions for improvement were also included. Furthermore, the physicians were given opportunity to provide the number and type of FP methods available at their center during the period of 2009–2013, according to cancer type. Most of the questions required an answer of either "yes" or "no". Certain topics required a response using a scale of 1–10 (low relevance to high relevance).

In this study, the survey population included children and adolescents aged below 18 years at the time of diagnosis either with a malignant disease, who were treated with radio-/chemotherapy or who underwent hematopoietic stem cell transplantation (HSCT), or with a nonmalignant disease who underwent an HSCT procedure. Patients who had undergone a cancer treatment or an HSCT procedure prior to 2009 were excluded. An ethical approval was obtained to perform this survey.

An exploratory analysis of the data was performed to evaluate the information provided by the pediatric hematology/oncology Swiss centers. Data were summarized in tables according to the principal characteristics of the center, such as the existence of an SOP. In addition, data were assessed visually using scatterplots, bar graphs, box plots, and maps to identify patterns, trends, and outliers. All analyses were performed using software R.

3. Results

All nine Swiss pediatric hematology/oncology centers agreed to participate in the survey and completed the questionnaire. Department characteristics and the number/proportion of counseling/procedures available during 2013 are described in Table 1. There were 308 new cases reported each year (including relapses); of them, 47 (16%) patients underwent an HSCT procedure as part of their therapy. An SOP for FP counseling and procedures was available in four out of nine (44%) centers (two for pre and postpubertal patients and two for postpubertal patients alone). These SOPs were in-house protocols based on the guidelines of American Society of Clinical Oncology (ASCO) (2006) or British Fertility Society (2004) and were written in collaboration with the university-based fertility team. The four centers that reported having an SOP were those with a larger number of treated cases (Table 1). In general, the use of SOPs was implemented recently (2010, 2011). Nevertheless, four out of five centers without an SOP performed FP counseling.

In the four centers with an SOP, counseling was performed by an interdisciplinary team consisting of a hematologist/oncologist, a pediatric endocrinologist, and a specialist in reproductive medicine, or at least by the hematologist together with the specialist in reproductive medicine. In three of the centers without an SOP, the hematologist performed FP counseling. In case of timing of counseling provided, in seven out of nine centers (four with an SOP), an FP counseling was conducted at the beginning of the treatment or procedure. However in three out of nine centers (all with an SOP) the FP counseling was conducted before performing HSCT procedure.

In 2013, out of 308 reported new cases, 36 (12%) patients underwent an FP procedure, whereas between 2009 and 2013, a total of 77 females and 75 males underwent an FP procedure. The most frequently used procedures in females were the use of a gonadotropin releasing hormone agonist (GnRHa) (42%) and ovarian tissue cryopreservation (47%) (Fig. 1A). In males, sperm cryopreservation (88%) was the most common procedure performed (Fig. 1B). Testicular sperm extraction was performed in three postpubertal males. No centers performed a cryopreservation of spermatogonial stem cells. Table 2 lists different procedures performed according to the type of cancer.

Table 3 summarizes the data on FP reimbursement for the year 2013. Costs were primarily covered by parents/patients (88%) and health insurance (66%). Some cases were subsidized by charitable institutions such as the Swiss cancer league.

According to the questionnaire, the study centers reported that parents and patients were indeed interested in discussing FP options (parents: 88% of prepubertal and 100% of postpubertal

Table 1
Demographic characteristics of centers and number/proportion of counseling/procedures in 2013.

Institution	New cases per year[a]	SOP	Counseling total	Procedure total
Zürich (including Chur)	77	Yes (post)	13/77 (17%)	13/77 (17%)
Lausanne	50	Yes (pre + post)	4/50 (8%)	4/50 (8%)
Berne	35	No	7/35 (20%)	7/35 (14%)
Geneva	32	Yes (pre + post)	3/32 (9%)	1/32 (3%)
Basel	32	Yes (post)	4/32 (12%)	4/32 (12%)
St. Gallen	30	No	7/30 (23%)	1/30 (3%)
Lucerne	25	No	0/25 (0%)	0
Aarau	15	No	4/15 (27%)	4/15 (27%)
Bellinzona	12	No	3/12 (25%)	2/12 (17%)

Note: pre = prepubertal; post = postpubertal; SOP: standard operating procedure.
[a] Including relapses.

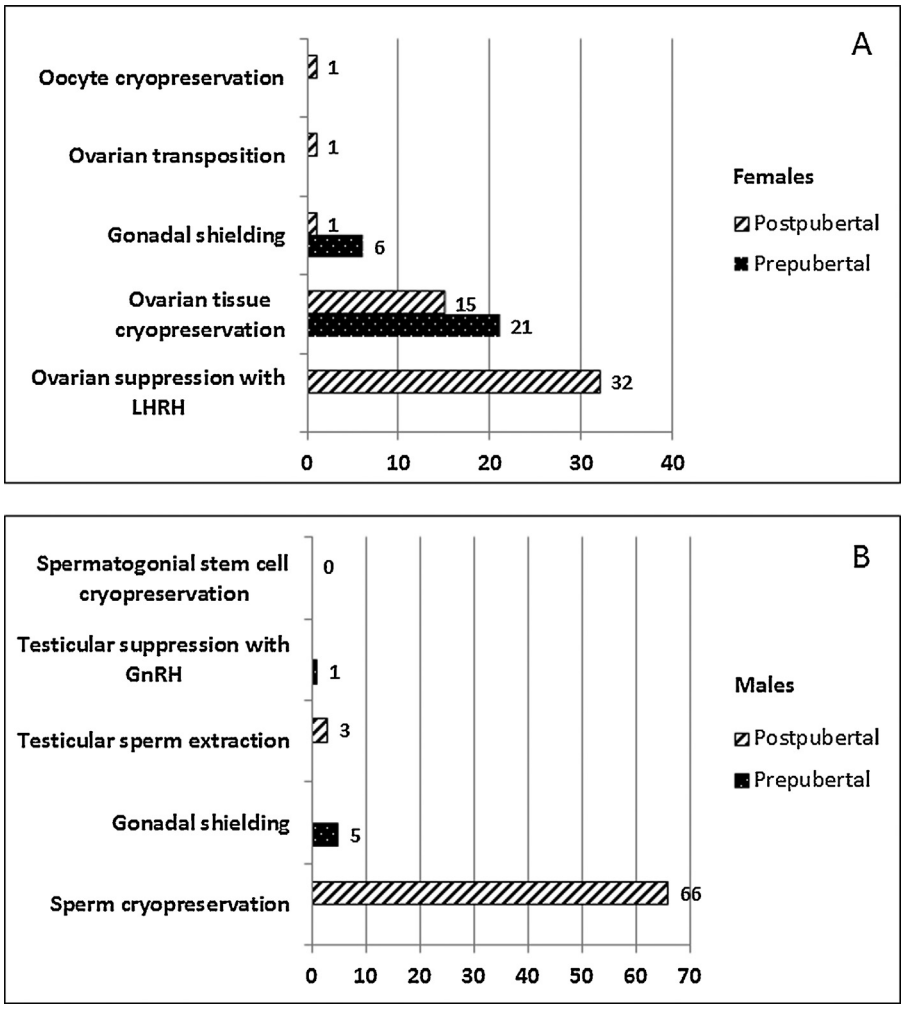

Fig. 1. (A) Number and type of fertility preservation procedures performed between 2009 and 2013 in females. (B) Number and type of fertility preservation procedures performed between 2009 and 2013 in males.

patients; patients: 88% of postpubertal patients). The most frequently provided reason for the lack of counseling was lack of time (3/9). Possible reasons for refusal of counseling by parents/patients (from the perspective of the 9 physicians) were reported to be lack of interest (6/9), overwhelming nature of the situation (6/9), and psychological distress (5/9) in a life-threatening situation. Doctors' views on the impact of FP counseling mentioned potential benefits for patients including relief of emotional distress (6/9) and a greater ability to cope with the diagnosis (3/9), less of the inquired considered no difference (3/9) Furthermore, in case of optimization of FP programs, all centers agreed that financial support is crucial; however, 90% of them indicated the need to promote education on the topic of FP and increase the availability of resources.

4. Discussion

FP has become an important topic of discussion in pediatric oncology, as demonstrated by the 100% response rate in this survey. However, till date, FP counseling and procedures are not being implemented routinely, with only four (44%) of the nine Swiss pediatric hematology/oncology centers having a standardized FP program. Our results agree with the results reported by Terenziani et al. in a European survey (42%) [7]. Those centers using an SOP counsel earlier and perform the counseling through a multidisciplinary team. According to our survey, the existence of a standardized process allows counseling and possible implementation of an FP procedure before starting the treatment. The absence of an SOP for FP did not exclude the possibility of counseling by some centers; however, the counseling was performed by a hematologist alone. Despite pediatric hematologists/oncologists playing a key role in the care of pediatric patients and their families, they are not always familiar with the current practice of FP. Interdisciplinary team work is a modern approach involving collaboration by a team of specialists to optimize the process and standard of care [5]. Thus, in case of FP in cancer therapy, an interdisciplinary team is necessary to work together to share expertise, knowledge, and skills to impact on patient care.

Our survey showed that the procedures most commonly performed on females during the period of 2009–2013 were hormonal suppression using GnRHa and ovarian tissue cryopreservation. GnRHa was often performed on postpubertal females despite the lack of substantiating evidence for its benefit [8,9]. Potential explanations for the use of this procedure may be that it is an easy procedure; some studies have shown a reduction in the risk of premature ovarian failure and an increase in the probability of achieving pregnancy [8,9]. Some of the limitations of these studies include the short and differing periods of follow-up, lack of randomization, small sample sizes, variations in GnRHa dosing regimens [10], and development of postmenopausal symptoms such as flush in some patients. Therefore, the use of GnRHa in postpubertal females remains controversial.

Table 2
Procedures used from 2009 to 2013 by disease type (report from 117 pediatric patients).

Procedure	Prepubertal females	Postpubertal females
Oocyte cryopreservation		1 ALL
Ovarian suppression		6 ALL 2 AML 1 NHL 8 M. Hodgkin lymphoma 1 Ewing sarcoma 3 Osteosarcoma 2 Localized soft tissue sarcoma 1 Nongerminomatous germ cell tumor 5 Nonmalignant diseases **20/26 in centers with SOP**
Ovarian tissue cryopreservation	8 ALL 1 Osteosarcoma 1 Ewing sarcoma 5 Neuroblastoma 1 Brain tumor 3 Nonmalignant diseases **19/19 in centers with SOP**	4 Hodgkin lymphoma 2 Osteosarcoma 2 Localized soft tissue sarcoma 1 Ewing sarcoma 1 Brain tumor 2 Nonmalignant diseases **7/12 in centers with SOP**
Gonadal shielding		1 Hodgkin lymphoma **0/1 in center with SOP**
Oophoropexy		1 Hodgkin lymphoma **0/1 in center with SOP**
Procedure	**Prepubertal males**	**Postpubertal males**
Spermbanking		16 Hodgkin lymphoma 4 Non Hodgkin lymphoma 7 Osteosarcoma 4 Ewing sarcoma 3 Localized soft tissue sarcoma 1 Metastatic soft tissue sarcoma 10 ALL 2 AML 3 Brain tumor 5 Nonmalignant diseases **37/55 in centers with SOP**
Testicular sperm extraction (TESE)		2 Nongerminomatous germ cell tumor 1 Hodgkin lymphoma **3/3 in centers with SOP**
Testicular spermatogonial cryopreservation		0
Gonadal shielding		0

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia.

Table 3
Payers of the cost of fertility preservation in nine centers in Switzerland in 2013 *(multiple answers possible)*.

Payer	Complete	Partial	Total
Insurance	1/9 (11%)	5/9 (55%)	6/9 (66%)
Parents/patients	1/9 (11%)	7/9 (77%)	8/9 (88%)
Others (funding, cancer league etc.)	0	5/9 (55%)	5/9 (55%)

Ovarian tissue cryopreservation, which is a promising novel method for FP and still considered to be experimental, was performed on 36 female patients, particularly in patients with sarcoma, Hodgkin lymphoma, and leukemia [11–16]. This method offers a number of advantages, such as omission for the need of hormonal hyperstimulation and immediate start of oncological treatment. In addition, it has the ability to restore the reproductive as well the endocrine functions of the ovary. However, especially in patients with leukemia, disseminated lymphoma, or neuroblastoma there is a potential risk of reintroduction of malignant cells by tissue re-implantation, in these patients, however, it would be acceptable to perform the procedure in the hope that science development will allow its use safely. The intervention itself also carries risks such as infection or bleeding. Therefore some researchers propose risk stratification before offering this procedure to high-risk patients [17–19].

Our survey showed that oocyte cryopreservation was performed only on one patient. This method cannot be performed on prepubertal females; moreover, its implementation requires at least 2 weeks of hormonal stimulation. The rarity of this procedure may be explained by the fact that from 2009 to 2013, two-thirds of the patients in pediatric hematology/oncology centers were prepubertal, and the urgent need to start treatment may have been the primary limitation for the use of this procedure in potential candidates.

In males, as expected, the most frequently performed FP procedure was semen cryopreservation. This method has been well established for several decades and is very successful in adult males. Semen cryopreservation is rapid and noninvasive, without delaying treatment start. Depending on the underlying disease and stress experienced during sample collection, the quantity and

quality of the sample might be reduced [20–22]. At the present moment, due to the young age of patients and the short follow up, no cryopreserved sperm were used yet.

Testicular sperm extraction, an established FP method in postpubertal males, was offered only by one center in 2013. Extraction of spermatozoa and subsequent cryopreservation requires a good deal of expertise, and this may have been a constraint for its use. In prepubertal males, the only FP procedure performed was testicular suppression with GnRHa in one case. To date, no data exist supporting this practice.

No center reported the use of cryopreservation of spermatogonial stem cells. This technique is very experimental in humans, although there is evidence for success in mouse models [23]. Furthermore, no protocol existed in 2013 for this method in Switzerland.

Costs for FP were either completely covered by parents/patients or partially covered by the health insurance schemes in Switzerland, which means that often part of the cost had to be covered by parents/patients or other institutions such as the Swiss cancer league. This is in contrast to other countries such as France or Israel, where there is a statutory right for FP to be covered by public health organizations [24]. For Switzerland, financial support by the state or through health insurance would likely provide additional support for the treatment costs.

All nine participating centers classified the topic of FP as important, whereas institutions with procedures outlined in an SOP considered it more important (mean 8.25 points) than those institutions without an SOP (mean 7.6 points). The awareness of the relevance of fertility prevention probably led to the development of FP program. This survey reported low percentage of patients (12%) receiving counseling and an appropriate procedure, and this might be explained by number of factors. Insufficient knowledge of the various FP options and low self-confidence in the pediatric hematology/oncology staff in introducing the topic and initiating discussion may represent a barrier for the implementation of these procedures, whereas lack of awareness of the FP issue per se may also play a role [25,26].

Knowledge concerned to different FP options is extremely variable among physicians. Loren et al. found that only 60% of surveyed pediatric and adult hematologists/oncologists were aware of the ASCO Guidelines on FP [27]. They noted that although risk of infertility and FP procedures were frequently part of the initial discussion with patients, half of them did not remember it, primarily because counseling was conducted during the initial conversation about diagnosis and therapy of the malignant disease [28–30]. This, again, supports the strategy of delivering FP counseling separately in a specific setting.

There is a widespread interest among parents and also postpubertal patients regarding FP. Often, the wish of the patient, who is still a child, may be underestimated [31]. Occasionally, parents refused a procedure. From physician's perspective possible reasons for parenteral refusal was the inability to consider the potential impact of fertility issues in the future of their child. The life-threatening situation reduced their capacity for decision-making, especially if an additional surgical procedure was required and the proposed options were experimental with unknown potential for fertility restoration. The additional barriers were religious, cultural, and ethical considerations [32]. In contrast, financial constraints did not seem to be a significant barrier on the part of parents who are considered supportive.

The health teams experienced a positive impact of counseling for FP, stating that patients who received counseling and/or a procedure were subsequently less distressed and felt that they were informed in a better way. Involvement in the decision-making process helped patients to cope with the disease and to deal with the problems of the disease in a better way.

The following three suggestions of the six possible options have been proposed to improve FP counseling: to secure the financial requirements, to enhance continuous medical education, and to provide access to specialist personnel. The coverage of cost by a public health system, as already available in some European countries, would guarantee better access to FP.

The majority of the centers recognized the need for more training in this area. Increased awareness and knowledge will strengthen the self-confidence of healthcare professionals to discuss the issue with patients and families. An underlying multidisciplinary team, including the collaboration of experts in reproductive medicine, seems to play a decisive role in this field.

We recognize that this study has some limitations in that the questionnaire was completed by only one professional person per institution, possibly leading to the introduction of some bias regarding the representativeness of the institution.

5. Summary and outlook

This is the first survey providing information on current practice in fertility counseling and FP procedures in children and adolescent cancer patients in Switzerland.

Data collected in this survey represent an initial effort to develop and harmonize practices in the field of FP counseling and procedures in Switzerland. Implementation of standardized procedures in all centers should help to offer a higher standard of care to cancer patients particularly to pediatric and adolescent patients.

Authors contribution

Tamara Diesch conceptualized the work, designed the survey, interpreted data and wrote the paper.

Alicia Rovo' and Nicolas von der Weid contributed to analysis and interpretation of data.

Gabor Szinai and Christian De Geyter revised critically the paper and gave specific inputs (endocrinological/reproductive medicine).

Sabine Schaedelin perfomed the statistic analysis.

Disclosure statement

The authors have nothing to disclose.

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