Female Fertility Preservation: Practical and Ethical Considerations of an Underused Procedure

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Purpose: Cancer treatments for young women can permanently or temporarily affect fertility. The purpose of this retrospective analysis was to present the clinical experience and ethical considerations of fertility preservation in female oncology patients in a tertiary gynaecological department.

Methods: Since 2002, in 37 patients fertility preservation was performed according to an institutional review board approved protocol in a University hospital in the Netherlands; 33 patients were not treated.

Results: Embryo cryopreservation was performed in 10 patients, ovarian tissue cryopreservation in 24, and an ovarian transposition was performed in 3 patients; in one patient combined with an ovarian transplantation and in one patient with ovarian tissue cryopreservation.

Discussion: Approved protocols and timing are essential in performing female fertility preservation. Referral for ovarian tissue and embryo cryopreservation is minimal in the Netherlands. Future research focuses on the psychosocial aspects of fertility preservation and explores patients' and professionals' expectations and attitudes regarding fertility preservation and aims to be in line with technical developments.

Key Words: female fertility preservation, ovarian tissue cryopreservation, infertility, malignancy, quality of life

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Medical advances in cancer therapy have increased survival rates for a variety of childhood and adult cancers resulting in increased attention to the possible long-term side effects of these therapies and quality of life (QoL) issues for cancer survivors.[1] It is even expected that by 2010, 1 in 250 young adults is a childhood cancer survivor.[2] Because of delayed childbearing and increased survival rates, more young adults are experiencing the consequences of infertility after cancer treatment.

Multidrug chemotherapy with alkylating agents such as cyclophosphamide, radiation therapy, or surgery can impair future fertility and have a great impact on QoL in men and women. For some patients, especially young women, loss of fertility after cancer treatment is almost as painful as facing the disease itself.[3,4] Studies show that cancer survivors do want to have children after cancer and some even valued parenthood more because of their experience with cancer.[4–8] Therefore, cancer patients would be motivated to undergo fertility preserving treatments.

In men and more recently in male adolescents, preservation of fertility using semen cryopreservation is a standard, safe technique and is very efficient in combination with assisted reproduction techniques (ART).[9] Cryopreservation of oocytes, the female equivalent of semen, is known for its reduced in vitro fertilization (IVF) success rates leaving it experimental at this moment and an inefficient technique to reliably preserve fertility.[10] Scientific research has therefore also focused on alternative fertility preserving methods like cryopreservation of ovarian tissue and embryo's. Embryo cryopreservation, like semen cryopreservation, is an established and efficient technique. However, the necessity of a male partner and time-consuming hormonal stimulation, possibly relatively contraindicated in estrogen receptor positive breast tumors, are possible limitations of this treatment.[11] Ovarian tissue cryopreservation (OTC), like oocyte cryopreservation, is an experimental technique. The lack of time-consuming hormonal stimulation and male involvement makes this technique an attractive alternative. OTC can therefore be proposed to prepubertal patients and patients without a partner; cancer treatment can start within days after the procedure.[12]

In contrast to the number of case reports and studies on the technical aspects of fertility preservation, only a few publications address the QoL and psychosocial aspects of fertility preservation in men or women. The American Society of Clinical Oncology and the British Fertility Society recommend to bring up the subject of induced infertility in patients treated during their reproductive years.[11,13,14] Discussion of infertility and fertility preservation options at the earliest possible opportunity, at least before initiation of cancer treatment, is stressed. This manuscript presents the clinical experience with fertility preserving techniques and

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the ethical considerations associated with them in a tertiary gynecologic department.

METHODS

From July 2002 to October 2007, 70 adult women, adolescents, and prepubertal girls were referred for fertility preservation. The patients and parents of patients under the age of 18 were informed of the risk of future infertility induced by cancer treatment. The various available methods of fertility preservation were discussed according to a treatment protocol approved by the local Ethical Committee. If gonadotoxic treatment consisted of pelvic radiation, ovarian transplantation, and transposition were discussed more specifically. Patients scheduled for chemotherapy were informed about embryo and/or OTC, depending on their age, tumor features, and marital status. Combinations of fertility preservation techniques were discussed on an individual basis.

Success rates and risks of the relevant techniques and procedures were subject of discussion. It was thoroughly explained that cryopreservation of ovarian tissue is still an experimental procedure, with no guarantees on fertility restoration or live birth and the small but present risk of reintroducing malignant cells with thawing and transplantation was underlined. OTC was performed after informed consent was signed.

Clinical charts were reviewed for disease evolution and ovarian function after gonadotoxic treatment. Disease evolution was specified as complete remission (CR) if all signs of cancer disappeared in response to treatment, partial remission if some but not all signs of cancer disappeared, no response if no improvement related to therapy was observed, and progression if signs of increasing tumor or cancer spread were present, not applicable if no primary malignant disease was present, and very recent if the patient was still receiving primary treatment. Ovarian function was based on cycle anamnesis and specified as chemotherapy-induced amenorrhea (CIA) whenever no menstruations occurred after gonadotoxic treatment; it was specified as therapy if a patient was still receiving primary or adjuvant hormonal treatment. In women receiving hormonal therapy, the ovarian function cannot be determined and CIA cannot be diagnosed. No women received hormonal therapy before or during fertility preserving treatment. Hormonal studies were performed postoperatively if signs of CIA were present. Normal ovarian function implied regular menstruations.

Cryopreservation Ovarian Tissue

Cryopreservation of ovarian tissue was discussed with selected patients after multidisciplinary evaluation of CIA and premature ovarian failure (POF) risk after gonadotoxic treatment. The inclusion and exclusion criteria are listed in Table 1. Before treatment, baseline endocrine studies were performed to exclude POF preoperatively. Consultation of the Ethical Committee occurred on individual basis whenever a girl under the age of 18 was referred. These girls were seen with at least 1 parent present.

Unilateral oophorectomy was performed under general anesthesia by laparoscopy or laparotomy, if possible combined with a necessary surgical procedure. In the operating room the ovarian tissue was dissected into small slices of ovarian cortex ($10 \times 5 \times 1$ mm), according to the description of Radford in 2001, and transferred in vials to the ART-laboratory.[15] A slow freezing protocol was used to cryopreserve the slices and they were plunged into liquid nitrogen and stored until required.

TABLE 1. Criteria Cryopreservation Ovarian Tissue

Inclusion Criteria	Exclusion Criteria
Written informed consent	Previous highly gonadotoxic treatment
18–35 yr	5-yr survival rate <50%
Very low chance of ovarian metastasis[52]	POF
Uterus and ovaries sonographically intact	Operative contra-indication
Risk of POF: >50%	Positive serology (HIV, hepatitis B and C)
	Severe comorbidity

POF, premature ovarian failure; HIV, human immunodeficiency virus.

Cryopreservation Embryos

Cryopreservation of embryos was discussed with patients of 18 to 40 years with a male partner. Before start of the IVF cycle, which is performed in 2 to 6 weeks, the possible consequences of delay in cancer treatment and use of hormonal stimulation, which starts on cycle day 2 to 3 were discussed with the oncologist. As described by Oktay et al,[16] in case of estrogen sensitive breast cancer a short protocol consisting of tamoxifen alone or tamoxifen plus low dose follicle-stimulating hormone (FSH) or letrozole plus FSH was given. However, since the appearance of literature on cardiac and bone malformations with letrozole, this protocol has been abandoned.[17] IVF during natural cycle was considered if hormonal stimulation was contraindicated or not wanted. The standard IVF protocol, FSH plus a gonadotropin releasing agonist, was used in patients without a hormone sensitive tumor.[18] Depending on the amount and quality of oocytes and semen, embryos were formed and cryopreserved until further use.[19]

Ovarian Transplantation and Transposition

Ovarian transplantation or transposition, in an attempt to preserve future fertility, is discussed with patients from 18 to 40 years in whom the risk of POF is greater than 20% after pelvic radiation therapy. Ovarian transplantation with its vascular pedicle, described by Hilders et al,[20] is a highly experimental procedure including a laparotomy. This procedure was therefore performed in only 1 patient with a gynecologic tumor, planned for laparotomy and pelvic radiation therapy. Ovarian transposition was preferably performed in a laparoscopic procedure. The utero-ovarian ligament, tube, and mesosalpinx were transected with bipolar cautery and sharp dissection, which was followed by the careful dissection of the vessels of the infundibulopelvic ligament. The ovary with its vascular pedicle and tube were mobilized out of the pelvis without tension. An irresolvable suture through the fascia superior was used to fixate the ovary at the level of the costal margin.[21] Metallic clips were applied to the borders of the ovary allowing radiologic visualization.

Statistical Analysis

Statistical Package for the Social Sciences, SPSS version 12.0.1, was used to perform descriptive statistics. Differences between groups were examined using the unpaired *t* test for interval variables and the chi-square test for nominal variables. *P* value <0.05 was considered statistically significant.

RESULTS

From July 2002 to October 2007, 77 requests for fertility preservation therapy (FPT) were evaluated and 37 were actually performed (Fig. 1). The 77 requests consisted of 70 patient contacts and 7 intercollegiate contacts (telephone), without final patient referral.

Fertility Preservation Therapy+

FPT was performed in 53% of referred patients of whom 65% was diagnosed with breast cancer. Sixteen percent of requests concerned patients with bone or soft tissue malignancies, 8% concerned Hodgkin disease or non-Hodgkin lymphoma, and 11% were related to single patients with rectal cancer, cervical cancer, and endometriosis with frozen pelvis or β-thalassemia major. Mean age was 28.2 years, varying from 13.8 to 35.7 years. The follow-up period, time from consultation to disease status and ovarian function assessment, varied from 0.9 to 57.0 months, mean 17.3 and median 12.8 months. Demographical features are listed in Table 2; data concerning a partner was missing for 15 patients.

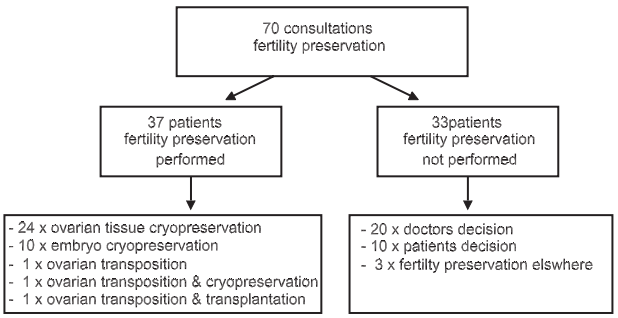

FIGURE 1. Extent of fertility preservation 2002–2007. Total number of patients referred for fertility preservation from 2002 to 2007, including the conducted fertility preserving treatments.

TABLE 2. Demographical Features

	Fertility Preservation	
	Performed, n = 37 (%)	**Not Performed, n = 33 (%)**
Partner	21 (57), 5 patients data missing	15 (45), 10 patients data missing
Parity*	3 (8)	10 (31)
Deceased	5 (14)	4 (13)
Pregnant	3 (8)	2 (6)

*Statistical significance $P = 0.01$.

In all patients who opted for cryopreservation of ovarian tissue, except for three, a laparoscopic procedure was performed and overall no surgical complications were observed. In the remaining 3 patients a laparotomy was performed because of the primary surgical treatment of rectal cancer, cervical cancer, or endometriosis. FPT was combined with other surgical procedures such as port catheter and intrauterine device (2) positioning. Patients were naive to chemotherapy or radiation treatment before fertility preserving treatment except for 3 patients with relapsing HD, breast cancer, and Ewing sarcoma. The relapsing HD patient received 6 cycles of epirubicin, bleomycin, prednison, and vinblastin 33 months before OTC. The breast cancer patient received 2 cycles of cyclophosphamide, epirubicin, and fluorouracil 2 months before OTC. Finally, the patient with a soft tissue malignancy received thoracic radiation therapy before undergoing surgery for OTC.

Most patients were referred by an oncologist (43%), gynecologist (21%), or surgeon (19%). Three children were referred by the pediatrician, 1 patient was referred by the radiotherapist, 1 patient was a self-referral, and 1 reference was unknown.

Nineteen patients (51%) were in CR at follow-up and 12 patients (33%) were still receiving primary treatment and therefore evolution of disease could not be determined (Fig. 2A). Eighteen patients (49%) still received adjuvant (hormonal) therapy at chart review (Fig. 2B). CIA occurred in 3 patients (8%) with amenorrhea for 3, 12, and 18 months. Two spontaneous pregnancies occurred 35 and 36 months after 6 cycles of cyclophosphamide, epirubicin, and fluorouracil and cyclophosphamide, doxorubicin, and fluorouracil. One pregnancy occurred after a request for thawing and transferring a cryopreserved embryo, 30 months after the cryopreservation procedure. The only request for ovarian tissue transplantation, 22 months after OTC, was rejected after multidisciplinary consultation, according to the protocol.

Five patients died in the follow-up period, after 6, 21, 22, and 34 months aged 17, 33, 26, and 20 years. The fifth patient who died of cervical cancer was lost to follow-up because of the emigration.

Fertility Preservation Therapy−

FPT was not performed in 47% of referred patients. Three patients decided to perform embryo cryopreservation elsewhere because of traveling time. Twenty-one patients were excluded by the gynecologist because of risk of ovarian metastasis (19%), previous highly gonadotoxic treatment (16%), low risk of POF after therapy (16%), and age (13%). Ten patients sustained the inclusion criteria and presented no exclusion criteria but decided not to undergo FPT for various reasons such as focus on disease and recovery, timing arguments, and poor efficiency of OTC.

Sixty-six percent of patients were diagnosed with breast cancer, 25% of requests were related to hematological disease. Three single patients with cervical cancer, sarcoma, and a mother who requested FPT for her daughters with POF were not included. The mean age was 30.2 years, varying from 15.1 to 45.2 years. The follow-up period, time from consultation to disease status and ovarian function assess-

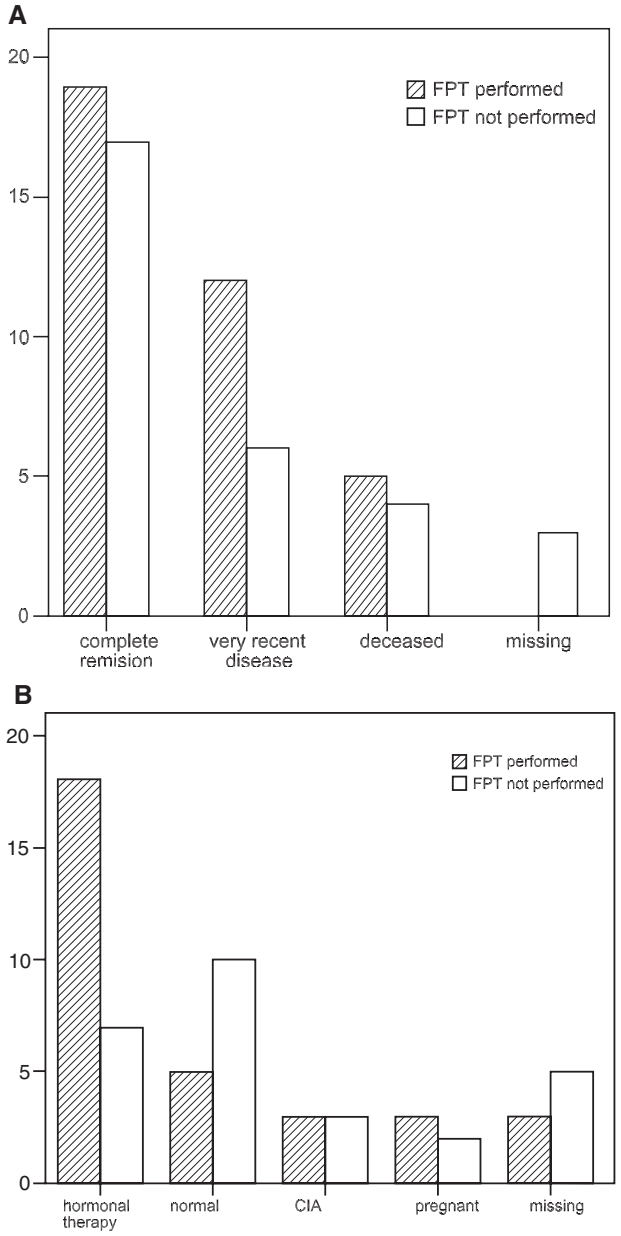

FIGURE 2. A, Evolution of disease of 70 patients at follow-up. Patients who were still receiving primary treatment, were classified as "very recent disease." FPT = fertility preservation therapy. B, Clinical ovarian function of 59 patients, 9 patients died and 2 used oral contraceptives, at follow-up. Normal function implies a regular menstrual cycle and chemotherapy-induced amenorrhea (CIA) implies absence of menstrual cycle.

ment, varied from 1.7 to 38.1 month, mean 13.1, and median 9.1 month. Demographical features are listed in Table 2.

Most patients were referred by their oncologist (41%), surgeon (16%), or gynecologist (13%). Three children were referred by their pediatrician, 2 patients were referred by the radiotherapist, 1 patient by the general practitioner, 4 were self-referrals, and 1 reference was unknown.

Seventeen patients (53%) were in CR at follow-up and 6 patients (18%) were still receiving primary treatment and therefore evolution of disease could not be determined (Fig. 2A). One patient was in progressive disease and in 1 patient a secondary tumor, acute leukemia, was present. CIA occurred in 3 patients (10%) and 6 patients were currently treated with adjuvant hormonal therapy (Fig. 2B). One woman was amenorrheic for 15 months and 2 women were amenorrheic for 1 month directly after chemotherapy. Two spontaneous pregnancies occurred, one of which after 6 cycles of cyclophosphamide, doxorubicin and fluorouracil at the age of 34 years. The other patient became pregnant at the age of 33 years during adjuvant hormonal treatment and gave birth to a healthy child. Three patients died in the follow-up period, after 2, 18, and 22 months aged 27, 36, and 34 years. One patient who had embryo cryopreservation performed elsewhere died after 6 months at the age of 24 years.

When comparing the demographical and medical data of both groups no statistically significant differences were observed except for parity, $P = 0.01$.

DISCUSSION

The ability to detect cancer in an early stage and the use of efficient therapies has improved the long-term survival rate for many childhood and adult cancer patients. However, the frequently used multidrug chemotherapy regimens are definitively associated with gonadotoxic effects. Patients treated with alkylating agents have a 4-fold higher risk of losing their ovarian function than patients who were treated with other agents.[22] The risk of early CIA is not only related to treatment regimen and dose, but also to the patient's age, and can be permanent or temporary.[23] However, clinical information, such as amenorrhea or resumption of menses post-treatment, is not an accurate predictor of ovarian reserve.[11] A high risk of developing POF later in life after apparently normal ovarian function can be present.[24] Furthermore, the ovarian function of women receiving adjuvant hormonal therapy cannot be assessed. POF should only be diagnosed if hormonal therapy is finished. An exact individual indication of risk concerning ovarian function is therefore difficult. However, the effect of treatment on future fertility, and options to try to preserve fertility should be adequately and timely discussed, preferably by the attending physician or oncologist before initiation of cancer treatment.

In this present series in 5½ years, 77 patients were considered candidates for FPT. However, in the Netherlands, according to the Dutch Cancer Registration, the incidence of newly diagnosed malignant disease is 3835 women aged 16 to 35 years. Only 2% of these patients was referred to this tertiary center for fertility preservation, despite the fact that these patients have an 8-fold increased risk of developing POF.[25,26] We therefore think that referral for fertility preservation is seriously underused in the Netherlands.

The inclusion and exclusion criteria applied for OTC differ from some other patient series.[27–29] There was a careful and somewhat restricted selection of patients for OTC, caused by the experimental status of this procedure. Age limitation, poor prognosis, and risk of ovarian metastasis

were added selection criteria. It was decided not to perform OTC in children because of lacking experience initially. Currently children are treated according to a revised protocol. Prognosis and genetic issues like breast cancer gene (BRCA) mutation carriage is important to consider, preceding the option of fertility preservation because it may imply a "message of hope." The doctors' role in this matter is of utmost importance and unrealistic expectations should be avoided. Reseeding malignancy is of major concern for thawing and transplanting ovarian tissue.[30] OTC was only performed in diseases with a low anticipated risk of ovarian metastasis; leukemia patients, for example, were not treated. Patients were considered candidates for ovarian tissue transplantation if the anticipated risk of POF was high (>50%), considering the need to operate and its experimental status. One ovary was always left in situ to enable natural fertility preservation because of difficulty in correct individual prediction of POF.

No complications of performing FPT, and only minimal cancer treatment postponement (up to 3 days, personal data) were observed. Timing, facilitated by protocol use and experience, was considered crucial to prevent cancer treatment delay. Both groups were comparable except for parity, perhaps already having a child or children plays a role in the decision whether or not to undergo FPT. Data of evolution of disease (24%) and ovarian function assessment (35%) were not complete because of ongoing primary or adjuvant hormonal treatment. Unfortunately, possible differences between the groups can only be confirmed definitively after completion of therapy.

Since the birth of a healthy baby girl after orthotopic transplantation of thawed ovarian tissue interest in fertility preservation has been raised tremendously. Currently, 4 births have been reported after ovarian tissue transplantation, 2 with and 2 without the use of ART.[31–33] Results of restored hormone production, cycles, and also early pregnancies were reported in other studies.[15,34–43] Despite these positive findings, OTC is still an experimental, promising but inefficient therapy which should be performed in a research setting under institutional review board approval and only if more efficient and standard care therapies are not possible.

This makes patients with insufficient time to perform FPT, patients in whom hormonal stimulation is unsuitable or contraindicated and patients without a partner, candidates for OTC. However, women of reproductive age should be counseled that IVF is their best approach to preserve fertility, in which the pregnancy rate is 18.6% per thawed embryo.[44] Occasionally, a standard and an experimental technique were combined. An ovarian transposition was combined in 2 patients with ovarian cryopreservation and ovarian transplantation for gonadotoxic treatment. For optimal treatment and fulfilling patients' psychologic needs, an individual approach in discussing, offering, and performing FPT is advised. Extensive collaboration between oncologists, fertility specialists, biologists, and psychologists is hereby strongly recommended.

Scientific interest in FPT has focused on its technical and functional aspects. Psychologic aspects of FPT and the consequence of infertility for cancer survivors are hardly reported even in men, for whom semen cryopreservation is standard care and a safe technique.[45,46]

Schover et al[8] conducted a study in men in which knowledge and experience regarding sperm banking was determined. Twenty-four percent banked sperm, 51% had been offered banking, and lack of information was the most common reason for failing to bank sperm. From this and other studies, it can be concluded that male and female cancer survivors want to have children and they feel that the experience of cancer increases the value of family life and would make them even better parents. Sperm banking helped in the emotional battle against cancer and encouraged the survivors. Unfortunately, it did not eliminate fear of infertility according to a study by Saito et al.[6]

According to studies by Partridge et al and Thewes et al, younger women experience greater psychosocial distress with the diagnosis and treatment of breast cancer.[47,48] Concerns about fertility and family planning, which are extraordinarily important issues for these women, contribute to this. Attitudes regarding fertility preservation in female adolescent cancer patient were studied by Burns et al.[49] These patients and their parents are willing to explore the possibilities of research options to preserve their fertility but they are not willing to postpone cancer therapy for this. Patients without children or an incomplete family find infertility after cancer treatment extremely important.[4,11] The American Society of Clinical Oncology therefore advises to study the psychosocial consequences of infertility and FPT in women. Research should also focus on the attitudes and expectations of patients and doctors regarding FPT. The psychosocial consequences of discussing the subjects too late or not at all are of current scientific interest together with improving psychologic counseling based on the patients' risk profile. In an ongoing retrospective interview study in the presented population, the fertility preserving treatment procedure is being evaluated, and the psychosocial consequences of this procedure are being discussed, to improve counseling and possibly adjust procedures. Finally, the technical aspects of fertility preservation should constantly be explored. Whole ovary cryopreservation and in vitro maturation techniques are hopeful developments in the search for an efficient and safe fertility preservation technique which can really preserve future fertility.[50,51]

Limitations of this study are the retrospective chart review design, the definition of CIA, and small patient numbers. It is known that amenorrhea and resumption of menses posttreatment are not accurate predictors of the ovarian reserve in women after cancer treatment. Hormonal studies, antimullerian hormone and inhibin B, should be performed in preferable prospective trials to confirm diagnosis of POF in patients after cancer treatment. After FPT only a few patients revisited the clinic and psychosocial consequences of FPT received only minimal attention. Although experience with patient selection has increased over the past years, experience with transplanting cryopreserved tissue is lacking and only minimal in embryo transfer in these patients.

Patients should be fully informed about the consequences of cancer treatment, preferably early during treat-

ment planning. If indicated, referral to a center with expertise on fertility preservation is of utmost importance. FPT is something that should always be considered in advance of gonadotoxic treatment but standard application in cancer patients should be avoided. The medical as well as the psychologic aspects in patient selection and counseling should be considered. On the basis of an individual risk benefit ratio the decision to undergo FPT should always be taken in the patients' best interest.

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