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Fertility Preservation in Pediatric Oncology Patients: New Perspectives

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Over the past 30 years, advances in antineoplastic treatment led to a significant increase in the survival of patients with childhood cancer. In Europe and the United States, 82% of children, adolescents, and young adults survive 5 years from the cancer diagnosis and the majority achieves long-term survival into adulthood. The impact of cancer therapy on fertility is related to the age of the patient and to the duration, dose/intensity, and type of treatment. Exposure to chemotherapy or to radiation to gonads or pituitary brings long-term complications of cancer-directed therapies that include effects on reproductive capacity. Different methods to preserve fertility can be offered. In prepubertal women, ovarian tissue freezing, *in vitro* maturation, and surgical movement of ovaries outside the field of irradiation are still experimental. In pubertal and postpubertal women, oocyte-embryo freezing is an established option. In men, the options are sperm cryopreservation, gonadal transposition, and testicular tissue or spermatogonial cryopreservation and reimplantation. Fertility risks and provision of strategies to minimize cancer treatment impact fertility include discussion of the tail of the option before cancer treatment. Having to make a decision in a limited time, while still coming to terms with a potentially life-threatening diagnosis, can cause patients to feel overwhelmed. To date, there are no uniform guidelines on how to approach this problem, so it is important to be aware of it for proper clinical practice.

Keywords: fertility preservation, survivors, chemotherapy, radiation

Introduction

The number of survivors of childhood cancers has increased over the past four decades. Many of the survivors are at risk of multi-faceted chronic morbidity as a result of their successful treatment; the loss of fertility is one of that and is a concern that affects patients, parents, and medical caregivers.[1]

The cancer treatment is the major determiner about the patient's fertility, and the entity of the damage is directly correlated with the nature of the treatment.[2] The impact of cancer therapy on gonadal function varies, ranging from no effect to total loss of function. These effects depend on several factors, including the type and dose of administered therapy (chemotherapy and/or radiation), type of surgical intervention (removal of a portion of one or all reproductive organs), and the field of radiation administered; also, the age at treatment initiation plays an important role.[3]

At the beginning, an active counseling about fertility preservation (FP) strategies, their risks, and success rates before the initiation of antineoplastic treatment is important, so FP should be incorporated into their designated treatment plan. It is, therefore, of utmost importance that effective collaboration between oncologists and gynecologists specialized in reproductive medicine is implemented to improve adolescent cancer patients' access to assisted reproductive technologies.[4]

At diagnosis, all patients deserve informed consultation about their fertility prognosis. For some, the prognosis is not clear, but for the majority of patients, it is clear whether the risk of compromising fertility with first-line treatment is low, medium, or high.[5] Patients report that fertility is an important aspect of the informed discussion about treatment options. Surveys of cancer survivors indicate that the great majority of patients desire families in the future and most feel that they are not sufficiently counseled at the time of their diagnosis about options for FP and the potential deleterious side effects of cancer therapy.[6,7]

The American Society of Clinical Oncology (ASCO) has developed FP guidelines to aid oncology providers in communicating with patients about potential threats to fertility as early as possible in the treatment process.[8]

The purpose of this study is to provide a synthesis of current evidence for pediatric oncology healthcare providers about FP options available for pediatric, adolescent, and young adult patients undergoing treatment for a pediatric malignancy; we

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also propose to discuss some of the problems associated with the use of these options and with the particular condition that these young patients are faced with.

Impact of Treatment on Fertility

The survival outcomes have been improved thanks to recent advances in cancer therapies: The combined 5-year survival rate for all cancers in young patients has improved to 80%, and the 10-year survival rate is 75%.[9]

The impact of cancer therapy on fertility is related to the age of the patient at treatment and to the duration, dose/intensity, and type of treatment (Tables 1 and 2). The most harmful regimens to the ovaries and testes are alkylating agent-based chemotherapy and high doses of cranial radiotherapy that impair hypothalamic pituitary function, resulting in the depletion of gonadotropin-releasing hormone (GnRH) (Table 3).[10–12]

Toxicity of chemotherapy on the ovary

In women, age has a central role to prospect the damage. Women have a fixed number of primordial follicles at birth that form the ovarian reservoir. Follicular depletion is physiologically age dependent; the pick of depletion is around the age of 38 years (when the reserve is about 10% the number present at menarche).[99] The damage depends on the agent (Table 1): Cell cycle nonspecific agents such as cyclophosphamide destroy primordial cells; instead, cell cycle specific agents such as methotrexate spare primordial cells, resulting in less gonadotoxicity. The incidence of gonadal failure is also dependent on the cumulative dose of chemotherapeutic agents and on age at diagnosis.[13]

Toxicity of chemotherapy on the testis

In men, spermatogenesis is the first target, more than testosterone production, this is due to the increased cytosensitivity

Table 1. Degree of Risk of Infertility in Women Related to Cytotoxic Drugs

Chemotherapy treatment	*Degree of risk*
Hematopoietic stem cell transplantation Total body irradiation Radiotherapy that includes ovaries	High risk (>80%)
CAAF, CMF, CEF× 6 (30–39 years of age), AC×4 (>40 years of age)	Intermediate risk (20%–80%)
ABVD, CHOP, CVP AML, ALL CAF, CMF, CEF× 6 (<30 years of age); AC× 4 (<40 years of age)	Low risk (<20%)
Vincristine, methotrexate, fluorouracil	Very low, no risk
Taxanes, irinotecan, oxaliplatin, monoclonal antibodies, tyrosine kinase inhibitors	Unknown risk

Modified from Zavras et al.[4]

C, cyclophosphamide 600–1200 mg/m^2; A, adriamycin 25–60 mg/m^2; F, fluorouracil 600 mg/m^2; E, epirubicin 60 mg/m^2; M, methotrexate 40 mg/m^2; B, bleomycin 10 U/m^2; V, vinblastin 6 mg/m^2; D, dacarbazine 375 mg/m^2; P, prednisolone 40 mg/m^2; H, hydroxydaunorubicin 50 mg/m^2; V (O), vincristine 1.2 mg/m^2; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia.

Table 2. Effect on Sperm Count in Men Related to Cytotoxic Drugs

Chemotherapy treatment	*Effect on sperm count*
Chlorambucil (1.4 g/m^2), cyclophosphamide (19 g/m^2), procarbazine (4 g/m^2), melphalan (140 mg/m^2), cisplatin (500 mg/m^2)	Prolonged-permanent azoospermia
Carmustine (1 g/m^2), lomustine (500 mg/m^2)	Azoospermia in adulthood if treated before puberty
Cusulfan (600 mg/m^2), ifosfamide (42 g/m^2), carmustine (300 mg/m^2), nitrogen mustard	Azoospermia likely
Doxorubicin (770 mg/m^2), thiotepa (8400 mg/m^2), cytarabine (1 g/m^2), vinblastine (50 mg/m^2), vincristine (8 g/m^2)	When used alone, cause temporary reductions in sperm count; in conjunction may be additive in causing azoospermia
Amsacrine, bleomycin, dacrbazine, daunorubicin, epirubicin, etoposide, fludarabine, fluorouracil, 6-mercaptopurine, methotrexate, mitoxantrone, thioguanine	When used alone, cause only temporary reductions in sperm count, in conjunction may be additive in causing azoospermia

Modified from Zavras et al.[4]

Table 3. Risk of Azoospermia in Men and Amenorrhea/Premature Ovarian Failure in Women After Radiotherapy

Men	*Women*
High risk	
• Total body irradiation	• Total body irradiation
• Radiotherapy of testis >2.5 Gy in men, >6 Gy in prepubertal boys	• Radiation treatment of whole abdomen or pelvis with >6 Gy in adult women, >15 Gy in prepubertal girls, and >10 Gy in postpubertal girls
• Irradiation of the brain >40 Gy	• Irradiation of the brain >40 Gy
Intermediate risk	
• Testicular radiation dose 1–6 Gy from scattered pelvic or abdominal radiation	• Radiation treatment of whole abdomen or pelvis at 10–15 Gy in prepubertal girls and 5–10 Gy in postpubertal girls
• Irradiation of the brain at 25–40 Gy	• Irradiation of the brain at 25–40 Gy

Modified from Suhag et al.[9]

of germinal epithelium compared with Leydig cells that appear more resistant to cytotoxic drugs.[9] The risk of azoospermia depends on the type of agent and on the dose as tabulated in Table 2.

Toxicity of radiotherapy in women

In women, irradiation of hypothalamic, pituitary, or pelvic regions is associated with acute ovarian failure and premature menopause. Effects are dose related: For example, a dose of 14.3 Gy in a woman >30 years of age will cause irreversible infertility; a dose of 6 Gy in a woman <30 years of age is usually reversible but will lead to premature menopause.[8,13]

Reproductive organs could be directly damaged by radiotherapy; in fact, although the uterus is relatively resistant to radiotherapy, uterine irradiation can result in a series of complications. An example of these are poor implantation, midtrimester losses, preterm labor, and intrauterine growth retardation; all these are related to reduced uterine volume and blood flow. Also, the irradiation of the vagina, even if it is relatively radio resistant, can bring loss of lubrification and stenosis, which may bring physical impairments to fertility.[13,14]

Toxicity of radiotherapy in men

In men, the effect of radiation is also dose dependent. A radiation >6 Gy, for example, will result in permanent azoospermia. The application of 3.5 Gy causes damage to the germinal epithelium and will bring sterility but it is commonly reversible in 1–2 years. Pretreatment sperm count is important to predict the entity of the damage. As already underlined, Leydig cells are more resistant but in prepubertal men, irradiation >20 Gy to the Leydig cells will reduce testosterone production; whereas in postpubertal men, >30 Gy is required to cause the same damage.[13] The physical damage of pelvic irradiation is a vascular disease that causes erectile dysfunction [13,15]

Gonadal Markers of Fertility

In clinical practice, small amounts of blood are sufficient to investigate hypothalamic-pituitary-gonadal interactions. The integrity of the hypothalamic-pituitary-gonadal axis in men and women can be assessed by measuring luteinizing hormone, follicle-stimulating hormone and sex steroid levels (estradiol in female or testosterone in male), basal and after subcutaneous administration of gonadotropin-releasing hormone analogs. In male infants, Leydig cell integrity can be determined by the testosterone response after human chorionic gonadotropin intramuscular administration.[16]

Recently, basal measurements of inhibin B and anti-Mullerian hormone (AMH) are getting involved in the study of fertility as part of a complete evaluation of possible reproductive organ damage.[17]

In men, the function of Sertoli cells could be investigated with AMH, whose secretion by these cells is usually suppressed by testosterone. Inhibin B is considered a marker of spermatogenesis.[18]

In women, AMH and inhibin B are secreted by the granulosa cells. The AMH concentration in blood in adult women directly correlates with the number of primordial follicles. In fertile women, AMH usually declines with age and it may, therefore, be of value in the prediction of the menopause. In young women with different cancers, AMH level was shown to decline steadily during repeated chemotherapy treatments, with variable recovery. A lower or an undetectable value of AMH after chemotherapy treatments is an indicator of premature primary ovarian insufficiency.[19]

These markers have the advantage of not requiring stimulus tests for their interpretation, but more studies are needed to better define normal values in prepubertal and pubertal children to correlate them with Tanner stages.

Table 4 summarizes a panel of gonadal markers that are useful for clinical practice for monitoring fertility function in patients undergoing a cancer therapy.

Table 4. Gonadal Markers Useful to Monitoring Fertility Function in Patients Undergoing Cancer Therapy

Hormonal evaluation	Gonadotropins (FSH, LH)[a] Sex steroids (estradiol in women, testosterone in men)[a] Basal level AMH Basal level inhibin B
Additional examination (for pubertal boys)	Semen analysis

[a]Basal levels and after stimulation test are required for the evaluation.
FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-Mullerian hormone.

Methods to Preserve Fertility in Patients with Cancer

Different methods to preserve fertility can be proposed depending on patient age, current success rate, and risk of reintroducing malignancy (Table 5).[20]

Table 5. Methods to Preserve the Reproductive Potential in Men and Women Undergoing Gonadotoxic Cancer Therapy

Established	*Investigational*
Men 1. Prepubertal • Gonadal shielding • Gonadal transposition 2. Postpubertal • Sperm cryopreservation • Gonadal shielding • Gonadal transposition	Men 1. Prepubertal and postpubertal • Cryopreservation of testicular tissue
Women 1. Prepubertal • Gonadal shielding • Oophoropexy 2. Postpubertal • Oocyte or embryo cryopreservation • Gonadal shielding • Oophoropexy	Women 1. Prepubertal • Cryopreservation of ovarian tissue • IVM • Orthotopic transplantation 2. Postpubertal • GnRH analog • Cryopreservation of ovarian tissue • IVM • Orthotopic transplantation

GnRH, gonadotropin-releasing hormone; IVM, *in vitro* maturation.

Techniques in prepubertal women

In young women, ovarian tissue freezing, *in vitro* maturation (IVM) of ovarian tissue (fresh or frozen-thawed),[21] and surgical movement of ovaries outside the field of irradiation (orthotopic sites) are still experimental; instead, gonadal shielding and oophoropexy are established. Ovarian tissue freezing and autotransplantation involves surgical ovarian tissue extraction, freezing-thawing, and transplantation. In prepubertal girls, extraction of less than half an ovary (20%–30%) may be enough.[22] Once levied, the ovarian cortex (that contains the majority of oocytes) is frozen and stored in liquid nitrogen at −196°C for up to 10 years. When the girl is healed, her ovarian tissue is autotransplantated in orthotopic (pelvis) or heterotopic (subcutaneous space of forearm or abdominal wall) sites. In spite of the fact that this technique is achievable in prepubertal girls, it has two disadvantages: the risk of reintroducing malignant cells and the short lifespan (about 10 years) of the ovarian tissue transplant.[23,24] To avoid the risk of reintroducing malignant cells, in this study, an artificial ovary was made with 3D alginate matrigel matrix loaded with ovarian follicles from the same patient; this technique has shown promising results in animal models.[25] IVM is mainly used in adult women to mature oocytes withdrawn transvaginally from unstimulated or stimulated ovaries. In orthotopic autotransplantation, the frozen-thawed ovarian tissue is retransplanted via laparoscopy or mini-laparotomy to the same girl once healed into pelvic sites (remaining ovary, broad ligament peritoneum of ovarian fossa). Gonadal shielding consists of physical protection of gonadal tissue with suitable shields during radiation. Oophoropexy is used when pelvic or abdominal irradiation is scheduled: Ovary is transposed via laparoscopy or mini-laparotomy toward the pelvic walls laterally or behind the uterus medially.[26]

Techniques in pubertal and postpubertal women

In pubertal and postpubertal women, oocyte-embryo freezing, gonadal shielding, and oophoropexy are established; whereas freezing of ovarian tissue, IVM, hormone injection (GnRH), and surgical movement of ovaries outside the field of irradiation (to an orthotopic site) are still experimental. Oocyte-embryo freezing and freezing of ovarian tissue require hormonal stimulation and are not feasible in prepubertal girls; in the past, doubts regarding the appropriate time to stimulate ovarian tissue precluded many cancer patients from pursuing FP. However, a new study has demonstrated that, in spite of the fact that a stimulus within 3 days of the start of the menstrual cycle is the gold standard, a random stimulation can also bring success.[27] Oophoropexy (laterally or behind the uterus) or pelvic shielding should be offered to adult and prepubertal girls undergoing pelvic or abdominal irradiation without chemotherapy.[28,29] The mechanism of GnRH analogs protection is doubtful and not very clear; in theory, GnRH analogs inhibit hypothalamic-pituitary-ovarian axis and, suppressing ovaries, they are less sensitive to gonadotoxicity.[26]

Techniques in prepubertal men

In prepubertal men, gonadal shielding and gonadal transposition are established, whereas testicular tissue or spermatogonial cryopreservation and reimplantation are still experimental.[20]

When gonadal transposition is in program, the placement of the testis should be decided in consultation with the radiation oncologists. Gonadal shielding should be recommended for men undergoing irradiation remembering that shielding does not completely protect testis, but it only reduces the dose.[30] The option of spermatogonial cryopreservation and reimplantation is not established, although testicular stem cell banking is being introduced into clinical practice.

Techniques in pubertal and postpubertal men

In pubertal and postpubertal men, the options for preservation of fertility include sperm cryopreservation (one or three samples), gonadal transposition, and gonadal shielding. Cryopreservation and reimplantation of testicular tissue is still experimental.[20] The first method is only indicated for pubertal and postpubertal boys since active spermatogenesis has not yet started in young boys. When patients cannot ejaculate, alternative methods are urine collection after retrograde ejaculation, rectal electroejaculation under anesthesia, and testicular sperm aspiration.[20] Once collected, the sperm can be used, for example, for intracytoplasmatic sperm injection. In men, there is no role of gonadal protection by any hormonal therapy.[31] If possible, pelvic shielding and fractionated doses of chemotherapy or radiotherapy could be considered in all patients.[32]

Discussion

Childhood cancers are rare diseases, as they represent 130–160 cases per million children, with considerable variation between countries.[33] Most of these cancers are embryonic tumors, the genesis of which is quite different from tumors encountered in adulthood. Improvements in therapy and intensive care have increased the overall 5-year survival rate from 45% for patients diagnosed in the mid-1970s to 80%.[34] When a patient is faced with cancer, the main concern is, after all, the cure of the disease.[20]

Due to the potentially detrimental effects of chemotherapy and radiotherapy on future fertility, international societies, including ASCO and the National Institute for Health and Care Excellence (NICE), recommend discussion on the risks of cancer therapy on fertility and options for preservation with all patients before the initiation of any therapy.[8,35]

Testicular or ovarian damage may be caused by radiation therapy directly to the gonads or brain (hypothalamic-pituitary axis damage) or by cytotoxic chemotherapy. The risk of infertility depends not only on the type of malignancy and its specific treatment but also on the age of the patient, as the effects of chemotherapy and radiation therapy manifest differently in the male and female reproductive systems.[36] Male and female survivors of childhood cancer are at increased risk for impaired fertility after exposure to alkylating agents in a dose-dependent fashion and high-dose chemotherapy preparatory to hematopoietic stem cell transplantation.[37]

FP includes discussion about future fertility risks and provision of strategies to minimize cancer treatment impacts on fertility. In children and adolescents, FP decisions pose unique challenges due to limited efficacy of the reproductive technologies (providing no guarantee of having a child), ethical and legal barriers, lack of models of care, cost, poor communication, and the triadic nature of discussions involving the clinician, parents, and young person.[38] Parents of children receiving oncology treatment may also benefit from counseling with

pediatric gynecologists and endocrinologists, who have a thorough understanding of the complexities of pediatric FP.

Having to make a decision about FP in a limited time, while still coming to terms with a potentially life-threatening diagnosis, can cause patients to feel overwhelmed.[38]

Ethical issues that arise in FP decision making in pediatric population cancer patients include: First, parents are making a decision for their children; therefore, adult factors are likely to have a role, such as desires for biological children; second, experimental procedures have uncertain outcomes and may leave both parties experiencing negative feelings in the longer term.

Key differences in the FP procedures offered to children and adults may impact the decision. In adults and adolescents, the procedures available have proved efficacy and are less invasive. However, gonadal tissue cryopreservation in children is invasive, experimental, and carries a risk of reimplantation of cancerous cells.[39] It is important to know the ''quality'' of the stored tissue before starting the procedure to predict the success of the preservation technique. In women, it depends on the number of follicles stored at the time of biopsy. If the quality is low, the probability of success decreases. A marker of follicular reserve could thus be used to assess whether the technique will be really effective. High levels of AHM were found in patients in whom the withdrawal was made before starting treatment compared with levels found in patients in whom the withdrawal was made after starting treatment.[40] Having proof of a high follicular reserve, this could be used as a predictive marker before starting any procedure. In the decision of FP, children should still be involved in discussion, despite being unable to consent legally, because parents may not be able to separate their own desires and beliefs from the decision-making process.[39,41] The decision to follow FP is difficult in the adult population and regret may be greater for parents who are making this decision for a child. For this reason, children should be involved in the discussion.

The benefit for prepubertal children remains speculative at this stage. Thus, there is a strong argument that the decision about FP remains essentially at the parents' discretion for this age group, so long as only experimental techniques are available. No FP procedure guarantees that the child will be able, as an adult, to parent a child who is genetically related to him or her. An FP procedure may be ''successful'' at the time of the child's illness, in the sense of collecting and freezing viable sperm or ovary or functional gonadal tissue. However, this may not progress to ''success''; there may still be no resultant pregnancy or birth of a child who is genetically related to the cancer survivor.

For the best possible results, FP needs to occur before the cancer treatment commences. Therefore, in some cases, undergoing FP procedures can result in the child's cancer treatment beginning later than it otherwise would have. For some types of FP procedures (particularly ovary harvest and freezing), a time delay of several weeks is a necessary part of the process. Delay to cancer treatment has been identified as a barrier to FP for female adolescent patients and their parents.

For certain types of cancer, the surgery involved in some FP procedures involves a risk of the cancer spreading. Further, if the cancer is of a type that involves a risk of ovarian metastases, reimplanting harvested tissue would risk a recurrence of the cancer. These two drawbacks are each potentially very significant, decreasing the patient's chance of survival; in the short term when the surgery itself risks spreading the cancer or in the longer term when reimplanting harvested tissue risks recurrence.[2]

There are small but real risks associated with FP procedures, varying according to the type of procedure. Surgical techniques for FP involve potential harm to the child. Anesthesia is necessary for the removal of gonadal tissue, the harvesting of ovaries, the surgical extraction of sperm in children, or moving the ovaries. A general anesthetic carries various low risks of side effects or adverse reactions. There is also the risk of infection associated with any surgery. Non-surgical techniques also involve potential harm to the child. Hormonal suppression of the ovaries precipitates menopausal symptoms. Freezing ejaculated sperm requires the patient to masturbate, which may involve embarrassment for young men.[2]

Survey data have indicated that many patients, especially women, are not or are inadequately counseled regarding the potential adverse effects of treatment on fertility and even fewer are referred for FP. Uniformity of counseling and standards for referral are lacking when FP is offered, which leads to variability in the uptake of these procedures.[42]

A study identified 25 clinical practice guidelines (CPGs) regarding FP for children, adolescents, and young adults (CAYAs) with cancer; only approximately one-third of the identified CPGs were found to be of sufficient quality. In these guidelines, there is a lot of variability in terms of recommendation about FP; this reflects a lack of consensus for specific recommendations and the consequent impossibility to provide high-quality care. CPGs. CPGs, including a transparent decision process for FP, can help healthcare providers to deliver optimal and uniform care, thus improving the quality of life of CAYAs with cancer and cancer survivors.[43]

Conclusions

Although major progress has been achieved in childhood cancer treatment, with a lower mortality and a better life expectancy, consequent loss of fertility remains a crucial issue to this day. The majority of young patients with cancer will not have their fertility significantly compromised by their planned treatment and so patient selection is essential. Patients should have active counseling about FP strategies, their risks and success rates before the initiation of antineoplastic treatment; FP can, thus, be incorporated into their designated treatment plan. Although such protocols are still experimental, they are very promising and remain the only method suitable for pre- and postpubertal children. We do not yet have enough results about the real success of these techniques but it will be important to see in the future whether those currently in use are actually effective. We realize that, mostly in young patients, several medical and ethical concerns could hinder the use in clinical practice of these methods; however, we think it is the clinician's duty to offer the possibility, if feasible, to preserve fertility in young patients with cancer, especially if life expectancy is long. It is also important to emphasize that the existence of uniform guidelines is essential for proper clinical practice and will make it possible to use a common and shared approach to this intricate subject.

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