Review paper

Oncofertility in pediatric patients: current perspectives

Rafael Marques[1], Maria João Oura[2], Rita Dionísio[3], Catarina Rodrigues[1], Joana Lorenzo[1]

[1]Centro Hospitalar Entre o Douro e Vouga, Santa Maria da Feira, Portugal
[2]Centro Hospitalar Universitário São João, Porto, Portugal
[3]Hospital Magalhães Lemos, Porto, Portugal

Cancer treatments may affect fertility in different ways. Oncofertility, i.e. the study of interactions between cancer, anti-cancer therapy, fertility, and reproductive health, is an emerging field that addresses cancer patients' concerns regarding their future reproductive ability. As the number of cancer survivors increases, fertility preservation is becoming an important quality of life issue for many survivors of childhood cancer. There is a wide array of fertility preservation options according to gender and pubertal status, and shared decisions must take place at the time of diagnosis. Even though there might be several barriers that can negatively affect this process, the presence of a dedicated fertility preservation team may help overcome them.

In this article, the authors aim to characterize what oncofertility is, the effects of cancer and its treatments on the fertility potential of pediatric patients and also on their mental health. Another goal is to expose the different fertility preservation therapeutic options and potential barriers.

Key words: cancer, fertility, oncofertility, fertility preservation techniques, pediatric cancer patients.

Contemp Oncol (Pozn) 2022; 26 (3): 165–173
DOI: https://doi.org/10.5114/wo.2022.120362

Introduction

The diagnosis of cancer in children and adolescents is a life-altering event for them and their families. Although advances in treatment have led to an overall 5-year survival rate for childhood cancers of approximately 80%, cancer is still the second leading cause of death (following accidents) in children aged 5 to 14 years[1]. Even though cancer is a leading cause of death in both adults and children, in terms of absolute numbers, pediatric cancer is a relatively rare disease [1].

The cancer incidence, worldwide, in both sexes, at 0–19 years of age, demonstrates that leukemia leads with 80 491 cases in 2020, followed by cerebral/central nervous system (CNS) (30 766 cases), non-Hodgkin lymphoma (25 100), kidney cancer and Hodgkin's lymphoma. Incidence is higher in males, but the three most frequent cancers are the same in both sexes. Regarding the number of deaths, in both sexes, worldwide, leukemia is the main cause of death, followed by brain/CNS, non-Hodgkin's lymphoma, kidney and liver cancer, with the number of deaths being higher in males [2].

Based on estimates of the number of new cancer cases in 2021, 4.6% of all new cancer cases will occur at 15–39 years of age, with 5-year relative survival of 85%. This percentage is also similar for children aged 0–14 years [2].

Depending on the type of cancer and treatment received, patients who survive 5 years may remain at risk of recurrence or progression of their primary cancer and be at an increased risk of developing subsequent malignant neoplasms, chronic diseases, and functional impairments. It is important that survivors of childhood and adolescent cancer are monitored for long-term and late effects [1].

Several studies have shown that fertility potential and reproductive health are major concerns for cancer survivors [3, 4]. Given the current epidemiological panorama, with the increase in the longevity of cancer survivors whose reproductive future is at risk, there was a need to create a new field at the intersection of reproductive medicine and oncology, which is oncofertility [5].

Oncofertility emerged in 2006 with the objective of implementing the search for options for the protection and/or preservation of fertility for patients diagnosed with cancer. Also it involves helping patients in decision making regarding preservation of fertility and the method to be used, in pre- and post-treatment preparation and dealing with associated psychological factors. So, oncofertility integrates several areas such as sexology, pediatrics, psychology and bioethics, in addition to oncology, urology and gynecology [6]. Furthermore, standardization of fertility preservation care for oncological patients is required [7].

This literature review discusses the effects of cancer and cancer treatment on fertility, options for fertility preservation in pediatric patients and potential barriers that can negatively affect them. We present the following article in accordance with the narrative review reporting checklist.

Effects of cancer on fertility

A cancer diagnosis by itself is a risk factor for infertility. Being a systemic disease, it can affect fertility through multiple mechanisms, even before initiating treatment. Infertility in cancer survivors can be caused by injury to the hypothalamic-pituitary-gonadal axis, as well as damage to the organs of the reproductive tract [8].

The hypothalamic-pituitary-gonadal axis is controlled by a classic feedback loop. Central hypogonadism occurs when there is damage to the hypothalamus or pituitary, due to tumors or their therapies; primary hypogonadism occurs when tumors or their therapies damage the testicles or ovaries. The major endocrine stimulators of human testes are luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are made by the pituitary and secreted into the systemic circulation. Luteinizing hormone and FSH secretion are stimulated by the pulsatile release of gonadotropin-releasing hormone (GnRH) from neurons in the hypothalamus. Gonadotropin-releasing hormone reaches the gonadotroph cells of the anterior pituitary *via* a portal vascular system. Dysfunction at any step of the axis can result in suppression of endogenous testosterone production and thus impair spermatogenesis. The same gonadal failure occurs in females, when failed hormonal production and infertility occur [9].

Testicular tumors can produce β-human chorionic gonadotropin (β-hCG) and α-fetoprotein (AFP). These tumors can alter the axis, since high levels of β-hCG are associated with poor quality semen, causing an inhibitory effect on spermatogenesis through negative feedback. Likewise, high levels of AFP are associated with decreased sperm count and inhibition of spermatogenesis [10, 11]. There are several studies that have examined semen parameters in male patients with testicular cancer and reported decreased sperm concentrations and parameters compared to male patients with different oncologic diagnoses [12, 13].

Several studies revealed that leukemia and lymphoma are risk factors for pre-treatment azoospermia [14]. Ragni *et al.* reported that more than 10% of cancer patients who banked sperm at their institution were azoospermic before treatment [15].

The immune response to the tumor can also affect fertility, as many cancers can generate lymphocytic infiltration causing an elevation of pro-inflammatory cytokines. The altered homeostasis of these cytokines (mainly IL-6, IL-8, and TNF-α) impairs the blood-testis barrier and can cause germ cell apoptosis and sloughing [10].

Systemic symptoms caused by the disease have an impact on the reproductive potential in several ways, highlighting severe malnutrition and fever (especially in Hodgkin's lymphoma), which promote alterations in spermatogenesis and changes in sperm motility, morphology and concentration, respectively [16, 17].

Effects of cancer treatment on fertility

The gonadotoxic potential of oncological therapies, increasingly efficient in controlling the disease and enabling longer survival, leads to a deterioration in the reproductive function of cancer survivors [18, 19].

In 2006, the American Society of Clinical Oncology (ASCO) established guidelines, updated in 2018, for the follow-up of cancer patients of childbearing age, with the creation of infertility risk calculation tools, taking into account several variables, including the type of cancer and treatment regimen [20].

Cancer treatments with gonadotoxic potential may have direct gonadotoxicity by injury or depletion of the seminiferous epithelium or the ovary; or indirect gonadotoxicity causing hormonal insufficiency, through the hypothalamic-pituitary-gonadal axis; and/or may cause functional alterations (uterine in women, ejaculatory or erectile in men) [21]. These effects can be permanent, transient or manifest late in relation to the end of treatment, specifically in women with premature ovarian failure [10, 20, 22].

Surgery

If feasible and without compromising the effectiveness of cancer treatment, conservative surgery should be chosen, in order to preserve reproductive function [23, 24].

Some types of surgery for adolescent male cancer can result in long-term negative influences on fertility potential and sexual function. Testicular surgery can affect sperm and hormone production or interfere with sperm transport [23, 25]. Unilateral orchiectomy in men with testis cancer may lead to a decrease in semen parameters following the surgery, though the majority of these men will recover [26]. Patients who have undergone a retroperitoneal lymph node dissection or prostatectomy as part of their cancer treatment plan may have an autonomic nervous system that is transiently or permanently damaged by sympathetic ganglia injury, responsible for emission and ejaculation, which may impair ejaculation. Other types of pelvic surgery can injure the parasympathetic and sympathetic nerves responsible for erection and ejaculation, through injury to the vas deferens, and put the patient at risk for erectile dysfunction or obstructive azoospermia [23]. Likewise, men who undergo radical surgery for non-testicular malignancies such as muscle-invasive bladder cancer, retroperitoneal sarcoma, paratesticular rhabdomyosarcoma, and colorectal cancer will often develop transient or permanent ejaculatory and erectile dysfunction despite modern techniques for preservation of sexual function [10].

In women, an oophorectomy or total hysterectomy permanently affects their fertility [23, 25]. Procedures that affect the bladder, large intestine, and rectum may impair a woman's ability to carry a pregnancy to term [27, 28].

Chemotherapy

Gonadotoxicity caused by chemotherapy occurs due to the fact that it targets rapidly proliferating cells. These effects depend on several parameters such as the type of chemotherapy, dosage, initial semen quality and the location of the toxicity in the spermatogenetic/menstrual cycle [29, 30].

For women, chemotherapy, especially cyclophosphamide and procarbazine, have effects on the loss of ovarian reserve, which can cause lesions in the ovarian stroma [31–33].

Table 1. Chemotherapeutic agents and gonadotoxicity. Adapted from Disparities in female pediatric, adolescent and young adult oncofertility: a needs assessment

High risk	Medium risk	Low or no risk	Unknown risk
Nitrogen mustard	Vinblastine	Methotrexate	Paclitaxel
Chlorambucil	Cytosine arabinoside	5-fluorouracil	Taxotere
Cyclophosphamide	Cisplatin	6-mercaptopurine	Oxaliplatin
Melphalan	Carboplatin	Vincristine	Irinotecan
Busulfan		Bleomycin	Trastuzumab
Procarbazine		Actinomycin D	Pertuzumab
Dacarbazine			Cetuximab
Doxorubicin			Erlotinib
Carmustine			Daunorubicin
Lomustine			Imatinib

In men, chemotherapy can damage the seminiferous epithelium and decrease testosterone levels by causing damage to Leydig cells [23]. The normal sperm count typically recovers by 12 weeks after therapy in patients treated with non-alkylating agents [30].

In general, alkylating agents are dose-dependently toxic to the testes, and in patients receiving these agents, calculating the correct equivalent dose can help quantify the risk of future infertility, although it was found that even at lower doses, some patients developed azoospermia [28, 34]. These agents interrupt DNA function and replication, being one of the most spermatotoxic agents, with infertility reaching 60% or higher (Table 1), and men being more susceptible than women. The effects on spermatogenesis are often irreversible, and a large percentage of patients may remain azoospermic even after 20 years of cessation of treatment [10, 30]. In women it leads to menstrual changes, acute ovarian failure, and diminished ovarian reserve [13]. For example, a cyclophosphamide equivalent dose greater than or equal to 8000 mg/m^2 has a high level of increased (greater than 80%) risk of premature ovarian insufficiency and infertility in the post-pubertal patient [13]. In men treated with a high dose of cisplatin 600 mg/m^2, 45% had Leydig cell dysfunction compared with 27% of patients treated with lower doses [21].

Studies of childhood cancer survivors indicate that premature menopause is most likely to occur in patients exposed to alkylating agents [35, 36]. In studies where female cancer survivors received treatments without alkylating agents no significant increase in premature menopause was observed and patients did not experience subfertility [27].

After receiving chemotherapy, many cancer survivors have growth hormone deficiency, hypothyroidism, or pubertal abnormalities. Thus, chemotherapy may damage fertility by affecting either the nervous system or pelvic reproductive organs [37, 38].

Heavy metal treatments (platinum-based) damage DNA and interfere with DNA replication and can result in a temporary or permanent suppression of spermatogenesis. However, these agents are associated with more favorable recovery of spermatogenesis over time, with approximately 80% of patients having successful sperm retrieval within 8 years of cisplatin cessation [10, 39] (Table 1).

Antimetabolite therapy and vinca alkaloids appear to have a lesser impact on male fertility [10].

Advances in chemotherapy regimens will hopefully allow targeted therapy with the minimal appropriate dose and toxicity [21].

Radiotherapy

Radiation therapy may impact the future reproductive ability of cancer survivors depending on the total dose of radiation and fractionation schedule, location of the treatment, and age of the patient [10, 27]. Also, the nearby regions can be affected by exposure to scattered radiation [25]. Ovarian follicles are sensitive to DNA damage from ionizing radiation. Radiation treatment induces massive DNA double strand breaks in primordial follicle oocytes and Chk2-dependent apoptotic death mechanisms. Ovarian radiation can result in the depletion of primordial follicle reserve as well as severe stromal scarring, which manifest as ovarian atrophy [40].

In women, the age at the time of exposure to pelvic or abdominal radiation and, consequently, ovarian reserve seem to be predictive factors of the potential effects of radiotherapy, because in older patients the risk of permanent ovarian failure is greater [41]. Younger women may be less susceptible and prepubescent girls have an even greater chance of achieving a healthy reproductive future after treatment [27, 42].

Pelvic radiation can also cause fibrosis of the uterus with damage to the musculature and vasculature of the endometrium, loss of lubrication and vaginal stenosis, which can result in an increased risk of miscarriage, mid-trimester pregnancy loss, premature delivery and low birth weight at birth, regardless of age of exposure [43, 44]. Direct ovarian radiation exposure causes menstrual irregularity, primary ovarian insufficiency and diminished ovarian reserve [13]. A study of childhood cancer survivors who received abdominal radiation indicated an increased risk of miscarriage and preterm birth later in life [45].

The hypothalamus and pituitary glands are especially sensitive to high levels of cranial or brain irradiation, which may prevent regulated secretion of GnRH, FSH and LH, which in turn affects release of estradiol, progesterone, and prolactin [45].

Spinal irradiation may also jeopardize reproduction after cancer, as higher rates of miscarriage have been reported after this treatment. Women whose cancer treatment causes damage to both the brain and pelvic regions are at

the highest risk for reproductive loss after cancer. Patients who undergo total body irradiation prior to hematopoietic stem cell transplantation should be informed of their fertility preservation options as early as possible. In fact, patients who undergo aggressive chemo-radiotherapy due to the need of transplantation are classified as at high risk for gonadotoxicity [27].

Cranial radiation disrupts hypothalamic and pituitary function, resulting in oligomenorrhea and hypogonadism. Scatter doses of radiation from abdominopelvic or craniospinal RT can cause ovarian failure in 50–70% of cases [13]. Craniospinal irradiation alone was not considered as a high gonadotoxicity risk [40].

In men, radiotherapy has implications for testicular function by potentially damaging both germ cells and Leydig cells, immature stem cells and spermatogonia, the latter being the most sensitive [30]. Leydig cells show variation in their radiosensitivity according to age, reaching its peak before puberty, which might affect the fertility potential. However, the sensitivity of sperm to radiation appears to be unrelated to age [25]. Testicular tissue is extremely radiosensitive and even smaller doses of direct radiation can impair spermatogenesis. Radiation doses begin to adversely affect spermatogenesis at 0.1–1.2 Gy; therefore doses greater than 6 Gy can cause total depletion of spermatogonial stem cells and permanent sterility [8].

Hormone therapy

Hormonal therapies are some of the oldest active systemic anticancer therapies in use today. Substantial evidence now exists that hormones play a key role in both the cause and the outcome of several cancers [46].

While fewer than one-third of women with newly diagnosed breast cancer are premenopausal, the choice of adjuvant endocrine therapy for hormone receptor-positive cancers is an important consideration regardless of menopausal status, particularly given the possibility of late recurrence with this subtype of breast cancer. Tamoxifen, a selective estrogen receptor modulator, has not typically been associated with cessation of ovulation. Furthermore, at higher doses, tamoxifen can stimulate ovulation. However, it is not recommended to become pregnant while taking tamoxifen. Despite this, tamoxifen may cause irregular or absent menses in some patients when given after gonadotoxic chemotherapy or when used alone. Tamoxifen-induced amenorrhea is thought to be reversible and temporary [47].

In men, hormone therapy is more commonly used in the treatment of prostate cancer, which occurs in most cases in older patients and necessarily involves azoospermia [22].

Immunotherapy

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatments due to their effectiveness, with the expectation that their use will increase even more in the near future. However, toxic effects on fertility, pregnancy and sexuality are poorly understood.

Based on currently known evidence, these compounds can cause primary hypogonadism especially in men, secondary hypogonadism, and theoretically, libido and sexual impairment. Despite the current knowledge gap, hypophysitis and panhypopituitarism are known adverse events of checkpoint inhibitors, so impairment of the pituitary gonadal axis can lead to reduced sex hormones. It is known that sex hormone deficiency can reduce fertility and lead to physical and psychological disorders of sexuality [48].

Tulchiner *et al.* reported that patients treated with anti-programmed death-1 (anti-PD1) checkpoint inhibitor anticancer drugs that block the activity of PD-1 and PD-L1 immune checkpoint proteins present on the surface of cells may show increases in LH-FSH ratio and estradiol levels, which only occurs in men for reasons not yet known [49].

In addition, conception and pregnancy should be avoided during treatment with ICIS [48].

Psychological effects

Hormonal changes leading to psychiatric disorders

Cancer diagnosis and treatment can be associated with sexual dysfunction of various etiologies, including testosterone deficiency [50]. Previous research showed that testosterone can affect the secretion of monoamine neurotransmitters associated with anxiety and depression [51]. Testosterone can increase dopamine neurotransmitter release in the limbic system of the midbrain. This may prevent not only depression-induced pleasure disorders but also a related reduction in dopamine activity in reward-related brain pathways. Additionally, blood testosterone levels inhibit re-uptake of serotonin, activate tyrosine hydroxylase, and increase the transport of 1-aminobutyric acid. Therefore, when blood levels of testosterone decrease, these neurotransmitter levels also decrease, eventually leading to depressive symptoms [52].

Psychiatric disorders leading to hormonal changes

The diagnosis of cancer, especially in young patients, is associated with a high level of distress, which is caused by many factors such as hypervigilance of symptoms, concerns about family and finances, the stress of managing health needs, changes in self-perceptions and body image, and feelings of vulnerability and worrying about recurrence [18].

The psychological distress is associated with symptoms of depression and anxiety. The incidence of depression in adolescent and young age (AYA) patients ranges between 13 and 25%, and anxiety is estimated to affect 15–20% of AYA patients [18]. This psychiatric conditions are proven to lead to a decrease in serum testosterone, an increase in FSH and, more specifically, to abnormal semen parameters, possibly leading to infertility [53].

Patients with infertility secondary to cancer treatment have increased risk of emotional distress [10] and the psychiatric disorders associated with it [54].

Cancer diagnosis and treatment may lead to psychological distress, which is associated with psychiatric conditions, such as anxiety and depression, that decrease the level of testosterone. On the other hand, this same oncologic disorder may lead to a testosterone deficien-

cy which is associated with depressive symptoms. This "dual" link between testosterone and depression might contribute greatly to infertility among oncologic patients, which is also a proven cause of depression [55, 56].

Fertility preservation

Over the past few decades, there have been significant advances in cancer research, namely in the pediatric field, leading to an improvement in survival rates. As a result, the number of patients reaching childbearing age is significant. Fertility preservation and protection is progressively becoming a pivotal topic when dealing with pediatric cancer patients. Several oncology organizations around the world, such as the ASCO and the European Society for Medical Oncology (ESMO), have already published guidelines on fertility preservation. It is well established that health professionals and patients should work together in the decision-making process before exposure to gonadotoxic agents takes place to allow the widest array of options [10]. During treatment, it is still possible to perform conservative surgery or to shield gonads from radiation. Several of these techniques can be performed in association to minimize their risk and maximize their success [57]. For instance, ovarian stimulation for oocyte cryopreservation can be combined with cryopreservation of ovarian tissue to increase success rates [58].

It is pivotal to assess pubertal status before initiating any fertility preservation technique. Through a detailed history and physical examination, it is important to analyze secondary sex characteristics and Tanner staging and evaluate, especially in the male group, if they already have experienced sexual thoughts or masturbation [10]. After an initial assessment, fertility preservation techniques can be offered according to gender and pubertal status. For post-pubertal children, it is possible to cryopreserve their gametes. For pre-pubertal patients, since they do not have mature gametes, they are not candidates for traditional cryopreservation. Regardless of the choice, these techniques should be performed at expertise centers.

Therapeutic options for male sex

Cryopreservation of sperm

For male post-pubertal children, cryopreservation of sperm is usually the best choice. Spermarche, the development of sperm in males, typically occurs during genital Tanner Stage 4. Sperm cryopreservation is generally offered to children who are at least Tanner Stage 3/4 in their development status, with a testicular volume of 10–12 ml and motile spermatozoa reported [59, 60]. A semen specimen can be obtained by masturbation but, in children who cannot perform it, it can be obtained by penile vibratory stimulation or electroejaculation [61]. Sperm is cryopreserved and later in life, when the patient desires, it can be used in intrauterine insemination, *in vitro* fertilization or intracytoplasmic sperm injection techniques [62, 63].

Hormonal suppression

The literature describes hormonal suppression to preserve gonadal tissue as a possible option, though not widely recommended since its success rate is not yet clearly proven [64].

Testicular tissue cryopreservation

For male pre-pubertal children, due to the lack of mature sperm, different techniques must be used. Testicular tissue cryopreservation, though experimental in pediatric patients, is currently the option with the greatest potential [64–67]. It consists in the surgical removal of immature testicular tissue through a biopsy and then cryopreserving it [61]. A prospective longitudinal study developed in the Karolinska University Hospital in 2020 examined prepubertal boys who underwent this procedure prior to hematological stem cell transplantation between 2003 and 2010. No long-term risk related with the procedure was reported. In adult age, patients reported normal testosterone levels but smaller testicles, elevated levels of LH and FSH and low levels of inhibin B and anti-Müllerian hormone [68]. However, this technique is still at the early stage of development [69], and it requires future development of techniques that allow maturation of spermatogonial stem cells into sperm [8, 61].

Therapeutic options for female sex

Cryopreservation of oocytes

For female post-pubertal children, cryopreservation of oocytes is the standard of care. It is more invasive and time-consuming when compared with the cryopreservation method for male patients, since it requires prior ovarian stimulation *via* multiple hormonal injections of GnRH antagonists [70]. Hormonal stimulation should start on the second or third day of the menstrual cycle and be maintained during a medium of 12 days. After that time, transvaginal oocyte removal is done, generally under sedation or anesthesia [61]. The whole process lasts about 14 days and cancer treatments can be initiated a couple of days after [22]. Later in life, if desired, it can be used in *in vitro* fertilization or intracytoplasmic sperm injection techniques [71, 72].

This technique is not the best choice for hormone-dependent cancers, such as breast cancer, since the importance of estrogen and its metabolites in breast cancer propagation is well recognized [73]. Recent studies demonstrated that controlled ovarian stimulation with letrozole supplementation is safer, even though its long-term safety has not been demonstrated yet [74].

Ovarian suppression

When cancer treatment has already started, the previously mentioned options should not be performed. A reasonable option to protect fertility during cancer treatments for post-pubertal patients is ovarian suppression using gonadotropin-releasing hormone agonist (GnRH-a) therapy [18]. It is still an experimental procedure, but several studies indicate that these agents may reduce ovarian toxicity by downregulating the secretion of FSH and LH from the pituitary, inhibiting follicular recruitment. It is believed to decrease sensitivity to chemotherapy since fewer primordial follicles attain the chemotherapy-sensitive stages

of proliferation and follicle maturation [18]. However, this is a controversial topic and there are concerns regarding the possible flare effect resulting in a rise in sex steroids and consequently in bleeding, which may be an important issue in children with pancytopenia [18].

Ovarian tissue cryopreservation

For both pre-pubertal and post-pubertal patients who require urgent treatment, time-consuming techniques that require ovarian stimulation are not recommended. In that case, ovarian tissue cryopreservation is currently the best choice [58, 75, 76]. It consists in the removal of ovarian tissue by laparoscopic surgery and its dissection, cryopreserving fragments of the cortex. This procedure does not require hormonal stimulation and it may be performed within days. It is important to perform a histological analysis to exclude ovarian metastasis [77]. In the future, if desired, the fragments are thawed and grafted onto the remaining ovary or to another location [18]. After transplantation, the ovarian tissue may restore endocrine function and fertility, enabling a natural conception. It is the only non-experimental option available for this group of children [78]. Due to the widespread utilization of this method internationally and consistent with the European Society of Human Reproductive and Embryology (ESHRE), ESMO and American Society for Reproductive Medicine (ASRM) guidelines, the experimental label has been removed and ovarian tissue cryopreservation is now standard of care [38, 79].

Oophoropexy

Another option for pre-pubertal and post-pubertal patients who require urgent treatment is ovarian tissue transplantation, also known as oophoropexy. It is a surgical procedure that is usually indicated in patients for whom pelvic irradiation is planned. It consists of an immediate reallocation of ovarian fragments away to the radiation field, instead of cryopreserving them. They can be allocated either to local structures, such as ovarian fossa, contralateral ovary and pelvic side wall, or to distant areas, such as subcutaneous areas of the forearm and retroperitoneal space under the abdominal wall [61]. When the treatment ends, the ovaries return to their original position to allow return of reproductive function [18]. However, it is also considered an experimental procedure and its success rate is not always the best due to radiation scatter [64].

Barriers to fertility preservation

There are several barriers that can negatively affect the discussion of fertility preservation in pediatric patients. A recent study performed in the Department of Women's and Children's Health in the Swedish Karolinska Institutet indicated that challenges regarding this topic may be mainly due to external and internal factors [71]. The first depend on the availability of health-care services and the organization of care. For instance, these treatments have high costs and some are experimental [80], not being available for everyone or covered by insurance [61, 64]. Internal factors are related to the clinicians' characteristics and values [81], and to the parents' perception and assumptions [82]. It is vital to assess the right of parental decision-making and the child's decisional capacity [83]. Patient autonomy is pivotal in the decision-making process [18]. However, there may be certain ethical considerations regarding consent and assent, since patients are under-aged. The lack of comprehension of the family about this topic might be an important obstacle [61], so it is also important to consider parents' concerns regarding the delay of cancer treatment to apply the fertility preservation technique [64]. The first consultation is the most critical barrier since the diagnosis is accompanied by anxiety and an urge to start treatment [10]. Certain pediatric cancers often require urgent initiation of treatment. Consequently, it might be a complicated decision to take under such difficult circumstances. Finally, it is equally important to evaluate the cultural and religious concerns regarding the collection method and fertility preservation technique, since certain religions hold bioethical concepts regarding fertility [61].

Additionally, the theoretical risk of cryopreserving and subsequently transplanting gonadal tissue with neoplastic cells, as well as the impact of the preservation treatment on future gonadal function and the health of the future baby, are both subjects that can negatively affect the process [61]. Infertility is not a life-threatening situation and fertility treatments are elective. For that reason, it is pivotal to ensure that the fertility preservation technique risk is null. Several techniques, such as polymerase chain reaction, flow cytometry and xenotransplantation, are being developed with the aim of excluding such a possibility.

The development of oncofertility programs might be a way to overcome several of these barriers [6, 71, 84–86]. However, formal programs that help to establish to whom and how fertility preservation techniques are applied are not yet common worldwide [87, 88].

Current recommendations and programs

There are several recommendations worldwide about fertility preservation, namely in the pediatric group. For instance, in 2013 the ESMO released a guideline regarding this topic [89]. In 2016, the Portuguese Society of Oncology also developed recommendations [90]. In 2017, Japan published its first guideline in cancer reproductive medicine, with an important emphasis on pediatric patients [28]. In the following year, the ASCO updated their guidelines on fertility preservation in cancer patients [91]. More recently, in 2021 a Spanish multidisciplinary consensus about this topic was published, and in 2022 similar recommendations were issued by the Oncology Association of Bosnia and Herzegovina [92]. Overall, all recommendations have similar points of view. It is widely stated that for post-pubertal boys receiving cancer treatments, sperm cryopreservation is effective and considered the gold standard. A semen sample can be obtained through masturbation or testicular sperm aspiration and cryopreserved. They also state that hormonal suppression to preserve gonadal tissue is not successful in preserving fertility, so it is not recommended. For post-pubertal girls, cryopreservation of oocytes is the current best option. Oophoropexy is an important option for girls who will be submitted to pelvic irradiation. How-

ever, it is important for patients to be aware that the procedure is not always successful since ovaries are not always protected because of radiation scatter. For prepubertal children, the only fertility preservation options are ovarian and testicular cryopreservation, which are still investigational.

It is believed that the development of formal fertility preservation programs might be the best way to ensure high-quality fertility preservation care [10, 71, 93]. Recently in Princess Máxima Center for Pediatric Oncology, in the Netherlands, a five-step oncofertility care plan for all newly diagnosed female patients was introduced [76]. The main goal was to identify, inform, triage and counsel patients at high risk of gonadal damage. It consisted of early identification of new patients, triage of gonadal damage, informing patients and family, counseling a selected subset of patients and finally submitting them to a fertility preservation technique. Nearly 88% of the 261 patients were timely identified and triaged, with 35 of them being counseled and more than half submitted to a technique. It did not lead to any complications or delay of cancer treatment. Also, a recent study assessed the current status of fertility preservation for pediatric patients in Australia and Asian countries [94]. According to it, Japan is at the forefront of this topic, as well as Australia. The latter is considered one of the most developed countries in the area and already has its own partial public funding and registration system for patients who desire fertility preservation techniques.

Conclusions

The growing number of cancer cases diagnosed at young ages and the effect of the disease and the antineoplastic treatment on the reproductive function justified the development of oncofertility. The survivors will experience long-term adverse outcomes from cancer therapies, such as infertility and poor reproductive outcomes that disrupt quality of life. To reduce risk, fertility preservation counseling is recommended as standard of care. Over the last 10 years, several organizations worldwide have published recommendations and guidelines on fertility preservation in cancer patients. It is widely agreed that pubertal status is a central factor when choosing the best technique. For post-pubertal children, since they have mature gametes, the preferential method is the cryopreservation of oocytes or sperm. For pre-pubertal patients several alternatives are still being developed. Recent scientific breakthroughs with use of spermatogonial stem cells and testicular tissue transplantation, for the male sex, and ovarian tissue preservation and oophoropexy, for the female sex, offer great promise for the future. It is also important to be aware of the several barriers regarding the oncofertility topic. Not only cultural, religious, and financial aspects, but also clinicians' characteristics and parents' perception of the method can negatively affect the process of fertility preservation in pediatric patients. The development of oncofertility programs, though still not common worldwide, might help overcome several of these aspects and ensure that patients perfect their future fertility potential.

The authors declare no conflict of interest.

References

1. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 2014; 64: 83-103.
2. Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon 2020, France.
3. Stal J, Yi SY, Cohen-Cutler S, et al. Fertility preservation discussions between young adult rectal cancer survivors and their providers: sex-specific prevalence and correlates. Oncologist 2022; 27: 579-586.
4. Lehmann V, Keim MC, Nahata L, et al. Fertility-related knowledge and reproductive goals in childhood cancer survivors: short communication. Hum Reprod 2017; 32: 2250-2253.
5. Rodriguez-Wallberg KA. Principles of Cancer Treatment: Impact on Reproduction BT – Reproductive Health and Cancer in Adolescents and Young Adults. In: Quinn GP, Vadaparampil ST, eds. Dordrecht: Springer Netherlands 2012, 1-8.
6. Moravek MB, Appiah LC, Anazodo A, et al. Development of a pediatric fertility preservation program: a report from the pediatric initiative network of the oncofertility consortium. J Adolesc Health 2019; 64: 563-573.
7. Tonorezos ES, Cohn RJ, Glaser AW, et al. Long-term care for people treated for cancer during childhood and adolescence. Lancet (London, England) 2022; 399: 1561-1572.
8. Bîcă O, Sârbu I, Ciongradi CI. Pediatric and adolescent oncofertility in male patients – from alpha to omega. Genes (Basel) 2021; 12: 701.
9. Huleihel M, AbuElhija M, Lunenfeld E. In vitro culture of testicular germ cells: regulatory factors and limitations. Growth Factors 2007; 25: 236-252.
10. Halpern JA, Das A, Faw CA, Brannigan RE. Oncofertility in adult and pediatric populations: options and barriers. Transl Androl Urol 2020; 9: S227-S238.
11. Hansen PV, Trykker H, Andersen J, Helkjaer PE. Germ cell function and hormonal status in patients with testicular cancer. Cancer 1989; 64: 956-961.
12. Williams DH, Karpman E, Sander JC, Spiess PE, Pisters LL, Lipshultz LI. Pretreatment semen parameters in men with cancer. J Urol 2009; 181: 736-740.
13. Rousset-Jablonski C, Chevillon F, Dhedin N, Poirot C. [Fertility preservation in adolescents and young adults with cancer]. Bull Cancer 2016; 103: 1019-1034.
14. Bahadur G, Ozturk O, Muneer A, et al. Semen quality before and after gonadotoxic treatment. Hum Reprod 2005; 20: 774-781.
15. Ragni G, Somigliana E, Restelli L, Salvi R, Arnoldi M, Paffoni A. Sperm banking and rate of assisted reproduction treatment: Insights from a 15-year cryopreservation program for male cancer patients. Cancer 2003; 97: 1624-1629.
16. Inui A. Cancer anorexia-cachexia syndrome: are neuropeptides the key? Cancer Res 1999; 59: 4493-4501.
17. Tarasiewicz M, Martynowicz I, Knapp P, Sieczyński P. "Oncofertility" procedures in children and adolescents. Pediatr Endocrinol Diabetes Metab 2019; 25: 144-149.
18. Appiah LC, Fei YF, Olsen M, Lindheim SR, Puccetti DM. Disparities in female pediatric, adolescent and young adult oncofertility: a needs assessment. Cancers (Basel) 2021; 13: 1-14.
19. Reinmuth S, Hohmann C, Rendtorff R, et al. Impact of chemotherapy and radiotherapy in childhood on fertility in adulthood: the FeCt-survey of childhood cancer survivors in Germany. J Cancer Res Clin Oncol 2013; 139: 2071-2078.
20. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 2006; 24: 2917-2931.
21. Van Dorp W, Haupt R, Anderson RA, et al. Reproductive function and outcomes in female survivors of childhood, adolescent, and young adult cancer: a review. J Clin Oncol 2018; 36: 2169-2180.
22. Teresa A, Santos A, Sousa G. Recomendações clínicas para a preservação da fertilidade no doente oncológico. Available from: https://www.spmr.pt/attachments/recom-spmr.pdf.
23. Djaladat H. Organ-sparing surgery for testicular tumours. Curr Opin Urol 2015; 25: 116-120.

24. Borghesi M, Brunocilla E, Schiavina R, et al. Role of testis sparing surgery in the conservative management of small testicular masses: oncological and functional perspectives. Actas Urol Esp 2015; 39: 57-62.
25. Rodriguez-Wallberg KA, Oktay K. Fertility preservation during cancer treatment: clinical guidelines. Cancer Manag Res 2014; 6: 105-117.
26. Jacobsen KD, Theodorsen L, Fossa SD. Spermatogenesis after unilateral orchiectomy for testicular cancer in patients following surveillance policy. J Urol 2001; 165: 93-96.
27. Waimey KE, Smith BM, Confino R, Jeruss JS, Pavone ME. Understanding fertility in young female cancer patients. J Womens Health (Larchmt) 2015; 24: 812-818.
28. Tozawa A, Kimura F, Takai Y, et al. Japan Society of Clinical Oncology Clinical Practice Guidelines 2017 for fertility preservation in childhood, adolescent, and young adult cancer patients: part 2. Int J Clin Oncol 2022; (0123456789).
29. Meistrich ML. Male gonadal toxicity. Pediatr Blood Cancer 2009; 53: 261-266.
30. Vakalopoulos I, Dimou P, Anagnostou I, Zeginiadou T. Impact of cancer and cancer treatment on male fertility. Hormones (Athens) 2015; 14: 579-589.
31. Oktem O, Oktay K. Quantitative assessment of the impact of chemotherapy on ovarian follicle reserve and stromal function. Cancer 2007; 110: 2222-2229.
32. Bates GE, Taub RN, West H. Fertility and cancer treatment. JAMA Oncol 2016; 2: 284.
33. Cioffi R, Fais ML, Bergamini A, et al. Ovarian failure risk in post-pubertal patients with cancer: a prognostic model. Future Oncol 2022; 18: 2391-2400.
34. Moss JL, Choi AW, Fitzgerald Keeter MK, Brannigan RE. Male adolescent fertility preservation. Fertil Steril 2016; 105: 267-273.
35. Green DM, Sklar CA, Boice Jr JD, et al. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. J Clin Oncol 2009; 27: 2374-2381.
36. Yu RN. Fertility preservation in the pediatric cancer patient. Curr Opin Urol 2019; 29: 477-480.
37. Rose SR, Schreiber RE, Kearney NS, et al. Hypothalamic dysfunction after chemotherapy. J Pediatr Endocrinol Metab 2004; 17: 55-66.
38. Committee P, Society A. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril 2019; 112: 1022-1033.
39. Hansen P V, Hansen SW. Gonadal function in men with testicular germ cell cancer: the influence of cisplatin-based chemotherapy. Eur Urol 1993; 23: 153-156.
40. Rinaldi VD, Hsieh K, Munroe R, Bolcun-Filas E, Schimenti JC. Pharmacological inhibition of the DNA damage checkpoint prevents radiation induced oocyte death. Genetics 2017; 206: 1823-1828.
41. Fenig E, Mishaeli M, Kalish Y, Lishner M. Pregnancy and radiation. Cancer Treat Rev 2001; 27: 1-7.
42. Wallace WHB, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys 2005; 62: 738-744.
43. Critchley HOD, Wallace WHB. Impact of cancer treatment on uterine function. J Natl Cancer Inst Monogr 2005; (34): 64-68.
44. Fukunaga H, Yokoya A, Prise KM. A brief overview of radiation-induced effects on spermatogenesis and oncofertility. Cancers (Basel) 2022; 14: 805.
45. Reulen RC, Zeegers MP, Wallace WHB, et al. Pregnancy outcomes among adult survivors of childhood cancer in the British Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev 2009; 18: 2239-2247.
46. Hanna L, Crosby T, Macbeth F. Practical Clinical Oncology. 2nd ed. Cambridge University Press 2016.
47. Hulvat MC, Jeruss JS. Maintaining fertility in young women with breast cancer. Curr Treat Options Oncol 2009; 10: 308-317.
48. Garutti M, Lambertini M, Puglisi F. Checkpoint inhibitors, fertility, pregnancy, and sexual life: a systematic review. ESMO Open 2021; 6: 100276.
49. Tulchiner G, Pichler R, Ulmer H, et al. Sex-specific hormone changes during immunotherapy and its influence on survival in metastatic renal cell carcinoma. Cancer Immunol Immunother 2021; 70: 2805-2817.
50. Salter CA, Mulhall JP. Oncosexology: Sexual Issues in the Male Cancer Survivor. Urol Clin North Am 2021; 48: 591-602.
51. Tham YL, Sexton K, Weiss H, Elledge R, Friedman LC, Kramer R. The rates of chemotherapy-induced amenorrhea in patients treated with adjuvant doxorubicin and cyclophosphamide followed by a taxane. Am J Clin Oncol 2007; 30: 126-132.
52. Chen Z, Shen X, Tian K, et al. Bioavailable testosterone is associated with symptoms of depression in adult men. J Int Med Res 2020; 48: 300060520941715.
53. Maharjan DT, Syed AAS, Lin GN, Ying W. Testosterone in female depression: a meta-analysis and mendelian randomization study. Biomolecules 2021; 11: 1-11.
54. Di Mattei VE, Perego G, Rancoita PMV, et al. Psychological aspects associated with fertility preservation in oncology: an exploratory study. Front Psychol 2020; 11: 608651.
55. Morgan TL, Young BP, Lipak KG, et al. "We can always adopt": perspectives of adolescent and young adult males with cancer and their family on alternatives to biological parenthood. J Adolesc Young Adult Oncol 2020; 9: 572-578.
56. Hudson JN, Stanley NB, Nahata L, Bowman-Curci M, Quinn GP. New promising strategies in oncofertility. Expert Rev Qual Life Cancer Care 2017; 2: 67-78.
57. Jiang M, Wang J, Yu R, Hu R, Li J. A narrative review on the research progress of gonadal function protection in children with cancer. Ann Transl Med 2022; 10: 374.
58. Dolmans MM, Marotta ML, Pirard C, Donnez J, Donnez O. Ovarian tissue cryopreservation followed by controlled ovarian stimulation and pick-up of mature oocytes does not impair the number or quality of retrieved oocytes. J Ovarian Res 2014; 7: 80.
59. DiNofia AM, Wang X, Yannekis G, et al. Analysis of semen parameters in a young cohort of cancer patients. Pediatr Blood Cancer 2017; 64: 381-386.
60. Salsman JM, Yanez B, Snyder MA, et al. Attitudes and practices about fertility preservation discussions among young adults with cancer treated at a comprehensive cancer center: patient and oncologist perspectives. Support Care Cancer 2021; 29: 5945-5955.
61. Burns KC, Hoefgen H, Strine A, Dasgupta R. Fertility preservation options in pediatric and adolescent patients with cancer. Cancer 2018; 124: 1867-1876.
62. Abram McBride J, Lipshultz LI. Male fertility preservation. Curr Urol Rep 2018; 19: 49.
63. Mitchell RT, Williams SA. A fertile future: fertility preservation special series. Reprod Fertil 2022; 3: C1-C3.
64. Lau GA, Schaeffer AJ. Current standing and future directions in pediatric oncofertility: a narrative review. Transl Androl Urol 2018; 7: S276-S282.
65. Valli-Pulaski H, Peters KA, Gassei K, et al. Testicular tissue cryopreservation: 8 years of experience from a coordinated network of academic centers. Hum Reprod 2019; 34: 966-977.
66. Ho WLC, Bourne H, Gook D, et al. A short report on current fertility preservation strategies for boys. Clin Endocrinol (Oxf) 2017; 87: 279-285.
67. Goossens E, Jahnukainen K, Mitchell R, et al. Fertility preservation in boys: recent developments and new insights. Hum Reprod Open 2020; 2020: 1-18.
68. Borgström B, Fridström M, Gustafsson B, Ljungman P, Rodriguez-Wallberg KA. A prospective study on the long-term outcome of prepubertal and pubertal boys undergoing testicular biopsy for fertility preservation prior to hematologic stem cell transplantation. Pediatr Blood Cancer 2020; 67: 1-11.
69. Tran KTD, Valli-Pulaski H, Colvin A, Orwig KE. Male fertility preservation and restoration strategies for patients undergoing gonadotoxic therapies. Biol Reprod 2022; 107: 382-405.
70. Porcu E, Cipriani L, Dirodi M, et al. Successful pregnancies, births, and children development following oocyte cryostorage in female cancer patients during 25 years of fertility preservation. Cancers (Basel) 2022; 14: 1429.
71. Lampic C, Wettergren L. Oncologists' and pediatric oncologists' perspectives and challenges for fertility preservation. Acta Obstet Gynecol Scand 2019; 98: 598-603.

72. Poli M, Capalbo A. Oocyte cryopreservation at a young age provides an effective strategy for expanding fertile lifespan. Front Reprod Health 2021; 3.
73. Diaz-Garcia C, Domingo J, Garcia-Velasco JA, et al. Oocyte vitrification versus ovarian cortex transplantation in fertility preservation for adult women undergoing gonadotoxic treatments: a prospective cohort study. Fertil Steril 2018; 109: 478-485.e2.
74. Kim J, Turan V, Oktay K. Long-term safety of letrozole and gonadotropin stimulation for fertility preservation in women with breast cancer. J Clin Endocrinol Metab 2016; 101: 1364-1371.
75. Takae S, Furuta S, Iwahataa H, et al. Cryopreservation of paediatric ovarian tissue with an updated version of the Edinburgh criteria for appropriate patient selection. Reprod Biomed Online 2022; 44: 667-676.
76. Madeleine van der Perk ME, van der Kooi ALLF, van de Wetering MD, et al. Oncofertility care for newly diagnosed girls with cancer in a national pediatric oncology setting, the first full year experience from the Princess Máxima Center, the PEARL study. PLoS One 2021; 16: 1-18.
77. Cariati F, Carbone L, Iorio GG, et al. Cryopreservation of ovarian tissue: the biggest challenge of oncofertility. Minerva Obstet Gynecol 2022.
78. Ní Dhonnabháin B, Elfaki N, Fraser K, et al. A comparison of fertility preservation outcomes in patients who froze oocytes, embryos, or ovarian tissue for medically indicated circumstances: a systematic review and meta-analysis. Fertil Steril 2022.
79. Nahata L, Woodruff TK, Quinn GP, et al. Ovarian tissue cryopreservation as standard of care: what does this mean for pediatric populations? J Assist Reprod Genet 2020; 37: 1323-1326.
80. Boone AN, Arbuckle JL, Ye Y, Wolfson JA. How accurate is oncologist knowledge of fertility preservation options, cost, and time in female adolescents and young adults? J Adolesc Young Adult Oncol 2022.
81. Vadaparampil S, Quinn G, King L, Wilson C, Nieder M. Barriers to fertility preservation among pediatric oncologists. Patient Educ Couns 2008; 72: 402-410.
82. Glazer TS, Schulte F. Barriers to oncofertility care among female adolescent cancer patients in Canada. Curr Oncol 2022; 29: 1583-1593.
83. Bayefsky M, Vieira D, Caplan A, Quinn G. Navigating parent-child disagreement about fertility preservation in minors: scoping review and ethical considerations. Hum Reprod Update 2022.
84. Dorfman CS, Stalls JM, Mills C, et al. Addressing barriers to fertility preservation for cancer patients: the role of oncofertility patient navigation. J Oncol Navig Surviv 2021; 12: 332-348.
85. Salama M, Anazodo A, Woodruff TK. Preserving fertility in female patients with hematological malignancies: a multidisciplinary oncofertility approach. Ann Oncol 2019; 30: 1760-1775.
86. Johnson R. Innovative fertility preservation strategies and programs for young adults with cancer. Clin Oncol Adolesc Young Adults 2016:1.
87. Frederick NN, Klosky JL, Meacham LR, et al. Infrastructure of fertility preservation services for pediatric cancer patients: a report from the Children's Oncology Group. JCO Oncol Pract 2021; 18: e325-e333.
88. Latif S, Martins Da Silva S, Davies M, et al. Fertility preservation provision in the NHS: a national assessment of care policies. Hum Fertil (Camb) 2022: 1-6.
89. Peccatori FA, Azim JA, Orecchia R, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24: vi160-70.
90. Teresa A, Santos A. Recomendações para a preservação do potencial reprodutivo no doente oncológico. Rev Port Oncol 2016; 2: 5-24.
91. Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol 2018; 36: 1994-2001.
92. Cerić T, Sokolović E, Hasanbegović B, et al. The Oncology Association of Bosnia and Herzegovina's Recommendations for fertility preservation in oncologic patients. Bosn J Basic Med Sci 2022.
93. Salama M, Laronda MM, Laura ER, et al. Installing oncofertility programs for common cancers in optimum resource settings (Repro-Can-OPEN Study Part II): a committee opinion. J Assist Reprod Genet 2021; 38: 163-176.
94. Takae S, Lee JR, Mahajan N, et al. Fertility preservation for child and adolescent cancer patients in Asian countries. Front Endocrinol (Lausanne) 2019; 10: 655.

Address for correspondence

Rafael Marques
Centro Hospitalar Entre o Douro e Vouga
Santa Maria da Feira, Portugal
e-mail: 7rafaelmarques@gmail.com

Submitted: 31.05.2022
Accepted: 14.09.2022