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Male fertility preservation at risk of gonadotoxicity

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Abstract

Background: Along with other aspects of male reproduction, fertility preservation has made significant advances in the past ten years. The overall survival rate for childhood cancer has greatly improved in recent decades, with a current 5-year survival rate of over 80%, compared to roughly 58% in the late 1970s. Many of the most common reproductive issues, such as cryptorchidism and hypospadias in newborns as well as testicular cancer and lower sperm quality in young adult males, have recently become increasingly common. Although the precise cause of these unfavorable effects on reproduction is yet unknown, it has been suggested that they may be related to the presence of common chemicals in the environment or exposure to specific drug classes during fetal life. Large progress has been achieved in recent years toward understanding the biology of male and female reproduction in both animals and humans and applying this information to the creation of methods for fertility preservation in a variety of clinical and ecological contexts.
Conclusions: A rapidly developing area, fertility preservation has a wide range of applications, from preserving the possibility of fertility in a child with cancer to preventing the extinction of an entire species. The emphasis on preserving fertility is now only placed on cancer patients who are of reproductive age, but its therapeutic importance may be extended to non-cancer patients as well.
Key words: prepubertal human testis, childhood cancer, gonadotoxicity, side effects, fertility preservation.

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Introduction

Along with other aspects of male reproduction, fertility preservation has made significant advances in the past ten years. Due to cultural changes that have delayed motherhood and the quick pace of scientific advancements spurred by advances in cancer therapy and cryobiology, it is regarded as a necessary service in the medical field. It is widely acknowledged that cancer is a serious situation in which fertility preservation is a crucial step. By 2025, there will be more than 20 million new cases of cancer annually, according to global demographic and epidemiologic data [1-3]. Also, while finding a cure is still our top priority, we are confronted with a difficult treatment outcome since an increasing percentage of patients have poor quality of life due to the presence of a tumor and the following treatment. The biggest quality of life concern for young cancer survivors continues to remain infertility. As a result, fertility preservation techniques are essential as the long-term survival rate for cancer has increased. The 5-year relative survival rate for all cancers combined is currently nearing 70% among adults and >80% among children, according to recent studies [4]. The emphasis on preserving fertility is now only placed on cancer patients who are of reproductive age, but its therapeutic importance may be extended to non-cancer patients as well. As a result, far more extensive applications are anticipated soon.

The overall survival rate for childhood cancer has greatly improved in recent decades, with a current 5-year survival rate of over 80%, compared to roughly 58% in the late 1970s [5]. This showed that as a result of advancements, primarily because of improved chemotherapy treatments, a growing number of long-term pediatric cancer survivors has arisen. However, chemotherapy drugs do not just target malignant cells; they can also destroy healthy tissues unintentionally, which might have unfavorable repercussions. To improve the quality of life for childhood cancer survivors, research is increasingly focusing on minimizing harm to healthy organs. The negative consequences of therapy on fertility can be particularly concerning for younger people [6].

Many of the most common reproductive issues, such as cryptorchidism and hypospadias in newborns as well as testicular cancer and lower sperm quality in young adult males, have recently become increasingly common. Additionally, the timing of puberty has changed over time. Although the precise cause of these unfavorable effects on reproduction is yet unknown, it has been suggested that they may be related to the presence of common chemicals in the environment or exposure to specific drug classes during fetal life [7].

The increased awareness of long-term treatment-related toxicities that impact reproductive and endocrine

function is a result of improved children cancer survival rates [8]. For prepubertal boys who are not yet producing mature germ cells, sperm cryobanking is not practical prior to beginning life-saving medications, which presents a problem for fertility preservation in this cohort of patients [9]. Prepubescent males currently do not have any treatment choices that will safeguard and preserve their future fertility. Cryopreserving testicular tissues that contain spermatogonial stem cells (SSCs) before starting any gonadotoxic cancer therapy becomes a possible solution to this issue [10].

Fayomi A. P. and associates have shown that intracytoplasmic sperm injection using autologous transplantation of cryopreserved prepubertal non-human monkey testis tissue can result in the production of functional sperm [11]. Applications using cryopreserved prepubertal human testis tissue are still at the experimental stage, despite the fact that this study is particularly positive and represents an opportunity for young boys.

Factors that affect the fertility of cancer survivors and their offspring: an overview

After cancer therapy, there is a great degree of variability in the risk and severity of infertility, which is influenced by numerous patient and therapeutic variables. Patient factors include aspects like age at diagnosis, length of time since treatment, sex, pretreatment fertility, and the location and stage of the cancer, while treatment factors include matters like drug type, administration route, location and dosage of radiation therapy, dose, and dose intensity [12]. Sterilization surgery could be necessary for the treatment of some malignancies. Additionally, by impairing potency and ejaculation, nonsterilizing surgery for malignancies of the bladder, prostate, and rectum may also have an impact on fertility [13].

Although there are obvious dose, medication, gender, and age-dependent effects, chemotherapy, and especially alkylating drugs like cyclophosphamide and procarbazine, can have a major impact on fertility [12, 13]. Whole-body radiation, radiation at or near reproductive organs, radiation at or near the pituitary gland, which produces FSH and LH, and other reproductive hormones, may all have a significant impact on fertility [12, 13].

In a large cohort study from the Childhood Cancer Survivor Study (CCSS), 6224 male subjects without surgical sterility aged 15-44 who were diagnosed with cancer before the age of 21 between 1970 and 1986 and survived for at least 5 years after diagnosis were examined for predictors of ever siring a pregnancy [14]. This investigation discovered a relationship between the dose of alkylating agents, the dose of radiation to the hypothalamus and pituitary, the dose of radiation to the testicles, the type of cancer, and the kind of chemotherapy [14]. Subjects who were not exposed to hypothalamic/pituitary/testes radiation or alkylating chemicals had a similar chance of siring a pregnancy to that of their control siblings. While a substantial difference in effect was seen based on the type of chemotherapy agent, increasing doses of each of these exposures were significantly associated with a declining risk of siring a pregnancy. In contrast to those identified between the ages of 15 and 20, those diagnosed between the ages of 0 and 4 had an HR of siring of 1.80 (95% CI: 1.31-2.47), suggesting that earlier diagnosis may increase fertility [14].

Chemotherapy and radiotherapy in non-sterile cancer survivors who do not have cryopreserved sperm or embryos raise the possibility of treatment-related germline alterations having an adverse effect on progeny's health. Theoretically, these germline mutations could cause the child to have genetic abnormalities and a higher chance of developing cancer. This can be a typical worry for cancer survivors and a possible obstacle to wanting children [15]. Evidence demonstrating that cancer survivors are actually susceptible to treatment-induced somatic mutations that raise the chance of developing later malignancies may underline this issue [16].

However, research to date suggests that, if cases of hereditary cancer syndromes are taken into account, there is no increased risk of cancer in offspring of cancer survivors. After excluding people with hereditary cancer syndromes, a population-based study of cancer patients in Finland who were diagnosed before the age of 35 discovered that children born more than nine months after their parents' diagnosis did not exhibit an elevated risk of developing the disease in comparison to children of the cancer survivors' siblings [17]. Furthermore, stratifying by the child's cancer site did not reveal any appreciable increased risks. The risk of cancer increased, as anticipated, if hereditary cancer cases were not eliminated. Similar results were obtained from a population-based study conducted in the Nordic countries between 1943 and 1994, which excluded likely cases of hereditary cancers and found a nonsignificant risk of all cancer sites among children of cancer survivors [18]. When stratified by age at diagnosis and gender, the same result was obtained. Nearly every participant in this study had children, and follow-up on the children continued until they were 43 years old. The children were all born at least 8 years following their mothers' cancer diagnoses. The results of earlier research have also demonstrated that any increased risk of cancer in offspring results from familial aggregation rather than mutagenic effects [19]. However, the size of these investigations was constrained by the small case numbers and short follow-up periods.

Other signs of transgenerational genetic impacts, such as single-gene abnormalities (Mendelian disorders) and genomic instability, do not seem to be more prevalent in the offspring of cancer survivors [20]. Finally, according to the majority of research [21], there are no appreciable differences between male and female cancer survivors in terms of gender. Despite the fact that one major investigation did find a significantly altered ratio [22], the authors hypothesized that this difference was not brought on by a rise in deadly X chromosomal mutations but rather by the decreased testosterone levels. According to studies done on mice, chemotherapeutic drugs like cyclophosphamide may cause aneuploidy in oocytes, early

embryonic death, and fetal malformation. However, it was hypothesized that these risks are most likely to occur in oocytes that are maturing at the time of exposure and that they are diminished by allowing enough time to pass between exposure and pregnancy [23]. Although aneuploidy in human spermatozoa has also been linked to chemotherapy, this connection has only been proven to be temporary, lasting less than 100 days [24].

It doesn't seem that the general health of children born to cancer survivors differs from what is expected. Children of cancer survivors did not exhibit an elevated risk of hospitalization compared to the control group after a median follow-up time to age 9.6, according to a population-based analysis of kids born in Denmark between 1977 and 2003 [25]. This remained true for all diagnoses associated with discharges, including those connected to injuries, infections, issues with any organ or metabolic system, and issues with the mind or behavior. Malignant and benign neoplasms were more likely to develop, although these risks were explained by inherited malignancies and greater surveillance, respectively.

Ethical discussions in approaching fertility preservation

Using previously frozen gametes or gonadal tissue, cancer survivors who have lost their reproductive ability could still want to have children. Due to the large spectrum of medico-social conditions that fertility preservation treats, some of which are highly unusual, patient care necessitates a personalized and multidisciplinary approach. Particularly, fertility experts who provide fertility preservation choices to cancer patients should be sufficiently educated and experienced in order to address the patient's treatment plan, prognosis, as well as unusual health risks for future offspring and the potential negative effects of pregnancy. Since these treatments are provided with the intention of protecting future fertility, there shouldn't generally be any ethical issues with offering them. In actuality, there are drawbacks: many options are still in the experimental stage; posthumous use of stored tissue or gametes has some legal repercussions; worries about the welfare of offspring due to an anticipated shorter life span of the parent; worries about the welfare of children born using gametes frozen after chemotherapy already started; and the possibility of cancer reseeding after transplanting cryopreserved tissue [26].

The five principle-based ethics serve as the basis for the majority of ethical norms employed in ethical analyses. These values include justice, beneficence, no malfeasance, autonomy, and authenticity.

Respect for humans, also known as autonomy, recognizes a person's right to have opinions, make decisions, and behave in accordance with their own personal values and beliefs. Informed consent and respect for privacy are based on this idea. This concept forms the basis for both reproductive rights and choices: if a woman's outlook for long-term survival is questionable, should fertility preservation be offered to her? Should a husband be allowed to use frozen embryos stored while his wife was still living and to use a member of her family to carry the embryos to term? In order to create an informed agreement, it is crucial to consider these possibilities and request disposal instructions for cryopreserved reproductive tissue, gametes, or embryos. Both beneficence and nonmaleficence may overlap, as in the case of a patient who wants to delay the start of chemotherapy treatments yet insists on undergoing fertility preservation against the advice of the oncologist. Justice is concerned with fairness and equality, i.e., the requirement to be fair in the burden-sharing and resource-distribution to all community members. The idea of fair treatment is frequently used, in particular, in circumstances when a choice must be made about the fair distribution of resources. However, the existing method of IVF, and specifically fertility preservation, is unfair. Insurance companies do not fund these procedures because many methods of fertility preservation are still considered experimental. The majority of patients are unable to obtain these treatments since they are only provided on an institutional grant basis or on a philanthropic basis, especially for low-income individuals [26].

Although there are numerous methods for preserving fertility, only embryo and sperm freezing have been shown effective; all other methods, such as oocyte and ovarian tissue freezing, *in vitro* oocyte maturation, and *in vitro* folliculogenesis, are still considered experimental. The collection and separation of spermatogonial cells from testicular biopsies, the freezing of testicular tissue for later transplantation or even xenografting, are being tested but remain extremely experimental for men when the option of semen cryopreservation is not accessible as for prepubertal boys. The right of both men and women to be informed about all alternatives for fertility preservation, their ramifications, including risks and costs, is important when utilizing experimental treatments. Additionally, as experimental techniques fall under the category of research protocols, institutional review boards should also review and approve them.

Restoring personal autonomy to persons who may eventually lose the ability to conceive is the main ethical justification for fertility preservation [27]. The possibility of both the parent and their progeny being affected makes it difficult to communicate danger information. Do no harm is a cornerstone of medical ethics. A team of medical oncologists, andrologist, reproductive endocrinologists, pathologists, and psychologists should ideally decide who is a candidate for fertility preservation, guided by documented protocols that may be communicated with patients [28]. False hopes shouldn't be given to patients. Alternative strategies, such as abstaining from intervention with the possibility of adoption or childlessness, should also be discussed.

Even for children, exposure to cancer treatments may lead to impaired future fertility. Children may be unable to comprehend these risks, but when they grow up, they

could experience trauma from them. Since children's sexual immaturity restricts the options open to them for retaining their fertility, all of them are regarded as experimental. Testicular stem cell collection and cryopreservation with the intention of future autologous transplantation or *in vitro* maturation represent prospective techniques of fertility preservation for prepubertal boys who are unable to produce mature sperm. Someone might presume that fertility preservation for children is morally acceptable because it protects their reproductive autonomy and reduces morbidity (both reproductive and psychosocial) [29]. The primary ethical issue therefore relates to the procedures and methods required to safeguard fertility. The unique scenario of using children as both research subjects and patients leaves the provider vulnerable to possible technology abuse in the pursuit of a breakthrough [28]. It is advisable to involve several caregivers in the consent procedure to reduce this risk. In terms of medical research, children are a special and sensitive group. They lack the ability to give consent for research investigations, have reduced autonomy, and have diminished capacity to appreciate the risks and advantages of the research objectives. They need specific protection against possible rights violations that could happen during research investigations as a result [27].

How does chemotherapy treatment damage the prepubertal testis?

Today, chemotherapy and radiotherapy are both used as anticancer treatments with increasing success, and over the past 30 years, the survival rate has increased from less than 20% to around 80%. However, 10–100% of cancer survivors will have diminished semen parameters, and 15–30% will ultimately stay sterile over the long run, depending on the doses used and the length of the treatment. Any prediction of an individual's fertility is practically impossible because there is interindividual variability in the spermatogenetic recovery following any gonadotoxic treatment. Additionally, even while the initial course of treatment is established when beginning cancer therapy, the treatment plan may alter over time, making it much more challenging to determine the risk for sterility. Therefore, sperm cryopreservation should be made available on a regular basis to all male patients receiving gonadotoxic therapies. Since there are numerous techniques for obtaining sperm from patients who are post pubertal, age should not be a decisive factor. After a patient has been treated, assisted reproduction techniques, such as intracytoplasmic sperm injection, can be used to give the patient the best chance to father their genetically matched children. Testicular stem cell banking may be an option for boys in the prepubescent stage.

At all stages of life, radiation and chemotherapy have a high potential for damaging the testis. It is one of the most radiosensitive tissues, and radiation damage can result from either direct exposure to radiation or radiation that is diffused to other tissues [30]. Testicular damage following chemotherapy depends on the medication and dose [31, 32]. It's equally vital to consider what age a patient receives chemotherapy and radiation treatment. Prepubertal testis germinal epithelium could be less vulnerable to injury than adult testis, according to certain research [33]. However, if chemotherapy doses are calculated per square meter and radiation doses to the gonad given during childhood and adolescence are measured, some chemotherapy agents and radiotherapy doses that cause nonreversible azoospermia in those patients appear to be the same as those for adults [34]. In the testis, there are two significant endocrinologically active cells called Sertoli cells (SCs) and Leydig cells (LCs).

It is crucial to comprehend the precise processes by which various chemotherapy drug classes directly target and harm the prepubertal testis in order to aid in the development of preventative measures. Chemotherapy-related damage might significantly affect a patient's ability to conceive later in life, with possible implications for fertility as well as delayed sexual maturation [35]. The long-term viability of male germ cells, specifically SSCs, and of functional supporting somatic cells, is necessary for fertility [36]. Testis tissue biopsy is not typically done prior to or following chemotherapy treatment, hence research on direct injury to the testis is sparse in a clinical context. Studies employing this tissue should become more prevalent in the future because there has been a recent focus on cryopreserving prepubertal testis samples before the start of cytotoxic therapy for potential fertility preservation in the future. In fact, a recent study histologically investigated testis biopsies from prepubescent patients who were chosen for tissue cryopreservation due to the cytotoxicity of their cancer treatment regimens [37]. Though few have been conducted to date, animal studies have the potential to shed light on the gonadal toxicity of various medications and their mechanisms of action, as well as the effects of therapeutically relevant combination therapies. The research, both human and animal, concentrates on chemotherapy administered during the prepubertal stage, when the effects of the treatment can be observed afterward or deduced from examination of the adult testis later on.

Larger studies have confirmed earlier histological findings seen in early case reports, showing a link between testicular tissue damage and the use of alkylating drugs in treatment plans [38]. Particularly, testicular injury has been connected to the use of the cancer therapy medication cyclophosphamide in prepubertal animals. The studies included under "immediate evaluation" differed in the length of their analyses, looking at testicular injury both during and up to a year after the end of therapy, as well as soon before cessation or at the end of the treatment period. These studies have shown a dose- and time-dependent relationship between cyclophosphamide treatment and testicular injury. Where there is a reduction in the number of germ cells, resulting in Sertoli cell-only tubules, interstitial fibrosis, and basement membrane, treatment can shrink the testis overall [39]. Since comparison between the limited studies that are now available is limited due to

the constraints previously mentioned as well as the variety of treatment regimens, it is difficult to determine a cut-off dose at which such harm is obvious. The duration of the treatment regimens may also affect how severe the impairment is, with shorter treatment times and higher cumulative doses lowering chemotherapy-induced damage [40].

The somatic and germ cells that make up the testis may react differently to chemotherapeutic medicines than one another. Chemotherapy-induced somatic cell damage may have a negative impact on germ cells and vice versa [41]. As evidenced by alterations in the gene expression of particular spermatogonial markers (MAGE A4 and CD9), it has been observed that cyclophosphamide targets both SSCs and more differentiated spermatogonia in the prepubertal testes [40]. With one study describing the occurrence of immature Leydig and Sertoli cells after cyclophosphamide treatment, this being reliable with the majority of papers that reported effects on germ cells [37].

Assessing pubertal/adult patients who received chemotherapy as children can reveal whether or not the prepubertal testes were injured as a result of the treatment. It can also reveal whether the testes have a chance of recovering and undergoing active spermatogenesis in the future. Sertoli cell only tubules were still present nine years following therapy in patients receiving relatively high doses of cyclophosphamide, resulting in serious testicular injury [42]. The disruption to the prepubertal testes may also depend on the length of the treatment regimen [43]. However, these variations may ultimately be caused by larger cumulative dosages or the age of the patient at the time of treatment, with younger patients possibly being more susceptible to a decreased tubular fertility index and suboptimal Sertoli and Leydig cell development [44, 45]. A case study of a 31-year-old man who received a cyclophosphamide-containing chemotherapy treatment as a child described somatic cell damage in the testis as a result of the chemotherapy, along with the presence of immature Sertoli cells; however, correlation cannot be concluded from a case report [46, 47].

Fertility-preservation methods

Depending on whether pediatric oncological therapy begins before or after puberty, different fertility preservation techniques are available [48, 49]. In addition to well-established metrics, experimental ones are also available.

The preventive treatment option for male adolescents and adults who have a reproductive issue or who are at risk of infertility is cryopreservation of semen. Recent studies have shown that only 39% of affected oncological patients are informed about the possibility of cryopreservation prior to a treatment that could be gonadotoxic [50, 51]. However, non-oncological conditions might also be connected to a surgical procedure that could be gonadotoxic or reduce the number of germ cells, which is a reason to talk about fertility preservation strategies like sperm cryopreservation.

The World Health Organization (WHO) also suggests that men who are interested in having an elective vasectomy be informed about preoperative sperm cryopreservation [52, 53]. It is possible to retrieve and cryopreserve sperm from the testicular tissue in males who have azoospermia or are unable to ejaculate by performing surgical scrotal exploration and testicular sperm extraction, ideally microsurgically [49, 54, 55]. Retrograde ejaculation (post-traumatic, post-operative, or post-radiogenic) permits the cryopreservation of sperm from urine or following rectal stimulation in extremely uncommon circumstances [56, 57].

The only experimental alternative currently accessible for prepubertal boys or early teenage boys whose spermatogenesis is not yet complete is the excision of testicular tissue from the immature tissue in which the spermatogonial stem cells rest and can be cryopreserved.

All systemic treatments that may have gonadotoxic effects as well as all local treatments that may have an impact on gonadal function directly or via their regulatory mechanisms are indications for cryopreservation of sperm and testicular tissue. Additionally, while undergoing surgery that affects sperm deposition negatively over the long term (ejaculation and/or erection), it is medically necessary to preserve fertility. Cryopreservation is also advised for males who are engaged in a risky activity, such as military service, in nations where the use of cryopreserved semen samples is also permitted posthumously [49]. The creation of a reproductive reserve (also known as "social freezing") is theoretically attainable for every man [58].

Sperm Cryopreservation

Prior to any potentially fertility-damaging operation or exposure, an adult male or teenage male should collect and retain his ejaculate for fertility preservation. From the age of 13, Tanner 3, and a testicular volume of less than 10 mL, sperm can be cryopreserved using ejaculation, electrostimulation, and testicular biopsy or testicular sperm extraction (TESE) as a fertility reserve for subsequent assisted reproductive techniques.

The sample is taken while being masturbated. Rectal electrostimulation is an unusual approach for obtaining a semen sample, but it can be discussed, particularly in early to late adolescence. Testicular sperm cell extraction under anesthesia should be preferred in these situations because anesthesia is necessary in these circumstances and the ability to ejaculate is also a sign of maturity in adolescents during puberty development. This is because cryopreservation of stem cells is also an option when the germinal epithelium has not yet fully developed [56, 57].

The WHO advises that in order to increase the likelihood of conception, enough normal semen samples should be cryopreserved to last for at least 10 or more inseminations [52, 53]. The pooling of several samples has not proven to be helpful in the case of the extremely frequent limitations in ejaculate quality, both in oncological patients for fertility preservation and in infertile patients. With conventional sets for ejaculate cryopreservation, which contain 36 straws with 300 L of volume apiece, this is generally ensured. The possibility of creating a second depot should be discussed

with the patient and made possible if the quality of the semen is noticeably lowered (either very few sperm or extremely few motile or vital sperm).

Cryopreservation of Immature Testicular Tissue

Under local or general anesthesia, and following the proper preoperative conversation with the patient, testicular tissue removal with the goal of testicular sperm extraction (TESE) is carried out after opening the scrotal skin and exposing the testicles on both sides. It is ideal to extract the testicle using microsurgical or microscopically assisted techniques (micro-TESE), but it is also possible to do so from different testicular locations (standard-TESE). In either case, the testicular blood flow must be preserved, and bleeding must be carefully controlled throughout the procedure. Multilocular tissue sample is sufficient in patients whose azoospermia is brought on by an obstruction.

Microsurgical epididymal sperm aspiration (MESA) may also be employed in specific circumstances (for uncorrectable obstruction). Regarding sperm production and postoperative scarring, fine needle aspiration is inferior to open testicular tissue removal and is not advised [55].

There is only the experimental option of eliminating spermatogonial stem cells (SSCs) using testicular biopsy in prepubertal boys because spermatogenesis has not yet begun [56, 57]. When taking testicular tissue for the cryopreservation of spermatogonial stem cells from prepubertal boys or early adolescents, the open biopsy is preferably performed only on one testicle. It is still experimental to cryopreserve surgically excised immature testicular tissue before puberty. It is currently not feasible for humans to undergo the further sperm maturation required from the testicular stem cells. There is also a chance of retransplanting cancerous cells, depending on the malignancy.

Conclusions

Although sperm cryopreservation from the ejaculate is a successful treatment, there is a 50% loss of critical cells. A testicular tumor affects 40% of patients who come in for sperm cryopreservation, followed by people with leukemia, lymphoma, or sarcoma [49]. 20% of all tumor patients are azoospermic at the time of the illness, or unable to ejaculate. The only preventative therapy option for these patients is surgical sperm extraction using testicular sperm extraction, ideally employing microsurgical methods. 60-70% of these individuals will have the opportunity to freeze fertile sperm thanks to this treatment [49].

Because patients with oncological diseases are frequently young when a partnership does not yet exist and frequently only reach the "cured" stage years after the end of therapy, the use of cryopreserved sperm samples is particularly beneficial for these individuals. Cryopreserved sperm is used in roughly 8–11% of patients, according to both recent and older studies [48, 59, 60]. Unfortunately, the severity of the sickness causes about 12% of patients to pass away [59]. A meta-analysis found that 16% of cryodepots were damaged by the dissolution of the cryodepots due to a temporal recovery of spermatogenesis, which can be delayed for years at a time [60]. Nearly half of the men who used their cryodepots gave birth to at least one child, with intracytoplasmic sperm injection (ICSI) therapy having the best success rates [59, 60].

Applying the information, the risk of gonadal injury should first be assessed. Prior to beginning gonadotoxic therapy, fertility-preservation procedures are strongly advised if there is a high risk of gonadal toxicity. If there is a medium risk, fertility preservation should be explored. If there is a low risk, fertility preservation can also be discussed. The decision-making process should actively involve young patients.

It is important to thoroughly communicate the risk of a reproductive disease to those who are affected and their family members. Additionally, the dangers of fertility preservation techniques must be described, and future options like sperm donation (if legal in the relevant country) must be taken into account. It's crucial to remember that gonadotoxic therapies do not enhance the incidence of congenital defects or non-hereditary cancer in the progeny. After the oncological therapy is finished, precautions must be taken to guarantee appropriate pubertal growth. A fertility assessment should be performed after puberty or at the latest in young adulthood.

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IA collected the data, wrote the first version of the manuscript; MM, IE, DM conceptualized the idea, completed the final text; ID revised critically the manuscript. All the authors approved the final version of the manuscript.

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Ethics approval and consent to participate
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Conflict of interests
The authors have no conflict of interests to declare.