Fertility Risk Assessment and Preservation in Male and Female Prepubertal and Adolescent Cancer Patients

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ABSTRACT: Cancer represents the second cause of death in prepubertal children and adolescents, although it is currently associated with an overall survival rate of 80%-85%. The annual incidence rate is 186.6 per 1 million children and adolescents aged up to 19 years. Both disease and treatment options are associated with life-altering, long-term effects that require monitoring. Infertility is a common issue, and as such, fertility preservation represents an essential part in the management of young patients with cancer who are at risk of premature gonadal failure. This review deals with the up-to-date available data on fertility risk assessment and preservation strategies that should be addressed prior to antineoplastic therapy in this vulnerable subgroup of cancer patients.

KEYWORDS: fertility, risk assessment, preservation, adolescents, cancer, radiotherapy, chemotherapy, surgery

Introduction

As a result of advances in cancer treatment, the five-year overall survival rate of adolescents and young adults currently stands at 80%-87% for both Europe1 and the United States of America.2 The American Cancer Society estimated that 10,380 new cases of cancer and 1,250 deaths from cancer would occur in 2016 among males and females aged 0–14 years.2 The most common cancers that occur in this age group include leukemias and lymphomas, brain and central nervous system tumors, embryonal tumors, sarcomas of bone and soft tissue, and gonadal germ cell tumors.2 Despite recent advances in the treatments of malignancies that may cure these young cancer patients,3–5 infertility is an important long-term toxicity in both females6 and males.7,8 Infertility is associated with significant psychological distress, with levels of depression twice that of the normal population in both young female9 and male cancer survivors.10 Even for patients who may have not planned to have children, most commonly due to their very young age, the threat of infertility can result in a deep sense of loss and anger.11

Since post-therapy recovery of gonadal function remains unpredictable, it is important to inform patients facing infertility of this possible side effect of their treatment and all the options available to prevent it.12 As survival worries may deviate from important life dreams, it is advisable to anticipate and facilitate the long-term perspectives that may not be readily apparent to young patients in this sensitive situation.13 Not surprisingly, fertility preservation concerns in many instances may influence patients’ treatment decisions, as for example in cases of breast cancer,14,15 although the general tendency of both patients and their parents is opposite.16,17

Herein, we present a comprehensive review of fertility risk assessment strategies including medical and surgical strategies that can preserve fertility in prepubertal and pubertal cancer patients.

Fertility Risk Assessment and Strategic Planning

Recent advances in cancer therapies have led to increased cure rates of male and female prepubertal and adolescent patients with malignant disease. As the likelihood of being long-term survivors is very high, it has become of utmost importance to assess the risk of infertility caused by treatment and to communicate this with the young patients and their parents, right at the beginning of their cancer journey (Fig. 1). Risk assessment for fertility preservation of a young patient includes the evaluation of both extrinsic and intrinsic factors that when combined assign patients into a group category of high, medium, and low risk (Table 1). Nevertheless, the exact assessment of

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individual factors is confounded by the constantly evolving treatment schedules and the difficulty to assess the gonadal reserve of each patient. The effect of chemotherapy on male and female gonads varies significantly among different drug combinations (Tables 2 and 3).

A special consideration includes the role of anti-Mullerian hormone (AMH) in predicting poor outcome in assisted reproduction, as shown by data from studies conducted more than 10 years ago. Of note, AMH values physiologically peak around the age of 26 years, so that its use is limited in females ≤25 years of age. Although there are limited data to reach robust conclusions on the relationship between AMH and the ovarian reserve in children and adolescents, there is growing evidence of its value as a potential marker of chemotherapy-induced ovarian follicular depletion. Recent studies indicate that AMH serves as an early plasma marker of chemotherapy-induced gonadal damage and is closely related to the ovarian reserve of patients before and after cancer treatment. In a prospective study including 22 females (17 prepubertal) of median age 4.4 years (range 0.3–15 years), it was shown that AMH was detectable prior to treatment in girls of all ages but fell rapidly during cancer treatment in both prepubertal and pubertal girls. Both the fall during treatment and recovery thereafter were linked with the risk of gonadotoxicity qualifying AMH as a clinically useful marker of damage to the ovarian reserve.

For prepubertal patients, the American Society Clinical Oncology guidelines on fertility preservation recommend to use established methods of fertility preservation (gonadal tissue cryopreservation, radiation shielding, or ovarian transposition), with patient assent, if appropriate, and parent or guardian consent. Additionally, for adolescent patients, the American Society Clinical Oncology recommends to present information on additional methods that are investigational and refer for experimental protocols when available. The National Comprehensive Cancer Network (NCCN) guidelines also suggest the referral of all patients who choose it to fertility preservation clinics within 24 hours and to a mental health professional to assist with complex decision-making, if needed (NCCN guidelines version 1.2016; Adolescent and young adult

### Table 1. Extrinsic and intrinsic risk factors associated with infertility in adolescent cancer patients. Reprinted with permission, from: Wallace WH et al. J Clin Oncol. 30(1);2012:3–5. © 2012 American Society of Clinical Oncology. All rights reserved.

| INTRINSIC FACTORS | EXTRINSIC FACTORS |
|--------------------|-------------------|
| **Health status of patient** | • Treatment options |
| • Consent (patient/parent) | • Radiotherapy |
| • Assessment of pubertal stage in young males (including testicular volume) | • Surgery |
| • Assessment of ovarian reserve in young females | • Chemotherapy (high/medium/low/uncertain risk for game) |
| • Tumor type, stage and location | • Dose and topology |
| • Performance status | • Time available for the procedure |
| • Ability to undergo fertility-sparing procedures | • Access to Fertility Centers with specific expertise |

### Table 2. Classification of infertility risk induced by chemotherapy in females.

| CHEMOTHERAPY TREATMENT | DEGREE OF RISK |
|-------------------------|----------------|
| Hematopoietic stem cell transplantation and total body irradiation Radiotherapy to a field including the ovaries | High risk >80% |
| CAF, CMF, CEF x6 30–39 years of age Ax4 >40 years of age | Intermediate risk |
| ABVD,CHOP,CVP,AML, ALL CAF, CMF, CEF x6 <30 years of age Ax4 <40 years of age | Lower Risk (<20%) |
| Vincristine Methotrexate Fluourouracil | Very Low or No Risk |
| Taxanes Irinotecan Oxaliplatin Monoclonal antibodies Tyrosine kinase inhibitors | Unknown Risk |

**Abbreviations:** C, cyclophosphamide 600–1200 mg/m²; A, Adriamycin 25–60 mg/m²; F, fluorouracil 600 mg/m²; E, epirubicin 60 mg/m²; M, methotrexate 40 mg/m²; B, bleomycin 10 U/m²; V, vinblastine 6 mg/m²; D, dacarbazine 375 mg/m²; V (Q), vincristine 1.2 mg/m²–2 mg; P, prednisolone 40 mg/m²; H, hydroxydaunorubicin 50 mg/m².
Effect of anticancer therapy in prepubertal and pubertal testicular function. The testicular effects of cancer therapy in prepubertal boys are heterogeneous due to the various cancer diseases and therapeutic strategies, including surgery, chemotherapy, or radiotherapy. A recent systematic review indicated that testicular germ cell tumors are associated with semen abnormalities before orchietomy and outside the treatment effects of orchietomy, radiation, or chemotherapy.

Prepubertal, adolescent, and adult male gonads exhibit similar sensitivity to chemotherapeutic agents (Table 3). Differentiating spermatogonia proliferate rapidly and are thus extremely vulnerable to cytotoxic agents, although the less active stem cell pool may also be depleted (Fig. 2). Modern adjuvant treatments for testicular germ cell tumor have drastic effects on spermatogenesis and sperm chromatin quality that decrease at 3–6 months and recover at 12 months following treatment with less than two cycles of bleomycin, etoposide, and cisplatin. However, the recovery period may become longer depending on treatment modalities, such as radiotherapy and more than two cycles of bleomycin, etoposide, and cisplatin, and patient’s characteristics such as pretreatment sperm production. Furthermore, despite lack of spermatogenesis completion in the prepubertal testis, cytotoxic treatment affects fertility by direct effect on early germ cells that undergo spontaneous degeneration before the haploid stage is reached.

Recovery of sperm production after a cytotoxic therapy depends on the survival and ability of mitotically quiescent stem spermatogonia (type A dark) to transform into actively

**Table 3. Classification of infertility risk induced by chemotherapy in males.**

| CHEMOTHERAPY TREATMENT | EFFECT ON SPERM COUNT |
|------------------------|-----------------------|
| Chlorambucil (1.4 g/m²) | Prolonged or permanent azoospermia |
| Cyclophosphamide (19 g/m²) | |
| Procarbazine (4 g/m²) | |
| Melphalan (140 mg/m²) | |
| Cisplatin (500 mg/m²) | |
| BCNU (1 g/m²) | Azoospermia in adulthood if treated before puberty |
| CCNU (500 mg/m²) | Azoospermia likely, and are often given with other highly sterilizing agents, adding to the effect |
| Busulfan (600 mg/m²) | When used alone, cause only temporary reductions in sperm count. In conjunction with above agents, may be additive in causing azoospermia |
| Ifosfamide (42 g/m²) | |
| BCNU (300 mg/m²) | |
| Nitrogen mustard | |
| Doxorubicin (770 mg/m²) | |
| Thiotepa (400 mg/m²) | |
| Cytarabine (1 g/m²) | |
| Vinblastine (50 g/m²) | |
| Vincristine (8 g/m³) | |
| Amsacrine | When used in conventional regimens, cause only temporary reductions in sperm count. In conjunction with above agents, may be additive in causing azoospermia |
| Bleomycin | |
| DaCarbazine | |
| Daunorubicin | |
| Epirubicin | |
| Etoposide | |
| Fludarabine | |
| Fluorouracil | |
| 6-mercaptopurine | |
| Methotrexate | |
| Mitoxantrone | |
| Thioguanine | |

oncology; Fertility and endocrine considerations; http://www.nccn.org).
administration with chemotherapy was associated with less prospective phase III randomized study concluded that GnRHa induced ovarian failure in young cancer patients. Similarly, a 2014 meta-analysis of randomized trials showed associated with significant differences in pregnancy rates. The use of GnRHa should be considered in women of reproductive age receiving chemotherapy, as it seems to be effective in protecting ovaries during chemotherapy and should be given before or during treatment, although it was not associated with significant differences in pregnancy rates. Although two recently published randomized phase III studies indicated that the administration of GnRHa with chemotherapy may protect against ovarian failure, the trials did not include females under 18 years of age. Until today, there is no evidence supporting the role of GnRHa in prepubertal or pubertal male or female patients, and its use remains controversial.

**Fertility-sparing surgery.** Surgical techniques for preserving fertility in adolescents and young women include fertility-sparing surgery (FSS), ovarian transposition, modalities of ovarian transplantation, and ovarian tissue harvesting for cryopreservation.

**Conservative unilateral salpingo-oophorectomy.** Up to date, the exact data from worldwide FSS modalities in adolescent cancer patients have not been reported, but an ongoing interest has been emerged, particularly for young patients with borderline ovarian tumors. One-half to two-thirds of ovarian malignancies in females up to 18 years derive from germ cells, most commonly dysgerminomas. Fertility-preserving surgery followed by chemotherapy, even in advanced-stage malignant germ cell tumors of the ovary, is effective in conserving the reproductive function of these women. It consists of a conservative unilateral salpingo-oophorectomy with preservation of the contralateral ovary and uterus. Removal of the ipsilateral fallopian tube is indicated because of the presence of lymphovascular connections between the tube and the ovary. Although the possibility of occult contralateral ovarian involvement is about 5%–10%, a wedge biopsy of a normal-appearing contralateral ovary is not indicated, as these tumors are sensitive to chemotherapy, and salvage rates are up to 94% even in the presence of advanced disease. In addition, a surgical intervention on a normal ovary, even with a biopsy, may lead to postoperative adhesions, and further fertility impairment. A retrospective study reported on 169 women (age range: 8–41 years) with various histological subtypes of malignant germ cell ovarian tumors (70 dysgerminomas, 28 endodermal sinus tumors, 24 mixed tumors, and 47 immature teratomas) and stages of the disease. In 138 patients (81.6%), a FSS was performed, and 81% of them received chemotherapy postoperatively. The survival rate was

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**Figure 2.** The pathway of spermatogenesis. From Heller CG, Clermont Y. Spermatogenesis in man: an estimate of its duration. Science. 1963;140(3563):184–6. Reprinted with permission from AAAS.

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Female Fertility Preservation Approaches

**Ovarian protection by GnRH analogs.** One method of pharmacologic gonadal function preservation is based on the theory that germ cells are damaged by chemotherapy because they are rapidly dividing and reproducing; by administering a medical agent to stop the reproduction of these cells, the damage could be alleviated or even prevented. The temporary ovarian suppression with gonadotropin-releasing hormone analogs (GnRHa) targets for the prevention of chemotherapy-induced premature ovarian failure and for fertility preservation. A recent Cochrane systematic review concluded that the use of GnRHa should be considered in women of reproductive age receiving chemotherapy, as it seems to be effective in protecting ovaries during chemotherapy and should be given before or during treatment, although it was not associated with significant differences in pregnancy rates. Similarly, a 2014 meta-analysis of randomized trials showed that GnRHa significantly reduces the risk of chemotherapy-induced ovarian failure in young cancer patients. A new prospective phase III randomized study concluded that GnRHa administration with chemotherapy was associated with less premature ovarian failure and more pregnancies. Although ovarian transplantation, and ovarian tissue harvesting for cryopreservation.

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94% for dysgerminoma, 89% for endodermal sinus tumors, 100% for mixed tumors, and 98% for immature teratomas. With regard to fertility, the authors reported 14 conceptions in 12 patients who did not receive chemotherapy postoperatively and 41 conceptions in 16 patients who received.

Another common subtype of ovarian tumors in adolescents is borderline ovarian tumors that have low-malignant potential and account for 30% of all ovarian tumors. A substantial number of these tumors are presented as stage I disease with a five-year survival rate of 95%–97%. In the past, hysterectomy with bilateral salpingo-oophorectomy, peritoneal washing, omentectomy, and peritoneal biopsies was the treatment of choice. However, many reports have demonstrated that conservative surgery, through either unilateral cystectomy or a unilateral oophorectomy, exerts no effect on the overall survival rate. A retrospective study indicated that women with borderline ovarian tumors undergoing minimal surgery with ovarian cyst excision had almost comparable recurrence rates to those treated with unilateral salpingo-oophorectomy. Concerning fertility, 25 (40.3%) of 62 patients attained 38 pregnancies, resulting in 35 deliveries. Another retrospective study indicated high disease relapse rates, but no difference in the mortality and an overall 63.6% pregnancy rate, in women undergoing FSS. A prospective randomized trial in patients with bilateral borderline ovarian tumors indicated that the ultraconservative fertility-sparing approach is more effective than the standard approach in terms of reproductive outcomes, but presents a higher oncological risk. In the case of borderline tumors, careful assessment of the ovaries and close follow-up are mandatory when conservative treatment is employed.

**Ovarian transposition.** Radiation therapy is a commonly applied treatment to adolescents with various tumors, such as sarcomas, medulloblastomas, and Hodgkin’s lymphomas, involving the genitourinary tract and the pelvis. However, there is a risk of ovarian damage after exposure of the gonadal tissue to radiation, especially when combined with alkylating chemotherapy drugs such as cyclophosphamide. The failure of the ovarian function has been related to the radiation dose, the age of the patient, the type of the chemotherapeutic drugs used, and the type of radiation. Wallace et al showed that a single dose of radiation of <4 Gy is able to destroy 50% of primordial follicles, while a single dose of 10 Gy for a total body irradiation may cause complete cessation of ovarian function in 55%–80% of patients before entering puberty.

Ovarian transposition was first described in 1958 as a method of preserving ovarian function. In this context, the ovaries are transferred outside the field of radiation, through laparotomy, laparoscopy, or robotic surgery and are fixed in the paracolic gutters above the pelvic brim and the psoas muscle when central radiation is indicated, or medially behind the uterus, when lateral pelvic lymph node radiation is designed. Whatever is the reason of transposition, caution should be made in order to avoid any damage of the ovarian blood supply. After transposition, the ovarian vessels should be examined for the presence of any kinking, and hemoclips should be placed to secure their location during future abdominal X-rays. However, in 10%–14% of cases, the procedure can fail to protect the ovaries. Common complications of ovarian transposition include intestinal obstruction, dyspareunia, functional ovarian cysts, and tubal obstruction caused by adhesions. Spontaneous pregnancies are possible if tubal function is preserved as part of the oophoropexy; otherwise, in vitro fertilization is applied.

**Orthotopic transplantation of cryopreserved ovarian tissue.** Cryopreservation and orthotopic transplantation of ovarian tissue is a breakthrough option for fertility preservation in young female cancer patients facing sterilizing anti-neoplastic therapy. Based on small case series, there have been more than 30 pregnancies after ovarian tissue cryopreservation and transplantation. The success rate is unclear as the denominator that corresponds to the exact number of women who had frozen-thawed ovarian tissue reimplemented is unknown. With the given age-related decline from birth until menopause, in the number of non-growing follicles, and the difficulties associated with ovarian stimulation and oocyte collection, young adolescents facing gonadotoxic treatment are potentially ideal candidates for ovarian cortex harvesting before the initiation of therapy and reimplantation at a later time. The answer is probably hidden behind the medical axiom: “to do good or to do no harm”.

Reports on orthotopic reimplantation of cryopreserved ovarian tissue are encouraging, in terms of safety, feasibility, and efficacy, as it is performed through laparoscopy or laparotomy under general anesthesia and is the only method that may lead to spontaneous pregnancies. Consent for harvesting ovarian tissue is usually obtained from their parents, whereas informed consent for its reimplantation is obtained from the patients much later, when they are competent to assess the complex issues by themselves. Excision of the ovary is followed by freezing of the ovarian cortex with the prospect of reimplantation or in vitro maturation of oocytes at a later time. The frozen ovarian cortex reimplantation takes place either orthotopically (at the site of the remaining ovary) or heterotopically (in the subcutaneous tissue of the abdomen or forearm). In a series of 30 reimplanted, frozen, and thawed ovarian tissue specimens, the birth of six live newborns was reported. In another study of 45 young patients aged 4.4–17.8 years, in whom cryopreservation of the ovarian tissue was performed before chemotherapy, a high correlation between follicular density and age and a decrease in follicular quality after chemotherapy were reported. Authors suggested that ovarian tissue cryopreservation is the optimal method to preserve fertility in young patients with cancer, and the only option for prepubertal females. An important point of concern is the transplantation of cancer cells, requiring careful evaluation by preoperative imaging and histological/molecular investigation of fresh ovarian tissue for cancer cells. Another important question that has not been answered as
yet is whether ovarian cortical strips are sufficient enough as an entire ovary.\textsuperscript{74,76} Although ovarian tissue cryopreservation is not a widely available procedure, it should be considered for fertility preservation in prepubertal girls and young patients who must urgently undergo aggressive chemotherapy and/or radiotherapy.\textsuperscript{81}

**Ovarian implantation and uterine transplantation.** Given the largely avascular environment of ovarian follicles in the ovaries, the use of ovarian cortical grafts is associated with minimal oocyte loss from ischemia time; thus, there is no need for total ovarian removal.\textsuperscript{71} However, various malignant conditions in young adolescents such as sarcoma botryoides, cervical cancer, and adenocarcinoma of the vagina require more aggressive surgical approaches (total hysterectomy, subtotal hysterectomy with preservation of the ovaries, elective vaginal hysterectomy) and radiotherapy. Studies have proven that a whole ovary cryopreservation for future reimplantation is feasible and without signs of apoptosis or ultrastructural alterations in cells type.\textsuperscript{82–84} In cases where treatment modalities such as radiation may affect the capacity of the uterus to receive a fertilized egg, additional uterine transplantation could be the only possible option for this group of young women who wish to conceive.\textsuperscript{85} Although each year in the United States 5,000 hysterectomies are performed in women under the age of 24 years for various reasons, uterine transplantation remains under consideration for medical and ethical reasons and until now only one live birth has been reported.\textsuperscript{85,86}

**Male Fertility Preservation Approaches**

Surgical methods preserving male fertility have been adopted including testis-sparing surgery, testicle transposition, and operative sperm retrieval strategies (testicular stem cell transplantation). On the other hand, no effective gonadal function preserving drugs are so far available for use in male patients.\textsuperscript{87} A recent animal study reported the protective effect of humanin analog on germ cells during chemotherapy in male mice,\textsuperscript{88} but no clinical studies are underway.

**Testis-sparing surgery.** The most common type of cancer of the testis in young men is germ cell tumors.\textsuperscript{97} Synchronous and metachronous bilateral germ cell tumors occur in 2%–5% of patients and bilateral radical orchiectomy will lead not only to infertility but also to increased cumulative risk of metabolic syndrome and cardiovascular events,\textsuperscript{90} everlasting dependency on exogenous testosterone replacement, and severe psychological disorders due to bilateral castration at such a young age. Organ-sparing surgery with tumor enucleation has resulted in fertility preservation of 10 patients who achieved spontaneous pregnancies and 5 who used the *in vitro* fertilization technique.\textsuperscript{91} Two major conditions that allow for testis-sparing surgery are the small size (20 mm or less) of the tumor and its confinement to the testis.\textsuperscript{89} As adjacent foci of testicular intraepithelial neoplasia may occur in up to 85% of the entire population,\textsuperscript{92,93} and local recurrence of invasive malignancy in 5% of patients treated with enucleation, close monitoring during follow-up is required.\textsuperscript{94} According to the European Society of Medical Oncology guidelines for testicular intraepithelial neoplasia patients who are willing to father children, definitive treatment by radiotherapy could be deferred until resolution, although substituted by close surveillance.\textsuperscript{94,95} The same guidelines also emphasize the need of semen sample before surgery and that a postponement of radiotherapy should be discussed only with patients with confirmed normal semen. Alternative options of sperm donation or testicular sperm extraction should also be discussed at the same consultation. In the less frequent case of bilateral germ cell testicular cancer, fertility preservation strategies should be similar as the survival rate matches that of unilateral disease. Similar to germ cell tumors, Leydig cell tumors that account for 0.8%–3% of all testicular neoplasms are traditionally treated by radical orchietomy.\textsuperscript{96} However, in two studies including a total of 61 patients treated with testicular conservative surgery, no recurrence was noted.\textsuperscript{97,98} Authors’ criteria for a sparing surgery included no symptoms at presentation, laboratory data, the size of the tumor, and frozen-section analysis during surgery.\textsuperscript{97}

Of note, testicular or paratesticular neoplasms are rare in children and adolescent males,\textsuperscript{99} but if proven, careful surveillance is mandatory.\textsuperscript{100} In all cases, the written informed consent of the patient is of paramount significance, concerning the right treatment option, including orchietomy, and alternative strategies of organ preservation, including chemotherapy and radiotherapy.\textsuperscript{101}

**Testicular transposition.** Radiation may damage the testicular function in a dose-dependent mode; if the dose is between 20 and 200 cGy, the damage may be reversible, but total irreversible azoospermia will be developed at a dose over 400 cGy.\textsuperscript{102} Testicular transposition was first described in a young male with a paratesticular rhabdomyosarcoma of the left testis. After left orchietomy and radical retroperitoneal lymphadenectomy, a course of radiation was suggested. To avoid damage from radiation of the right normal testis, transposition of the testis to the right thigh was performed.\textsuperscript{103} Following radiotherapy completion, the testis was replaced in the scrotum. This approach could also enable fatherhood in young males with rhabdomyosarcoma of the bladder or prostate where radiotherapy is necessary.\textsuperscript{103} Furthermore, Acosta et al.\textsuperscript{104} modified the abovementioned technique by wrapping the testis in a Silastic\textregistered sheath to prevent adhesions between the spermatic structures/testis and the surrounding anatomical tissues. In addition, they proposed to relocate the testes in the upper medial thighs in the case of the whole abdominal region that needs to be exposed to irradiation.\textsuperscript{104} However, the clinical role of these methods warrants further investigation.\textsuperscript{105}

**Sperm extraction and banking.** Sperm banking from adolescents scheduled for cancer therapy may be produced by masturbation.\textsuperscript{106,107} In a study of 238 adolescents patients (aged 12–19 years) with various types of cancer (Hodgkin’s and non-Hodgkin’s lymphoma, osteosarcoma, Ewing’s sarcoma, acute
myeloid leukemia, acute lymphoblastic leukemia, testicular cancer, leukemia, and lymphoma), the majority of patients (86.1%) were able to offer adequate semen sample for future fertilization with modern assisted reproductive technologies. However, in the cases of failure to deliver a semen sample because of masturbation problems, other alternative methods such as vibrostimulation or electroejaculation could be performed under general anesthesia. Novel techniques for sperm extraction are currently available. These include: (a) removal of seminiferous tubules with their sperm included within them, after an incision in the scrotum and testis, testicular sperm aspiration by using a needle sized 16–22 G from seminiferous tubules, and (b) extraction of sperm from the epididymis, which represents the primary site of sperm maturation and motility gaining. Percutaneous epididymal sperm aspiration can be performed either by using a small-caliber needle (23–25 G) or with the use of an operating microscope.

All in all, prior to orchiectomy, in order to avoid fertility impairment, semen cryopreservation remains the appropriate option. A recent study from France indicated a large inter-center variation in practices involving young patients seeking to preserve their fertility before cancer therapy pointing an urgent need for decisive changes in public health policy to facilitate the access to reproductive health care for all young cancer patients.

Female and Male Fertility Preservation by in vitro Procedures

Gametes and embryo cryopreservation. Gametes and embryo cryopreservation are considered as standard practice in young individuals with cancer and are widely accessible. For young males, oocyte cryopreservation is a currently offered method, through either controlled ovarian stimulation or no stimulation at all, via in vitro maturation. This method is of particular importance for women who do not have a male partner or do not want to use donor sperm. Embryo cryopreservation is the most used method of fertility preservation, further enhancing its capabilities through the freezing method of vitrification. The latter is a standardized, simple, reproducible, and efficient option, easily applied in the storage of all the mentioned specimens. In addition, newer strategies in the form of mild stimulation regimens, such as letrozole, constitute an important advance in the field of reproductive endocrinology.

Notably, even though results from both the cryopreservation of ovarian cortical strips and in vitro maturation, mentioned above, are encouraging, both approaches are not routinely performed and thus cannot be considered as standard of care at the moment. Prepubertal boys cannot benefit from sperm banking; a potential alternative strategy for preserving their fertility involves storage of immature gametes and gonadal stem cells after testicular tissue sampling in the hope that future technologies will allow its safe utilization. A recent review indicates that the generation of male gametes from stem cells is a promising option for the future.

Conclusions

Based on recent improvements on the survival of adolescent patients with cancer and the progress of reproductive techniques, oncologists can assess the risk of infertility and discuss the options of fertility preservation with both young patients and their parents. Patients should have active counseling about fertility preservation strategies, their risks, and success rates before the initiation of antineoplastic treatment, so that fertility preservation can be incorporated into their designated treatment plan. It is therefore of utmost importance that an effective collaboration between oncologists and gynecologists specialized in reproductive medicine is implemented to improve adolescent cancer patients’ access to assisted reproductive technologies. Nevertheless, more effort is required to improve the efficacy and safety of the available strategies and advance the field of fertility preservation in cancer patients.

Author Contributions

Conceived and designed the review: NZ, AK. Analyzed the data: CS, AK. Wrote the first draft of the manuscript: NZ, AS. Contributed to the writing of the manuscript: CS, AK. Agree with manuscript results and conclusions: NZ, AS, CS, AK. Jointly developed the structure and arguments for the paper: NZ, CS. Made critical revisions and approved the final version of the manuscript: NZ, AS, CS, AK. All authors have contributed to the preparation of the manuscript and approved its final version.

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