Chapter 5
Fertility Risk in Pediatric and Adolescent Cancers

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Recent diagnostic and therapeutic advances in pediatric oncology have led to greater survival rates in children with malignancies. However, while childhood and adolescent cancer therapies improve long-term survival, such treatments may lead to abnormal pubertal development, infertility, and gonadal failure. As more children and young adults survive childhood cancer and lead productive lives, these concerns are becoming increasingly important. Clinicians and researchers must be aware of current research in the area of fertility preservation in order to best guide patients through cancer treatment towards a healthy, fulfilled life. This chapter will review the effects of cancer treatments on reproductive potential, describe current methods of monitoring reproductive potential, and describe the fertility-sparing options available to young cancer patients of reproductive age. Specific attention will be paid to gaps in research pertinent to this topic.

Scope of the Problem

The number of childhood cancer survivors has increased dramatically over the last 25 years as substantial therapeutic advances have been made. Today, 75% of children with cancer can be expected to survive. Since the prevalence of cancer in children and adolescents up to 20 years of age is approximately 1 in 300, survivors can be expected to comprise 1 of 450 individuals in the young adult population [1]. Improvements in cancer treatments have prolonged survival and hence the focus has shifted from treating the cancer to improving the long-term health and quality of life among childhood cancer survivors [2].

The Importance of Fertility to Cancer Patients

The ability to lead full reproductive lives is very important to young cancer survivors [3–5] (for further discussion, see Kinahan, Didwania and Nieman, this volume). Web sites devoted to young cancer survivors contain patient testimonials related to fertility concerns and other quality-of-life issues after cancer. In fact, three fourths of cancer

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patients surveyed discussed fertility issues with their physician. One third of young women with breast cancer admitted that infertility concerns influenced their treatment decisions. Sadly, however, only 51% of cancer survivors surveyed felt that their concerns were addressed adequately, highlighting the need to focus counseling efforts on fertility preservation and treatment [3]. While childbearing is often considered a "woman's issue", there is evidence to suggest that this issue is important to males as well. Indeed, a retrospective survey of testicular cancer survivors and a small qualitative study of young male cancer survivors have demonstrated that infertility among cancer survivors can cause substantial distress [6,7].

Common Cancers in Children and their Treatment

The most common cancers of childhood in the order of decreasing incidence include: leukemia, central nervous system (CNS) malignancies, lymphomas, soft tissue sarcoma, renal cancer, and bone tumors. Leukemia is by far the most common cancer in children, accounting for 31% of all cancer cases in children under 15 years of age. Acute lymphocytic leukemia (ALL) commonly occurs in children ages 2–6. Treatment involves multi-agent chemotherapy, including a small dose of alkylating agent given over a 2–3–year period. The incidence of acute myelogenous leukemia (AML) peaks at 2 years and again at 16 years. Most effective therapy for AML involves chemotherapy with anthracyclines. Allogenic bone marrow transplantation is the best treatment option for AML patients in first remission.

Central nervous system malignancies are the second most frequent malignancy in children, accounting for 17% of childhood cancers. Treatment is multimodal and often involves surgery and chemotherapy.

Lymphomas account for 15% of childhood cancer cases. Therapy for Hodgkin's lymphoma includes combination chemotherapy with alkylating agents such as cyclophosphamide. The need for radiation is based on response to chemotherapy, tumor burden, and potential complications. Similarly, therapy for non-Hodgkin's lymphoma includes multiple chemotherapeutic agents including alkylator therapy with cyclophosphamide. Radiation is generally reserved for emergent therapy only.

With respect to other childhood malignancies, 7% of children with cancer are diagnosed with soft tissue sarcomas, 6.3% have renal cancer (most commonly Wilm's tumor), and 6% have bone tumors such as osteosarcoma and Ewing's sarcoma [8].

Fertility Risks for Young Females

Gonadotoxicity of Cancer Treatments

In the female, the ovary is particularly sensitive to the adverse effects of chemotherapy and radiation due to its finite number of unrenewable germ cells [9,10]. A woman's reproductive lifespan is determined by the size of the follicular

pool. Cancer treatments that cause follicular atresia and destruction of the follicular pool can lead to premature menopause and infertility [11]. Such decreased reproductive potential can be unpredictable and can lead to long-term health problems, including osteoporosis, cardiovascular disease, and sexual problems.

Limited data exist that provide reliable estimates of female infertility and premature ovarian failure for counseling pediatric cancer survivors. The Childhood Cancer Survivor Study (CCSS) recently reported findings from a study of over 3,000 childhood and adolescent cancer survivors and their siblings. They found that 6.3% of childhood survivors experienced acute ovarian failure, that is, ovarian failure that occurred during or immediately after cancer treatment [12]. A comparison of the incidence of non-acute premature ovarian failure in childhood cancer survivors compared with their siblings revealed a significantly higher incidence of premature menopause in survivors (8% vs. 0.8%). Specifically, the risk of premature menopause was 13-fold higher in survivors compared with siblings. Risk factors identified in this study for premature menopause included increased age, exposure to pelvic radiation, increased number of cycles and cumulative dose of alkylating agent therapy, and a diagnosis of Hodgkin's disease. Women who had undergone treatment with alkylating agents and pelvic irradiation had a 30% incidence of premature menopause [13].

Chemotherapy

Ovarian function is affected by chemotherapy. Alkylating agents such as cyclophosphamide and ifosfamide are particularly toxic to the oocyte [14–17]. Alkylating agents are commonly used in treating childhood sarcomas, leukemia, and lymphomas. By cross-linking DNA and introducing single-stranded DNA breaks, alkylating agents destroy cells in a dose-dependent fashion [18]. In patients with chemotherapy-related ovarian failure, histological sections of the ovary show a spectrum of changes ranging from decreased numbers of follicles to complete absence of follicles and stromal fibrosis [19–21]. Age is strongly associated with gonadotoxicity of chemotherapy. In particular, the effects are more pronounced in post-pubertal females than in prepubertal females. This can be explained by the presence of fewer primordial oocytes in the ovaries at baseline and hence, less ovarian reserve to offset the cytotoxicity of cancer treatment. For instance, the risk of ovarian failure in women treated for Hodgkin's disease is 13% in girls treated before the age of 15, 60% in women less than 30 years of age, and close to 100% of women over 30 years of age [22].

Radiation

Females who receive abdominal, pelvic, or spinal radiation are at risk of developing ovarian failure, especially if the ovaries are within the treatment field. Data suggests that the ovary of an older individual is more susceptible to damage from radiation than is

the ovary of a young individual. In women over 40 years of age, radiation doses of 600 cGy may be sufficient to produce ovarian failure, whereas in the majority of females treated during childhood, doses in excess of 2,000 cGy are needed to induce permanent ovarian failure [23–25]. The effect of radiation on ovarian function is compounded if radiation is given in conjunction with alkylator-based chemotherapy. In this case, ovarian dysfunction may occur despite the use of lower doses of radiation [26].

Using mathematical models that assume the age of natural menopause to be 51 years, 2,000 cGy represents a critical dose at which 50% of primordial oocytes are destroyed, and ovarian failure risk is increased [27]. Similar to the trends seen with alkylating chemoagents, older ovaries are more vulnerable to radiation damage than younger ovaries in that much smaller doses of radiation will render sterility in the setting of a diminishing primordial oocyte pool [28]. Taking into account different ages at treatment and various doses ranging from 3 to 9 Gy, Wallace et al. devised a table for predicting the age of ovarian failure and the maximum doses at any age that would render a patient sterile. These tools can be valuable in counseling patients about their reproductive potential.

Girls treated with whole abdominal and/or pelvic irradiation (total dose 2,200–3,000 cGy) for Hodgkin's disease or another solid tumor were evaluated by Wallace et al. Twenty-seven of 38 girls failed to undergo or complete pubertal development. An addiitonal 10 girls experienced early menopause at a median of 23.5 years of age [24]. Patients who receive a bone marrow transplant (BMT) with total body irradiation (TBI) are at the greatest risk of developing permanent ovarian failure. Almost all female patients who undergo a marrow transplant after age 10 will develop premature ovarian failure, whereas 50% of girls transplanted before age 10 will suffer acute loss of ovarian function [29].

Other effects of pelvic irradiation on pelvic organs can also contribute to infertility, namely, a damaged, scarred uterus with severely diminished blood flow potentially compromised in its capacity to accommodate implantation and a growing gestation. The degree of uterine damage depends on the total irradiation dose and the site of irradiation [30]. Prepubertal girls in whom the uterus has not yet developed in response to rising levels of sex steroids seem the most vulnerable to pelvic irradiation and the most resistant to physiologic sex steroid replacement. Overall, average uterine volume following TBI is 40% smaller than normal adult size [31]. Bath et al. [32] showed that in a group of survivors who received TBI as children or adolescents, some uterine volume was gained with sex steroid replacement (from 6.8 to 17.3 ml^3), but still remained significantly smaller than healthy controls and survivors who did not receive pelvic irradiation (41.5 ml^3). While the endometrial lining can be cycled using exogenous sex steroids, suggesting adequate exposure and response to exogenous estrogen, it still remains thinner than normal uteri assessed at matched cycle time (5.9 vs. 8.7 mm). With the larger doses used in abdominopelvic irradiation, these sequelae are even more profound, and there is a subset of patients in whom the uterine musculature and vasculature have been so damaged that no restoration will be achieved with hormonal replacement [33]. In women treated with abdominopelvic radiation after puberty, limited data suggest that fertility is decreased 23% [34]. In addition, there is an increased risk

of spontaneous abortion, preterm labor, and delivery of low birthweight infants among women who have received pelvic irradiation [35,36].

Effects on the Hypothalamic-Pituitary-Ovarian Axis

Cranial irradiation can affect the hypothalamic-pituitary-ovarian axis. With respect to reproductive function, changes in gonadotropin secretion may lead to precocious or delayed puberty. Specifically, Bath et al. demonstrated ovulatory dysfunction in subjects who had cranial irradiation and chemotherapy for childhood ALL [37]. At times, it can be difficult to determine whether reproductive dysfunction is a result of impaired hypothalamic-pituitary function vs. evolving gonadal failure [38–40].

Time Course of Ovarian Dysfunction

Limited data exist that document the effects of chemotherapeutic agents on endocrine function prior to, during, and immediately following cancer treatment. In particular, there are no longitudinal studies assessing ovarian function in adolescents and young adults. Nonetheless, a recent study conducted in 50 adult breast cancer patients is informative. This longitudinal study collected endocrine and ultrasound measures of pituitary and ovarian function in women (median age 41) before treatment and every 3 months during chemotherapy for a total of 12 months. During this time, a significant fall in anti-Mullerian hormone (AMH) levels and inhibin B occurred, while an increase in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were observed by 3 months. Estradiol (E2) levels remained relatively unchanged during therapy. Ovarian volume and antral follicle counts declined over 12 months. Most women experienced irregular menstrual cycles [41]. This study and others support the theory that small preantral follicles are destroyed primarily by chemotherapy while larger follicles that produce E2 are less affected [41–43]. No longitudinal studies have been conducted assessing similar measures of ovarian function in adolescent and young cancer survivors. Presumably, the ovaries in such patients are more resistant to the effects of chemotherapy and smaller differences in measures would be detected. Being able to identify and predict when ovarian failure is expected to occur in particular patients would be helpful in determining fertility potential for family planning and the onset of menopause for bone and cardiovascular health.

Clinical Signs Occur after Fertility is Severely Compromised

Currently, it is difficult to predict whether, and to what extent, cancer survivors will experience infertility. Once clinical symptoms of ovarian dysfunction occur, such as irregular menses and vasomotor symptoms, pregnancy is usually not possible

even with aggressive fertility treatments. Even women who maintain cyclic menses after therapy are at risk of infertility, early menopause, and long-term health problems related to early ovarian failure [14,17,44–48]. Therefore, early detection of compromised ovarian function is necessary in order to offer cancer survivors viable fertility options and improve quality of life. Most exciting is the possibility of identifying women at highest risk for infertility and cryopreserving ovarian tissue for future use.

Ovarian Function Markers

Over the past decade, several clinical tests have been developed to evaluate a woman's fertility potential in the infertility clinic setting [49]. Serum levels of several reproductive hormones and ultrasound-based ovarian measurements are utilized routinely as counseling tools to select treatment protocols for infertility. Such ovarian reserve testing includes isolated serum measures of basal FSH, E2, inhibin B, and AMH; dynamic serum measures, such as the Clomiphene Citrate Challenge Test; and ultrasound measures of the ovary, including antral follicle count (AFC) and ovarian volume [49–57]. If premature ovarian failure secondary to gonadotoxic treatment is preceded by ovarian and hormonal changes analogous to those seen with age-related changes, such surrogate measures should reflect fertility potential in cancer survivors as well.

While somewhat inconsistent, the findings of several small studies conducted in European centers suggest that surrogate measures of fertility potential in cancer survivors are promising. Bath et al. compared measures of fertility potential in 10 cancer survivors and found that FSH levels were higher, AMH levels were lower, and ovarian volume was smaller in cancer survivors compared with controls. No differences in basal or stimulated inhibin B or AFC were observed [58]. However, when Larsen et al. compared hormone profiles and ultrasound measures in 70 cancer survivors with spontaneous menses and 21 controls, he was able to demonstrate lower inhibin B levels, smaller ovarian volumes, and decreased AFC in the cancer survivors [59]. In a follow-up study, he found that cancer survivors with normal FSH levels and regular menses reported shorter menstrual cycles and had smaller ovarian volumes and a lower AFC compared with controls, but that the two groups had similar hormone profiles [60].

It is important to emphasize that these studies are limited by several factors that may have substantially biased the results: small sample sizes, age disparities between cases and controls, diverse gonadotoxic treatments, and inclusion of subjects taking exogenous hormones. In addition, no study has simultaneously tested several measures, assessed novel markers of ovarian aging, or assessed changes in measures during and after cancer therapy. Such data would help to elucidate which test(s) may best predict the otherwise "invisible transition" toward decreased ovarian reserve and/or premature ovarian failure.

Pregnancy Outcomes in Cancer Survivors

A large-scale epidemiologic study, the CCSS, included over 20,000 childhood cancer survivors and offers some optimism in pregnancy outcomes. Comparing outcomes of over 4,000 pregnancies in survivors with 1,900 of their siblings, the authors found a small but significant decrease in live births in cancer survivors regardless of cancer diagnosis or treatment regimen received (relative risk, RR 0.52–0.87). The authors explained the decrease in live births with the finding that survivors were more likely to choose termination of pregnancy, perhaps due to concerns regarding pregnancy outcome or maternal medical effects. Importantly, risk for stillbirth was not increased across all cancer diagnoses and treatments. No specific chemotherapy agent was identified that contributed more to adverse pregnancy outcomes, including alkylating agents. Radiation to the ovaries, either directly or indirectly through scatter and inadequate shielding, resulted in higher risk of miscarriage, but no effect on live births. The CCSS found that low birth weight infants (<02,500 g) were twice as likely to be born to survivors compared with their siblings, and particularly to those who received pelvic irradiation. The increased risk of low birth weight infants primarily related to a history of pelvic irradiation has been confirmed by several other studies [34,61].

Fortunately, studies demonstrate that cancer survivors who conceive at least 5 years following cancer treatment are not at increased risk of having a child with major congenital abnormalities when compared with the general population [61–64]. In addition, children of cancer survivors do not appear to be at higher risk of developing cancer themselves [65]. While this data is reassuring, the majority of studies assessing pregnancy outcomes cannot be generalized to current populations, since some studies date as far back as the 1940s, when treatment protocols were drastically different than those of today. Future investigations of large, current databases of cancer survivors are needed to provide more information for patient counseling. At present, however, evidence suggests that if ovarian function is preserved and pregnancy is achieved, outcomes are encouraging enough to actively pursue fertility [65]. The prenatal and obstetrical care of the cancer survivor should be multi-disciplinary, since the spectrum of medical complications resulting from cancer treatment would certainly benefit from diverse expertise.

Options for Preserving Fertility in Girls and Young Women

Unfortunately, limited options are currently available for girls and young women suffering from cancer to ensure future reproductive capacity (see Table 5.1). The most successful option for fertility preservation in post-pubescent girls facing cancer is emergency in vitro fertilization (IVF) and embryo cryopreservation prior to chemotherapy. The pregnancy rate with this technique averages 30–40% [66,67]. While

Table 5.1 Options for fertility preservation in cancer patients

Before cancer treatment
• Medical
GnRH agonist concurrent with chemotherapy
• Surgical
Oophoropexy prior to pelvic irradiation
• Cryopreservation
Sperm cryopreservation*
Embryo cryopreservation*
Oocyte cryopreservation
Ovarian tissue cryopreservation
Testicular tissue cryopreservation
After cancer treatment
• IVF*donor oocyte*

*denotes established procedures

often successful, this option requires time for ovarian stimulation, oocyte retrieval, and in vitro embryo development, which delays cancer treatment 2–5 weeks [68]. Complications from IVF include ovarian hyperstimulation syndrome, which occurs in 5% of cycles. Embryo cryopreservation is ideally used when there is a male partner involved, but it can be performed in single, young cancer patients who are willing to use donor sperm. In addition, this procedure is not successful in prepubescent girls [34]. While emergency IVF is the preferred way to preserve fertility for young adults, the emotional and physical demands of the process, the duration of stimulation, and the financial burden often make it a suboptimal choice for fertility preservation.

Other options for minimizing the damaging effects of cancer treatments include oophoropexy or fertility-sparing cancer surgery [69–71]. In addition, co-administration of GnRH agonists may provide some protection against ovarian damage during chemotherapy, although prospective controlled trials are needed to establish any real benefit [72–76]. Anti-apoptotic agents like S1P have substantial promise and are currently under investigation [77–79]. While still considered experimental, other potential options for fertility preservation include cryopreservation of oocytes or ovarian tissue [80–84]. These options are particularly desirable for young single women and will be discussed in detail in Agarwal and Chang, this volume. After reproductive potential has been significantly compromised by cancer treatments, aggressive treatment with IVF may improve pregnancy rates. Oocyte donation and embryo donation offer excellent chances of pregnancy after ovarian failure has occurred, but may not be acceptable to many couples.

Fertility Risks for Young Men

Cancer therapy can interfere with reproductive ability and libido in men. The differential sensitivity of spermatozoa-producing Sertoli cells compared with the testosterone-producing Leydig cells allows for greater effects in on the

reproductive capacity of men than effects on their sexual function. Moreover, since the testes are more sensitive than the ovary to cytotoxic therapies, the ensuing injury is more damaging to male fertility than to female fertility. Comparison of fertility in treated men and women revealed a 0.76 adjusted relative fertility [85]. The testes are extremely sensitive to chemotherapy, radiation, and surgical interventions.

Chemotherapy

Testicular dysfunction is among the most common long-term side effects of chemotherapy in men. Testicular damage is agent-specific and dose-related. The germinal epithelium is particularly susceptible to injury by cytotoxic drugs secondary to a high mitotic rate. In contrast, Leydig cells appear relatively resistant to the effects of chemotherapy [86]. In 1948, azoospermia after exposure to an alkylating agent (nitrogen mustard) was described in 27 of 30 men treated for lymphoma [87]. Subsequently, it has become apparent that all alkylating agents such as cyclophosphamide, ifosfamide, and procarbazine are gonadotoxic [88–90]. Conversely, antimetabolite therapy, such as methotrexate and mercaptopurine, does not have an adverse impact on male fertility. Cisplatin-based regimens including velban, bleomycin, and etoposide result in temporary impairment of spermatogenesis in all patients but with recovery in a significant percentage [91].

Initial reports suggested that the younger the boy the more resistant he was to the gonadotoxicity of the chemotherapy [92]. More recently, however, it has become apparent that both the prepubertal and pubertal testes are vulnerable to cytotoxic drugs [93–95]. Impairment of spermatogenesis may be irreversible in the months to years following chemotherapy. However, late recovery of spermatogenesis up to 14 years following chemotherapy has been reported [96,97]. The chance of recovery of spermatogenesis following cytotoxic chemotherapy and the extent and speed of recovery are related to the agent used and the dose received [97–100]. In contrast to the germinal epithelium, Leydig cells appear relatively resistant to the effects of chemotherapy [101]. However, a few studies have demonstrated a reduction in testosterone concentrations following treatment with gonadotoxic agents, and there is evidence to suggest that Leydig cell impairment following chemotherapy may be relevant clinically.

While chemotherapy lowers sperm counts and may disrupt DNA integrity, it appears that sperm integrity is re-established over time [102,103]. In addition, as reviewed previously, there does not appear to be any increased risk of congenital anomalies among children born of cancer survivors [104].

Radiotherapy

Spermatogenesis is exquisitely sensitive to radiation [105]. The testes are directly irradiated in rare situations, such as testicular relapse of ALL. Although the testes are usually not directly in the radiation field, they can still receive irradiation via

body scatter. The amount of scattered radiation is a function of the proximity of the radiation field to the target, the field size and shape, the X-ray energy, and the depth of the target. Of these, distance from the field edge is the most important factor. Scatter dose to the testes becomes a real issue when treating a field that extends into the pelvis, as in some cases of Hodgkin's disease, seminoma, or soft tissue sarcoma of the thigh. Small children, because of their short trunk length, can be at greater risk from scattered radiation than larger individuals.

The germinal epithelium is most sensitive to radiation effects and some effect on spermatogenesis will be seen at doses of 10 cGy. Permanent sterilization may be seen with doses as low as 100 cGy [105]. Ash summarized data from several older studies that examined testicular function following radiation in patients who were treated for a range of cancers, including Hodgkin's disease, prostate cancer, and testicular cancer [105]. The author found that oligospermia occurred at doses as low as 10 cGy and azoospermia at 35 cGy, which was generally reversible. However, 200–300 cGy could result in azoospermia that did not reverse even years after irradiation. Leydig cells in the testes are more resistant to radiation than germ cells. The available data indicate that chemical changes in Leydig cell function are observable following direct testicular irradiation, with the effect more pronounced with 2,400 cGy than with 1,200 cGy [106]. The severity of the effect is more marked the younger the patient is at the time of radiotherapy [107]. In general, progression through puberty and testosterone production proceeds normally in males subjected to radiation therapy.

Options for Preserving Fertility in Boys and Young Men

Sperm cryopreservation after masturbation remains the best option for fertility preservation in the post-pubertal male diagnosed with cancer. All adolescents and young adults facing cancer therapy should be offered sperm cryopreservation as a way to preserve future fertility. Multiple samples should be cryopreserved before cancer treatment begins. Since sperm production begins around the age of 12–13, adolescent boys who are unable to produce a specimen via ejaculation can undergo electroejaculation or testicular sperm extraction under anesthesia [108]. Although sperm banking is a relatively simple process, there is evidence that oncologists do not routinely discuss this option with their patients [109]. In addition, even when sperm is banked, many men do not use the specimens. A study of 422 testicular cancer survivors with cryopreserved semen reported that while only 29 (7%) used the cryopreserved samples for artificial reproductive techniques, 48% (14/29) were successful [110].

Unfortunately, at this time there are no feasible options for preserving fertility of prepubertal male patients. There has been no demonstrated protective effect of using GnRH analogues with and without testosterone to suppress testicular function during chemotherapy [111,112]. In cooperation with pediatric oncologists, we must continue to attempt to reduce the gonadotoxicity of treatment regimens while maintaining superior cure rates.

Fertility preservation in prepubertal boys remains problematic and is an active area of investigation. Extracting and cryopreserving spermatogonial stem cells from boys in order to use later in autografts, xenografts, or maturation in vitro are exciting and promising avenues of investigation. While transplantation of cryopreserved testicular tissue has been successful in mice and rats, data in humans is lacking [113,114].

Ethical Issues in Pediatric Patients

The use of novel methods of assisted reproductive technologies (ART), such as oocyte and ovarian tissue cryopreservation, raise ethical challenges for the informed consent process in the pediatric and adolescent patient. As discussed, while these methods are experimental and may offer no guarantee of future fertility, they involve invasive procedures that have a small but significant potential for medical complications. The decision-making process is complex since it involves the need to weigh complex options (ovarian tissue, oocyte, and embryo cryopreservation; future donor oocyte; future adoption), in order to achieve a potential future goal (childbearing). Whether the authority to make such a decision rests with the parent or the cancer patient is not clear and depends on the age and maturity of the patient and state law. It is possible that parental judgment may not reflect the future best interests of the patient, but the patient may not have the capacity to truly consent or refuse the fertility-preserving procedures. Informed choice is also challenging in this area since there is limited evidence on the safety and efficacy of novel fertility-preserving technologies (for further discussion, see Zoloth and Backhus, this volume).

Another issue that must be considered is ownership of cryopreserved tissue in the case of a pediatric patient's death. Who should decide on ownership? Should parents or guardians be permitted to use this tissue to undergo ART in the case of the child's death? Such ethical issues must be carefully considered when counseling patients and families about fertility preserving options [115].

Conclusion

The scope of the "problem" of fertility preservation in cancer survivors will only continue to grow as cancer treatments improve disease-free survival. Therefore, quality-of-life issues, including reproduction and avoiding premature menopause, will certainly become even more prominent concerns, and much of pre-cancer treatment counseling will need to broaden to cover these issues. We must work together in the medical and research community to find ways to minimize the gonadotoxicity of cancer treatments, develop novel and effective fertility preserving techniques, improve the detection of impaired fertility potential in cancer survivors, improve

patient counseling about available fertility options, and assist those interested in pursuing fertility preserving therapies prior to treatment. Ultimately, a multi-faceted team approach that includes the expertise of a reproductive endocrinologist and oncologist will culminate in the best treatment plan possible, encompassing not just cancer treatment but also fertility preservation. We are optimistic that more choices will soon be available to help cancer survivors lead full reproductive lives.

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