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The scope of potential fertility issues for pediatric cancer patients is broad and difficult to predict. Both genders are susceptible to central dysregulation of the hypothalamic axis. For boys, chemotherapy and radiation can affect production of both sex hormones and sperm. These effects can be reversible or permanent. For girls, the ovary can be similarly affected, with inadequate or absent hormone production and depletion of ovarian follicle reserve. Additionally, even in a young woman with normal puberty and early fertility, premature menopause is a possibility after certain exposures. Finally, the uterus can be affected by radiation and create problems in carrying a normal pregnancy to term, even if hormonal fertility is achieved.

Radiation is a clearly established risk to the hormone- and gamete-producing tissues. What is more difficult to predict are the fertility outcomes after chemotherapeutic exposures. The main exposures implicated for pediatric patients are cyclophosphamide and other alkylating agents; large cumulative doses have been shown to irreversibly impair fertility in both male and female patients. However, the variability in gonadal function between different individuals after therapy with an alkylating agent is quite large, making prediction of fertility outcomes after many protocols extremely difficult. Furthermore, evidence suggests that males are more susceptible than females, and spermatogenesis is impaired at lower doses than is testosterone production.

Many pediatric patients who are survivors of cancer are never offered fertility-sparing interventions, so it is important for health care personnel to monitor the fertility status of survivors of childhood cancers. Management should focus on assessment of gonadal function via patient history, physical examination, and laboratory screening. Below, I discuss guidelines from the Children’s Oncology Group (COG) that identify high-risk patients who should receive more careful monitoring and counseling regarding long-term issues such as premature menopause and bone density concerns. Future challenges include better definition of patients at risk of infertility pretreatment in order to target fertility preservation schemes accordingly. (For further discussion of fertility risk among pediatric cancer patients, see Garcia and Ginsburg, this volume.)

Follow-up Guidelines Related to Male Fertility

Risk Factors

Radiation, even without concomitant chemotherapy, can impact the gonadal axis in a number of ways. Radiation doses of 40 Gy or more to a field that includes the hypothalamus can lead to gonadotropin deficiency [1]. Radiation directly to the testes, including pelvic irradiation and total body irradiation (TBI), can cause germ cell failure. After doses of 1–3 Gy, azospermia may be reversible, but reversibility is unlikely at higher doses, especially >6 Gy [2]. Pelvic or testicular radiation at doses of 20 Gy or higher, especially if combined with alkylating agents or head/
brain irradiation, is a risk factor for Leydig cell dysfunction leading to delayed or arrested puberty and hypogonadism [3].

Use of alkylating agents can place the male gonads at risk of delayed or arrested puberty, hypogonadism, oligospermia or azospermia, and infertility [4]. The risk factors include higher cumulative doses, particularly of cyclophosphamide or busulfan, and combinations with other alkylators or with radiation in a field that affects the testes directly or that affects the neuroendocrine axis. Leydig cell dysfunction can occur after alkylating agent exposure at any age [5].

Finally, surgical procedures related either to tumor removal or to complications during treatment can also affect fertility. Bilateral or unilateral orchiectomy can cause hypogonadism or infertility if combined with radiation or alkylating agents [6]. Pelvic surgery could also place a male patient at risk for mechanical sexual dysfunction including retrograde ejaculation, anejaculation, or erectile dysfunction.

**Surveillance and Screening**

After any of the exposures discussed above, a yearly patient history should monitor the onset and timing of puberty, sexual function as age appropriate, including erections and nocturnal emissions, and medications that may impact sexual function. Frothy white urine at first void after intercourse suggests retrograde ejaculation [7].

The annual physical examination should include overall assessment of growth and development. A genitourinary exam specifically involves Tanner stage (sexual maturity rating or SMR), including testicular volume, until sexual maturity (SMR 5) has been reached.

In patients at risk for hypogonadism, laboratory screening should include measurement of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), as well as testosterone at age 14 as a baseline. These studies should be repeated as clinically indicated due to signs of delayed puberty or testosterone deficiency [1,3,4]. Semen analysis should be performed for evaluation of infertility or at the request of the patient in family planning [2–4,6].

**Additional Management Issues**

Those males at risk of azospermia and their sexual partners should be counseled to use appropriate birth control methods as sperm production can resume spontaneously up to 10 years after treatment. For this same reason, periodic reassessment by semen analysis may be indicated for those desiring to start a family. Patients who have testosterone deficiency will also be at risk for low bone mineral density (BMD) in addition to abnormal development of secondary sexual characteristics, so testosterone replacement is warranted.

In the current treatment era, optimal care for pediatric patients with cancer would include fertility-preservation options at diagnosis prior to therapeutic exposures that can cause azospermia. Sperm banking can be offered to even early pubertal patients, while development of
methods to preserve spermatogonia from prepubertal patients represents an area of active research.

Follow-up Guidelines Related to Female Fertility

Risk Factors

The number of ways in which female fertility can be affected by exposure to cancer therapies is quite large and complex. Not only are there potential effects parallel to those seen in males on the hypothalamic-gonadal axis, on the gonads themselves, and on sexual function, even in a “fertile” female with functioning gonads there are potential problems carrying a pregnancy to term due to direct effects on the uterus.

Radiation doses to the head of \( \geq 40 \) Gy confer a risk for gonadotropin deficiency in females [1]. Radiation fields that expose the ovaries, including TBI, can also cause ovarian dysfunction, resulting in delayed or arrested puberty (both secondary sexual characteristic development and menstruation) as well as infertility [8]. Of additional concern for females is that even if puberty development and early fertility were normal, premature menopause can occur. While surgical premature menopause is the most common etiology in cancer survivors, as well as in patients never treated for cancer, the risk of nonsurgical premature menopause for a cancer survivor is 13 times higher than in sibling controls [9]. Cumulative incidence is highest in those women who, when treated for cancer as children, received both radiation to the ovaries and alkylating agent chemotherapy.

Radiation can also affect the vascular supply to and growth of the uterus [10]. The highest risk is conferred by prepubertal age at treatment and by radiation dose \( \geq 30 \) Gy or TBI. In addition, girls with Wilm’s tumor are at high risk of congenital uterine anomalies that would further impact uterine sufficiency. The implications for uterine vascular insufficiency can include adverse pregnancy outcomes, such as spontaneous abortion, premature labor, and low birth weight. An additional treatment effect, particularly from radiation to the vagina or from chronic graft vs. host disease in stem cell transplant recipients, can include vaginal fibrosis or stenosis, which in turn lead to problems such as dyspareunia and postcoital pain, as well as possible psychosocial consequences of sexual functioning difficulties [11].

Chemotherapy effects on ovarian function can be highly variable. Alkylating agents, particularly cyclophosphamide, busulfan, and procarbazine, have been implicated in different patient populations and different studies [12]. Older age at treatment appears to be a risk for girls as well, especially when combined with high cumulative doses of cyclophosphamide [13]. Ovarian failure can be temporary or permanent, and chemotherapy is also implicated, as discussed above, in premature menopause even for those women who experienced some post-treatment period of normal gonadal function.

The surgical procedures that can impact fertility for girls include hysterectomy and oophorectomy. Hysterectomy not only prevents a woman from carrying her own pregnancy, it can also cause problems with pain or urinary leakage that may impact a survivor’s psychological well-being [14]. Bilateral oophorectomy is a cause of hypogonadism and infertility, but these
women may still be able to carry a pregnancy with hormone replacement therapy (HRT) if the uterus is intact [15]. Unilateral oophorectomy, particularly in patients who smoke or had other treatments that affect gonadal function, can increase the risk for premature menopause [16]. Oophoropexy is sometimes used to shield the ovaries from radiation to nearby structures, but it can result in late effects such as the inability to conceive even with normal ovarian function [17]. Spinal or pelvic surgery can also impact sexual functioning in females with an indirect impact on fertility [18].

**Surveillance and Screening**

For females, a yearly patient history should monitor the onset and timing of puberty, including menstrual and pregnancy history, sexual function as age appropriate, including vaginal dryness, and medications that may impact sexual function. Family history of pubertal development timing may also be helpful in judging whether puberty is delayed. Physical examination should include overall assessment of growth and development. SMR should be documented yearly until sexual maturity has been reached.

In female patients at risk for hypogonadism, laboratory screening should include FSH and LH, as well as estradiol at age 13 as a baseline. These studies should be repeated as clinically indicated due to signs of delayed puberty, irregular menses, primary or secondary amenorrhea, or clinical signs of estrogen deficiency [1,8,12,16].

The various potential genitourinary tract abnormalities that may be due to radiation are generally found by history and physical examination. When contemplating pregnancy, high-level ultrasound can be considered for female patients who received radiation in a field impacting the uterus [10]. High-risk obstetrical care is warranted for a patient who conceives after abdominopelvic or lumbosacral spine radiation or TBI.

**Additional Management Issues**

Recovery of fertility and normal gonadal function is highly variable in females as well as males. Patients should be counseled to use birth control to avoid unintended pregnancy because recovery of fertility can occur even years after therapy ends. For patients with ovarian failure who have been on HRT, clinicians should consider a 2-month trial off of hormones to assess whether ovarian function has resumed. Conversely, patients who experience normal gonadal function and fertility after treatment with potentially gonadotoxic therapy should be counseled to be cautious about deliberately delaying childbearing as premature menopause can also occur [1,8,12,16].

Patients with abnormal hormone levels or delayed puberty should be referred to endocrinology. Estrogen deficiency is also a risk factor for osteoporosis, so assessment of bone density is important and hormone replacement should be at least partially protective. Reproductive endocrinology referral is warranted for patients who experience infertility [1,8,12,16].

For female patients with sexual dysfunction due to treatment, including dyspareunia or vaginal dryness, gynecologic consultation for symptom management can be helpful, but psychological
distress due to these difficulties may also need attention. Referral to a psychologist may also be warranted for patients experiencing infertility.

Fertility preservation options that can be offered to female patients prior to gonadotoxic therapy are more invasive and time-consuming than the options for males. Adult women with a male partner or who choose to use donor sperm and who can safely delay cancer therapy can undergo stimulation and in vitro fertilization with a high efficiency of pregnancy using cryopreserved embryos. However, the ability to cryopreserve oocytes with successful fertilization and implantation later has been technically difficult. Many programs are currently focusing on cryopreservation of intact ovarian tissue, which requires surgical removal of all or part of an ovary. However, newer methods such as reimplantation and in vitro follicle maturation that would allow clinical use of oocytes after freezing are still in the experimental stage. (For further discussion of cryopreservation, see Mullen and Critser, this volume and see Appendix A for currently available oncofertility options.)

Optimal Care for Pediatric Cancer Patients

Dealing with fertility preservation upon diagnosis of cancer is challenging even for a young adult patient. This issue is even more complex for pediatric patients where decision making generally falls to the parents but where high cancer survival rates increase the possibility of survivors needing to confront infertility later in life (See Clayman, Galvin, and Arntson, this volume). Parents and adolescent patients report that achieving a healthy state is most important, and that while they are interested in fertility preservation options, they may not be willing to delay treatment for pursuit of those options [19] (for further discussion, see Kinahan, Didwania, and Nieman, this volume).

Fertility preservation options will only be offered to patients if the knowledge of oncology providers leads them to appropriately identify patients at risk and if they have appropriate resources to support their patients in fertility preservation decision making. Most pediatric clinicians in one pediatric hematology/oncology clinic were aware that radiation and chemotherapy can affect fertility, but only half were aware of gender differences in toxicity, and only about one third currently consult with specialists regarding fertility preservation [20].

Optimal care of pediatric cancer patients undergoing gonadotoxic therapy should include enrollment in available trials that will continue to refine knowledge of the effects of therapy on fertility for both male and female patients. Patients and families need information at diagnosis regarding the potential impact of therapy on fertility as well as referral to appropriate specialists for fertility preservation when desired. Studies and resources that allow potentially fertility-sparing interventions such as ovarian cryopreservation will not only need to be expanded, but adequate education and support for oncology providers who screen for patients at risk will be key. For patients that did not undergo fertility-sparing procedures prior to treatment, careful monitoring of reproductive function is warranted and current technologies will still allow many of those patients to parent their own biological children.
References


