Female Reproductive Health After Childhood, Adolescent, and Young Adult Cancers: Guidelines for the Assessment and Management of Female Reproductive Complications

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ABSTRACT

Purpose

As more young female patients with cancer survive their primary disease, concerns about reproductive health related to primary therapy gain relevance. Cancer therapy can often affect reproductive organs, leading to impaired pubertal development, hormonal regulation, fertility, and sexual function, affecting quality of life.

Methods

The Children’s Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer (COG-LTFU Guidelines) are evidence-based recommendations for screening and management of late effects of therapeutic exposures. The guidelines are updated every 2 years by a multidisciplinary panel based on current literature review and expert consensus.

Results

This review summarizes the current task force recommendations for the assessment and management of female reproductive complications after treatment for childhood, adolescent, and young adult cancers. Experimental pretreatment as well as post-treatment fertility preservation strategies, including barriers and ethical considerations, which are not included in the COG-LTFU Guidelines, are also discussed.

Conclusion

Ongoing research will continue to inform COG-LTFU Guideline recommendations for follow-up care of female survivors of childhood cancer to improve their health and quality of life.

INTRODUCTION

Although the goal of treating young female patients with cancer is cure, long-term effects of therapy should be considered at diagnosis, before and during therapy, and during long-term follow-up. Alkylating chemotherapy, irradiation of the CNS and/or ovaries, and pelvic or genitourinary surgery, used to treat common childhood cancers, can adversely affect reproductive organs, altering pubertal development, hormonal regulation, fertility, and sexual function and significantly reducing quality of life. The risk of these complications is linked to age at diagnosis, primary diagnosis and disease site, and treatment modality and intensity. Oncologists can sometimes tailor therapy to optimize reproductive health.

In 2003, the Children’s Oncology Group (COG) released risk-based, exposure-related guidelines for follow-up care after pediatric cancer treatment.1 The COG Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer (COG-LTFU Guidelines)2 are evidence-based recommendations for screening of late effects of therapeutic exposures. The sections on female reproductive health are updated regularly, based on the current literature and consensus by an expert panel (representatives of pediatric oncology, endocrinology, nursing, urology, gynecologic oncology, and radiation oncology).3 The guideline screening recommendations are appropriate for asymptomatic survivors receiving routine exposure-based medical follow-up > 2 years after completion of therapy. More-extensive evaluations are suggested, as clinically indicated. Patient education materials (provided under Health Links at http://www.survivorshipguidelines.org) complement several topics addressed in the guidelines. Here we review the literature that informed our 2012 recommendations for all aspects of female
reproductive and sexual health, including hypogonadism, precocious puberty (PP), and reduced fertility. We also review current knowledge in other relevant areas, including investigational fertility preservation, interventions for infertility, and sexual function.

**HYPOGONADISM**

Primary (ovary-specific) hypogonadism, defined by low ovarian estrogen and progesterone levels, is caused by oophorectomy or toxic radiotherapy and/or chemotherapy. Hypothalamic/pituitary (HP) damage caused by tumor, radiation, or surgery may result in central hypogonadism with impaired release of ovarian-stimulating hormones (gonadotropin-releasing hormone [GnRH], luteinizing hormone [LH], and follicle-stimulating hormone [FSH]).

**Risk Factors**

*Primary hypogonadism.* Chemotherapy-induced ovarian failure is associated mainly with alkylating agents (classical and nonclassical) and heavy metals and is directly correlated with cumulative dose and age at exposure.4,5 Primary ovarian failure (POF) after gonadal radiotherapy has similar risk profiles for hormonal function and fertility. Risk-associated irradiation fields include the spine (lumbar, sacral, or whole spine), flank, hemiabdomen below the iliac crest, whole abdomen, inverted Y, pelvis, vagina, bladder, iliac lymph nodes, total lymphoid system, and total body. Abdominal and pelvic irradiation are associated with acute ovarian failure (AOF)6 and POF.7 Irradiation at an older age confers greater dose-related risk, with increased risk resulting from smaller oocyte pool.8,9 Doses as low as 5 Gy can affect ovarian function in postpubertal girls,10 and doses ≥ 10 Gy confer higher risk. In prepubertal girls, higher radiation dose (ie, ≥ 10 Gy) is associated with impaired ovarian function, and dose ≥ 15 Gy confers higher risk. Mathematical modeling based on data on the rate of oocyte decline suggests that the sterilizing dose is 20.3 Gy in infants, 18.4 Gy at age 10 years, and 16.5 Gy at age 20 years.11 Risk is increased by alkylating chemotherapy.7

Young survivors who have never menstruated or who ceased menstruating < 5 years after diagnosis have AOF.4 AOF was reported in 215 (6.3%) of 3,390 female participants in the Childhood Cancer Survivor Study (CCSS)12 who were age ≥ 18 years. Multivariable logistic regression showed ovarian irradiation of > 10 Gy, procarbazine exposure at any age, and cyclophosphamide exposure from age 13 to 20 years to be independent risk factors for AOF.6

Female survivors who retain ovarian function after ovary-toxic therapy are at risk of POF (age < 40 years).13-15 POF was reported by 126 (4.5%) of 2,819 CCSS survivors age > 18 years and by 33 (3.1%) of 1,065 sibling controls; 95% of POF cases among controls were attributed to surgery. Cumulative incidence of nonsurgical POF was substantially higher in CCSS survivors than in their siblings (8% vs 0.8%; P < .001). Risk factors for nonsurgical POF were: older age (relative risk [RR], 1.15), higher ovarian radiation dose (RR, 6.7 to 12.3), higher alkylating agent dose (RR, 1 to 5.8), and Hodgkin lymphoma (RR, 9.2). Survivors treated with alkylating agents and abdominal-pelvic irradiation had a cumulative incidence of nonsurgical POF approaching 30%.7

Bilateral oophorectomy invariably results in hypogonadism. Adult women who undergo unilateral oophorectomy have reduced ovarian reserve and greater risk of POF than controls.16 Unfortunately, no similar study in childhood cancer survivors is available.

**Central hypogonadism.** Direct irradiation of the HP may induce central hypogonadism by impairing secretion of FSH and LH, especially at doses > 40 Gy.2,17-22 Cranial irradiation doses described to cause lower pregnancy rates vary significantly by study, but even low doses (18 to 24 Gy), as used prophylactically in acute lymphoblastic leukemia, have been reported to decrease fertility rates compared with rates among sibling controls.23,24 A report from the CCSS group showed highest risk at doses > 30 Gy.23,26

**Assessment**

The COG-LTFU Guidelines (Table 1) recommend regular screening of patients at risk of hypogonadism to identify gonadotropin deficiency, delayed or arrested puberty, AOF, or POF. In prepubertal survivors, onset and tempo of puberty, menstrual history, and Tanner stage are evaluated annually until sexual maturity. Baseline LH, FSH, and estradiol levels should be assessed at age 13 years. In sexually mature patients, evaluation should include menstrual and pregnancy history and history of sexual difficulties or changes. Patients with delayed puberty, irregular menses, primary or secondary amenorrhea, and/or clinical signs and symptoms of estrogen deficiency should have LH, FSH, and estradiol levels screened. Bone mineral density tests should be considered for hypogonadal patients. Referral to an endocrinologist or gynecologist is warranted by signs and symptoms of ovarian dysfunction and/or abnormal hormone levels.

It is vital to counsel women who received gonadotoxic therapy regarding their risk of POF. Although antral follicle count by transvaginal ultrasound is the most established method for assessing ovarian reserve in adult women,27,28 anti-Müllerian hormone (AMH) correlates well with it and is better than age, basal FSH, estradiol, and inhibin B in healthy women;29-32 AMH generally does not vary by menstrual day, nor is it affected by use of exogenous estrogen or progesterone.33,34 Very low AMH levels are indicative of ovarian failure; however, there is a wide range of normal values in healthy young adult women. Normative data in pediatric patients are limited.35 AMH levels, which have recently entered into routine use by reproductive endocrinologists, have been reported to be decreased in both adult and pediatric patients with cancer,36-41 with potential recovery in patients after low doses of alkylating chemotherapy.39 AMH shows promise to be useful as a predictor of ovarian reserve and timing of onset of menopause in pediatric patients with cancer; it will likely be included in the recommendations for long-term follow-up in the near future.42-44

**Treatment**

Treatment of hypogonadism seeks to normalize ovarian hormone levels. Estrogen may be replaced with oral, micronized, or transdermal preparations.45 Progesterone therapy is also needed to avoid an unopposed estrogen effect and maintain endometrial health in women with a uterus. Oral contraceptives and transdermal devices provide a variety of estrogen and progesterone forms and dosing options.

Ovarian hormone replacement therapy (HRT) regimens differ for survivors who were prepubertal before cancer therapy and those who experience gonadal failure after menarche.46-50 Timing and tempo of estrogen HRT in the pubertal patient are crucial to ensure an acceptable final height and should be managed by a provider with
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### Precocious puberty

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#### Radiotherapy:

- Cranial, orbital/eye
- Ear/infratemporal
- Nasopharyngeal
- Waldeyer’s ring

#### Host factors:

- Younger age at treatment
- Treatment factor: Radiation dose \( \geq 18 \text{ Gy} \)

#### Physical examination (yearly until sexual maturity): Height/weight

#### Tanner staging

### Uterine vascular insufficiency

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#### Radiotherapy:

- Spine (lumbar, sacral, whole)
- Flank/hemabdomen below iliac crest
- Whole abdomen/TLI/TBI
- Inverted Y
- Pelvic/iliac/bladder

#### Host factor:

- Women with Wilms tumor and associated Müllerian anomalies

#### History (yearly and as clinically indicated): Adverse pregnancy outcomes

#### Low-birth weight infant

#### Sponatenous abortions

#### Fetal malposition

#### Premature labor

### Sexual dysfunction

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#### Radiotherapy:

- Flank/hemabdomen below iliac crest
- Whole abdomen/TLI
- Inverted Y
- Pelvic/iliac
- Vaginal/bladder

#### Hematopoietic cell transplantation:

- GVHD

#### Surgery:

- Pelvic surgery
- Ictometry
- Neurosurgey (spinal cord)

#### Host factors:

- Chronic GVHD
- Hypogonadism
- Tumor adjacent to spinal cord or cauda equina
- Vaginal tumor or pelvic tumor adjacent to vagina

#### Treatment factors:

- Prepubertal (onset \( \geq 25 \text{ Gy} \))
- Postpubertal (onset \( \geq 50 \text{ Gy} \))
- GVHD plus pelvic irradiation

#### History (yearly): Psychosocial assessment

#### Altered or diminished sensation

#### Medication use

#### Dyspareunia

#### Vulvar pain

#### Postcoital bleeding

#### Difficulty with tampon insertion

### Abbreviations:

COG, Children’s Oncology Group; FSH, follicle-stimulating hormone; GVHD, graft-versus-host disease; HRT, hormone-replacement therapy; HSCT, hematopoietic stem-cell transplantation; LH, luteinizing hormone; TBI, total body irradiation; TLI, total lymphoid irradiation.
expertise in pediatric development (eg, pediatric endocrinologist, adolescent gynecologist).

Postmenarchal women who cease menstruating during or after cancer therapy can be monitored for resumption of menses for 1 year. Those who remain amenorrheic, have symptoms of gonadal failure, or have elevated gonadotropins should be offered HRT in consultation with a specialist.

Ovarian function cannot be reliably assessed during HRT for contraception or gonadal failure. Many patients erroneously assume that menstrual cycles indicate fertility. Because gonadotoxic therapy can cause POF, the HP-gonadal (HPG) axis should be periodically assessed without any HRT. HRT can also benefit cardiovascular and bone health. Ovarian failure reduces risk of radiation-associated breast cancer, but the effect of HRT on breast cancer risk in childhood cancer survivors is unknown.

**Reduced Fertility**

Fertility may be reduced by removal or damage of the reproductive organs or disruption of the HPG axis. Young adult survivors with normal ovarian function after ovary-toxic therapy have diminished ovarian reserve and are at risk of POF and reduced fertility. Furthermore, onset of POF may be masked by regular menstrual cycles with oral contraceptives.

**Risk Factors**

Fertility can be impaired by factors that impede conception, implantation, and carriage of pregnancy to term. In the CCSS, RR of a pregnancy was 0.81 (95% CI, 0.73 to 0.90; P < .001) in 5,149 female survivors age 15 to 44 years, as compared with 1,441 age-matched siblings. In multivariate models, survivors treated with an HP radiation dose ≥ 30 Gy or ovarian/uterine dose > 5 Gy were less likely to have been pregnant than those treated with lower doses, and survivors who experienced higher cumulative alkylating agent exposure had less likelihood of pregnancy than those who received no alkylating agents. Survivors with normal ovarian function at risk of therapy-related orophorectomy on fertility in childhood cancer survivors is unknown. Those with a single ovary (congenital or otherwise) have normal potential to conceive, either naturally or by in vitro fertilization (IVF), but should expect a shorter reproductive period.

**Assessment**

The COG-LTFU Guidelines recommend yearly height, height velocity, and Tanner stage evaluations for survivors at risk of PP. Some, but not all, survivors with PP experience accelerated height velocity. Patients with Tanner 2 breast development before age 8 years should be referred to a pediatric endocrinologist after LH, FSH, and estradiol levels are assessed. Bone age should be assessed in rapidly growing children, and where possible, a pelvic ultrasound should be included to assess ovarian volume and uterine size and stimulation. Premature activation of the HPG axis is indicated by elevated basal LH, advanced bone age, and ultrasonic evidence of uterine stimulation. The endocrinologist may perform a GnRH-stimulation test to identify elevation of peak LH level. Diagnostic imaging of the head may be considered for patients with neurologic symptoms suggestive of other intracranial pathologies.

**Treatment**

Treatment for PP uses GnRH analogs to preserve final adult height, delay menarche, and optimize development of secondary sex characteristics. Through continuous stimulation, these analogs desensitize the gonadotrophs and reduce LH release, thus halting ovarian stimulation. Treatment usually continues until the normal age of puberty.
**Pretreatment Fertility Preservation**

Modification of primary treatment to preserve fertility (tailoring/shielding radiation fields around the gonads, gonad-sparing surgery) should always be discussed by the treating oncologist. Fertility-sparing surgery may be attempted in gynecologic cancer, but other treatment-related factors may adversely affect fertility.83 Pretreatment oophoropexy may decrease risk of radiation-induced ovarian dysfunction.84,85 Use of GnRH analogs (for suppression of LH and FSH production) for ovarian chemoprotection is experimental and controversial and should only be used in randomized controlled trials.41,86-98 It is questionable if GnRH treatment will work, because primordial follicles are not gonadotropin sensitive,93 and although other alternative mechanisms have been offered, all are theoretic and unproven.99,100 Apoptosis inhibitors, which may induce ovarian dormancy by obstructing genetically programmed cell death, are experimental; their effect on cancer treatment outcome is unknown, and their effect on fertility is unproven.101

Most successful assisted reproductive techniques depend on harvesting and banking the postpubertal patient’s oocytes and cryopreserving102,103 unfertilized oocytes or embryos before gonadotoxic therapy. Options for prepubertal patients are limited. Ovarian tissue cryopreservation for later autotransplantation104 may be offered to girls with nonovarian, nonhematologic cancers, but this is still experimental.105-107 In vitro maturation of ovarian follicles to produce mature oocytes eliminates the risk of cancer cell reintroduction; however, this is still technically challenging and in its early phases of research.108 Because the field of fertility preservation is rapidly evolving, enrollment in experimental protocols that harvest ovarian tissue for future in vitro maturation may be considered, even when there is risk for ovarian cancer involvement.

A significant barrier may lie in the treating oncologists’ lack of awareness or knowledge about facilitating expedited preservation. In a nationwide survey of pediatric oncologists, 73% agreed that all pubertal female patients should see a fertility preservation specialist before cancer therapy, but only 23% consistently made a referral.109 Only 44% were familiar with the 2006 American Society of Clinical Oncology fertility preservation recommendations,80 and most used them in fewer than one quarter of patient cases.109

Fertility preservation may not be feasible for patients with rapid disease progression who require immediate therapy. The advanced planning necessary for some of these procedures, such as ovarian stimulation for emergency IVF and oocyte cryopreservation, can take 2 to 4 weeks.110 Embryo cryopreservation may not be appropriate for patients age < 18 years because of concerns about informed consent and use of donor sperm. Furthermore, costs may be prohibitive, especially if the physician is unaware of available support resources. Decisions about fertility preservation in prepubertal girls are complicated by biologic, psychosocial, and ethical implications.111

**Post-Treatment Reproductive Options**

For survivors who experience infertility or POF, third-party reproduction through egg donation or surrogacy may be an option.112,113 Other survivors may consider adoption. However, expense is a barrier to both these options. IVF may be partially covered by health insurance, but out-of-pocket expenses may be prohibitive, and multiple rounds of IVF treatment may be necessary.114 The cost of adoption can be comparable, although domestic agencies may have a sliding scale based on household income. Significant legal fees may be incurred to find a child for private adoption and finalize the adoption. Cancer survivors in some countries may encounter exclusionary policies related to cancer history or be required to document ≥ 5 years of disease-free survival or obtain their oncologist’s certification of a predicted normal lifespan.112 Oncologists and centers caring for young patients with cancer should know the resources available to patients who wish to become parents, such as FertileHOPE (www.fertileHOPE.org) and the Young Survival Coalition (www.youngsurvival.org).

**Ethical Considerations in Fertility Preservation**

Fertility discussions can be challenging to both patients and providers. The few fertility preservation options available may be considered inappropriate topics for discussion with children, adolescents, or young adults who are not yet sexually active.115 Adolescent survivors and their parents have reported low satisfaction with the information received about infertility risks.116 Infertility can cause emotional distress, affect overall quality of life,117 and lead to psychosocial problems118,119 and symptoms of mild posttraumatic stress disorder.120 Experimental fertility preservation is a sensitive topic, especially for minors, because ethical and legal norms require that minors should only undergo procedures that serve their best interests.121 An invasive experimental procedure requires the assent of a minor.122 Parents are not allowed to provide consent for procedures with more than minimal risk without proven net benefit to a child too young to assent.122,123

A survey showed that 81% of teenage girls with cancer and 93% of their parents were interested in using research-based methods to preserve fertility.124 Although most survivors desire to bear their own children and believe their cancer experience will make them better parents,117 many have unnecessary anxiety about the risk of birth defects,117,125,126 which are not more frequent among their offspring.127,128 A study of 4,699 children born to 1,128 male and 1,627 female participants in the CCSS found no association between parenteral mutagenic exposure (alkylating agent doses, gonadal irradiation) and risk of congenital anomalies.129,130

Other ethical considerations concern potential harm to the offspring from being born to a cancer survivor. For example, the parent may face a significantly shortened lifespan or impaired ability to care for the child (because of physical and/or cognitive disability).121 Ethical analyses suggest that these would not be reasonable grounds to deny survivors the opportunity to reproduce.131 A more extreme question is the posthumous use of stored tissue for reproduction. It is paramount that the disposition of tissue in case of death be clearly documented at the time of collection. Although many courts recognize children born after posthumous conception or implantation as the legal offspring of the parent who consented to reproduction after his or her death,121 a recent US Supreme Court hearing denied social security benefits to posthumously born children.

**SEXUAL DYSFUNCTION**

Cancer and its treatment may predispose survivors to sexual dysfunction.132-135 There is limited information about sexual function and sexuality in childhood cancer survivors. In a study of 23 survivors of pediatric pelvic rhabdomyosarcoma,136 11 who had not undergone
bilateral oophorectomy experienced ovarian failure: four had fistulas, four required vaginal dilation for stenosis, and three underwent vaginal reconstruction. These outcomes could profoundly affect sexuality. Additional research is needed to elucidate the impact of childhood cancer on sexual function.

**Risk Factors**

Cancer treatment may alter the female reproductive system both anatomically and hormonally. After pelvic irradiation, blood flow to the vagina and vulva may be impaired, and scarring may develop. Vaginal scarring caused by post-transplantation graft-versus-host disease can result in vaginal and vulval dryness and vaginal shortening that can cause dyspareunia. Surgery and irradiation may affect the vestibular glands, causing dryness. Removal of all or part of the vulva and vagina may reduce sensation or cause dyspareunia. Sexual dysfunction after surgical procedures such as radical hysterectomy in adults seems to be related to prior sexual difficulties or depression and not related to the procedures themselves. This suggests that hysterectomy alone in this young population may not explain future risk of sexual dysfunction.

Hormones are important in female sexual functioning, and low serum estrogen causes vaginal atrophy and higher vaginal pH, which can result in infections, incontinence, and sexual dysfunction. Lack of estrogen can reduce vaginal lubrication and expansion on stimulation. Estrogen also indirectly regulates vaginal and ditoral nitric oxide, which promotes vaginal mucosal health and mediates relaxation of smooth muscle; thus, medications that promote nitric oxide–mediated smooth muscle relaxation may help to treat female sexual arousal disorder.

**Assessment**

Sexual functioning should be assessed annually in adult survivors at risk of sexual dysfunction and should include genital sensation level, dyspareunia, vulvar pain, postcoital bleeding, and difficulty with tampon insertion. Current medications should be listed to identify any that may affect sexual function. Domains of sexual functioning, such as desire, arousal, lubrication, orgasm, satisfaction, and pain, should be assessed to rule out sexual dysfunction. Standardized questionnaires (eg, the Female Sexual Function Index and Brief Index of Sexual Functioning–Women) can be helpful. Providers should initiate discussions, because patients may be too embarrassed or believe there is no treatment. Sexual evaluation can be complex in survivors who have never had so-called normal sexual function or whose understanding of normal female anatomy and sexual function is limited.

**Treatment**

Sexual rehabilitation should incorporate both the physical and psychosocial aspects of sex. Both providers and patients tend to avoid this topic, although 80% of women report a desire to discuss sexual issues. No medications are currently available to assist women with loss of sexual desire, but gynecologic consultation can include discussion of low-dose vaginal estrogen or lubricants. Unfortunately, vaginal stenosis and agglutination are difficult to reverse. In adults, vaginal dilators can be used as preventives after pelvic irradiation or grafted host disease; their use in children has not been described. Pelvic floor dysfunction, which can cause urinary and bowel incontinence, pelvic pain, and sexual dysfunction, is treatable with physical therapy.

Survivors may have depression, poor body image, or other psychosocial or psychoemotional issues that can be addressed by counseling, sex therapy, or both. Because sexual function and satisfaction are important aspects of quality of life, psychoeducational interventions should be considered to help survivors understand and cope with the physical and sexual changes caused by treatment.

**REFERENCES**


**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

The author(s) indicated no potential conflicts of interest.

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