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SPECIAL ARTICLE

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

Monika L. Metzger, Lillian R. Meacham, Briana Patterson, Jacqueline S. Casillas, Louis S. Constine, Nobuko Hijiya, Lisa B. Kenney, Marcia Leonard, Barbara A. Lockart, Wendy Likes, and Daniel M. Green

Monika L. Metzger and Daniel M. Green, St Jude Children's Research Hospital, Memphis, TN; Monika L. Metzger and Wendy Likes, University of Tennessee, Memphis, TN; Lillian R. Meacham and Briana Patterson, Emory University, Atlanta, GA; Jacqueline S. Casillas, University of California at Los Angeles, Los Angeles, CA; Louis S. Constine, University of Rochester, Rochester, NY; Nobuko Hijiya, Northwestern University; Barbara A. Lockart, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL; Lisa B. Kenney, Dana-Farber Cancer Institute and Children's Hospital Boston, Boston, MA; and Marcia Leonard, University of Michigan, Ann Arbor, MI.

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Corresponding author: Monika L. Metzger, MD, MSc, 262 Danny Thomas Pl, Memphis, TN 38105; e-mail: monika.metzger@stjude.org.

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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.

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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 $\geq$ 10 Gy confer higher risk. In prepubertal girls, higher radiation dose (ie, $\geq$ 10 Gy) is associated with impaired ovarian function, and dose $>$ 15 Gy confers higher risk. Mathematic 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 $\geq$ 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% *v* 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.[25,26]

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,[28,36-41] 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

Table 1. Recommended Assessment of Treatment-Associated Female Reproductive and Sexual Function: Summary of COG Guidelines

Late Effect or Complication	Associated Therapies	Risk Factors	Assessment	Counseling and Additional Considerations
Hypogonadism Gonadotropin deficiency Delayed/arrested puberty Acute ovarian failure Premature menopause Infertility	Chemotherapy: · Alkylating agents · Heavy metals · Nonclassical alkylators Radiotherapy: · Cranial (≥ 40 Gy) · Cranial, orbital/eye · Ear/infratemporal · Nasopharyngeal · Waldeyer's ring · Ovarian (any dose) · Spine (lumbar, sacral, whole) · Flank/hemiabdomen below iliac crest · Whole abdomen/TLI/TBI · Inverted Y · Pelvic/iliac/vaginal/bladder Surgery · Oophorectomy	Host factors: · Older age at gonadal irradiation Treatment factors: · Higher cumulative doses or combinations of alkylators (busulfan > 600 mg/m^2, cyclophosphamide > 7.5 g/m^2 or as conditioning for HSCT) · Prepubertal gonadal irradiation (≥ 10 Gy) · Pubertal gonadal irradiation (≥ 5 Gy) · Alkylators plus irradiation of: —Abdomen/pelvis —Lumbar or sacral spine —Neuroendocrine axis —TBI · Longer time since treatment Health behaviors: · Smoking	History (yearly): · Pubertal (onset, tempo) · Menstrual/pregnancy · Sexual function (vaginal dryness, libido) · Medications relevant to sexual function Physical examination (yearly until sexual maturity): · Tanner staging Screening: · LH, FSH, and estradiol (baseline at age 13 years and as clinically indicated by delayed puberty, irregular menses, primary or secondary amenorrhea, and/or clinical signs and symptoms of estrogen deficiency)	Referral: · Endocrinology/gynecology for delayed puberty, persistently abnormal hormone levels, or hypogonadism · Reproductive endocrinology for infertility evaluation and consultation on assisted reproduction or gestational surrogate · Consider oocyte cryopreservation for patients who wish to preserve fertility options Associated considerations: · Evaluation of bone mineral density in hypogonadal patients Counseling: · Counsel menstruating women at risk of early menopause about risk of delaying childbearing · Counsel all patients on need for contraception because alkylator-associated gonadal toxicity is extremely variable · Counsel regarding benefits of HRT in promoting pubertal progression and bone and cardiovascular health Resources: · American Society for Reproductive Medicine (www.asrm.org) · Fertile Hope (www.fertilehope.org)
Precocious puberty	Radiotherapy: · Cranial, orbital/eye · Ear/infratemporal · Nasopharyngeal · Waldeyer's ring	Host factor: · Younger age at treatment Treatment factor: · Radiation dose ≥ 18 Gy	Physical examination (yearly until sexual maturity): · Height/weight · Tanner staging	Referral: · Endocrine consultation for accelerated puberty (age < 8 years) Laboratory: · FSH, LH, and estradiol as clinically indicated by accelerated pubertal progression and growth Radiology: · X-ray for bone age in rapidly growing children · Consider pelvic ultrasound to rule out ovarian tumor Resource: · Magic Foundation (www.magicfoundation.org)
Uterine vascular insufficiency	Radiotherapy: · Spine (lumbar, sacral, whole) · Flank/hemiabdomen below iliac crest · Whole abdomen/TLI/TBI · Inverted Y · Pelvic/iliac · Vaginal/bladder	Host factor: · Women with Wilms tumor and associated Müllerian anomalies Treatment factors: · Higher pelvic radiation dose · Radiation dose ≥ 30 Gy	History (yearly and as clinically indicated): · Adverse pregnancy outcomes · Low–birth weight infant · Sponatenous abortions · Fetal malposition · Premature labor	Radiology · High-level ultrasound evaluation of genitourinary tract after pubertal development as clinically indicated in patients contemplating pregnancy
Sexual dysfunction Vaginal fibrosis/stenosis	Radiotherapy: · Flank/hemiabdomen below iliac crest · Whole abdomen/TLI · Inverted Y · Pelvic/iliac · Vaginal/bladder Hematopoietic cell transplantation: · GVHD Surgery: · Pelvic surgery (cystectomy) · Neurosurgery (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 (≥ 25 Gy) · Postpubertal (≥ 50 Gy) · GVHD plus pelvic irradiation	History (yearly): · Psychosocial assessment · Altered or diminished sensation · Medication use · Dyspareunia · Vulvar pain · Postcoital bleeding · Difficulty with tampon insertion	Referral: · Gynecologic consultation for management · Psychological consultation for patients with emotional difficulties

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.[51,52] 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.[53,54]

PRECOCIOUS PUBERTY

PP is early activation of the HPG axis. Premature pulsatile secretion of GnRH induces release of LH and FSH. Importantly, adrenarche (pubic or axillary hair) is not a sign of activation of the HPG axis in girls, whose first physical sign of puberty is breast development (thelarche). Although some healthy girls experience thelarche before age 8 years, its timing differs with ethnicity[55] and may be accelerating among US girls.[56] Tanner stage 2 breast development before 8 years of age is a reasonable definition of PP.[55,57,58]

Risk Factors

PP may occur after cranial irradiation that includes the hypothalamus (Table 1).[2] Radiation doses $\geq$ 18 Gy administered to the cranium, orbit/eye, ear/infratemporal region, nasopharynx, or Waldeyer's ring are a significant risk factor, and risk increases with younger age at time of irradiation.[59-62]

Assessment

The COG-LTFU Guidelines recommend yearly height, height velocity, weight, and Tanner stage evaluations for survivors at risk of PP.[2] 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 assayed. 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.[63,64]

Treatment

Treatment for PP uses GnRH analogs to preserve final adult height, delay menarche, and optimize development of secondary sex characteristics.[65] Through continuous stimulation, these analogs desensitize the gonadotrophs and reduce LH release, thus halting ovarian stimulation.[66] Treatment usually continues until the normal age of puberty.[67-69]

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.[25] In multivariate models, survivors treated with an HP radiation dose $\geq$ 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.[70] Lomustine and cyclophosphamide reduced the likelihood of pregnancy in a dose-dependent manner.[71] Survivors who become pregnant after pelvic irradiation at an early age are at risk of spontaneous abortion, low–birth weight infant, fetal malposition, and premature labor resulting from uterine dysfunction (restricted blood flow and/or impaired growth).[71,72] Survivors of Wilms tumor, who may have associated Müllerian abnormalities and/or may receive $\geq$ 30 Gy of pelvic irradiation, are at greatest risk of adverse pregnancy outcomes.[73-75]

Fertility outcomes after oophoropexy are uncertain. The procedure protects the ovaries by transposing them out of the radiation field. If shielding is successful, normal ovarian function and fertility can be expected[25]; however, overall pregnancy success rate is felt to be approximately 50% because of a combination of scatter radiation, alteration of ovarian blood supply, and fallopian tube damage.[76-80]

The effect of unilateral oophorectomy 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),[81,82] but should expect a shorter reproductive period.[16]

Assessment

The COG-LTFU Guidelines recommend annual pregnancy and childbirth history in survivors at risk of reduced fertility or adverse pregnancy outcomes. History of menstrual cycles, sexual function and libido, and evaluation of Tanner stage and external genitalia can detect early problems. Laboratory screening should include LH, FSH, and estradiol levels for all women who wish to become pregnant. Recommendation to assess AMH is not yet included in the guidelines but may be in the future after additional investigations have been completed. Diagnostic imaging of genitourinary anomalies, ovarian reserve, uterine blood flow, and tubal patency should also be considered. Women unable to conceive spontaneously should be referred to a reproductive endocrinologist. Survivors with normal ovarian function at risk of therapy-associated POF should be counseled about this risk.

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 cryopreserving[102,103] unfertilized oocytes or embryos before gonadotoxic therapy. Options for prepubertal patients are limited. Ovarian tissue cryopreservation for later autotransplantation[104] 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 $\geq$ 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 problems[118,119] 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 parental 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.[136] Vaginal scarring caused by post-transplantation graft-versus-host disease can result in vaginal and vulval dryness and vaginal shortening that can cause dyspareunia.[137] 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.[138] 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.[139] Lack of estrogen can reduce vaginal lubrication and expansion on stimulation. Estrogen also indirectly regulates vaginal and clitoral 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.[140]

Assessment

Sexual functioning should be assessed annually in adult survivors at risk of sexual dysfunction and should include genital sensation level,[141] dyspareunia, vulvar pain, postcoital bleeding, and difficulty with tampon insertion.[142] 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.[143] 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.[144] 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.[145] Unfortunately, vaginal stenosis and agglutination are difficult to reverse. In adults, vaginal dilators can be used as preventives after pelvic irradiation or graft-versus-host disease[146]; 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.[147]

DISCUSSION

Risk of gonadal, reproductive, and sexual complications in female cancer survivors varies according to cancer type, age at diagnosis, and therapeutic exposure. Oncologists should be aware of potential complications that may affect long-term reproductive and sexual health and discuss them in a developmentally appropriate way with patients and families before treatment. Fertility preservation options for prepubertal girls are experimental and should be offered only within a research study. It is important to review potential sexual and reproductive health risks after completion of therapy and during long-term follow-up and to plan ongoing surveillance measures. After cancer therapy, all patients should have regular assessments of pubertal development, sexual health and function, and pregnancy attempts and outcomes. Survivors at risk of reproductive and sexual complications should be offered the recommended screening and counseling reviewed in this article and may benefit from endocrine, gynecologic, or reproductive consultation. Ongoing research on gonadoprotective drugs and improved shielding of reproductive organs may increase the effectiveness of fertility preservation for prepubertal and postpubertal female patients and optimize long-term reproductive health in childhood cancer survivors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception and design: Monika L. Metzger, Lillian R. Meacham, Jacqueline S. Casillas, Nobuko Hijiya, Lisa B. Kenney, Marcia Leonard, Barbara A. Lockart, Wendy Likes, Daniel M. Green
Collection and assembly of data: Monika L. Metzger, Briana Patterson, Jacqueline S. Casillas, Wendy Likes
Data analysis and interpretation: Monika L. Metzger, Briana Patterson, Jacqueline S. Casillas, Louis S. Constine, Nobuko Hijiya, Barbara A. Lockart, Wendy Likes
Manuscript writing: All authors
Final approval of manuscript: All authors

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