Childhood, Adolescent, and Young Adult Cancer: Fertility Implications and Clinical Practice

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Key Points

- Gonadal toxicity from chemotherapeutic agents and gonadal radiation has been identified.
- CAYA cancer patients should be offered fertility preservation options prior to initiating therapy.
- Reproductive endocrine and urology providers can assist with fertility preservation and evaluate a patient's fertility potential.
- A multidisciplinary approach for cancer patients is optimal to address patient's medical, psychological, and fertility health.

2.1 Introduction

Each year more than 15,000 children age 19 and younger are diagnosed with cancer in the United States [46]. In recent years, adolescent and young adult (AYA) oncology has become a national and international focus as a cohort of patients with special needs at diagnosis, as well as during treatment and survivorship [7]. In general, this selection of cancer patients includes those diagnosed from 15 to 39 years of age and includes approximately 70,000 cancer diagnoses per year in the United States alone [7]. In Europe, the number of children diagnosed with cancer each year ages 0–14 is 15,000, and there is an additional 30,000 who are 15–24 years old at diagnosis [21]. Together, this group of patients are referred to as childhood, adolescent and young adult (CAYA) cancer patients and comprise a wide spectrum of malignancies, and outcomes are dependent upon histology type, disease origin and site, race, sex, and age at diagnosis [16, 63]. Fortunately, advances in treatment and supportive care have led to a significant increase in survival rates for CAYA cancer patients [21, 46]. For purposes of this chapter, we will focus on patients diagnosed at age 30 and younger, but some of the information may be applicable for older patients as well. Patients in this age group are treated on The Children's Oncology Group (COG) cancer treatment protocols as well as adult treatment protocols and clinical trials. The standard of care in CAYA oncology has now changed from prior decades of thinking primarily of cure at all cost. The standard now includes fertility preservation when possible prior to starting treatment for protocols with surgery, radiation, or chemotherapy that negatively affect any component of the hypothalamic-pituitary-gonadal axis and may adversely impact future fertility [29].

Long-term cohort studies of adult survivors of childhood cancer show significant morbidity from cancer treatment, but late mortality rates have improved with reductions of radiotherapy being delivered in treatment protocols [1–3, 6]. Recent studies demonstrate that while more CAYA cancer patients are surviving and thriving, a high percentage of survivors are encountering serious "late effects" from their therapy. These late effects include, but are not limited to, cardiac, pulmonary, and endocrine disorders including impaired fertility, increased morbidity and mortality, and moderately to severely affected status in one or more of the primary domains of health (i.e., general health, mental health, functional status, limitations in activity, fear, or anxiety) [30, 42, 43].

This chapter will not go into detail on the myriad of late effects of CAYA cancer treatment. Rather, we will focus on the fertility effects of treatment which include use of alkylating agents and newer chemotherapeutic agents, radiotherapy with potential exposure to the ovaries, and surgery that involves the reproductive organs that can lead to permanent sterilization or premature ovarian failure in female survivors. These same treatments can cause altered spermatogenesis, testosterone deficiency, and physical sexual dysfunction in male patients who have reached puberty [63]. We will cover research into the psychosocial impact of potential or lost fertility for both males and females and how providers can become their advocates. We will discuss processes for assessment and treatment of impaired fertility with adult survivors of childhood cancer and adult-onset cancer. Lastly, we will review fertility preservation practices for newly diagnosed or relapsed CAYA cancer patients.

2.2 Recent Research on Late Effects and Infertility

The 2007 Woodruff and Synder's Oncofertility book introduced early studies identifying late effects of childhood cancer treatment impacting fertility [71]. Notably, Dr. Julie Byrne, one of the

pioneer investigators in this field, and her 1999 study provided some of the first data on this important complication and found that the principal risk factors for early menopause after cancer were related to treatment after the onset of puberty, treatment with radiation below the diaphragm, and the use of alkylating agent chemotherapy. Byrne found that survivors were twice as likely (RR = 2.32, $p < 0.01$) as their control siblings to reach menopause during their 20s. However, there was no excess risk during their 30s (RR = 0.78). Survivors diagnosed after puberty and treated with radiation below the diaphragm were nearly ten times more likely to reach menopause during their 20s than controls, regardless of their primary diagnosis. The RR was 9.6 for Hodgkin lymphoma survivors and 8.56 for all other cancers [9]. Advances in pediatric and adolescent research have expanded our understanding of fertility outcomes and directed clinical trials research. Recent studies from the Childhood Cancer Survivor Study (CCSS) have demonstrated a higher incidence of infertility rates and reproductive interventions in female survivors enrolled in the CCSS compared to their sibling cohort. When compared to 1366 female sibling controls, 3531 5+ year survivors who enrolled in the study between November 1992 and April 2004 had an increased risk (RR 1.48 [95% CI 1.23–1.78]; $p < 0.0001$) of clinical infertility that was most pronounced at early reproductive ages in participants less than or equal to 24 years old (RR 2.92 [95% CI 1.18–7.20]; $p = 0.020$), in survivors aged 25–29 years (RR 1.61 [95% CI 1.05–2.48]; $p = 0.029$) and in those aged 30–40 years (RR 1.37 [95% CI 1.11–1.69]; $p = 0.0035$). As other studies have demonstrated, the authors reported increasing doses of uterine radiation and alkylating agent chemotherapy were strongly associated with infertility [4].

A 2016 study from the CCSS reported on pregnancy after chemotherapy in 10,938 male and female survivors after receiving treatment with one or more of 14 alkylating and similar DNA interstrand cross-linking drugs of interest without exposure to cranial or abdominal radiation. Results were compared to 3949 sibling controls. Five thousand nine hundred and twenty-two (54%) survivors received at least one alkylating or similar DNA interstrand cross-linking drugs such as cisplatin. Results of a multivariable analysis showed survivors having a decreased likelihood of siring or having a pregnancy versus siblings (male survivors, hazard ratio [HR] 0.63; 95% CI 0.58–0.68; $p < 0.0001$; female survivors, HR 0.87; 95% CI 0.81–0.94; $p < 0.0001$). Their results showed that male survivors who received ifosfamide doses of more than 25,000 mg/m^2, procarbazine doses of more than 3000 mg/m^2, and cisplatin doses of more than 475 mg/m^2 had a significantly reduced chance of siring pregnancies and livebirth compared to survivors with no exposure [12]. For female survivors, data demonstrated that only busulfan of any dose category and lomustine ≥411 mg/m^2) were associated with significantly decreased achievement of pregnancy. Further subanalyses showed female survivors exposed to cyclophosphamide in the upper quartile (≥11,295 mg/m^2) had a lower likelihood of pregnancy than did those not exposed (HR 0.85, 95% CI 0.74–0.98; $p = 0.023$) [12].

The adverse effects of high-dose cranial radiation and direct gonadal radiation on fertility have been widely described [25, 57]. A study from St. Jude Lifetime Cohort Study (SJLIFE) assessed the effect of low doses (<26 Gy) of cranial radiation on sperm concentration of 241 adult survivors of childhood acute lymphocytic leukemia (ALL). Results show that cranial radiation doses (<26 Gy) typically used for central nervous system prophylaxis in patients with ALL had no demonstrable adverse effect on spermatogenesis although a cyclophosphamide equivalent dose (CED) exceeding 8 g/m^2 and an age at diagnosis of 5–9 years did increase the risk of oligospermia and azoospermia [26]. Other studies have demonstrated Leydig cell function being preserved after cancer treatment, but germ cell failure is common in men treated with high cumulative doses of cyclophosphamide (>7500 mg/m^2) [34, 41] and with more than 3 months of combination alkylating agent therapy [22, 27].

The ability of female survivors to carry a pregnancy to term and health of the offspring have been investigated. At-risk groups include patients treated with flank and abdominal radiation such as with patients with Wilm's tumor who have been shown to have early or threatened labor, fetal malposition, and low birth weight, all of which are increased with flank radiation dosages [11, 24]. Female CAYA cancer survivors who received flank or abdominal radiation and are fortunate enough to become pregnant should be managed by a high-risk multidisciplinary team or maternal-

fetal medicine [18]. Other survivors such as those treated for leukemia and lymphoma with anthracycline therapy and/or chest irradiation need to be aware of maternal cardiopulmonary risks and should also be evaluated by a maternal-fetal medicine practice for close surveillance including echocardiograms during pregnancy and delivery and postpartum [37, 61].

A great deal of progress has been made in understanding the effects of chemotherapeutic agents and irradiation on gonadal function. As new chemotherapy agents and other therapies are discovered, research must continue with a focus on their role in not only curing cancer but also the life-altering effects such as infertility and premature menopause they may cause. These same factors and their relationship to the CAYA cancer survivor's quality of life must be investigated and addressed.

2.3 Providers Addressing Psychosocial Implications

Great importance is placed on fertility by adolescent and young adult cancer survivors themselves and by the parents of childhood cancer survivors [45, 64]. Information regarding the impact of diagnosis and treatment on fertility is one of the most cited unmet needs among adolescent and young adult survivors [39, 70, 74]. It is important for providers to recognize this need and address the concern felt by survivors even if medical treatment may not affect fertility. Fertility implications of diagnosis and treatment need to be addressed at the time of diagnosis but also after treatment has been completed as many CAYA cancer patients do not process their concerns until they are actively thinking about having children.

Reproductive concerns in survivors have been associated with depression and anxiety symptoms, grief, lowered self-esteem, and an altered sense of identity [14]. Fertility-related distress may become more acute as these survivor populations move past their treatment and consider building a family, and many survivors do not know their fertility status [48]. An exploratory study looking at the experiences of 38 survivors over time in terms of managing fertility matters following cancer treatment in their teens found that professional and social networks did not provide many opportunities for these survivors to ask questions, receive information, process feelings, or develop handling strategies. The study also found that for some survivors, fertility matters affected identity, well-being, and life planning as well as reproductive function [15].

Providers who are aware of survivors' concerns about fertility, whether founded or imagined, can have a great impact on the well-being of their patients. Secondary analyses of a qualitative study of young adult survivors of adolescent cancers by Benedict et al. concluded that females may be more at risk for distress than males, particularly in situations of uncertainty and limited knowledge regarding fertility implications of their primary disease or secondary to treatment [5]. How and when to address fertility issues may be some of the barriers to providing information to survivors. CAYA cancer survivors may still be developing cognitive and emotional abilities to manage stress and cope effectively as they mature [75]. This limitation along with parental buffering and clinicians' discomfort addressing fertility issues may result in survivors not receiving adequate information and support around fertility issues [28, 55]. Increased attention to fertility may help to alleviate CAYA's distress, facilitate engagement in decision-making about their reproductive future, and improve long-term well-being in survivorship.

Benedict et al. also found that discussing fertility elicited emotional reactions for most participants ranging from expressions of distress to feelings of hope and positivity [5]. The distress felt by participants included feeling upset, nervous, overwhelmed, and angry. Those participants who were unsure of the gonadotoxic effects of their treatment anticipated feeling devastated, hurt, and lonely if they were unable to have children. For some of the participants, this distress was associated with feeling different from their peers and excluded from normalcy in reaching parenthood [5]. Eighteen percent of participants in this study reported little to no concern about their fertility, and surprisingly, this lack of concern was not limited to those who knew that their fertility had not been affected [5]. Care providers who assume they can predict whether their survivors will have psychosocial effects from fertility concerns will miss opportunities to provide comprehensive care if they do not address the issue with their patients. Care providers will also have to build relationships with their survivors in

efforts to understand the survivor's maturity and their ability to process fertility-related issues and concerns.

Survivors in the Benedict et al. study used a variety of strategies in dealing with fertility concerns including acceptance, avoidance, and taking comfort in the availability or success of assisted reproductive technology [5]. Therefore, counseling should include a balanced approach of allowing for optimism as well as setting realistic expectations. Some CAYAs may still worry about their reproductive health even if their treatment was not gonadotoxic despite provider reassurance [33]. A qualitative study by Quinn et al. found that female adolescent participants had two categories of coping styles in reaction to questions regarding loss of fertility: emotion-focused and problem-focused [56]. Wishful thinking, externalizing, and other emotion-focused coping styles are traditionally viewed as maladaptive when compared to information-seeking and other active coping styles [68]. Although these concepts are not universally held, providers aiming for successful interventions should seek to uncover CAYAs' values and presumptions about future parenthood and reproduction in hopes of assisting the psychosocial stressors and development of adaptive coping mechanisms.

The individuals within the CAYA cancer population are unique in their reaction to the gonadotoxic effects of treatment, their ability to address their concerns, and the adaptive mechanisms they employ to deal with these stressors. Practitioners should strive to become comfortable with addressing fertility effects of treatment but most importantly develop strategies to gauge their survivors' needs and limitations.

2.4 Assessment of Fertility Status in CAYA Survivors of Cancer

Many survivors of CAYA cancer are aware that their prior treatment had potentially gonadotoxic effects. However, if and when they were counseled in the past, clinicians were unlikely to have given them a definitive prediction on their future fertility status. As previously mentioned, how robustly cancer treatment affects reproductive function depends on the type and total dose of chemotherapy and if they received pelvic radiation. As female and male survivors begin to inquire more actively about their fertility status and consider building a family, they should be encouraged to consult with their primary care physicians and also consider seeking specialized consultations with a reproductive endocrinology and fertility specialist or a reproductive urologist. In the United States, there are more than 384 fertility centers in 49 states that are members of the Society for Assisted Reproductive Technology. Of these, 77 are committed members of the Oncofertility Consortium, which is a national, interdisciplinary initiative designed to explore the reproductive future of cancer survivors, and many more centers provide this care outside of the consortium.

Table 2.1 Semen analysis

Parameter	Reference value
Ejaculate volume	1.5 mL
Sperm concentration	15 million sperm/mL
Total sperm	39 million sperm/mL
Motile sperm	40%
Progressively motile sperm	32%
Normal morphology	4%

Data derived from World Health Organization [72]

For men, a clinical assessment of the current health status, reproductive history, medications, prior chemotherapy, radiation, or abdominal or genitourinary surgery should be made [53]. Symptoms of low testosterone, including low libido, erectile or ejaculatory dysfunction, inability to gain muscle mass, etc., can also be signs of poor reproductive function. Next, a semen analysis should be performed. As shown in Table 2.1, a semen analysis evaluates the volume of the ejaculate, the concentration of sperm, and the proportion of sperm that are motile and are morphologically normal [72]. At a minimum, a primary care physician can perform a medical and reproductive history and at least one semen analysis. If abnormal, the patient should be referred to a reproductive specialist, who will perform a physical exam focusing on secondary sex characteristics and the genitourinary anatomy. The etiology of abnormal sperm parameters should be further explored by an endocrinology evaluation,

specifically looking at follicle-stimulating hormone (FSH) and luteinizing hormone, testosterone, and estradiol, while also excluding other etiologies for abnormal hormone levels by assessing both prolactin and thyroid-stimulating hormone. A normal semen analysis in the setting of normal hormone levels is reassuring that the survivors' fertility is minimally affected by his prior therapy.

In contrast to men, who have stem cells in their testes and create new sperm regularly, women are born with a finite number of oocytes that decrease in quantity and quality over time. While women's fertility assessment can be initiated with their primary care physician, assessing ovarian reserve is complex and prompt referral should be made to their gynecologist or reproductive endocrinology and infertility specialist. A fertility evaluation should start with a clinical history assessing overall health, prior surgeries (specifically abdominal or pelvic), prior chemotherapy, and prior radiation [52]. Focus should then be placed on her reproductive health, including prior pregnancies, pregnancy outcomes, and history of pelvic infections, and, most importantly, a careful menstrual history should be elicited. While normal menstrual cycles seem reassuring, cycling every 28 days is not a predictor of fertility. An abnormal menstrual cycle length is defined as less than 21 or greater than 35 days [51]. However, subtle changes, such as premenstrual spotting and shortening cycles, can be indicators of diminishing ovarian reserve and should not be ignored. Absence of menstrual cycles may be a sign of primary ovarian insufficiency and should be further evaluated.

Ovarian reserve is best assessed by both serum analysis and pelvic ultrasound [54, 67]. Anti-Müllerian hormone (AMH) is a protein secreted by the granulosa cells surrounding oocytes early in the process of folliculogenesis. AMH is the most sensitive assessment of the ovarian reserve, and normative values are adjusted by age; the lower the number, the smaller the pool of remaining oocytes [60]. Interestingly, the AMH value does not predict a woman's current fertility, but a lower than expected value could suggest that her reproductive time span will be shortened and her fertility will decline earlier than would be expected [65]. In addition, this value is most useful as a predictor of ovarian response to stimulation by exogenous gonadotropins, which is particularly relevant when considering fertility preservation via egg or embryo freezing or if actively seeking fertility treatment [60] (Table 2.2). Pelvic ultrasound counting the number of antral follicles is similarly sensitive and usually corroborates the interpretation of AMH. Measuring basal serum FSH early in the menstrual cycle (ideally cycle day 3) is also predictive of ovarian reserve. While less sensitive than AMH, FSH is more specific in diagnosing severely diminished ovarian reserve or primary ovarian insufficiency. FSH levels above 15 mIU/mL are suggestive of this diagnosis and, most importantly, suggest that fertility treatments have limited benefits above spontaneous conception. Even when fertility treatments are not successful, conception is possible as long as spontaneous ovulation continues to occur [50].

Table 2.2 Anti-Müllerian hormone values by age

Age (years)	Median (ng/mL)	Mean (ng/mL)	1 Standard deviation
25	3.2	4.1	4
30	2.4	3.2	3.2
35	1.3	2.1	2.5
40	0.7	1.1	1.3
45	0.3	0.5	0.9

Data derived from 17,120 women in US Fertility Centers

Ultimately, no clinical history or laboratory test is a perfect predictor of current or future fertility. Only attempting pregnancy will give patients their definitive answer. However, if patients are not yet ready to conceive but desire information, further testing is a reasonable approach and can help with family planning.

2.5 Fertility Preservation for CAYA Cancer Patients

As survival rates for CAYA cancers have risen over the last decades, many adult survivors of are left to deal with sequelae of treatment years and even decades after completion of therapy. Research shows patients are troubled by the potential of infertility during and after cancer

treatment [8, 59]. In an effort to improve the health and quality of life for survivors, advances in reproductive medicine and the emergence of oncofertility as a discipline prompted the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) to develop clinical guidelines for healthcare providers working with these patient populations [13, 38]. From 2006 to 2016, over a hundred articles were published in the field of fertility preservation alone in the childhood and adolescent cancer population, and multidisciplinary fertility preservation programs are being developed around the country [10, 32].

Fertility preservation in pediatric and adolescent patients is more complex than in young adult patients for a multitude of reasons. Prepubertal patients only have experimental fertility preservation options available to them. Children and adolescents may lack capacity to envision a future in which they want children but in adulthood regret a decision to not pursue fertility preservation when offered. There are ethical concerns regarding parents making generational choices for their children and potentially future grandchildren [40]. Additionally, the literature expresses concern that offering fertility preservation may create false hope which can be of particular concern with prepubertal patients where long-term survival and the likelihood of pregnancy in adulthood are distant and dependent on future studies and advances in available reproductive technologies and medicine [19].

Fertility preservation options available to CAYA cancer patients may be limited for several reasons. Experimental options available to prepubertal patients require Institutional Review Board (IRB) approval and are offered at a small number of pediatric institutions. Young adult patients diagnosed with a "pediatric" malignancy such as acute lymphoblastic leukemia or rhabdomyosarcoma may receive care at a pediatric institution due to pediatric oncology team's expertise treating pediatric cancers. The patient's access to fertility preservation may be limited due to the providers' lack of knowledge of fertility preservation options or due to challenges coordinating care between the pediatric institution and reproductive medicine team. Refer to Table 2.3 for a brief overview of fertility preservation options [19].

The majority of pediatric oncology physicians, advanced practice providers (APPs), and registered nurses (RNs) support educating patients and families on the risk of infertility and options for fertility preservation. Referral practices for fertility preservation in CAYAs show a discrepancy between the providers' beliefs and practices [35]. There are a multitude of factors that influence the practice of fertility preservation as identified by physicians, APPs, and RNs. Most commonly acknowledged issues are an urgency to start treatment, lack of clarity about a patient's and family's desire for the information, and concerns about cost. Lack of educational materials, unfamiliarity with options, and no relationship

Table 2.3 Fertility preservation options

	Fertility preservation option	Experimental
Prepubertal males	Testicular tissue cryopreservation	Yes
Postpubertal males		
Prepubertal males	Orchiopexy	No
Postpubertal males	Testicular shielding	
Postpubertal males	Sperm banking	No
	Testicular sperm extraction	
	Post-masturbation sperm banking	
	Electroejaculation	
Prepubertal females	Ovarian tissue cryopreservation	Yes
Postpubertal females		
Postpubertal females	Oocyte cryopreservation	No
	Embryo cryopreservation	
Pre- and postpubertal females	Oophoropexy	No
	Ovarian shielding	
Pre- and postpubertal females	GnRH agonists	No consensus

Fernbach et al. [19]

with a reproductive medicine team are also identified as obstacles to fertility care in CAYA patient populations [20, 23, 69]. Two studies report nonwhite patients are less likely than Caucasian patients to receive fertility preservation counseling [58, 62].

Other challenges to education and access for fertility preservation include the patients' and families' culture, religion, race, language, health literacy, and cognitive level of the patient and parents. Stressors such as child care, parental relationship, and access to healthcare may all impact the individual's ability to process information and influence decision-making. Concerns regarding when a child should be included in medical decision-making and what influence the child should exert, especially regarding experimental options, impact the pursuit of fertility preservation. Adolescents are more likely than children to identify concerns about infertility make them uneasy, rather than having concerns about the procedure. Parents are shown to influence the fertility preservation decision more than physicians [73].

The burden of consent is greater when a family is considering an experimental procedure, rather than a standard treatment such as sperm banking, or when consenting for life-saving medical treatment. Neither child nor parent should feel they are coerced to make a decision. Weighing the child's ability to grasp the risk versus benefit of an experimental procedure and the parents' ability to make a decision in the child's best interest is paramount. The depth of information provided to patients is adjusted to age and cognitive level. Providing information in developmental appropriate terms may require assistance from psychologists, social workers, or child life therapists adept at sexual health discussions. Genetic counseling prior to fertility preservation should be considered if the family has a known hereditary cancer syndrome or if the patient is undergoing stem cell transplant for a condition such as sickle cell disease or thalassemia [49].

Discussions surrounding fertility preservation and consenting for procedure must be performed in the patient's and family's native language by a medical interpreter. A quiet room free of distractions is needed to improve the patient and family's understanding. Information should be free of medical speak and paced to optimize comprehension. Confidentiality is vital, and adolescents and young adults must be given the opportunity to meet privately with providers if requested.

Families of pediatric and adolescent cancer patients are concerned about the treatment's impact on fertility. Regardless of whether a family decides to pursue any fertility preservation, families do want information on risk of infertility and available fertility preservation options. Counseling and services often require coordination of care between multiple disciplines and services and possibly between pediatric and adult institutions. Reproductive health discussions in CAYA cancer patients do not end at the time of diagnosis. As the patient matures, it is imperative the medical team provides patients with developmentally appropriate information from diagnosis to survivorship.

2.6 Conclusion and Next Steps

A cancer diagnosis is an overwhelming, stressful, and life-altering time for CAYA cancer patients and their families. In an increasing number of patients, improvements in treatment and supportive care shift the cancer experience from a terminal disease to a chronic illness [17]. As a result, healthcare providers caring for survivors of CAYA cancer need to become aware of unique medical and psychosocial risks from their past treatment exposures and cancer journey experiences. Fertility implications from cancer treatment are only one adverse issue many survivors must deal with [29, 47]. As discussed, advances and details in gonadal toxicity have been discovered, and as a result, CAYA treatment protocols have been amended to promote health and quality of life of survivors [3, 66]. Nevertheless, while advances have been made in the field of oncofertility as outlined in this chapter and others, we still have an immense amount of work to do.

As providers, we need to appreciate a true understanding of the impact of infertility and sterility on our patients, as it is often an extremely difficult consequence of cancer treatment. The discussion of fertility preservation needs to occur prior to cancer treatment, but also an inquiry about patient's readiness to find out about their own fertility status needs to be brought up by providers at

every encounter. This starts with oncology providers including physicians, RNs, and APPs abstracting the patient's treatment details and providing them with a Survivorship Care Plan (SCP) or treatment summary. This document serves as a conduit of information for the current medical team to understand actual or potential late effects of treatment, including fertility implications. The SCP can be shared with current and future providers such as primary care providers. As CAYA cancer patients enter into the "adult" medical world, there is a known lack of knowledge about late effects of therapy, and it becomes a barrier to care for patients and providers [31, 36, 44]. Arming our self with available resources is critical for our own knowledge and also enables us to educate our patients. An excellent resource is *The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers* and their accompanying patient education materials called "Health Links." These are available for no cost at ► http://www.survivorshipguidelines.org [37]. Another useful resource for the CAYA population is ASCO's "Focus Under 40" found at ► http://university.asco.org/focus-under-forty which has information on male and female fertility preservation, survivorship, and supportive care. We continue to recognize the importance of quality of life for survivors, and it is our ultimate goal to have CAYA survivors a long and fulfilling life, which includes the opportunity to become a parent if desired.

Review Questions and Answers

Q1. Which class of chemotherapeutic agents is best known for their gonadal toxicity and associated infertility/sterility?

A1. Alkylating agents such as cyclophosphamide, ifosfamide, procarbazine, and busulfan are known to be associated with reduced fertility.

Q2. A 32-year-old female treated at age 15 for Hodgkin lymphoma with MOPP (nitrogen mustard (melphalan), oncovorin, procarbazine, and prednisone) without radiation arrives in your office and wants to discuss a fertility workup. She has attempted pregnancy for 9 months without success. What type of doctor would you ideally refer her to?

A2. This patient should be referred to a reproductive endocrine specialist who can counsel her on an evaluation, review results, and make appropriate referrals.

Q3. True or false? All patients who received cancer treatment are at risk for infertility/sterility.

A3. False. Many patients treated with chemotherapy and direct radiation not encompassing the abdomen or gonads may conceive or sire a pregnancy. This notion of cancer = infertility reiterates the importance for obtaining detailed cancer treatment records including cumulative dosages of alkylating agents if possible.

Q4. What are some reliable resources for physicians and advanced practice providers to access to educate themselves about advances in reproductive medicine and counseling CAYA survivors on their risk of infertility?

A4. The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) have developed clinical guidelines and education materials for providers (► asco.org, ► NCCN.org). The ASCO website offers Focus Under 40 which includes education programs for male and female fertility preservation and survivorship at ► https://university.asco.org/focus-under-forty. The Children's Oncology Group Long-Term Follow-Up Guidelines available at ► http://www.survivorshipguidelines.org offer health links on male and female reproductive system issues.

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