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Oncofertility: Meeting the fertility goals of adolescents and young adults with cancer

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Abstract

Adolescents and young adults ages 15 to 39 who are diagnosed with cancer (AYA survivors) undergo a range of therapies for cancer cure, but subsequently may be at risk of treatment-related infertility and, for female AYA survivors, adverse pregnancy outcomes. Future fertility is important to AYA survivors. Meeting their fertility goals requires awareness of this importance, knowledge of cancer treatment-related fertility risks, appropriate fertility counseling on these risks, and access to fertility care. Epidemiologic and dissemination and implementation research are needed to estimate more precise risks of traditional and novel cancer therapies on fertility and pregnancy outcomes and improve the delivery of fertility care.

Keywords

Oncofertility; AYA cancer; fertility preservation; cancer survivor; adolescents and young adults

Introduction

In the United States, more than 90,000 adolescents and young adults ages 15 to 39 are diagnosed with cancer each year (AYA survivors), with nearly 1 million cancer survivors who are currently of reproductive age.^{1,2} Long-term survival for AYAs with cancer is high, 82% at 5 years.¹ These individuals undergo a range of therapies for cancer cure, but subsequently may be at risk of treatment-related infertility and, for female AYA survivors, adverse pregnancy outcomes. Future fertility is important to AYA survivors. Meeting their fertility goals requires awareness of this priority to AYA survivors, knowledge of cancer treatment-related fertility risks, appropriate fertility counseling on these risks, and access to

fertility care. Accordingly, the primary goal of this review is to summarize evidence on fertility needs, known and unknown risks of cancer treatments on fertility and pregnancy, as well as fertility treatment strategies at diagnosis and in survivorship for male and female AYA survivors. A second goal is to highlight current gaps in knowledge in this area and barriers to fertility care. Where possible, we present AYA-specific data, but the preponderance of fertility data on young people are derived from childhood cancer survivors. Risks of abnormal puberty and hypogonadism are beyond the scope of this review.

The importance of fertility to AYA survivors

Having children is a priority for the majority of male and female AYA cancer survivors.^{3–5} When asked to prioritize life goals, 44% of newly diagnosed male AYAs recruited in a multi-institutional study (n=187) ranked having children among their top 3 life goals, along with health and education; a separate single-institution study found post-treatment survivors ranked having children as 6th of 8 life goals.^{3,6} Post-treatment, one-third of a cohort of 201 male AYA survivors reported worry about cancer-related infertility.⁷ Among female AYAs with cancer, fertility concerns are also highly prevalent at diagnosis and in survivorship. In a multi-institutional study of 620 breast cancer patients younger than 40 years of age, 51% were concerned about fertility at diagnosis; among 200 post-treatment female AYA survivors, 29% reported high concerns about their fertility potential.^{8,9} Across studies, it is evident that a moderate proportion of AYA survivors are concerned about fertility. Current data are limited by largely cross-sectional studies, which are unable to capture fluctuations in fertility concerns over the course of cancer survivorship which is needed to guide the timing of clinical screening.

Fertility concerns negatively impact quality of life. In long-term male and female AYA transplant survivors (n=37), 54% reported moderate to high concerns on how infertility had negatively impacted their emotions, relationships and self-worth.¹⁰ Similarly, fertility distress was reported in 30% of long-term testicular cancer survivors and was related to younger age, single relationship status and childlessness.¹¹ Perceived infertility has been observed to adversely affect sense of masculinity, self-esteem, as well as relationships, but this distress was not associated with mood in male testicular cancer survivors.^{12,13} Females have greater infertility-related distress than males, perhaps in part because they are at higher risk of not receiving fertility information.^{14,15} For female AYA survivors, reproductive concerns extend beyond fertility concerns and span worries about offspring health, personal health, pregnancy health, and partner disclosure.^{4,8} These domains have been captured in measures such as the Reproductive Concerns After Cancer scale.¹⁶ Female AYA survivors who have higher reproductive concerns were more likely to experience moderate to severe depression and lower quality of life.^{8,17}

How is fertility measured in AYA survivors?

There are multiple clinically used fertility measures in AYA survivors. For postpubertal males, methods have included clinical infertility, ever siring a pregnancy or a live birth, semen analyses, and measurement of hypothalamic-pituitary-testicular axis hormone activity via FSH and LH, testosterone, and inhibin B. For postpubertal females, fertility has been measured by time to pregnancy, ever having a pregnancy or live birth, menstrual pattern, and

ovarian reserve markers (gonadotropins FSH and LH, anti-Mullerian hormone [AMH], FSH, inhibin B, antral follicle count [AFC]). Clinical infertility for males and females is defined as the failure to achieve pregnancy after at least 12 months of pregnancy attempt.¹⁸

Among these measures, the clinical outcomes are infertility, gonadal failure, and history of pregnancy, live birth or siring a pregnancy or live birth. Because serum, semen, and ultrasound measures are surrogates, where possible we present the data on clinical outcomes. Of note, clinical infertility and ever pregnancy/siring a pregnancy are related but distinct measures of fertility. The limitation of using ever having or siring a pregnancy/live birth as the outcome is the inability to distinguish survivors who choose not to pursue pregnancy due to factors unrelated to fertility from survivors who are infertile. Consequently, ever having or siring pregnancy/live birth may overestimate fertility risk. The limitation of clinical infertility is that this measure will underestimate the proportion of AYA survivors who will ultimately become pregnant or sire a pregnancy beyond 12 months of attempts. It is also important to know the age at which these outcomes were assessed, as prevalence of (or proportion of individuals with) pregnancy, live birth, and clinical infertility will be lower at younger ages of assessment. For clinical care, awareness of data on both measures can help clinicians counsel on the range of threat to fertility.

Data on infertility and gonadal failure in AYA survivors are limited. In male childhood cancer survivors in the Childhood Cancer Survivor Study, inclusive of adolescents up to age 21, the prevalence of infertility was 46% at a mean age of 38. These men had a 2.6-fold higher risk of infertility (95% CI 1.9–3.7) and 2.1-fold higher odds of primary hypogonadism, compared to controls.^{19,20} Among more than 6000 male childhood cancer survivors who were not surgically sterile, three-quarters of whom were younger than 30 at assessment, 941 (15%) had sired a pregnancy in survivorship; this was half as likely as their male siblings (HR 0.56, 95% CI 0.49–0.63).²¹

Clinical infertility in female childhood cancer survivors, reported by the Childhood Cancer Survivor Study, was 13% at a median age of 27 years.²² These young women had a 1.5-fold higher risk of infertility (95% CI 1.3–1.8) and 10.5-fold higher risk for non-surgical ovarian insufficiency before age 40 (95% CI 4.2–26.3), compared to their female siblings.^{22,23} Importantly, infertility and gonadal failure rates are hypothesized to be higher in female AYA survivors than in childhood cancer survivors, because ovarian reserve at the time of cancer treatment is lower with increasing age. Several large cohort studies have shown rates of pregnancy and live birth in female childhood and AYA survivors to be 60 to 80% of those in control populations.^{24–29}

Cancer treatment-related fertility risks

Chemotherapy, radiation, surgery and targeted therapy pose differential threats to fertility by disrupting the hypothalamic-pituitary-gonadal (HPG) axis, incurring gonadotoxicity to both gametes and supporting cells, impairing uterine function, and causing cardiopulmonary comorbidities that would threaten pregnancy health in females (Figure 1). With accelerated development of novel targeted cancer therapies, there are extremely limited human data on associated reproductive risks, despite pre-clinical data showing expression of the majority of targets in the pituitary, gonads and uterus;³⁰ animal data in female and male rodents, dogs,

and primates show abnormal ovarian follicular development and spermatogenesis, decreased gonadal and uterine weights, lower pregnancy rates and litter sizes, and nearly uniform teratogenicity; and concerning human reports of infertility and gonadal failure.^{31–34} As human data on targeted therapy are sparse, we summarize the fertility risks of traditional chemotherapy, radiation and surgical treatment.

Gametogenesis requires an intact HPG axis. For both males and females, cancer treatments that disrupt the HPG axis include surgery and radiation. Cranial radiation in cumulative doses higher than 30Gy is associated with central hypogonadism and infertility as a result of FSH/LH deficiency.^{35–38} Infertility as a result of central hypogonadism following these treatments may be overcome with exogenous gonadotropins.

For male AYA survivors, testicular radiation, chemotherapy, and bilateral orchiectomy can incur infertility as a result of gonadotoxicity, and retroperitoneal lymph node dissection can incur infertility as a result of ejaculatory dysfunction. Radiation exposure to the testes poses a considerable fertility risk. Radiation in amounts as small as 0.1Gy diminishes spermatogenesis, with fractionated doses of 2Gy causing permanent damage.³⁹ Infertility risk is 1.99 fold (95% CI 1.52–2.61) higher in childhood cancer survivors who had received a dose of 4Gy testicular radiation, compared with sibling controls.¹⁹ Doses of 7.5Gy are associated with a decreased likelihood to sire a pregnancy (HR 0.12 95% CI 0.02–0.64).³⁸ Exposure to alkylating drugs is associated with infertility in a dose dependent manner.¹⁹ More recently, the cyclophosphamide equivalent dose (CED) was developed to allow comparisons across studies.⁴⁰ Compared with males whose cumulative CED exposure was less than 4.9 grams, men who were exposed to 4.9 to 9.6 grams (HR 0.84, 95% CI 0.72–0.97) and > 9.6 grams (HR 0.53, 95% CI 0.44–0.62) as children and adolescents were less likely to sire a live birth.²⁶ However, azoospermia is unlikely when CED is less than 4 grams.²⁶ Bilateral orchiectomy, or the surgical removal of both testes, renders males infertile. In addition, retroperitoneal lymph node dissection, commonly used as a preventative measure for cancer metastasis, presents a higher risk of infertility secondary to retrograde ejaculation and ejaculatory failure.⁴¹

For female AYA survivors, uterine radiation, ovarian radiation, and alkylating chemotherapy exposures are risk factors for longer time to pregnancy and/or infertility. Among childhood cancer survivors, >5 Gy radiation to the uterus raises the risk of infertility more than 2-fold.²² The risk of ovarian insufficiency from radiation is age- and dose-dependent.⁴² A dose of 20 Gy or greater is estimated to cause ovarian insufficiency in infants; threshold doses that result in ovarian insufficiency for girls and young women who are older are progressively lower.⁴² The observation that alkylating agents were associated with destruction of the ovarian follicle pool motivated efforts to derive a summary measure of alkylator exposure. Initially, alkylator exposures were expressed by quantiles within a study; the highest tertile in alkylating chemotherapy exposure increased the risk of infertility in girls by 1.5 fold, 95% CI 1.1–2.0, compared to no alkylating chemotherapy exposure.²² Data are mixed on whether CED is a good predictor of ever pregnancy/live birth or ovarian insufficiency in female childhood cancer survivors, and no reports for CED and infertility have been published to date.^{23,26,43}

Fertility options at cancer diagnosis

Major professional organizations including the American Society of Clinical Oncology, American Society of Reproductive Medicine, American Academy of Pediatrics and the National Comprehensive Cancer Network recommend that healthcare providers discuss the possibility of infertility with patients who will undergo cancer treatment before or during their reproductive years.^{44–47} For AYAs at risk of infertility, there are effective fertility preservation methods that render infertility preventable. Male and female fertility specialists (urologists and reproductive endocrinologists) are able to discuss and perform fertility preservation procedures. Fertility preservation methods are divided into standard of care and experimental methods (Table).

For male patients, mature fertility preservation technology involves cryopreservation of sperm in postpubertal males.^{44,45} Testicular tissue cryopreservation in prepubertal males, grafting human testicular tissue, and gonadal suppression with GnRH analogs are experimental.^{44,45} Ejaculated sperm cryopreservation is feasible and can be highly successful. In a prospective study, 53.5% of newly diagnosed adolescent males attempted to bank their sperm before treatment initiation, with an 82.1% success rate.⁴⁸ A caveat for treating AYA males, however, is that collection of sperm may be compromised by the inability to ejaculate—a phenomenon more common in younger than older men.^{45,46} Alternative methods of sperm collection for cryopreservation include use of PDE-5 inhibitors, vibratory stimulation, electroejaculation, as well as surgical extraction of sperm or testicular tissue.⁴⁵ Of note, some cancers, including testicular cancer, lymphoma, and leukemia, are associated with poorer semen parameters even before cancer treatment, limiting the quantity of banked sperm. Because of limited female fertility delineated below, banking multiple sperm samples will provide the male AYA survivors with more fertility options in the future.^{49–52}

Frozen sperm may be used for inseminating a female partner or for in vitro fertilization (IVF). For intrauterine inseminations, cycle fecundity is related to female partner age. In contemporary time to pregnancy studies in the general population, cumulative pregnancy rates by 6 months range from 77% (95% CI 72–81%) in women who are age 30–31 to 47% (95% CI 31–66) in women who are age 40–41.⁵³ For female partners of male AYA survivors who are sterile after cancer therapy, each insemination, generally one per month, requires one frozen specimen. Therefore, it is important for sperm samples to be frozen in multiple aliquots, each with at least 5 million total motile sperm. For male survivors with less sperm, consideration of using the sperm for IVF will be more efficient, as only a single spermatozoon is needed per oocyte retrieved.

For female patients, embryo or oocyte banking following controlled ovarian stimulation, fertility sparing surgery in early stage cervical, uterine and ovarian cancer, ovarian transposition away from the radiation field and gonadal shielding to minimize radiation exposure to ovaries are considered standard of care methods.⁴⁴ Ovarian tissue freezing and in vitro maturation of oocytes or ovarian follicles are experimental. Recently, the ASCO Clinical Guidelines for Fertility Preservation delineated GnRH agonist use for ovarian suppression during chemotherapy as a potential fertility preservation method to offer young women with breast cancer, if more proven methods such as oocyte or embryo

cryopreservation are not feasible.⁴⁴ This recommendation was informed by two randomized controlled trials in breast cancer survivors (POEMS and PROMISE), in which the odds of ovarian insufficiency in survivors who received GnRH agonists were one-third of the odds in controls.^{54,55} In POEMS, 16 of 105 survivors who underwent GnRH agonist therapy had at least one delivery, compared to 8 of 113 survivors who did not receive a GnRH agonist (OR 2.5, $p=0.05$).⁵⁵ In a smaller randomized controlled trial of 129 lymphoma patients, neither ovarian insufficiency (OR 0.7, $p=0.76$) nor pregnancies (OR 1.5, $p=0.47$) were improved in patients who received a GnRH agonist during chemotherapy compared to controls, but this study was underpowered.

Controlled ovarian stimulation (COS) uses injectable gonadotropins to grow multiple ovarian follicles over approximately two weeks, culminating in an oocyte retrieval that is most commonly performed transvaginally. Oocytes that are retrieved may be frozen, or fertilized and cultured to embryos prior to freezing. The most significant limitation to oocyte freezing is thaw rate, which will vary by the laboratory, but embryos derived from frozen oocytes appear to have similar fertility potential to embryos derived from fresh oocytes.⁵⁶ For example, if fertilization of mature oocytes is at least 67%, and development of blastocysts is 50% of fertilized oocytes, then 10 oocytes undergoing fertilization will yield 3–4 blastocyst embryos to freeze. In vitrification protocols, more than 95% of blastocysts survive the thaw, yielding a final 3–4 blastocysts to transfer. In comparison, if the thaw rate of frozen oocytes is 80–90%,^{56,57} then the same 10 oocytes that are initially frozen would yield 8 thawed oocytes and subsequently 2–3 blastocysts given the same attrition with fertilization and embryo culture, or one fewer blastocyst to transfer. The live birth rate of each transferred blastocyst is dependent on oocyte age, and the vast majority of assisted reproductive technology centers in the U.S. publicly report center-specific outcomes through the Centers for Disease Control and the Society for Assisted Reproductive Technology (www.sart.org).

Several advances in fertility treatments have clinical implications for female AYA cancer patients considering fertility preservation. First, ample data support starting COS on any day of a menstrual cycle, which decreases the time to start cancer treatment.^{58–61} Second, consecutive COS cycles during which a second COS cycle is begun within a few days following the first oocyte retrieval have been reported, in order to increase the number of oocytes retrieved within the same menstrual cycle.^{62–64} Third, aromatase-inhibitor- or tamoxifen-based COS protocols are commonly used to reduce estradiol exposure in cancer patients with estrogen-sensitive tumors with early evidence of safety.^{65–67} Fourth, use of GnRH agonists to induce ovulation in COS cycles greatly reduces the risk of ovarian hyperstimulation syndrome, rendering COS safer in young patients.⁶⁸ Finally, emerging case reports suggest the feasibility of obtaining mature oocytes through COS in premenarchal girls who have initiated puberty.⁶⁹

Ovarian tissue banking with subsequent transplantation remains experimental, but has potential clinical application in pre-pubertal children and women who do not have enough time to undergo COS. To date, there are more than 86 births from re-transplantation of frozen ovarian tissue, one from a post-pubertal but pre-menarchal girl.^{70–73} There are no reported pregnancies or live births from transplanting ovarian tissue frozen during pre-

pubertal years. Most transplants are orthotopic, surgically sewing ovarian tissue back into the ovarian fossa. But there is a reported ongoing pregnancy from heterotopic transplantation into the abdominal wall.⁷²

Taken together, AYA females who have initiated puberty have several valid options for fertility preservation. Importantly, an improved ability to estimate future fertility risk is needed to delineate which AYA patients actually need to undergo these procedures.

Post-treatment fertility and pregnancy considerations

Following completion of cancer treatment, AYA survivors seek information on whether they are fertile, how to measure fertility, fertility treatment options, and safety of pregnancy. Specialists in fertility (reproductive urologists and reproductive endocrinologists) and pregnancy (perinatologists) can provide fertility care to post-treatment AYA survivors. For both male and female AYA survivors, the best measure of fertility is the outcome of unassisted pregnancy attempts, as abnormal measures of semen parameters or ovarian reserve markers do not definitively preclude pregnancy in cancer survivors.

For post-pubertal male AYA survivors, surrogate measures of fertility include semen analyses, and measurement of hypothalamic-pituitary-testicular axis hormones (FSH, testosterone, and inhibin B). Recovery of spermatogenesis requires residual spermatogonial stem cells and their differentiation. The duration of post-treatment azoospermia secondary to gonadotoxic therapy is highly variable, and recovery of spermatogenesis may occur years after therapy.⁷⁴ Recovery more than 10 years after treatment is unlikely, but has been reported.⁷⁵ Importantly, even in azoospermic AYA survivors, microdissection testicular sperm extraction procedures by reproductive urologists can result in sperm recovery in up to 43% of cases.⁷⁶ Testicular sperm would be sufficient for IVF via intracytoplasmic injection of partner oocytes.

What do practice guidelines recommend for male AYA survivors? Recently, the International Late Effects of Childhood Cancer Guideline Harmonization Group, in collaboration with the PanCareSurFup Consortium, published surveillance recommendations for impaired spermatogenesis in male childhood and AYA survivors up to 25 years old. The panel recommended semen analysis as the gold standard surveillance modality, with testicular volume, FSH and inhibin B as additional reasonable screening tests. As no studies were available on timing of changes in spermatogenesis, the group recommended surveillance in survivors treated with alkylating agents or testicular radiation at the request of survivors or when paternity is desired in the foreseeable future.⁷⁷ NCCN Guidelines on AYA oncology recommend semen analysis with infertility or when requested by patients, with periodic evaluation over time to account for resumption of spermatogenesis.⁴⁷

For postpubertal female AYA survivors, surrogate measures of fertility include menstrual pattern, and ovarian reserve markers (gonadotropins FSH and LH, anti-Müllerian hormone [AMH], FSH, inhibin B, antral follicle count [AFC]). FSH, AMH, AFC are associated with response to ovarian stimulation, time to pregnancy and age at natural menopause in the general population.^{78–80} However, longitudinal data demonstrate that AYA survivors have very different trajectories in these markers than females who do not undergo cancer therapy.

Following exposure to gonadotoxic therapy, AMH levels and AFC fall while FSH levels increase initially. For those with remaining ovarian follicles, a subsequent rise in AMH and AFC and fall of FSH ensues, though generally not back to pre-treatment levels.^{81–84} This pattern of change suggests a residual window of ovarian function and fertility, but data are lacking on when ovarian recovery plateaus and subsequent decline begin. If this were known, then the residual ovarian function window may offer another opportunity to attempt fertility or undergo fertility preservation. Clinically, providers and AYA survivors who are considering measuring ovarian reserve should be aware that these markers have not been tested in predicting fertility or time to pregnancy in cancer survivors. If ovarian reserve is to be measured, then serial measurements are likely more helpful than single measures.

What do the guidelines recommend for female AYA survivors? The International Late Effects of Childhood Cancer Guideline Harmonization Group and PanCareSurFup Consortium collaboration published the following recommendations on primary ovarian insufficiency for post-pubertal survivors; no separate fertility-specific guideline has been generated from this group.⁸⁵ FSH and estradiol are recommended screening tools for female survivors with menstrual cycle dysfunction or who desire assessment about future fertility. AMH is a reasonable screening tool in conjunction with FSH and estradiol. On the basis of fertility concerns causing significant distress and evidence that ovarian reserve markers may decline prior to menstrual changes in the general population, we caution against screening only symptomatic patients, i.e. female survivors with irregular menses, amenorrhea, or estrogen deficiency signs and symptoms.⁴⁷

Female AYA survivors frequently express concerns on personal and offspring health when considering pregnancy. Radiation to the brain, abdomen or pelvis increases spontaneous abortion risk 1.5 to 3-fold.^{86–88} Spontaneous abortion rates do not appear increased with chemotherapy exposure. In addition, no increased incidence of birth defects or congenital abnormalities has been observed in the offspring of AYA survivors compared to sibling controls.^{89,90} Interestingly, despite increased sperm aneuploidy rates following gonadotoxic chemotherapy in men, studies have demonstrated that rates of birth defects are universally low for male and female AYA survivors irrespective of cancer type and treatments received.^{91–93} Compared to controls, female childhood and AYA survivors experience 1.5 to 2.8-fold higher rates of preterm delivery, a magnitude of risk that is similar to the strongest clinical risk factor in the general population, i.e. prior preterm delivery.^{87,88,94–101} Currently, there is a lack of understanding of 1) how early these preterm births occur, 2) whether preterm births are medically indicated or spontaneous, and 3) what specific cancer treatments increase risk. Until these factors are elucidated and interventions developed accordingly, AYA survivors and their obstetricians need to be aware of these sequelae. Finally, prior anthracycline and/or chest radiation exposures increase the risk of pregnancy-associated cardiomyopathy. In limited studies, the incidence is low (<1%),¹⁰² but given catastrophic consequences, COG Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers advise pre-conception cardiac evaluations in women exposed to a cumulative dose of 300 mg/m² of cardiotoxic anthracyclines or high-dose cyclophosphamide, e.g. a cumulative dose of > 20 g/m² plus chest radiation or, 30 Gy chest radiation.¹⁰³

Barriers to fertility care for AYA survivors

Despite long-standing clinical guidelines and selection of fertility counseling as a quality measure, a significant gap in care exists.¹⁰⁴ Aggregate data from the U.S. Quality of Oncology Practice Initiative show a stagnant 40% rate of fertility risk discussion and <30% rate of discussing fertility preservation options at diagnosis from 2013–2016. Recent data from our own institution showed a 32% rate of fertility risk discussion and 10% rate of referral to fertility specialists. Barriers to fertility care have been well-characterized and consistent across a variety of care settings and developed countries; these data have been summarized in systematic reviews.^{104,105} For AYA survivors and their families, the lack of *high quality* information on fertility risk and fertility preservation is the most common theme. AYA survivors report not receiving or receiving inadequate fertility information at cancer diagnosis from their oncology providers.^{106,107} Additional intrinsic factors influence patients' decisions on fertility preservation, such as concerns about delaying cancer treatment, personal health and offspring health and desire for parenthood.^{4,106,108,109} The role of the oncology provider in fertility care is pivotal, as AYA survivors not only desire guidance from their oncology providers, but also want fertility information and options from reproductive specialists.^{4,110} Among oncology providers, patients' cancer characteristics such as poor physical health, psychological state, or prognosis, influence fertility counseling. Gaps in knowledge on fertility risk and fertility preservation options and safety are additional barriers.^{111–113} However, research also shows that providers' assumptions about their patients' fertility interest, sex, financial capability, relationship status, and existing family size, influence whether and how fertility counseling/referral is undertaken, but problematically, these assumptions can be incongruent with the patient perspective.¹⁰⁵ Finally both institutional and societal structure present significant barriers to fertility care. At the institutional level, a lack of collaboration and communication between oncology and fertility, institutional guidelines, educational materials for patients and providers, and support for language barriers hinder consistent delivery of fertility care.^{111–113} In the U.S., the lack of financial support and insurance coverage for fertility care in this setting is, without doubt, a key barrier for AYA survivors.^{114,115} These data strongly support that successful implementation of fertility care will require careful consideration of the complex interplay of patient needs, provider needs, institutional structures and health policies.

Interventions to improve fertility care have been undertaken but are early and limited in scope. For patients, written educational and decisional aid supports have been developed with stakeholder engagement and user-centered design,^{116–120} but lack testing and replicative studies for efficacy. At the provider level, a web-based communication-skill-building curriculum on fertility care for oncology nurses improved reproductive knowledge, increased involvement in fertility-related activities, and led to implementation of institutional/policy changes.¹²¹ At the institutional level, development of toolkits and dedicated AYA and/or oncofertility services to include provider education, patient education, and identification of fertility providers has been undertaken.^{122,123} In single institutions, interventions increase documentation of fertility counseling and fertility specialist referral, and decrease time to fertility counseling by a fertility specialist.^{124,125} In the past year, three states in the United States (Connecticut, Delaware and Maryland) have passed mandates for insurance coverage of fertility preservation for iatrogenic infertility risk. The initial results

are promising, and several observations can be made for future implementation efforts. While clinical outcomes such as specialist referral are improved, the absolute rates are low, suggesting limited penetrance. There is considerable heterogeneity in these multi-level interventions with lack of clarity on the key ingredients, level of fidelity and adaptations necessary for improving fertility care. Approaching these limitations via implementation science research methods will be informative to improve care in a systematic and generalizable manner.¹²⁶

Conclusion

As researchers and clinical providers who work with AYA survivors, we have observed that the occurrence of infertility as well as uncertainty around reproductive risks result in distress, depression, and poorer quality of life in this population.^{4,8,127–130} Meeting the fertility goals of this population requires not only sound epidemiologic research to estimate risks of traditional and novel cancer therapies on fertility and pregnancy outcomes, but also better dissemination and implementation strategies to improve the delivery of fertility care.

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Figure 1:
Cancer therapies incur female and male fertility risks

Table.Standard and Experimental Fertility Preservation Options for Male and Female AYA Survivors^{44,45}

Sex	Procedures	Timing
Male	Standard of care	
	• Sperm cryopreservation	• 1–2 days before cancer therapy
	Experimental	
	• Gonadal suppression (GnRH Analogs)	• Concomitant with cancer therapy
	• Testicular tissue cryopreservation	• Before cancer therapy
Female	Standard of care	
	• Embryo or oocyte cryopreservation	• 2 weeks before cancer therapy; possible second opportunity at least 4–6 months post-treatment
	• Fertility-sparing surgery	• Concomitant with cancer surgery
	• Ovarian transposition	• Before abdomino-pelvic radiation
	• Ovarian shielding	• Concomitant with abdomino-pelvic radiation
	Experimental	
	• Gonadal suppression (GnRH Analogs)	• During chemotherapy
	• Ovarian tissue cryopreservation	• Before cancer therapy