Fertility Assessment and Treatment in Adolescent and Young Adult (AYA) Cancer Survivors

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Abstract

In the survivorship setting, adolescent and young adult (AYA) cancer survivors frequently demonstrate little knowledge of infertility risk, are unclear regarding their fertility status and may under- or over-estimate their treatment-related risk for infertility. In female AYA survivors, ovarian function usually parallels fertility, and can be assessed with serum hormone levels and ultrasonography. Post-treatment fertility preservation may be appropriate for survivors at risk for primary ovarian insufficiency. In male AYA survivors, fertility and gonadal function are not always equally affected, and can be assessed with a semen analysis and serum hormones, respectively. As reproductive health issues are commonly cited as an important concern by survivors of AYA cancer, multidisciplinary care teams including oncology, endocrinology, psychology, and reproductive medicine are advocated, with the aim of optimal provision of fertility advice and care for AYA cancer survivors.

Introduction

Infertility, defined as the inability to achieve a pregnancy after 12 months of unprotected intercourse, is an important late effect of cancer therapy, although the prevalence is challenging to capture accurately. Infertility after childhood cancer therapy typically occurs years after the completion of treatment and often after the patient has transitioned away from pediatric survivor care. As such, most studies evaluating infertility in childhood cancer survivors use surrogate measures such as reduced fertility rates, acute ovarian failure, premature ovarian insufficiency, diminished ovarian reserve, oligo/azoospermia or elevated gonadotropins (1–8). In two studies from the Childhood Cancer Survivor Study, infertility was self-reported by 46% of male survivors compared to 17.5% of healthy siblings (RR 2.64 95% CI 1.88-3.70, p<0.001) and by 13% of female survivors compared to 10% of healthy siblings (RR 1.34 95% CI 1.12-1.60, P= 0.0015).(9,10) National and international working groups have identified cancer therapeutic exposures which place patients at risk for gonadal damage and infertility and have formulated guidelines to assist providers in assessing the extent

of injury.(11–13) The exposures identified to result in gonadal dysfunction include: traditional alkylating agent chemotherapy, heavy metal chemotherapy, abdomino-pelvic exposure to radiation, cranial radiation > 30 Gy, surgeries on the reproductive organs and hematopoietic stem cell transplant preparative regimens that include alkylators and/or total body irradiation.(11)

In the survivorship setting, AYA survivors frequently demonstrate little knowledge of infertility risk, are unclear regarding their fertility status and may under- or over-estimate their treatment-related risk for infertility.(14–17) Discussions of infertility risk secondary to cancer treatment should first occur at diagnosis and prior to the initiation of cancer treatment. These discussions should include assessment of fertility preservation candidacy and referrals for appropriate fertility preservation options.(18–20) However, data suggest that these discussions do not uniformly occur as a component of comprehensive oncology care, with great variability occurring among practitioners and across institutions and countries.(21–24) Furthermore, documentation of fertility preservation discussions is generally poor when they do occur.(25,26) Consequently, it is almost impossible to ascertain what information about risk for infertility an individual patient and family actually received at the time of diagnosis. In addition, many AYA survivors do not recall conversations or recall inadequate conversations about infertility risk as part of the initial informed consent for cancer therapy.(14,27,28) Because of these knowledge deficits and misperceptions, most survivors will need to review their level of risk for infertility after completion of treatment at least once and, for many, multiple times in long-term follow-up.

It is also important to realize that survivor care varies significantly between institutions and countries. In the US, it is recommended that survivors are seen regularly and long-term follow-up care be guided by the use of the Children's Oncology Group (COG) Long-Term Follow-Up Guideline for Survivors of Childhood Adolescent and Young Adult Cancers. The COG guidelines provide recommendations for surveillance to detect sex hormone deficiencies and impaired spermatogenesis and diminished ovarian reserve.(29) International guidelines for surveillance are also available for both males and females. (30,31) The guidelines provide information for consideration of further gonadal testing and referral to specialists. Some centers provide regular comprehensive multidisciplinary follow-up from two years after the completion of therapy throughout life. Other centers do not have providers trained in screening for or identifying specific late, while some centers only follow patients until they transition to adult care. In many cases, adult survivors are followed by generalists with limited knowledge about previous therapies.(32) Additionally, some centers rely upon survivorship clinics to monitor fertility, while others rely upon reproductive endocrinologists and urologists for assessment and counseling of all fertility-related effects. All of these variables result in wide variations in opportunities for survivors to gain meaningful knowledge about their personal risk for infertility or current fertility status.

Fertility Considerations in Female AYA Cancer Survivors

Several studies indicate that female AYA cancer patients are less likely to be offered counseling and to be referred to centers for fertility preservation than their male counterparts.(33,34) Thus, a larger population of female patients may not have received information about the impact of cancer treatment on future fertility or have undergone fertility preservation procedures before cancer treatment. After completion of therapy, the extent of ovarian damage is difficult to ascertain. Regular menses and traditional measures of ovarian function, FSH and estradiol, may not reflect the extent of damage to the primordial follicle pool and the decrease in ovarian reserve from cancer treatment. Understanding the level of risk for ovarian dysfunction related to cancer treatment therapy may help in counseling and identifying patients who need more careful or specialized surveillance. The types of surveillance offered and the frequency should be tailored to the survivor's age, developmental stage, desire to know their fertility status and willingness to consider post treatment fertility preservation when indicated.

Assessment of Ovarian Reserve

Current reproductive function can be subdivided into whether it is apparently normal, absent, or compromised. When there is evidence of ongoing ovarian function, there are difficulties in the accurate assessment

of whether there is damage, although measures of ovarian reserve can provide some data and are summarized in table 1. Measurement of Follicle Stimulating Hormone (FSH) in the early follicular phase shows significant inter-cycle variation and is a late indicator of reduced ovarian reserve. A high result, i.e. over 10 IU/L, even if not present on a repeated sample, remains an important indicator of at least some loss of ovarian reserve. Low Anti-Müllerian hormone (AMH), traditionally used to predict poor response to ovarian stimulation, is increasingly used to indicate diminished ovarian reserve and correlates well with antral follicle count.(35) It is important to realize that low AMH is not predictive of the inability to conceive in regular cycling women who are actively trying to become pregnant.(36,37) Recent data show the value of AMH in prediction of natural menopause, but its accuracy falls sharply with decreasing age.(38) While AMH can distinguish categories of gonadotoxic risk in AYA cancer survivors its use in predicting duration of future fertility is unclear (39,40). Furthermore, concurrent treatment with exogenous hormones, either as replacement or as contraception, makes FSH levels uninterpretable and may suppress AMH by up to 30%.(41) As such, there are few reliable measure of ovarian reserve that can aid in predicting future fecundity in AYA survivors. The ideal variable would progressively decrease in a linear manner and allow for a window of time after crossing a threshold when oocyte preservation might be attempted after cancer treatment. It may be more helpful to trend measures such as AMH over time. Additionally, due weight should be given to predicted fertility risk based on therapy received.(42) Conversely, it is also essential to discuss the need for contraception when patients are at risk of unplanned and unwanted pregnancy.

Post-Treatment Fertility Preservation

Some survivors may maintain ovarian function for a number of years following cancer therapy, and thus may have the possibility to undergo oocyte or embryo cryopreservation in survivorship if deemed to be at increased risk for future primary ovarian insufficiency (POI). Unfortunately, there are limited to no data in humans on the ideal amount of time to wait between completion of chemotherapy or radiation and ovarian stimulation for oocyte retrieval, with many centers recommending waiting at least 6 months post completion of therapy based on risk of malformation and fetal loss reported in animal studies.(43,44) There is also a delicate balance between intervening with fertility preservation before oocyte yield becomes extremely limited or POI occurs, and avoiding unnecessary procedures in patients who may maintain adequate ovarian function during their reproductive years. Age and maturity of the patient, as well as family building goals should also be taken into account when considering timing of post-treatment fertility preservation. Data from the 2017 Society for Assisted Reproductive Technology (sart.org) show a 46.8% live birth rate per in-vitro fertilization (IVF) cycle for women under 35 in the United States, but it is unknown how having a history of cancer impacts these results. Unfortunately, the out-of-pocket costs of IVF can be prohibitive for many, and insurance coverage is quite variable, which further complicates the decision.

Grafting Cryopreserved Ovarian Tissue

Some survivors presenting with POI who previously cryopreserved ovarian tissue may consider ovarian tissue grafting. There is extreme hesitance to graft tissue in patients who were treated for leukemia and some lymphomas, due to concern for reintroducing cancer cells that may have been harbored in the ovary. In patients for whom grafting is considered safe, sites that can be used include the remaining contralateral ovary, pelvic side wall, abdominal wall, and other peripheral locations with adequate blood flow and accessibility for subsequent follicle aspiration if required.(45) Restoration of fertility with ovarian tissue harvested from post pubertal patients and grafting is no longer considered experimental as there have been over 140 births reported.(46) There has been one live birth from ovarian tissue harvested from a prepubertal girl, and another birth from tissue harvested in a peripubertal girl prior to menarche.(47) There are limited but reassuring data on follow up studies of thawed and engrafted ovarian tissue, in regards to safety, hormonal function, and restoration of fertility.(48–51) Ovarian endocrine function usually resumes two to five months after surgery and duration of function depends on many factors including the age of the patient at the time of retrieval, tissue volume, and follicle density.(52–54) Unfortunately, even with demonstrated restoration of endocrine function, pregnancy may not ensue after grafting, either from spontaneous conception or assisted by *in vitro* fertilization, and procurement of good quality embryos can be difficult. Current data suggest an

approximately 25-30% chance of live birth where ovarian tissue was cryopreserved in adulthood.(48,49)

For those patients in whom risk exists for malignant cell transmission from grafting, various strategies including *in vitro* maturation, use of an "artificial" ovary, and xenotransplantation are currently being explored in multiple centers.(55,56) Testing of ovarian tissue using appropriate histological, immunological and molecular modalities is essential prior to transplantation, but does not provide total reassurance.(57) International registries with robust follow-up are needed to advance this field of fertility preservation safely and effectively.

Pregnancy Risks in Female AYA Survivors

Pre-conception consultation with a Maternal-Fetal Medicine specialist is recommended for female cancer survivors at risk of end-organ damage from cancer treatment. Survivors who received anthracycline chemotherapy or chest radiation are at increased risk for cardiomyopathy, thus closer monitoring of cardiac function before and during pregnancy may be warranted in higher risk patients.(58) Additionally, women who received abdominal radiation, nephrectomy, hematopoietic cell transplantation, ifosfamide, or platinum containing compounds are at risk for renal insufficiency,(11) and pregnancy associated hypertension, eclampsia, or pre-eclampsia may be exacerbated by pre-existing kidney disease.

Women who received radiation to the uterus also have increased pregnancy risks,(59,60) as radiation induced injury may not allow the uterus to accommodate the necessary growth that occurs during pregnancy. A large study of offspring of women who received uterine radiation doses of more than 5 Gy were more likely to be small for gestational age (birth weight <10 percentile for gestational age; 18.2% v 7.8%).(60) Survivors treated with abdominal radiotherapy may also be at higher risk for preterm delivery, low birth weight, and peripartum hemorrhage.(61,62) Typically uterine and ovarian doses of radiotherapy are highly correlated,(10) and thus patients who received substantial doses of radiation to the uterus would also be less likely to have preserved ovarian function and natural fertility due to high ovarian doses. However, in the present age of oocyte or ovarian tissue cryopreservation, oophoropexy prior to radiotherapy, and oocyte/embryo donation, there may be a greater likelihood of these women attempting and achieving pregnancy. Donor uterine transplantation is also an active area of research that may benefit these survivors in the future.(63)

Data on pregnancy risks, including hypertensive diseases of pregnancy, gestational diabetes, maternal anemia, preterm birth, low birth weight, and peripartum hemorrhage, in otherwise healthy AYA cancer survivors who did not receive abdominopelvic radiation are limited, with mixed results. Importantly, studies examining risks of congenital anomalies or genetic abnormalities in the offspring of female AYA cancer survivors have shown no increase risk compared to that of the general population.(64)

Fertility Considerations in Male AYA Cancer Survivors

Many male patients entering survivorship will have already had a fertility consult at the time of diagnosis or relapse of their disease. Post-pubertal males may have opted to cryopreserve sperm prior to therapy, while younger males or males unable to cryopreserve sperm may have opted to participate in a research trial for testicular tissue cryopreservation. Males who receive gonadotoxic therapy may have loss of spermatogonial stem cells, but for those who are able to produce sperm after the completion of treatment do not have the same risk for early senescence of germ cell production that their female cancer survivor counterparts experience. Survivorship is a time to revisit cancer treatment related infertility risks and fertility status assessment conversations with all patients.

Semen Analysis

The semen analysis is currently the gold standard for assessing fertility status in males, although it must be recognized that a normal semen analysis does not assure fertility. A semen analysis is quick, cost-effective, and non-invasive, and can be performed at any age after puberty. In 2010 the WHO published the 5th edition of*Laboratory Manual for the Examination and Processing of Human Semen* , providing normal reference ranges based on semen parameters of men whose partners became pregnant within 12 months of trying to

conceive. Cutoffs above the 5th percentile are considered normal by WHO criteria, and men with abnormal parameters should be counseled as to future fertility options (Table 2).(65)

Since chemotherapy easily penetrates the blood-testis barrier, spermatogonial stem cells are at risk for damage by certain chemotherapeutic agents.(66) It is well established that degree of fertility impairment and azoospermia is directly proportionate to type of cancer treatment; specifically, the dose of alkylating agent. Semen analyses from 214 male survivors of childhood cancer who had been treated with alkylating agents revealed rates of 28% and 25% for oligospermia and azoospermia respectively; in addition, if the cumulative cyclophosphamide equivalent dose was < 4 gm/m^2, 89% of males were normospermic.(67) Radiation therapy is also known to cause impaired spermatogenesis in a dose dependent manner.(68) Transient effects on spermatogenesis have been seen in low doses of radiation therapy with cumulative doses as low as 2 Gy causing transient or even permanent azoospermia.(68) While some men may permanently lose sperm production as a result of their cancer treatment, others may have the return of sperm to the ejaculate over a period of months to years.(69)

While semen analysis is optimal in males desiring information about fertility status, FSH and Inhibin B may provide information about germ cell function if patients are unable to provide a semen specimen.(62) FSH, a hormone produced in the anterior pituitary, can help predict normal sperm production when its value is normal. FSH values poorly correlate with specific sperm concentrations,(70) but a systematic review and combined analysis of individual patient data showed that FSH above 10.4 IU/L predicted azoospermia in AYA survivors with specificity 81% (95% CI 76%-86%) and sensitivity 83% (95% CI 76%-89%).(71) Inhibin B has been shown to be decreased in some adult male survivors of childhood cancer, and is associated with decreased sperm concentration in males treated for Hodgkin Lymphoma.(72,73) However, Inhibin B does not perform as well as semen analysis in predicting fecundity and is not often tested.(74)

Assessment of Testicular Function

An intact, functioning hypothalamic-pituitary-gonadal axis is also required for normal spermatogenesis and reproduction. FSH and LH support testicular Sertoli cell and Leydig cell function, respectively, and are responsible for testicular reproductive and androgenic function. Cancer treatment has been shown to potentially affect both aspects of testicular function in a dose-dependent and treatment-dependent manner.(67,75–77) Leydig cells (testosterone-producing cells) are generally more tolerant of chemotherapy and radiation, and androgen deficiency is much less common than impaired spermatogenesis in cancer survivors. As such, a normal testosterone level should not be interpreted as indicative of normal fertility. After high dose cranial radiation, high dose alkylating chemotherapy, or high dose testicular radiation, androgen deficiency can occur with specific symptomatology including loss of libido and with long-term health consequences, and will also negatively impact spermatogenesis.(30) Unfortunately, treatment of androgen deficiency with exogenous testosterone will impair spermatogenesis, and thus is not an appropriate treatment for men seeking fertility. Patients with hypogonadotropic hypogonadism following cranial radiation may have restored ability to sire children after treatment with gonadotropins.(78) It is for these reasons that early referral to urology or endocrinology is warranted.

Surgical Sperm Retrieval

Testis tissue sampling is indicated in men with non-obstructive azoospermia (lack of sperm due to failure of spermatogenesis) desiring to conceive. This may be accomplished with testicular sperm aspiration (TESA), testicular sperm extraction (TESE) or micro-dissection testicular sperm extraction (microTESE). Open biopsy (TESE or microTESE) remains the gold standard in cases of non-obstructive azoospermia because it provides an optimal amount of tissue both for accurate diagnosis and retrieval of sperm for use in assisted reproduction. MicroTESE remains the most accurate and reliable method for retrieving sperm in men with non-obstructive azoospermia.(79) In the general infertile population, microTESE has been shown to yield successful sperm retrieval 1.5 times more often than conventional TESE, and TESE has been shown to yield sperm retrieval 2 times more often than TESA.(80)

In a study by Shin et al, successful sperm retrieval with microTESE was noted in 47 % of adult males with

azoopermia after chemotherapy, with a 35% clinical pregnancy rate after IVF/ICSI, yielding a 27% live birth rate.(81) These authors found no significant differences in outcomes between patients with a history of testicular cancer, lymphoma and leukemia. Hsiao et al demonstrated similar successful sperm retrieval rates in men who had a mean time from chemotherapy treatment of 18.6 years.(82) Sperm retrieval rates were demonstrated to be 37%, with a history of testicular cancer treatment having the highest sperm retrieval rates and exposure to alkylating agents resulting in a significantly lower sperm retrieval rate.

Counseling Adolescents About Fertility

There are a variety of factors which affect the content and timing of fertility counseling among adolescent cancer survivors. These factors may include patient sex, pubertal status, developmental level, cognitive capacity, psychological functioning and patient/family desire for information. Studies suggest that AYA patients prefer that information about their disease and cancer-related risks are communicated in a positive, respectful, and non-judgmental manner.(83) As adolescents are familiar with searching for information on the internet, it may also be helpful to provide them with reliable and recommended age-appropriate online resources, translated to their native languages if needed.(20,84) Peer support programs to assist adolescent survivors have been shown to promote positive psychosocial growth,(20) and may also be an option for broaching the topic of fertility. Key considerations for discussing fertility with AYA cancer survivors are outlined in table 3.

Conclusions

Regardless of whether infertility risk and fertility preservation options were presented to children and families at the time of cancer diagnosis, fertility is an important issue to address in survivorship. The type of fertility information may morph over time, from risk of gonadal damage due to cancer treatment, to fertility status assessment, to pregnancy risks and risks to offspring, to fertility options/assisted reproductive technologies, alternative options for family building. While counseling about risks needs to be individualized, patients should be reassured that survivors who conceive remote from therapy do not have an increased risk of congenital or genetic abnormalities. As reproductive health issues are commonly cited as an important concern by survivors of AYA cancer, multidisciplinary care teams including oncology, endocrinology, psychology, and reproductive medicine are advocated, with the aim of optimal provision of fertility advice and care after cancer.

Conflict of Interest Statement: Dr. Pavone serves on the Ferring advisory board; Dr. Kashanian is a medical advisor for Roman Health; Dr. Anderson consults and lectures for Roche Diagnostics, IBSA, Ferring, and Merck Serono; no other authors have any disclosures.

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