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Chapter 18

Fertility and Sexuality

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INTRODUCTION

From the perspective of the adolescent and young adult survivor, alterations in gonadal function and the loss of fertility (or even the fear of impaired fertility) are perhaps the most life altering sequelae of childhood cancer influencing a survivor's developing body image, sexuality, dating relationships, marriage patterns, and sense of well-being. Fertility is also one of the most difficult outcomes to study in survivors, as the primary endpoint is pregnancy, an outcome that is influenced by many physical and societal factors beyond the direct effect of the cancer therapy on the reproductive organs. This is particularly true in males, as many men are not willing to have a semen analysis and self-reporting a successful impregnation is subject to both over- and under-reporting biases. Further compounding the investigation of fertility in both genders are the often overlapping effects of different cancer therapies on the reproductive system and the sometimes late recovery of function.

A survivor's (and a parent's) understanding of fertility and sexuality and how it is impacted by the cancer and the cancer therapy evolves through the stages of survivorship. When a child or adolescent is diagnosed with cancer, the discussion of cancer therapy is difficult and complicated as the oncologist describes to the parent (and patient) the response rates of various protocols, the associated acute toxicities of therapy, and the potential for future health problems related to the therapy. During this stress laden period when therapeutic decisions are made, as a parent faces the potential of losing a child, details regarding the potential for infertility and gonadal dysfunction are often not understood or remembered by families and sometimes are not adequately provided by the cancer treating team. Later, as the cancer is cured and the patient matures into adulthood, issues of fertility and sexuality become more immediate and prevalent.

Following is an overview of fertility and sexuality, by gender, including therapies associated with gonadal dysfunction, methods of fertility preservation, and sexuality. For further reading, two superbly written chapters in *Late Effects of Childhood Cancer*, edited by Wallace and Green, discuss ovarian and uterine function and reproductive potential in women and testicular function in men (1, 2).

Table 18.1 Acute Ovarian Failure and Premature Menopause in Female Survivors of Childhood Cancer

Acute Ovarian Failure

- Definition: loss of ovarian function during or shortly following completion of therapy
- Occurs in 5-7% of females treated in childhood or adolescence
- High risk groups:
 - Stem cell transplant recipients
 - Total body irradiation (TBI) - nearly all women treated with TBI after age 10 years; about 50% of those treated prior to 10 years of age
 - High dose myeloablative therapy (e.g., busulfan, melphalan, thiotepa)
 - Ovarian (pelvic or abdominal) irradiation > 1000 cGy
 - Ovarian irradiation < 1000 cGy with concomitant alkylating agents (e.g., cyclophosphamide) or older age at exposure

Non-surgical Premature Menopause

- Female survivors who do not develop acute ovarian failure are potentially at risk of developing premature menopause.
- Definition: menopause prior to age 40 years
- High risk groups:
 - older attained age
 - increasing dose of radiation to the ovaries
 - increasing dose of alkylating agents
 - diagnosis of Hodgkin lymphoma

- cranial radiation doses ≥ 3000 cGy to the hypothalamic-pituitary axis may lead to gonadotropin deficiency affecting fertility
- For women treated with an alkylating agent plus abdominopelvic radiation, the cumulative incidence of nonsurgical menopause approaches 30% by forty years of age.

Evaluation for Ovarian Dysfunction

- Detailed history of menstrual cycle:
 - age at menarche
 - for women with cancer prior to menarche - precocious or delayed puberty
 - for women with cancer following menarche - change in menstrual history during and following cancer therapy
 - frequency, duration, intensity of menstruation
 - use of estrogen replacement
- Symptoms of hypo estrogen state
 - hot flashes
 - night sweats
 - vaginal dryness
 - variable sexual interest
 - altered, depressed, or irritable mood
- Laboratory evaluation of ovarian potential and reserve:
 - Difficult to predict premature menopause by biochemical testing
 - Follicle stimulating hormone (FSH) and estradiol levels
 - if menstruating, obtain on day 3 of cycle

- FSH will be elevated and estradiol level low during perimenopause and menopause.
 - FSH levels often fluctuate and may need repeating
- B-inhibin (if menstruating, obtain on day 3 of cycle) and anti-Mullerian hormone (AMH) are newer methods that may provide additional information regarding ovarian reserve.
- Further testing should be conducted by a reproductive specialist and may include a pelvic ultrasound (transvaginal).

Table 18.2 Infertility and Androgen Deficiency in Male Survivors of Childhood Cancer

Infertility

- Germinal epithelium of the testis is sensitive to radiation
- Germinal epithelium of the testis is also sensitive to chemotherapeutic drugs, including alkylating agents (e.g., cyclophosphamide and ifosfamide), procarbazine, and cisplatin. Outcomes are agent specific and dose-dependent.
- High risk groups:
- Radiation doses (to the testes) above 200 cGy invariably cause oligospermia or azoospermia
 - TBI - fractionated dose of 1200 to 1500 cGy often results in infertility.
 - Males with ALL who are treated with irradiation of the testis for a testicular relapse will almost always be azoospermic.
 - Though the testes are shielded with modern techniques, scatter radiation from high dose radiation can result in oligospermia or azoospermia. Examples include pelvic, inguinal, or spinal radiation for a sarcoma, Hodgkin lymphoma, or CNS tumor, respectively.
- Chemotherapy
 - Moderate to high dose cyclophosphamide or ifosfamide often results in azoospermia. The combination of these two agents, used in the treatment of patients with Ewing sarcoma, causes infertility in virtually all males.

- Combination of cisplatin with either ifosfamide or cyclophosphamide, used in the contemporary treatment of osteosarcoma, results in oligospermia or azospermia in over 90% of males.
- High dose melphalan or busulfan used in preconditioning regimens prior to a stem cell transplant causes impaired spermatogenesis in the majority of males.
- Early chemotherapeutic regimens used for Hodgkin lymphoma, including six courses of MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) generally resulted in a high incidence of azospermia.
- Radiation to the hypothalamic-pituitary axis with doses > 3000 cGy (e.g., cranial radiotherapy for a brain tumor) may result in a gonadotropin deficiency, thus indirectly affecting spermatogenesis and reproductive potential.

Evaluation for Infertility in Males

- Pubertal staging - reduced testicular volume (< 12 ml), measured by Prader orchidometer, is strongly suggestive of impaired spermatogenesis
- An elevated FSH suggests impaired spermatogenesis
- Semen analysis

Androgen Deficiency

- In comparison with the germinal epithelium, the Leydig cells are less affected by chemotherapy and radiotherapy.
- Testicular irradiation with doses of greater than 2000 and 3000 cGy are associated with Leydig cell dysfunction in prepubertal and sexually mature males, respectively.
- Even with high dose cyclophosphamide, frankly subnormal levels of testosterone are rare, though Leydig cell dysfunction may be evidenced by an elevated luteinizing hormone

(LH) level. Whether or not mild Leydig cell dysfunction will lead to premature androgen deficiency as this population ages is not known.

- Androgen deficiency can also result from hypogonadotropic hypogonadism following cranial radiotherapy.

Evaluation of Androgen Deficiency

- In postpubertal males, elevated LH and decreased testosterone levels indicate Leydig cell dysfunction.

Table 18.3 Fertility Preservation

American Society of Clinical Oncology (ASCO) recommends that oncologists discuss fertility preservation options as appropriate and to refer interested patients and their families to reproductive specialists (3).

Females

- When radiation fields include the pelvis, the ovaries can be surgically transposed to a more protected location. However, even after transposition of the ovaries, some women will develop premature menopause secondary to their chemotherapy.
- Hormonal protection of the ovaries with a GnRH analogue has been attempted with varying success in small uncontrolled trials in patients undergoing therapy with moderate to high dose alkylating agents. Because the success rate of cryopreservation of unfertilized oocytes is very low and the necessary ovarian hormonal stimulation prior to removal of the oocytes may delay cancer therapy, this approach is used infrequently in adolescents with cancer.
- Ovarian tissue cryopreservation is an investigational method of fertility preservation that has the advantage of requiring neither a sperm donor nor ovarian stimulation.

Males

- Sperm cryopreservation is an effective method of fertility preservation in males.
- In a sample of 162 oncology physicians, 91% agreed that sperm banking should be offered to all male patients about to have cancer treatment that could impair their fertility. Yet, only 10% said they always mention sperm banking to eligible patients during treatment planning. Another 18% mentioned it in more than 85% of their cases (4).

- In a companion survey of recent male oncology patients in the same setting, 20% said they did not bank sperm because it was never mentioned as an option, and another 5% had been interested, but did not know how to find out more information in time (5).
- Spermarche does not occur until about 13 to 14 years of age, thus limiting sperm banking to adolescent males.
- Methods to preserve fertility in younger males, including testicular tissue cryopreservation, have had little successful.

Table 18.4 Body Image

- Definition: Mental perception one has of one's physical body and its function. It forms an important part of one's entire self-image.
- Develops gradually from positive experiences of satisfaction in early childhood
- In adolescence, the altered, sexually mature body and images of it are integrated into an individual's identity. This integration and development can be influenced by experience of physical illness.
- Two-thirds of pediatric cancer survivors have been found to have impaired body image; body image has been found to be inferior in childhood cancer survivors as compared to peers.
- Most disturbing physical changes for adolescents includes: hair loss, presence of a central venous catheter, weight changes, scars from surgery, amputation, acne (typically medication induced), limited growth
- Body image concerns persist and may even appear for the first time after treatment, even when many of the physical changes are no longer apparent.
- Body altering side effect of cancer treatments (both in the short- and long-term) are reported by adolescents and young adults to be one of the worst aspects of the diseases
- Physical changes are distressing for children and adolescents with cancer of all ages. Self-consciousness about appearance can lead to social withdrawal.
- High risk groups:
 - Those who report physical late-effects that interfere substantially with daily activities

- Older age at diagnosis (especially adolescence and young adulthood)
- Undergoing active treatment
- Cranial irradiation
- Treatment that limits growth or is associated with infertility

Table 18.5 Sexuality

- Definition: The development of one's sexuality and sexual identity is a process that occurs during adolescence and leads to an understanding and appreciation of who one is as a sexual being
- WHO Definition of sexual health: state of physical, emotional, mental and social well-being related to sexuality which requires a positive and respectful approach to sexuality and sexual relationships as well as the possibility of having pleasurable and safe sexual experiences.
- Sexuality is positively associated with body image and self-esteem and inversely associated with depressed mood.
- Establishing positive sexual identity depends on obtaining sexual health knowledge, developing interpersonal relationships, and dealing with body image concerns. All of these are challenged by the cancer experience.
 - Survivors may have relatively limited sexual knowledge which may impair the development of a healthy sexual identity.
 - Barriers to interpersonal relationships include: feelings of being unattractive or different, possible impairments in social skills, fears felt by potential partners about the cancer diagnosis, isolation from peers, and treatment-related cognitive impairments.
 - Positive body image is an integral element of sexual health.
- Hormonal, interpersonal or psychological problems can affect sexuality
- High risk groups:

- May be associated with high dose chemotherapy and bone marrow transplantation
- Those with impaired fertility
- Body image disturbance
- Delayed puberty

Table 18.6 Practical Applications

- A majority of parents do not recall receiving information on fertility despite having been informed.
- Additionally, many patients are unaware of their fertility status.
- Patients want their treatment team to tell them the facts about cancer-related infertility and sperm banking, directly and openly. Patients (older adolescents and young adults) want to make their own choice of whether or not to bank sperm.
- It is important to discuss fertility and fertility concerns several times throughout treatment and post-treatment as they may become more relevant as the patient gets older and further out from treatment. Additionally, diagnosis and treatment planning create tremendous anxiety for patients and their families. It makes it difficult for patients and families to remember all the new medical information they receive.
- Since most sexual information adolescents and young adults possess is either learned at school or from peers, missing educational and social experiences because of treatment may affect sexual identity formation as well. If this is the case, sexual health education similar to the information being provided in school should be offered to the patient.
- It is important to take into account the patient's developmental stage when deciding whether to discuss certain aspects of the treatment effects (sexual health and body image issues such as scaring). Involving parents may be beneficial for younger adolescents whereas it may hinder self-esteem and growth in older ones.

- Teenagers interviewed about sperm banking preferred to hear about sperm banking privately, without having their parents present

Tips and Suggestions:

- Acknowledge the sensitivity of the topic in terms of emotions and values.
- Don't try to minimize the grief of infertility
- Separate sexuality and fertility
- Tips on making the discussion easier:
 - Try to find a place for the discussion where you have privacy and will not be overheard. Plan ahead for privacy as much as possible
 - Make sure to set aside enough time for discussion
 - Make eye contact with your patient
 - If the patient and/or family get upset, be supportive. You cannot take away the pain and loss of potential infertility but you can let them know you empathize
 - Avoid minimize or negating the importance of infertility
 - This topic can bring up a lot of emotions. Would you like to discuss your feelings with a social worker or psychologist? With clergy?

SUMMARY

Infertility and premature gonadal dysfunction are common outcomes following therapy for childhood cancer and influence a survivor's quality of life, body image, and sexuality. It is imperative that clinicians address the fears and concerns of survivors in a sensitive manner. Moreover, recognizing the complexity of this topic and the evolving options for fertility preservation, a multidisciplinary team that includes a reproductive specialist and a psychologist familiar with the issues of cancer survivors (or ready availability by referral) is preferred.

Oncology teams can facilitate the development of positive self-esteem and development of sexual health in several ways: facilitating personal control and individuation, offer opportunities for sexual health education, connect the patient/survivor with other teens diagnosed with cancer. Evaluate sexual development to ensure puberty is proceeding normally. Those with late effects that alter sexual functioning, physical appearance or fertility should be referred to health care providers who specialize in these issues

Any patient or survivor with sexual problems that result from treatment for childhood cancer needs both medical and psychological follow-up. A team approach that provides rehabilitation and psychological assistance to address concerns about body image, fertility and sexuality is crucial.

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ADDITIONAL RECOMMENDED READING

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