In Weiner, LS, Pao, M, Kazak, AE, Kupst, MJ, Patenaude, AF, Holland, JC (Eds.) Pediatric Psycho-Oncology: The Quick Reference for Pediatric Oncology Clinicians. The Psychiatric and Psychological Dimensions of Pediatric Cancer Symptom Management on Fertility and Sexuality (2nd Edition). Oxford University Press. 2015.

18 Fertility and Sexuality

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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 one of the most difficult outcomes to study in survivors, as the primary endpoint is pregnancy, which is influenced by many physical and societal factors beyond the direct effect of the cancer therapy on the reproductive organs.

• 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.

• The investigation of fertility in both genders is hampered by the often overlapping effects of different cancer therapies on the reproductive system, and the sometimes late recovery of function.

• Pregnancies may occur when survivors are no longer in contact with treating physicians or long term follow up clinics therefore limiting accurate assessment of this outcome.

A survivor's (and a parent's) understanding of fertility and sexuality and how it is impacted by cancer and cancer therapy evolves through the stages of survivorship. During the stress laden period of diagnosis, when therapeutic decisions are made and as a parent faces the possibility 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. This chapter presents an overview of fertility (including therapies associated with gonadal dysfunction and methods of fertility preservation) and sexuality. Further reading on the effects of cancer treatment on ovarian and uterine function and reproductive potential in women and testicular function in men is available.[1, 2]

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

Acute Ovarian Failure	**Evaluation for Ovarian Dysfunction**

- Definition: loss of ovarian function during or shortly following completion of therapy
- Occurs in 5-7% of females treated in childhood or adolescence[3]
- 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, cytoxan, 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

- 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 hypoestrogen 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

Non-surgical Premature Menopause

- Female survivors who do not develop acute ovarian failure are potentially at risk of developing premature menopause.[4]
- 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 testing
    - Affected by use of oral contraceptives.
    - 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.
    - Anti-Mullerian hormone (AMH) is a newer methods that may provide additional information regarding ovarian reserve.
- Further testing should be conducted by a reproductive specialist and may include a pelvic or transvaginal ultrasound to assess ovarian volume and antral follicle count.

menopause approaches 30% by forty years of age.	

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. o TBI - fractionated dose of 1200 to 1500 cGy often results in infertility.	• 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 azoospermia in over 90% of males. • High dose melphalan or busulfan used in preconditioning regimens prior to a

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Males with ALL who are treated with irradiation of the testis
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.

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stem cell transplant causes impaired spermatogenesis in the majority of males.

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.

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<td colspan="2">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 is the gold standard to evaluate sperm count, motility, mobility and volume

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<td>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

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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

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associated with Leydig cell dysfunction in prepubertal and sexually mature males, respectively.	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 Options
The American Society of Clinical Oncology (ASCO) recommends that oncologists discuss fertility preservation options as appropriate and refer interested patients and their families to reproductive specialists.[5] In a recent survey of pediatric oncology practitioners 75% of respondents indicated that they offer sperm banking to post pubertal male patients ≥ 50% of the time. Twelve percent of practitioners responded that they referred post pubertal female patients to a fertility specialist ≥ 50% of the time.[6]
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.

- Radical trachelectomy, in which the cervix but not the entire uterus is surgically removed, may preserve fertility in patients with early stage cervical cancer.
- There is insufficient evidence to support the use of gonadotropin releasing hormone (GnRH) analogues in protecting the ovaries during cancer directed treatment.
- Oocyte cryopreservation is now considered a non-experimental intervention. This process requires hormonal hyperstimulation for approximately 10-12 days with subsequent oocyte retrieval under anesthesia. Unfertilized oocytes are then cryopreserved and can be thawed and fertilized utilizing assisted reproductive techniques in the future. The cost is not usually covered by insurance.
- 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 post-pubertal males. Spermarche does not occur until about 13 to 14 years of age, thus limiting sperm banking to adolescents.
- Anterograde ejaculation is the most common method for obtaining sperm. In individuals who cannot ejaculate via masturbation, alternative methods of obtaining sperm for cryopreservation include vibrostimulatory ejaculation and testicular sperm extraction (TESE). TESE is a surgical procedure performed under anesthesia.
- Methods to preserve fertility in younger males, including testicular tissue cryopreservation, have had little success to date.

Table 18.4 Body Image

- Definition: Mental perception 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.
- Body image has been found to be inferior in survivors of childhood leukemia as compared to peers.[7]
- 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) and 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[8], and can affect both the formation of romantic relationships and the development of physical and emotional intimacy within those relationships.[9]
- 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 oneself 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.[10]
- Sexuality is positively associated with body image and self-esteem and inversely associated with depressed mood.[11] An association also exists between sexual function and health status. Survivors of childhood cancer often have persistent health concerns.[12]
- 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.
- Recent studies have identified some degree of difficulty in sexual functioning in 41-43% of young adult survivors of childhood cancer survivors, with women experiencing a greater degree of dysfunction [13, 14]
- High risk groups:
  - Those who have had high dose chemotherapy and bone marrow transplantation
  - Those with impaired fertility
  - Body image disturbance
  - Delayed puberty
- Sexual dysfunction (problems with libido, arousal, orgasm, resolution) can occur as a result of treatment (radiation/surgery in the pelvic area), physical symptoms (fatigue, pain, nausea), psychological factors (anxiety, depression, guilt), and social and interpersonal factors. It is important that adolescent and young adult cancer patients are given permission to talk about sexuality, as well as concerns about fertility with knowledgeable providers. (Cf. corresponding handbook for adults.[15]

(Cf. MMQL-AF measurement of health-related quality of life in the Appendix.)

Practical Applications

- A majority of patients and parents do not recall receiving information on fertility, despite having been informed.
- 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, because they may become more relevant as the patient gets older and further out from treatment. Also, diagnosis and treatment planning create tremendous anxiety for patients and their families. It is difficult for patients and families to remember all the new medical information they receive.
- Since most sexual information processed by adolescents and young adults is either learned at school or from peers, missing educational and social experiences because of treatment may affect sexual identity formation. 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.
- Do not try to minimize the grief of infertility.
- Separate sexuality and fertility.
- Provide information on contraception and sexually transmitted infections.
- 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 minimizing or negating the importance of infertility.
    - This topic can bring up a lot of emotions. Ask patients if they would like to discuss their feelings with a social worker, psychologist or with clergy.
- Have information readily available about regionally appropriate referrals to sperm banks or reproductive specialists.
- Have information readily available about multiple pathways and options regarding family building.
- Have information readily available for local therapists and/or counselors with a specialty in body image dysfunction and/or sexual dysfunction.
- Provide links to relevant websites for information and financial assistance, e.g. http://www.fertilehope.org/index.cfm

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 mental health provider who is 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 heath 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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