Chapter 1
Reproductive Health After Cancer

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Introduction

Recent diagnostic and therapeutic advances in oncology have led to greater survival rates in children and reproductive aged adults with malignancies. However, while cancer therapies improve long-term survival, such treatments can lead to a variety of reproductive problems including abnormal pubertal development, infertility, premature gonadal failure, and sexual dysfunction [1, 2]. As more children and young adults survive cancer and lead productive lives, these concerns are becoming increasingly important. However, the treatment of these conditions can be complicated both by the previous diagnosis of cancer and by comorbidities related to previous cancer therapy. Collaboration with a subspecialist in the area of reproductive endocrinology before and after cancer treatment can be helpful in managing the reproductive needs of cancer survivors [3]. Clinicians must be aware of the reproductive consequences of cancer therapies in order to anticipate and address the needs of cancer survivors so that they can lead healthy, fulfilled lives.

Gonadotoxicity of Treatments

In the female, the ovary is particularly sensitive to the adverse effects of chemotherapy and radiation due to its finite number of un-renewable germ cells [4, 5]. A woman's reproductive life span is determined by the size of the follicular pool. Cancer treatments that cause follicular atresia and destruction of the follicular pool can lead to premature menopause and infertility [6, 7]. Alkylating agents and pelvic irradiation pose the greatest threat to ovarian function [6–11]. In addition, the uterine effects of pelvic irradiation may contribute to infertility and increase the risk of pregnancy loss [12]. Premature ovarian failure not only causes infertility but can

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lead to long-term health problems such as osteoporosis, cardiovascular disease, and sexual problems in women.

Cancer therapies also affect reproductive function in males. The mechanism for impaired spermatogenesis involves not only damage to the somatic cells that support spermatogenesis (Sertoli and Leydig cells) but also apoptosis of the germ cells themselves. Both chemotherapy, particularly alkylating agents and cisplatin, and testicular radiation pose a threat to future fertility. In addition, some surgical treatments for cancer can have an effect on transport of sperm and ejaculatory function [13]. In both males and females, cranial irradiation can have a profound effect on pubertal development and long-term reproductive function by disrupting the hypothalamic–pituitary–ovarian axis [14, 15].

Fertility

The ability to lead full reproductive lives is very important to both female and male reproductive aged cancer survivors [16–18]. There is evidence that reproductive problems lead to substantial anxiety, which negatively affects quality of life in cancer survivors [19]. The reproductive risks of cancer therapies and fertility preservation options should be routinely discussed with patients prior to treatment. Consultation with a reproductive endocrinologist may be very helpful to provide adequate counseling regarding the reproductive consequences of cancer therapies and the risks and success rates of various fertility preservation strategies. A recent survey of cancer survivors reported that almost 30% of patients less than 50 years of age wanted more information about premature ovarian failure or health risks for their children, and a third of patients would have liked a fertility consultation before cancer treatment [20]. Semen cryopreservation remains the best option for fertility preservation in the post-pubertal male diagnosed with cancer. Fertility preservation in prepubertal boys remains problematic and is an active area of investigation. Extracting and cryopreserving spermatogonial stem cells from such boys in order to later autograft, xenograft, or mature in vitro are exciting and promising avenues of investigation [21]. In females, the most successful option for fertility preservation is emergency IVF and embryo banking prior to cancer therapy. However, this method is not appropriate for young women without a partner, prepubertal girls, or those who do not have time to delay lifesaving treatment. Other less effective and still experimental options for fertility preservation in cancer patients include oocyte and ovarian tissue cryopreservation [22]. Other options for minimizing the damaging effects of cancer treatments include oophoropexy or fertility-sparing cancer surgery [23]. In addition, co-administration of GnRH agonists may provide some protection against ovarian damage during chemotherapy, although prospective controlled trials are needed to establish any real benefit.

Given the potential of cancer therapies to cause reproductive problems, it is important to monitor a patient's reproductive function after cancer therapy. For males this includes an assessment of sexual function and a semen analysis. In

women, it is important to monitor menstrual function, though hormonal contraception will mask any signs of ovarian failure. Importantly, menstrual function is not an adequate measure of fertility. Even women who maintain cyclic menses after therapy are at risk for early menopause, infertility, and long-term health problems related to early ovarian failure [7–9, 24–28]. Once clinical symptoms of ovarian dysfunction occur, such as irregular menses and vasomotor symptoms, pregnancy is usually not possible even with aggressive fertility treatments. Data suggest that measures of ovarian reserve, such as basal FSH, inhibin B, anti-mullerian hormone, and antral follicle counts, may be useful to monitor ovarian function in cancer survivors since they can reveal decreased ovarian reserve even in normally menstruating women [29, 30]. While such monitoring may be helpful particularly in patients who were unable to pursue fertility preservation techniques pretreatment and may benefit from fertility treatments or preservation post-treatment, these measures must be validated before routine use. In general, cancer survivors at risk for infertility should be counseled about pursuing pregnancy as soon as appropriate because the age-related decline in fertility may occur at an earlier age. In addition, cancer survivors experiencing delayed conception should be evaluated by a fertility specialist sooner than normally recommended (before 12 months of unprotected intercourse) given that such couples may have a shorter fertile window compared to couples without a history of cancer. Post-therapy options for having a family include fertility treatments including IVF, the use of donated gametes or embryos, or adoption.

Overall, data regarding the safety of pregnancy after cancer have been reassuring. Pregnancy does not appear to increase the risk of cancer recurrence in young patients, even for hormone sensitive tumors such as breast cancer [31]. While several studies of childhood cancer survivors have demonstrated an increased risk of low birthweight infants, primarily related to a history of pelvic irradiation [32, 33], cancer survivors who conceive at least 5 years following cancer treatment are not at increased risk of having a child with major congenital abnormalities [32, 34–36]. In addition, children of cancer survivors do not appear to be at higher risk of developing cancer themselves [37]. While these data are reassuring, further studies of large, current databases of cancer survivors are needed to provide more information for patient counseling. In general, the prenatal and obstetrical care of the cancer survivor should be multi-disciplinary, since the spectrum of medical complications resulting from cancer treatment benefits from diverse expertise. While many cancer survivors will be good candidates for carrying a pregnancy, others may be at high risk because of associated comorbidities. In such cases, a gestational carrier may be considered.

Contraception

While cancer therapies can lead to infertility, a history of cancer does not necessarily mean that a patient is sterile. An unplanned pregnancy in the setting of a cancer diagnosis can be devastating, making treatment decisions more complex and putting

the patient and pregnancy at high risk. Even after cancer treatment is completed, oncologists often recommend waiting at least 2 years before pursuing pregnancy. Many cancer survivors will never pursue pregnancy because of the perceived risk. Nonetheless, making a decision to continue or terminate an unplanned pregnancy in such cases can be very difficult. For these reasons, discussion of contraceptive options should be a priority after the diagnosis of cancer. Several factors should be considered when selecting among contraceptive options. The type of cancer may influence whether hormonal or nonhormonal agents are selected. For example, breast cancer is the most common malignancy in reproductive aged women in which hormonal contraception is contraindicated. A history of thromboembolic disease, significant liver dysfunction, or significant comorbidities may also make hormonal contraception a less desirable option. While barrier contraceptives are reasonable options for such patients, more effective methods include the nonhormonal intrauterine device (Paraguard) and permanent sterilization.

Menopausal Symptoms

Premature ovarian failure can result in vasomotor symptoms and vaginal dryness. Other symptoms associated with menopause include sexual dysfunction, mood symptoms, and sleep disturbance. These symptoms can be very troublesome for patients and can significantly interfere with quality of life. Hormone replacement therapy in the form of traditional postmenopausal low-dose estrogen and progestin therapy or combine contraceptives are commonly prescribed to cancer survivors not only for the treatment of menopausal symptoms but also for the prevention of bone loss. There are no clear guidelines regarding hormone replacement therapy in this population since little data exist comparing the long-term safety and efficacy of various different forms of therapy in cancer survivors. Importantly, the results of large HRT trials such as the Women's Health Initiative cannot be generalized to the population of young cancer survivors with premature ovarian failure. Alternative therapies such as lifestyle modification, selective serotonin receptor inhibitors (SSRI), venlaxafine, and gabapentin may be useful for the management of vasomotor symptoms in breast cancer survivors and in other situations where estrogen is contraindicated [38]. Vaginal estrogens and lubricants are effective for the treatment of atrophic vaginitis and dyspareunia, and appear to be safe in patients who are not candidates for systemic estrogen therapy [39].

Sexual Function

Overall, at least 20% of cancer survivors experience sexual dysfunction, and a higher proportion of survivors with a history of colorectal, prostate, gynecological, breast, and bladder cancer [1]. It appears that all phases of the sexual response cycle are affected by cancer. However, men are most likely to experience erectile

dysfunction and women experience decreased libido and vaginal dryness. Impaired body image after cancer may be an important factor influencing sexual function as well. Sexual rehabilitation after cancer may significantly improve quality of life [40]. Moreover, there is evidence that even adolescent and young adult cancer survivors benefit from education and support surrounding issues of sexual development and function, body image, fertility, prevention of sexually transmitted disease, and unwanted pregnancy. In one small pilot study, such an intervention increased cancer-specific knowledge regarding sexual issues, improved body image, lessened anxiety about sexual relationships, and decreased psychological distress [41].

As the number of young cancer survivors continues to increase, it is important for clinicians to be aware of the reproductive risks and concerns specific to this population. This chapter has reviewed some of the main reproductive consequences experienced by cancer survivors and provides guidance regarding the management of these conditions.

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