Effects of cancer treatment on ovarian function

Jaymeson S. Stroud, M.D.,[a] *David Mutch, M.D.,*[c,d] *Janet Rader, M.D.,*[c,d] *Matt Powell, M.D.,*[c,d] *Premal H. Thaker, M.D.,*[c,d] *and Perry W. Grigsby, M.D.*[a,b,c,d]

[a] Department of Radiation Oncology; [b] Department of Radiology, Division of Nuclear Medicine; [c] Department of Obstetrics and Gynecology, Division of Gynecologic Oncology; and the [d] Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, Missouri

Causes of primary ovarian failure are reviewed, focusing specifically on cancer treatment-related modalities. Strategies and future directions for protection of the ovaries during cancer therapy, including ovarian transposition, and conformal radiation techniques are presented. (Fertil Steril® 2009;92:417–27. ©2009 by American Society for Reproductive Medicine.)

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Although cancer incidence rates in women less than 50 years old continue to increase during recent years, mortality rates are dramatically decreasing due to modern advances in treatment (1, 2). In 1990 the prevalence of cancer survivors was 1 in 1,000 for young adults (15–45 years of age). By the year 2010, as many as 1 in 250 patients in this age group will have survived cancer (3). However, increasing numbers of survivors are now confronted with the long-term consequences of exposure to these treatments. Cancer therapy, which includes surgery, radiotherapy, and chemotherapy, can have a profound impact on ovarian function, leading to premature menopause and loss of fertility.

Acute ovarian failure can occur during or shortly after completion of irradiation or chemotherapy and may be transient or permanent. In contrast, premature ovarian failure (POF) or premature menopause typically manifests after a post-treatment return of regular menses with subsequent loss of ovarian function before the age of 40 years. As expected, surgical ablation of the ovaries leads to immediate and permanent loss of function.

Given that the pool of primordial follicles in the ovary is fixed and declines in a predictable manner, generalized models have been established to describe the natural decay of the ovary. Any injury to the ovary can potentially reduce this ovarian reserve, effectively advancing the patient's reproductive age, thus closing her window of reproductive opportunity. The radiosensitivity of the human oocyte has been studied and a model for predicting the age of ovarian failure after a known dose of radiation has been proposed (4–7). Those women not receiving a sterilizing dose of radiation or chemotherapy may be at increased risk for complications during pregnancy, including spontaneous abortions and delivery of low birth weight babies (8).

Particularly challenging are similar consequences of cancer treatment in the pediatric population. At a time when cancer *survival* is the first priority, questions regarding future reproductive ability and childbearing are difficult issues for physicians, patients, and parents. Nevertheless, having foreknowledge of potential treatment-related ovarian failure will allow the physician to better counsel the patient and her family regarding the importance and timing of fertility preservation given an estimated window of fertility. In prepubertal girls, in whom clinical, biochemical, or radiological detection of ovarian failure is not reliably possible, estimating the risk and age of ovarian failure can potentially facilitate the initiation of hormone replacement therapy (HT) to induce secondary sex characteristics.

Modern techniques for prevention of treatment-induced ovarian ablation include better shielding of the ovaries from the damaging effects of radiation. This can be accomplished by implementing transposition procedures to move the ovaries outside of the area at risk. In addition, knowledge of the precise three-dimensional location of the ovaries allows the physician to limit the dose in these regions with novel beam arrangements, three-dimensional conformal radiation therapy or intensity-modulated radiation therapy. Prevention of the cytotoxic effects of chemotherapy by administering a concurrent GnRH agonist (GnRH-a) appears to be promising in early studies (9, 10).

In the modern era of improved antineoplastic agents and highly conformal, three-dimensionally planned radiation

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Reprint requests: Perry W. Grigsby, M.D., Department of Radiation Oncology, Box 8224, Mallinckrodt Institute of Radiology, Washington University School of Medicine, 4921 Parkview Place, Lower Level, St. Louis, MO 63110 (FAX: 314-747-9557; E-mail: pgrigsby@wustl.edu).

therapy, the possibility of limiting the ovaries from excess treatment-related toxicity in certain situations is becoming more of a reality. Herein we describe the effects of multimodal cancer treatment on ovarian function as published in the literature from a historic basis down through more recent efforts to characterize toxicity during this transition into a more technologically advanced age of cancer therapy.

PATHOPHYSIOLOGY

Primary ovarian failure is the loss of ovarian function caused by a process directly affecting the ovaries. In addition to multimodal cancer treatment, other processes including autoimmunity, chromosomal abnormalities, and natural aging can result in secondary ovarian failure, which is easily detected by an increase in serum gonadotropin levels (FSH and LH). Other markers like inhibin A or inhibin B and 17-β-E_2 have been shown in preliminary studies to be prognostic factors in predicting the return of ovarian function after cancer treatment (11, 12). Ovarian failure before menarche will preclude development of secondary sex characteristics as the patient ages. Loss of ovarian function at any age thereafter leads to menopausal symptoms including vasomotor instability (hot flashes), fatigue, irritability, anxiety, vaginal dryness, decreased libido, and atrophy of the breasts. Adverse health outcomes of POF include osteoporosis, cardiovascular disease, impaired fecundity, and psychosexual dysfunction.

Any injury to the dividing granulosa cells (GC) that line and support the developing follicles will affect the viability of the maturing oocyte. Inability of the follicle to develop into a mature oocyte available for ovulation indicates loss of ovarian function. The GCs appear to be the initial target for radiation injury. Within a few hours of irradiation, before any changes in the oocyte are detectable, pyknosis—indicating cell death—can be seen in GCs. With sufficient loss of GCs, the oocyte loses viability and the follicle atrophies (13).

Acute ovarian failure (AOF) occurs in those women receiving a dose of irradiation or chemotherapy sufficient to cause permanent sterility during or shortly after treatment. The ovaries of these women reveal complete or nearly complete disappearance of primordial follicles, occasionally with remnants of degenerating follicles. The ovarian cortical stromal cells are mostly replaced with collagen and the ovary shrinks in size. With normal aging, ovarian vessels develop spontaneous sclerosis and myointimal proliferation to the point of occlusion of the vessel lumen. The media may also show hyaline degeneration. Radiation injury accelerates this process of small vessel damage as demonstrated by the signature late effects of organizing thrombi or masses of fibrin around foamy histiocytes within the intima of small vessels (13, 14).

A retrospective cohort multicenter study by the Childhood Cancer Survivor Study assessed AOF in female childhood cancer survivors (15). Of the 3,390 survivors studied, 215 (6.3%) developed AOF defined as the loss of ovarian function (self-reported amenorrhea) within 5 years of cancer diagnosis. Factors associated with the development of AOF were increased age at the time of treatment, diagnosis of Hodgkin's disease, increased radiation doses (particularly >10 Gy), and exposure to alkylating agents (specifically procarbazine and cyclophosphamide). Women who developed AOF despite receiving doses of less than 10 Gy typically had additional risk factors, such as exposure to alkylating agents and older age.

In other women, fertility may remain transiently after treatment if some follicles are relatively radioresistant. This typically occurs in the late stages of maturation when the GCs are no longer rapidly proliferating. Temporary sterility may result because of loss of follicles in the intermediate stages of development when GC proliferation is most intense. Women receiving a dose of irradiation insufficient to result in immediate and permanent sterility may experience POF or premature menopause. Lower radiation doses can lead to a reduction in the total number of remaining follicles, which effectively shortens the reproductive period. The POF typically manifests after a post-treatment return of regular menses with subsequent loss of ovarian function before the age of 40 years.

The incidence and risk factors of POF were recently analyzed using a separate cohort of participants in the multicenter Childhood Cancer Survivor Study (16). Of the 2,819 female cancer survivors that met study entry criteria, 8% had experienced nonsurgical premature menopause compared with 0.8% in a cohort of control siblings. In women who received an alkylating agent and abdominopelvic irradiation, the cumulative incidence of nonsurgical premature menopause approached 30%.

TREATMENT FACTORS

Ultimate fertility depends not only on the reproductive age of the patient and the corresponding ovarian reserve or size of the remaining pool of primordial follicles, but also on treatment-related factors such as the dose of radiotherapy, the dose and class of chemotherapy, and the use of a combination of treatment modalities. In a retrospective analysis of 100 female childhood cancer survivors and 21 age-matched controls from Denmark, the effects of cancer treatment on ovarian function were evaluated (17). Detailed menstrual histories, hormonal measurements, and timed transvaginal ultrasound measurements (menstrual cycle days 2–5) were performed. The median age was 5.4 years at diagnosis and 25.7 years at study entry. All patients received chemotherapy, including 44 who received alkylating agents. Fifty-six patients received radiotherapy with 20 undergoing infradiaphragmatic irradiation (12–40.5 Gy). Cranial (16 patients), supradiaphragmatic (12 patients), and total body irradiation (10 patients) were among the other sites treated. Premature ovarian failure was recorded in 17 patients who were noted to have follicle-depleted or undetectable ovaries, elevated FSH and LH, and reduced inhibin B levels. Thirteen patients used oral contraception (OC) and 70 women had spontaneous menstruation. Compared with the controls, the women