Impact of Cancer Treatment on Uterine Function

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Fertility and future pregnancy potential are of concern to survivors of childhood cancer. Radiotherapy causes both ovarian and uterine damage. There are no reports of uterine damage after chemotherapy. The magnitude of risk is related to age at treatment, dose, and schedule. The dose of radiation required to destroy fifty percent of immature oocytes is <2 Gy. Reduced ovarian volume and low inhibin B and anti-Mullerian hormone concentrations in survivors with regular menses may be markers of incipient ovarian failure. Uterine damage, manifest by impaired growth and blood flow, is a likely consequence of pelvic irradiation. Uterine volume correlates with age at irradiation. Exposure of the pelvis to radiation is associated with an increased risk of miscarriage, midtrimester pregnancy loss, preterm birth, and low birthweight. The optimal dose and delivery route of estrogen replacement required to facilitate uterine growth in adolescent women treated with total body irradiation in childhood needs to be established. If female survivors of childhood cancer do achieve a pregnancy, then these pregnancies are high risk, pose a challenge for optimal mode of delivery, and require a multidisciplinary approach to management. [J Natl Cancer Inst Monogr 2005;34:64–8]

Cancer in childhood is rare; within the United Kingdom there are approximately 1400 new cases per year and a cumulative risk of around 1 in 500 by the age of 15 years. With long-term survival rates approaching 73%, it has been estimated that, by the year 2010, about 1 in 715 of those in the adult population will be a long-term survivor of childhood cancer (1).

The challenge is to maintain the excellent survival rates and to minimize the incidence and severity of modern treatment-related late effects. The treatment of childhood cancer will involve a combination of surgery, radiotherapy, chemotherapy, and bone marrow transplantation. A major issue is the effect of treatment on reproductive function and implications for the health of offspring (1). A successful pregnancy is dependant upon a functioning hypothalamic-pituitary-ovarian axis and an uterine environment that is not only receptive to implantation but, in addition, able to accommodate normal growth of the fetus to term. Adverse effects on pregnancy potential may be mediated through the hypothalamic-pituitary-ovarian axis (2), the ovary (3–5), or the uterus (6, 7). Chemotherapy and radiotherapy may damage the ovary and hasten oocyte depletion, resulting in loss of hormone production, curtailed fecundity, and a premature menopause (8, 9). It is the recognition of the impact of cancer treatment on reproductive potential that has driven the pursuit of strategies to preserve fertility, as reviewed by Critchley et al. (10, 11).

Radiosensitivity of the Ovarian Primordial Follicle

It had been estimated that the dose of radiation required to destroy 50% of immature oocytes (lethal dose; LD50) is less than 4 Gy (12). More recently, by including a group of women who had developed premature ovarian failure after total body irradiation (TBI; 14.4 Gy) and finding a mathematical solution to the Faddy-Gosden equation (13), it has been possible to determine the surviving fraction of primordial follicles following irradiation, and the LD50 of the human oocyte has now been estimated to be less than 2 Gy (Figs. 1 and 2).

It should thus now be possible to provide accurate fertility counselling for women by knowing the total dose of radiotherapy administered to the ovary and age at treatment and the likely window of opportunity for fertility (5, 14). A premature loss of primordial follicles will result in impaired ovarian hormone production, uterine dysfunction due to inadequate estrogen exposure, and an early menopause.

Radiation-Induced Pelvic Damage

The degree of impairment of ovarian function is related to the radiation dose, fractionation schedule, and age at time of cancer treatment (7, 12, 15). TBI, either alone or in combination with chemotherapy, may result in impairment or loss of ovarian function. Ovarian failure has been reported in 97% of women after total abdominal irradiation (20–30 Gy) in childhood (4) and in 72% of patients in a cohort of girls treated prepuberty (16). Long-term follow-up of women post-TBI (10–15.75 Gy, single exposure or fractionated) has shown that ovarian failure develops in 90% of patients.
Abdominal and pelvic irradiation may be part of the therapy for management of Wilms tumor, pelvic rhabdomyosarcoma, and Ewing sarcoma of the pelvis or spine. Young women exposed to flank irradiation (20–30 Gy) may have preservation of ovarian function. If women do conceive after exposure to 20–30 Gy of abdominal irradiation, there is a high risk of midtrimester miscarriage and subsequent early menopause. Furthermore, the risk of early menopause increases significantly with an increasing dose of abdominal irradiation (17). Abdominal irradiation, pelvic irradiation, and TBI may all lead to impaired ovarian function (4, 9, 18–20). Byrne and colleagues (21, 22) followed survivors between 1945 and 1975. Their study demonstrated an adjusted relative fertility in survivors of 0.85 (95% confidence interval = 0.78 to 0.92) when compared to their siblings. Most damaging to the ovary, with consequent early menopause, was treatment with infradiaphragmatic irradiation and alkylating agents. The average age of menopause was 31 years, and the risk of early loss of ovarian function increased with increasing age at the time of treatment.

Impairment of ovarian function may be the result of exposure to cranial irradiation via effects on the function of the hypothalamic-pituitary-ovarian axis. High-dose (greater than 24 Gy) radiation to the hypothalamus and pituitary (management of brain tumors) is associated with a risk of delayed puberty. Lower doses of cranial radiotherapy (less than 24 Gy) are more often accompanied by early or precocious puberty. It is therefore essential that young girls treated with cranial irradiation have their puberty status monitored at regular intervals after the completion of treatment (1, 23).

Late effects to the hypothalamic-pituitary-ovarian axis may be progressive with time and difficult to detect clinically. Decreased luteinizing hormone secretion, an attenuated luteinizing hormone surge, and shorter luteal phases have been reported among a group of women exposed to low-dose (18–24 Gy) cranial irradiation. There is an association between short luteal phases and incipient ovarian failure and early pregnancy loss (2, 24).

**Uterine Damage After Pelvic Irradiation**

The degree of uterine damage depends on the total radiation dose and the site of irradiation. The prepubertal uterus is more vulnerable to the effects of pelvic irradiation. At puberty, in response to increases in ovarian estrogen production, uterine shape alters from a tubular to pear-shaped organ with an increase in all dimensions (25, 26). Doses of radiation between 14 and 30 Gy have been reported to result in uterine dysfunction (6, 7). It is likely that there are long-term effects of high-dose pelvic radiotherapy on the uterine vasculature and development of the uterus.

Holm and colleagues (27) reported that young women exposed to TBI also suffer with impaired uterine growth and blood flow. Uterine function was studied in 12 women between 4 and 10.9 years after TBI and bone marrow transplantation for childhood leukemia and lymphoma. In this study (27), three subjects experienced spontaneous puberty and eight girls suffered a premature menopause and required sex steroid replacement. A fourth subject reported symptoms of estrogen deficiency. Average uterine volume was reduced to 40% that of normal adult size in the women on sex steroid replacement. Although the women on hormone replacement therapy experienced withdrawal bleeding (a reflection of adequate endometrial estrogen exposure), the dose of sex steroids administered was insufficient to establish normal uterine growth and development.

**Adverse Pregnancy Outcomes After Pelvic Irradiation**

Adverse pregnancy outcomes have been described for women treated with TBI and include an increased risk of early pregnancy loss, preterm birth, and delivery of low- or very-low-birthweight infants. An excess risk of low-birthweight infants
(<2500 g) and preterm birth among mothers who received abdominal irradiation for Wilms tumor in childhood has also been described (28, 29).

Thus far, there are no reports of increased incidence of either congenital abnormalities or childhood malignancy in children born to long-term survivors of childhood cancer (6,30,31). However, these successful pregnancies mostly result from natural conception. Neither the consequences of circumventing the natural selection processes of normal sexual reproduction by using assisted reproduction techniques nor the effects of assisted reproduction techniques on the complex cascade of precisely timed molecular interactions of early embryonic development are known. Continued surveillance of the progeny of survivors of childhood cancer remains essential (32).

It is the age and pubertal status at the time of irradiation that determines final uterine volume (7) (Fig. 3). An important study has described the outcome of ovum donation in three childhood cancer survivors with premature menopause after TBI and marrow transplantation (33). One woman, treated postpubertally, whose uterine volume was in the normal range (41.8 mL) delivered a healthy infant at 37 weeks gestation. The second patient, treated prepubertally (aged 12.9 years), had a small uterus (9.4 mL) and miscarried in the second trimester. The third patient, treated postpubertally, also with a smaller uterine volume (31.9 mL), had not achieved a pregnancy at the time of the publication.

**SEX HORMONE REPLACEMENT THERAPY FOR CHILDHOOD CANCER SURVIVORS**

The most appropriate dose and route of administration of sex hormone replacement to young women with ovarian failure after pelvic irradiation that provides adequate concentrations of estrogen to ensure optimal uterine growth during adolescence has not yet been established. Bath and colleagues (7) studied ovarian and uterine characteristics in cancer survivors treated with TBI. The women were administered a physiological regimen of sex steroid replacement (34) if ovarian function was absent. Pelvic ultrasound assessed uterine blood flow, uterine size, and endometrial thickness. The physiological sex steroid replacement regimen involved a transdermal route of estrogen delivery that had previously been demonstrated to simulate endogenous cyclical ovarian estrogen and progesterone profiles. The regimen was administered for 3 months. At a baseline assessment of uterine volume (performed 4 weeks after discontinuation of a standard hormone replacement regimen) in the women with ovarian failure, there was undetectable blood flow in the uterine arteries and a reduction in uterine volume. These observations were in contrast to those for the women with residual endogenous ovarian function after treatment with chemotherapy or cranial...
irradiation or in a control group of healthy women with regular menstrual cycles. The subsequent assessment was conducted after 3 months of exposure to physiological concentrations of estrogen and progesterone. At baseline, uterine volume was 6.5 mL, and at 3 months of physiological hormone replacement, uterine volume had increased to 16.3 mL (significant increase) but remained significantly lower than measurements in the control group (median, 41.5 mL; range, 28.1–57.9 mL). An important observation was that the young girls exposed to irradiation prepuberty exhibited a far smaller increase in uterine volume than the girls exposed to irradiation postpuberty. In addition, there were also demonstrable increases in endometrial thickness and the detection of uterine blood flow after 3 months of physiological sex steroid replacement. Furthermore, it was of interest that a preliminary study of characteristics of the endometrial tissue collected at the time of physiological sex steroid replacement revealed an appropriate functional response as determined by the immunohistochemical demonstration of endometrial sex steroid receptors (35).

Very recently, Larsen and colleagues (36) measured uterine volume in a cohort of 100 childhood cancer survivors and assessed uterine response to a high-dose estrogen replacement regimen in three patients with ovarian failure and markedly reduced uterine volume after abdominal and/or pelvic irradiation. These three subjects had received high-dose (30–54 Gy) whole abdominal or pelvic irradiation. There was no significant increase in uterine volume, endometrial thickness, or uterine artery blood flow. Thus, for a cohort of radiation-treated subjects, the radiation-induced damage may be irreversible. These authors concluded that higher irradiation doses, as delivered with abdominal and pelvic irradiation, compared to the lower doses with TBI [the radiation exposure to subjects in the study by Bath et al. (7) was 14.4 Gy] are more likely to cause damage (possibly irreversible) to the uterine musculature and vasculature. In contrast, cytotoxic treatment among this cohort of childhood cancer survivors did not affect adult uterine size (36). Taken together, these data indicate that physiological sex steroid replacement may have the potential to improve uterine characteristics in some patients. The precise dose of sex steroids and administration regimens are as yet not established. Furthermore, long-term effects of these novel hormone replacement approaches are unknown. Current data on hormone replacement regimens have been derived from women in the usual, older menopausal age range (fifth decade). It will be essential to carefully evaluate the optimal delivery route, formulation of sex steroid, and administration regimen required to minimize adverse effects and optimize beneficial effects.

Pregnancy Potential

In order to minimize the risk of ovarian failure and preserve fertility, strategies that include translocation of the ovaries in order to reduce the exposure to radiotherapy (37–39) and, more recently, cryopreservation of ovarian cortical tissue (40–43) have been employed. The cryopreservation of ovarian cortical tissue has significant ethical and legal implications and remains at present at an experimental stage only. Our group (44) has described a spontaneous conception in a teenager in whom ovarian cortical tissue was stored prior to gonadotoxic therapy for a pelvic tumor (Ewing sarcoma on the superior pubic ramus). Her cancer treatment was completed at age 15.8 years and, following completion of radiotherapy, the patient had symptomatic and biochemical evidence of ovarian failure. She used a low-dose combined oral contraceptive pill for hormone replacement. At the age of 19.7 years, the patient raised the issue of fertility but continued on hormone replacement therapy. She presented at age 20.2 years with an unexpected early intrauterine pregnancy. Her pregnancy and fetal growth progressed normally. She was delivered by elective cesarean section at term. Her infant, a healthy boy, weighed 2940 g (3rd–10th percentile). At the time of delivery, an inspection of the pelvis revealed normal ovaries and pelvic bones and no evidence of radiation damage. She had a spontaneous return of regular menstrual cycles postdelivery.

Several important issues for young women treated with chemotherapy and/or radiotherapy are raised by this case study. Ovarian function may be preserved after radiation exposure prepuberty, although spontaneous conceptions have been associated with first- and second-trimester pregnancy loss. radiation postpuberty has a less damaging effect on uterine function. The return of ovarian function after gonadal toxic chemotherapy and biochemical evidence of absent ovarian function is reported. If ovarian cortical strips had been replaced in the pelvis of this patient, her spontaneous conception would have reasonably been attributed to a presumed reengraftment and function of stored ovarian cortical tissue.

In conclusion, the challenges that face the multidisciplinary team responsible for the ongoing care of childhood cancer survivors include the management of disorders of ovarian and uterine function. The problems will include risk of pubertal delay or failure, premature ovarian failure, and subfertility. Among those survivors who do achieve a pregnancy, there is an increased risk of loss of pregnancy, preterm birth, and low-birthweight infants. Pregnancy in a cancer survivor must be recognized as high risk, and a multidisciplinary approach to management is essential.

References


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