Radiotherapy and chemotherapy are deleterious to the uterus. . . but how and why?

The objective of the study of Courbiere et al. (1) was to evaluate the impact of hematopoietic stem cell transplantation (HSCT) on the uterine volume of childhood acute leukemia (AL) survivors according to age at HSCT and type of myeloablative conditioning (MAC) applied. The most commonly used MAC regimens for childhood AL are either chemotherapy plus total body irradiation (TBI) based regimen, or a combination of high-dose chemotherapy containing alkylating agents.

The existing literature concurs that gonadotoxic high-dose chemotherapy essentially causes massive loss of ovarian follicles, whereas TBI-based protocols induce radiation-related damage to the ovaries and uterus. Radiation-induced fibrosis and uterine vasculature injury (2–4) indeed are thought to be responsible for reduced uterine volume after childhood TBI and consequently adverse obstetric outcomes. Some studies (2, 3) also have suggested that alkylating agent-only regimens are harmful to the ovaries as well as the uterus. Therefore, it was vital to determine the impact of HSCT on the uterine volume of childhood AL survivors based on the type of MAC regimen they were subjected to and their age at HSCT.

This was the primary objective of investigations by Courbiere et al. (1), who report data from the FERTILEA study, a multicentric prospective trial conducted across 13 French university teaching hospitals. Selection criteria were strict, the most important being age >18 years in subjects who had undergone HSCT during childhood or adolescence for AL after a MAC regimen, including either TBI or alkylating agents. Magnetic resonance imaging (MRI) was used to assess uterine volume. Mean age at HSCT was 9.1 ± 0.3 years, and 26.5 ± 63 years on evaluation.

The mean cyclophosphamide equivalent dose was 3.834 mg/m^2 in 54 women undergoing a TBI-based protocol, and 11.217 mg/m^2 in 34 women given alkylating agent-containing treatment. The primary endpoint was uterine volume. In the TBI group, uterine volume was 19.6 ± 1.9 vs. 45.3 ± 5.6 mL after an alkylating agent-based regimen, which amounts to a significant reduction of 75% and 43%, respectively, compared with the control group (79.7 ± 3.3 mL).

Interestingly, in the alkylating-agent group, uterine volume was significantly lower in women with premature ovarian insufficiency who had not received hormone replacement therapy (HRT; 15.2 ± 2.6 mL) than in those who had (49.3 ± 6 mL). In contrast, no positive effect of the added hormones was observed in the TBI group. Age at HSCT was a key factor in the TBI group, the uterus being smaller if TBI was performed before 10 years of age.

Radiotherapy is well known to cause damage to the uterus. Courbiere et al. (1) used MRI to prove that HSCT after alkylating agent-based therapy also has a deleterious effect on the myometrium and uterine volume. Two studies (2, 3) already have reported pernicious consequences, but the results were obtained by 2- or 3-dimensional ultrasound and the population was more heterogeneous.

The key question to address is how does high-dose chemotherapy induce a significant decrease in uterine volume? As noted by the investigators (1), high doses of chemotherapy may result in microvascular damage to blood vessels, with subsequent fibrosis of the myometrium, as happens in the ovarian stroma. Their argument supporting this hypothesis is the significant decrease in the apparent diffusion coefficient in the myometrium observed in their study, suggesting reorganization of the tissue and possibly a chemotherapy-generated stroma. In the alkylating agent-based regimen group, uterine volume decreased less when the patient was under hormone therapy. This is an interesting observation, but one limitation of this study is the lack of accurate information on possible protective effects of hormones, as some data are missing and compliance issues cannot be ruled out.

In an extensive review, Griffith et al. (4) concluded that uterine growth is stunted and resistant to HRT in prepubertal girls undergoing abdominal or pelvic radiotherapy or TBI, while postpubertal adolescents can benefit from HRT, as demonstrated by increased uterine volume and function. Evidence that radiotherapy may damage the uterus was put forward first in 1989, but the mechanisms remain poorly understood and further research is required to elucidate the effects of radiotherapy on the endometrium, myometrium, uterine vasculature and endometrial stem cell niche.

Courbiere et al. (1) clearly showed the impact of high-dose alkylating agents to be highest when treatment is administered after puberty. However, as stressed by the investigators, data on why uterine volume would be more affected in the case of chemotherapy exposure after puberty are lacking. Are differentiated myometrial cells or endo/myometrial stem cells of the growing postpubertal uterus more sensitive to high doses of alkylating agents? Is estrogen deprivation the cause? Future research should focus on the repercussions of chemotherapy on the myometrium and uterine vasculature to be able to prevent impairment.

Moreover, the high incidence of premature ovarian insufficiency after HSCT should not be overlooked and also requires strategies to preserve fertility. Ovarian tissue cryopreservation allows women to conceive, but here too, the impact of radiotherapy on uterine function is crucial. Indeed, Dolmans et al. (5) clearly demonstrated that with high doses of pelvic irradiation, the live birth rate after ovarian tissue transplantation was 0% compared with 50% with low doses. This shows a negative impact on the uterus and pelvic environment, which is not an ideal site for grafting because of fibrosis of the retroperitoneal vasculature. As underlined by the investigators (1) and others (2–4), obstetrical outcomes should not be disregarded and all pregnancies after HSCT should be managed as at high risk of complications.

In conclusion, this very interesting and sizable study by Courbiere et al. (1) is the first to demonstrate by MRI, a highly objective method that is not operator dependent, that high doses of alkylating agents are deleterious to uterine volume and function, especially when exposure occurs after puberty.

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