Adolescent and adult uterine volume and uterine artery Doppler blood flow among subjects treated with bone marrow transplantation or chemotherapy in pediatric age: a case-control study

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Objective: To compare uterine and ovarian volumes and uterine artery (UA) Doppler blood flow among women who were treated with antineoplastic regimens when pediatric aged versus healthy controls.
Design: Case-control study.
Setting: Tertiary obstetric and gynecologic center.
Patient(s): One hundred twenty-seven women who were treated for childhood cancer with bone marrow transplantation (BMT) and\or chemotherapy and total body irradiation (TBI) and 64 age-matched healthy controls.
Intervention(s): Ultrasonographic and clinical evaluations.
Main Outcome Measure(s): Uterine and ovarian volume, detection of follicles, and UA pulsatility index (PI).
Result(s): Median uterus and ovarian volumes were reduced by 64% (95% CI, 56.6–70.6) and 83.6% (95% CI, 79.6–86.7), respectively, among cases compared with controls. Median UA PI among cases was increased by 30.3% (95% CI, 19.6–40.8) compared with controls. Ovarian follicles were identified in 24 (18.9%) of 127 cases and 25 (39%) of 64 controls. Uterine volume was reduced after TBI (percent reduction 81.9%; 95% CI, 71.8–87.8) or busulfan (percentage reduction 67.4%; 95% CI, 58.5–75.6) compared with those who had not received a conditioning regimen (percentage reduction 24.4%; 95% CI, 7.6–38.2). The only factors independently associated with reduced uterine and ovarian volumes compared with controls were TBI, busulfan, and BMT. The worst effect on UA PI resulted from BMT and a diagnosis of hematologic disease.
Conclusion(s): Bone marrow transplantation as main treatment and TBI and busulfan as conditioning regimens had the worst effect on uterine and ovarian sizes compared with controls. These data should be considered in counseling families on preserving future fertility in children undergoing BMT. (Fertil Steril® 2015;103:455–61. ©2015 by American Society for Reproductive Medicine.)
Key Words: Bone marrow transplantation, chemotherapy, total body irradiation, uterine artery, uterine volume

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Survival after childhood cancers is now generally good and better than for adults, with 5-year survival ranging from 60% to 82% (1–3). Chemotherapies and ionizing radiation could reduce fertility in almost 80% of cancer patients (4, 5).

Gonadal insufficiency with impairment of the hypothalamic-pituitary axis and irreversible loss of ovarian follicles is the main long-term endocrine consequence of antineoplastic treatments (6). Bone marrow transplantation (BMT) poses high reproductive risks because of conditioning treatments, as do alkylating agents or total body irradiation (TBI). In post-pubertal females, ovarian insufficiency has been observed in 65%–84% of pediatric transplant recipients (7, 8), whereas in prepubertal stages incomplete pubertal development or pubertal insufficiency has been reported in 57% of girls after BMT (9).

Besides the risk of premature ovarian insufficiency, female survivors who received TBI may experience disruption of normal uterine function, with reduced uterine volume, impaired uterine blood flow, and an increased risk of infertility or adverse obstetric outcomes such as miscarriages, preterm delivery, and low-birth-weight infants (10–12). Methods to preserve fertility are now available in many centers, but reduced uterine volume and inappropriate uterine blood supply in these patients have been linked to poor outcomes even during assisted reproduction therapies (13–17).

Although the deleterious effect on fertility of conditioning therapies are well known, the data in the literature are mostly based on a small number of participants (18) or do not include an appropriate control group of healthy women of similar age (11). These data could be important for reproductive counseling of survivors from BMT before assisted reproductive techniques, including oocyte donation. Our study compared uterine and ovarian volumes and uterine artery Doppler blood flow in women who received antineoplastic treatments at pediatric age and in healthy controls.

MATERIALS AND METHODS

The study was approved by the ethics committee of our hospital (ref. no. 20130003837, 22 August 2013) and written informed consent was obtained from patients or their parents\legal guardians. The cases included 127 women who had been treated for childhood malignancy or had received BMT for thalassemia major or sickle-cell disease during the period 1984 to 2011. The nonmalignant hematologic diseases (n = 31) included thalassemia major or sickle-cell anemia (n = 27), severe aplastic anemia (n = 1), mastocytosis (n = 1), Fanconi anemia (n = 1), and Blackfan-Diamond anemia (n = 1). The malignant hematologic diseases (n = 63) included acute myeloid leukemia (n = 26), chronic myeloid leukemia (n = 1), acute lymphoblastic leukemia (n = 30), and myelodysplastic syndrome (n = 6). Lymphomas (n = 23) included Hodgkin disease (n = 19) and non-Hodgkin disease (n = 4). Solid tumors (n = 10) included neuroblastoma (n = 3), medulloblastoma (n = 2), rhabdomyosarcoma (n = 4), and melanoma (n = 1).

The conditioning regimens before BMT or other types of therapies included TBI (n = 37), or chemotherapy with busulfan (n = 44), treosulfan (n = 10), or other treatments (cyclophosphamide + fludarabine, etoposide + cytarabine + melphalan, thiothepa + melphalan, fludarabine + melphalan, or cyclophosphamide + melphalan). The dose of TBI was 1200 cGY in six fractions (two fractions of 200 cGy daily, for 3 days). The main treatments included BMT alone (n = 74), chemotherapy + BMT (n = 20), chemotherapy + radiotherapy + BMT (n = 6), chemotherapy + radiotherapy (n = 6), and chemotherapy alone (n = 21). Controls (n = 64) were healthy volunteers of similar age as the cases who were recruited among women attending a cytologic screening and human papillomavirus vaccination center of our department.

Each case subject had been included into an electronic database containing detailed information about the original disease, the treatment protocol employed for the original disease, and/or the type of conditioning therapy used before BMT. Variables describing the results of the physical examinations, hormone evaluations, stage of pubertal development, and drugs prescribed during follow-up visits were also available in this database. Patients had been treated with conventional chemotherapy, in some cases associated with radiotherapy, for their oncohematologic disorders or had received conditioning regimens before BMT, which included TBI, busulfan, treosulfan, or other cytotoxic drugs, in various combinations. When deemed necessary, hormone replacement therapy (HT) was administered from 14 years of age. Scheduled hormone treatment included estradiol supplementation given as biweekly patches in a dose of 100 mg/24 hours. Medroxyprogesterone acetate (MAP) was given orally in a dose of 10 mg, starting from cycle day 21, for 12 days. As an alternative to HT, a combination of estradiol 1.5 mg and nomegestrol 3.75 mg was used.

Oral contraceptives were administered according to the patients requirements, and included drospirenone 3 mg plus ethinyl estradiol 0.03 mg. Hormone therapy, if not otherwise contraindicated, was started in females who presented 17β-estradiol levels lower than 50 pg/mL and follicle-stimulating hormone (FSH) > 40 IU/L after gonadotoxic treatment. The choice of different regimens (oral contraceptives or HT) and different methods of delivery were influenced by clinical status, age, and by the individual desire of each patient. The gynecologic evaluation at enrollment included a standard gynecologic examination, transabdominal and/or transvaginal ultrasonography, and a structured interview about menstrual and reproductive history and drug use, including contraceptives and HT.

Ultrasonographic examination of cases and controls included the measurement of uterine volume, ovarian volume, detection of follicles (number and major diameter), and uterine artery Doppler blood flow evaluation. Uterine volume was calculated by measuring the length (d1) from the fundus uteri to the external orificium, the transverse diameter (d2), and the anteroposterior diameter (d3), and by using the formula based on an ellipsoid: d1 × d2 × d3 × 0.523. Endometrial thickness was measured in the longitudinal plane as the distance in millimeters between the myometrial/endometrial junctions on either side of the miduterine cavity. Ovarian volume was calculated by measuring the length and the height of the ovary in the sagittal section, and the width in the transverse section, and by using the formula of an ellipsoid: d1 × d2 × d3 × 0.523.

Uterine artery blood flow was evaluated using power Doppler ultrasonography. Uterine arteries were localized by