Female cancer survivors are low responders and have reduced success compared with other patients undergoing assisted reproductive technologies

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Objective: To investigate the effect of prior chemotherapy and radiation on assisted reproductive technology (ART) outcomes.
Design: Retrospective cohort study.
Setting: University-based infertility clinic.
Patient(s): Female cancer survivors who had received chemotherapy or radiation and all other women undergoing first-fresh IVF/intracytoplasmic sperm injection (ICSI) cycles.
Intervention(s): Survivors' ART outcomes were compared with all women undergoing first-fresh IVF/ICSI cycles and those with male-factor infertility only. Multivariate logistic and Poisson regression analyses were used to estimate the effect of cancer therapy on ART outcomes.
Main Outcomes Measure(s): Number of oocytes retrieved and embryos obtained; odds of cycle cancelation, clinical pregnancy, and live birth.
Result(s): Compared with others undergoing IVF/ICSI, survivors had significantly fewer oocytes retrieved and embryos available for transfer. In addition, survivors were significantly more likely to be canceled (odds ratio [OR] 5.60, 95% CI 2.94–10.66) and had lower pregnancy and live birth rates (OR 0.30, 95% CI 0.13–0.68; and OR 0.27, 95% CI 0.10–0.69; respectively). Odds ratios were stronger when the comparison group was restricted to those with male-factor infertility only.
Conclusion(s): Women who have received systemic therapy for malignancy should be considered to be low responders and counseled that their per-cycle live birth rate is lower than that of their peers. These data strongly support offering fertility preservation before cancer therapy when possible. (Fertil Steril® 2012;97:381–6. ©2012 by American Society for Reproductive Medicine.)
Key Words: Cancer, survivorship, fertility preservation, assisted reproduction, IVF, poor responder

Advances in cancer therapy have lead to increased survival of young people with malignancies. Recent estimates indicate that 80% of children now survive their cancer (1). Along with increasing cancer survival, considerable research efforts have investigated the late effects of cancer therapy on health outcomes (2).

Several large epidemiologic studies have investigated the association between cancer and fertility. Consistently, these studies have demonstrated that cancer survivors are less likely to ever become pregnant than control groups without a history of cancer (3–5). Furthermore, results from the Childhood Cancer Survivor Study, a cohort of more than 20,000 patients diagnosed with cancer in childhood and who survived for $\geq$5 years, demonstrated that the risk of premature menopause (at <40 years old) was tenfold higher for cancer survivors than sibling control subjects (6). Interestingly, the fertility effects of therapy may not be initially apparent, because many female survivors progress through puberty and resume menstruation. However, cancer survivors have biochemical evidence of decreased ovarian reserve compared with control subjects, even if they are having regular menstrual cycles (7, 8). Therefore, a disproportionate number of cancer survivors attempting to conceive after cancer treatment may require assisted reproduction.

Despite consistent reporting of the increased risk of infertility in survivors, few data exist regarding outcomes of infertility treatment in this population. Studies have shown a diminished response to stimulation and a lower pregnancy rate among those who had

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received systemic cancer therapy compared with local therapy, but the results were not statistically significant (9). To our knowledge, no study has been published comparing assisted reproductive technology (ART) outcomes between cancer survivors and a group of infertility patients who have not received cancer therapy. In the present study, we aimed to investigate the effect of systemic cancer therapy on ART outcomes in female cancer survivors.

MATERIALS AND METHODS

Institutional Review Board approval was obtained from Brigham and Women's Hospital. All women undergoing first-fresh IVF/intracytoplasmic sperm injection (ICSI) cycles from January 1, 1998, to December 31, 2009, at our center were reviewed from our prospectively maintained ART database. Women who were noted to have a history of any cancer diagnosis in their medical history underwent chart review. Type of malignancy, age at treatment, and treatment details were extracted from the medical records. Women who received chemotherapy or radiation therapy (RT) prior to starting ovarian stimulation were included in the survivor group. If the malignancy was treated with surgery alone or the woman was diagnosed with a malignancy and underwent IVF/ICSI for fertility preservation before any systemic therapy, they were excluded from the survivor group. All cancer survivors were required to have clearance from their oncologists and a maternal fetal medicine provider before undergoing ovarian stimulation or attempts at pregnancy.

Two comparison groups were constructed. The first comparison group included all women undergoing first-fresh IVF/ICSI cycles who were not considered survivors. The second included those women whose infertility diagnosis was only male-factor infertility without any apparent female infertility at the time of the first IVF/ICSI cycle. Women $\geq$44 years old, oocyte donors, intrauterine insemination conversions, and preimplantation genetic diagnosis cycles were excluded from both survivor and sibling groups. Cycles using gestational carriers were excluded from pregnancy and live birth analyses but retained in the analyses for number of oocytes and embryos obtained and cycle cancellation for poor response.

Baseline variables collected as covariates included female age at cycle start, early follicular FSH, and infertility diagnosis. IVF/ICSI cycle information extracted included type of ovarian stimulation protocol used, amount of gonadotropin used, total days of ovarian stimulation, peak E_2 level, use of ICSI, normal fertilization rate, number of embryos transferred, implantation rate, and cycle outcome. Luteal leuprolide down-regulation and antagonist cycles were considered to be standard stimulation protocols; microdose leuprolide cycles (microflare), luteal estrogen priming antagonist cycles, and ultra-low-dose luteal leuprolide down-regulation cycles were considered to be poor-responder protocols (10–14). Clinical pregnancy was defined as the presence of at least one gestational sac, and live birth was defined as the birth of at least one viable neonate. Cycle cancellation was defined as gonadotropin initiation but no oocyte retrieval owing to inadequate ovarian response. Generally at our institution, in the absence of concurrent letrozole use, it is our protocol that peak E_2 must be $\geq$500 pg/mL with at least four follicles $\geq$12 mm present on transvaginal ultrasound to proceed with oocyte retrieval.

To estimate the effect of prior cancer therapy, the number of oocytes retrieved and the number of embryos obtained were compared between groups with the use of Poisson regression; logistic regression was used to calculate odd ratios (ORs) and 95% confidence intervals (CIs) for cycle cancellation, clinical pregnancy, and live birth. Exploratory models adjusting for type of stimulation protocol and the use of ICSI did not change effect estimates by more than 10%; therefore, final models were adjusted only for age group ($\leq$34, 35–39, and $\geq$40 years) (15). Survivors with relapsed disease who were undergoing IVF/ICSI for fertility preservation and planning to freeze embryos before additional cancer therapy were excluded from the pregnancy and live birth models, because no attempt at pregnancy was planned at the time of ovarian stimulation (n = 14). They were retained in the analyses for number of oocytes and embryos obtained. Pregnancy and live birth rates were otherwise calculated per cycle start. Wald P values are two sided; $P<.05$ was considered to be significant.

RESULTS

Fifty-three women with a history of malignancy who had received chemotherapy, RT, or both were identified and included in the survivor group. Of these, 14 were undergoing IVF/ICSI for fertility preservation before additional treatment for relapsed disease, leaving 39 women attempting conception in the fresh cycle. In general, survivors were slightly younger than other women undergoing ART, and they were more often prescribed poor-responder protocols on the first IVF/ICSI attempt than other infertility patients. Results of ovarian reserve testing with early follicular FSH were similar. Survivors required higher doses of gonadotropins and had lower peak E_2 levels than comparison groups (Table 1).

Breast cancer and Hodgkin lymphoma comprised 57.6% of the cancer diagnoses. Approximately one-half of the survivors had received treatment with alkylating-agent chemotherapy, pelvic/abdominal RT, or total body irradiation (TBI), all of which are considered to be high risk for gonadal toxicity. The median age at which survivors had received treatment was 28 years with a range of 0.8 to 42 years. The median time from treatment for cancer and first IVF/ICSI cycle was 4.2 years, with a range of 0.2 to 40.2 years (Table 1).

Survivors had significantly fewer oocytes retrieved and embryos available for transfer compared with all other women undergoing IVF/ICSI. The unadjusted median number of oocytes and embryos retrieved was eight oocytes and four embryos in the survivors, compared with 13 oocytes and seven embryos in all other infertility patients, and 14 oocytes and eight embryos in the male-factor infertility group (Table 1). Adjusting for patient age, survivors had 29% and 34% fewer oocytes retrieved compared with all other infertility patients (rate ratio (RR) 0.71, 95% CI 0.56–0.90) and male-factor patients (RR 0.66, CI 0.52–0.83), respectively. Similarly, survivors had 34% and 36% fewer embryos available for