

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 ≥ 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 ≥ 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 ≥ 500 pg/mL with at least four follicles ≥ 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 (≤ 34 , 35–39, and ≥ 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

TABLE 1

Demographic and cycle characteristics of survivors and comparison groups.

	Survivors (n = 53)	All infertility (n = 7,030)	Male-factor infertility (n = 1,153)
Female age at cycle start (y)	34.2 (19.3–43.9)	35.8 (19.3–43.9)	35.0 (19.7–43.9)
Day 3 FSH (mIU/mL)	7.3 (2.6–43.0)	7.3 (0.1–52.0)	7.0 (1.0–10.0)
Poor-responder protocol	13 (24.5%)	1,048 (14.9%)	73 (6.3%)
Total dose of gonadotropins (IU)	5,025.0 (1,500.0–13,500.0)	3,300.0 (225.0–12,000.0)	2,700.0 (712.5–10,200.0)
Peak E ₂ (pg/mL)	1,186.5 (14.0–3,980.0)	1,748.0 (<assay–12,385.0)	1,978.0 (<assay–8,856.0)
Days of stimulation to hCG	11.0 (6.0–23.0)	11.0 (5.0–21.0)	10.0 (6.0–20.0)
No. of oocytes retrieved	8 (0–36)	13 (0–68)	14 (0–68)
No. of embryos obtained	4 (0–18)	7 (0–51)	8 (0–51)
No. of embryos transferred	2.0 (0.0–8.0)	2.0 (0.0–10.0)	2.0 (0.0–10.0)
Cancer type		NA	NA
Leukemia	4 (7.5%)		
Hodgkin lymphoma	13 (24.5%)		
Non-Hodgkin lymphoma	5 (9.4%)		
Sarcoma	2 (3.8%)		
Neuroblastoma	1 (1.9%)		
Kidney (Wilm)	3 (5.7%)		
Breast	17 (32.1%)		
Gynecologic	8 (15.1%)		
Treatment type		NA	NA
No alkylating agents nor pelvic/abdominal RT	24 (45.3%)		
Alkylating agents, no pelvic/abdominal RT	18 (34.0%)		
Pelvic/abdominal RT, no chemotherapy	5 (9.4%)		
Any chemotherapy with pelvic/abdominal RT	6 (11.3%)		
Age at treatment (y)	28.0 (0.8–42.0)		
Time since treatment (y)	4.2 (0.2–40.2)		

Note: Values are median (minimum – maximum) for continuous variables and n (%) for categoric variables.

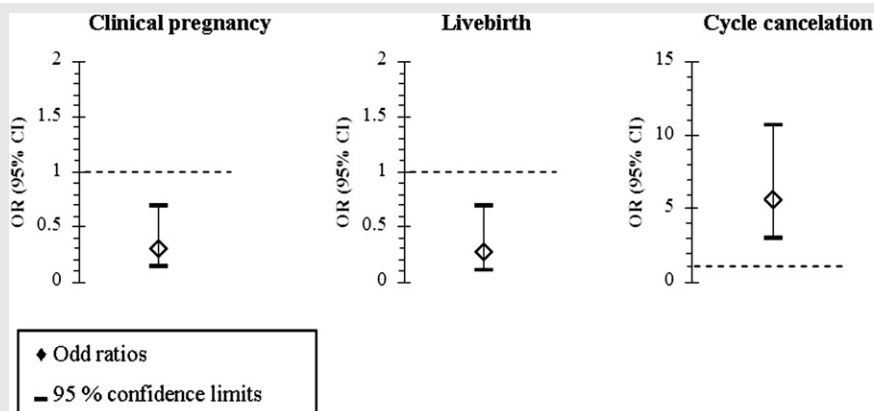
Barton. Assisted reproduction after cancer. *Fertil Steril* 2012.

transfer compared with all infertility patients (RR 0.66, 95% CI 0.51–0.85) and male factor infertility patients (RR 0.64, 95% CI 0.49–0.83), respectively.

The odds of clinical pregnancy and live birth were statistically significantly reduced in survivors compared with all others undergoing IVF/ICSI (OR 0.30, 95% CI 0.13–0.68; OR 0.27, 95% CI 0.10–0.69; respectively; Fig. 1). Odds ratios were stronger when survivors were compared with those

with male-factor infertility only (OR 0.23, 95% CI 0.10–0.53; OR 0.21, 95% CI 0.08–0.55; for clinical pregnancy and live birth, respectively). Among the 39 survivors not planning embryo freezing for fertility preservation, five live births resulted. None of the survivors with a history of pelvic or abdominal RT had a live birth, but three women who had received alkylating-agent chemotherapy had a live birth. Live births were seen in women remote from therapy (defined

FIGURE 1



Assisted reproductive technology outcomes in cancer survivors compared with all other infertility patients.

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as ≥ 5 years) as well as in those who had received therapy <5 years before ART. Finally, the odds of having a cycle canceled were markedly increased in survivors compared with all others undergoing IVF/ICSI (OR 5.60, 95% CI 2.94–10.66) and those with male-factor infertility (OR 9.83, 95% CI 4.82–20.05; Fig. 1).

DISCUSSION

Female cancer survivors undergoing their first IVF/ICSI attempt whose treatment included systemic chemotherapy or RT had significantly poorer outcomes compared with other couples undergoing ART. Despite more frequently being prescribed aggressive stimulation protocols and receiving higher doses of gonadotropins, they attained lower peak E_2 levels and had fewer oocytes and embryos obtained. The odds of pregnancy and live birth were more than three times lower than for other infertility patients. In addition, survivors were at higher risk of having an IVF/ICSI cycle canceled before oocyte retrieval because of poor ovarian response to stimulation.

A variety of factors influence the effect of therapy on fertility. In general, the risk of ovarian failure or premature menopause is associated with the total dose of chemotherapy or radiation as well as age and pubertal status at treatment. Increasing age at the time of therapy is directly correlated with rates of permanent amenorrhea (16, 17). Of the chemotherapeutic agents, alkylating agents such as cyclophosphamide and busulfan are known to confer the highest risk (18, 19). Interestingly, almost one-half of the survivors in the present cohort had not received therapy considered to be high risk for gonadotoxicity, such as pelvic/abdominal RT, TBI, or alkylating-agent chemotherapy, but outcomes were still significantly affected.

Those undergoing bone marrow or stem cell transplant, especially with TBI, are the highest-risk group for overt ovarian failure, with estimates of 70%–90% of patients (20, 21). Not surprisingly, the present study suggests a particularly poor prognosis for those who had received pelvic/abdominal RT or TBI, with no live births reported. These results should be interpreted with caution, because only nine patients in this study who had received pelvic/abdominal RT or TBI attempted conception on the first-fresh cycle.

This study highlights the difficulty in identifying survivors who will be at high risk for infertility. Generally, in the present cohort of cancer survivors, ovarian reserve testing with early follicular FSH did not demonstrate evidence of diminished ovarian reserve. In fact, early follicular FSH was very similar among survivors, all other infertility patients, and patients with male-factor infertility. Historically, ovarian toxicity after chemotherapy or RT was evaluated as the return of regular menses after treatment. Subsequent studies have shown that menstruation is not a sensitive marker for identifying the effect that therapy has had on ovarian reserve, because very few young women have frank ovarian failure after therapy, despite decreased fertility. Among cancer survivors who are menstruating after therapy, it appears to be prudent to use sensitive markers of ovarian reserve such as antimüllerian hormone (AMH) or antral follicle count,

because FSH may be normal and not reflect ovarian damage (7, 22). One-fourth of the survivors in the present cohort were prescribed poor-responder stimulations for the first IVF attempt based on a history of gonadotoxic therapy despite a normal-appearing FSH level in the majority. Even with more aggressive stimulation, the survivor group had five times the odds of cycle cancellation for poor response.

We compared ART outcomes in survivors to the male-factor infertility group as a surrogate measure of the direct impact of therapy on the female partner. With no detectable female-factor infertility present in the comparison group, we theoretically eliminated diminished ovarian reserve or other female infertility diagnoses and expected to see more dramatic changes in outcomes than in the general infertility population. As expected, when comparing ART outcomes between survivors and male factor infertility, magnitudes of effect were larger. We think that this is the best reflection of the impact of chemotherapy and RT on ovarian reserve and the endometrium.

It is important to note that 15% of the survivors in the present study underwent ovarian stimulation within 1 year of chemotherapy or radiation. These women all had relapsed hematologic malignancies or lymphoma and were awaiting stem cell transplantation. At diagnosis of relapse, chemotherapy was started very quickly, so that sufficient time for ovarian stimulation and oocyte harvesting before chemotherapy was not possible or referral for consultation for fertility preservation was made after therapy had begun. In these women, stem cell transplantation could not be delayed and was highly likely to render these women menopausal. Occasionally, breast cancer survivors underwent ovarian stimulation 1–2 years after therapy. Those cycling <2 years after therapy were >40 years of age or had evidence of diminished ovarian reserve, and waiting longer for ovarian stimulation was not deemed to be wise, owing to diminished ovarian reserve. These women received clearance from their oncologist before stimulation. We are aware that animal data have suggested that offspring created from gametes proximally exposed to chemotherapy have a higher incidence of birth defects (23), but observational studies including large numbers of offspring of cancer survivors have not confirmed this association in humans (24). With careful counseling, women recently treated for cancer that do not have time to wait 1–2 years after therapy for oocyte retrieval are allowed to undergo ART in our program. In these women, ovarian tissue harvesting is also emerging as a potentially viable option for fertility preservation. This may not be an option, however, in women with hematologic malignancies, owing to concern about reintroduction of the malignancy after reimplantation. In vitro maturation holds out promise to allow pregnancy without tissue reimplantation, but to date no live births have been reported using ovarian tissue harvesting without reimplantation.

Strategies for fertility preservation in reproductive-age women with cancer include emergency ovarian stimulation with either cryopreservation of embryos or oocytes, ovarian tissue harvesting, and ovarian transposition for those receiving pelvic radiation and possibly use of GnRH agonists during chemotherapy. Only embryo cryopreservation and ovarian transposition are considered to be standard of care, with other

options remaining experimental (25). Mounting evidence supports the use of GnRH agonists during chemotherapy in premenopausal women. A recent randomized trial comparing the incidence of menopause after therapy in premenopausal breast cancer patients receiving GnRH agonist during chemotherapy and those receiving chemotherapy alone reported a 17% decrease in menopause in those receiving GnRH agonists. This represented an OR of 0.28 for treatment-related menopause using GnRH agonists concurrently with chemotherapy (26). It was unusual that the investigators did not find an association of age with chemotherapy-related menopause or stratify randomization by those receiving tamoxifen, given the known association of amenorrhea and tamoxifen, which may limit the generalizability of those results (27). Other randomized trials of GnRH agonist use during chemotherapy have been negative (28). However, the present study is in agreement with the findings of earlier nonrandomized studies that collectively report a relative risk of preserved ovarian function of 1.68 with the use of GnRH agonists (29). It is important to appreciate that ongoing menstrual function, though important in these women, does not necessarily equate with preservation of fertility. In addition, because amenorrhea after chemotherapy for breast cancer is associated with improved long-term survival, it is unclear if maintenance of menstrual function is desirable in this patient population (30).

Study Limitations

We recognize several limitations to these data. First, this is a retrospective study and providers had knowledge about the survivors' cancer diagnoses and treatments. This may have influenced them to stimulate the patients more aggressively, as evidenced by the higher percentage of survivors on poor-responder protocols. They may also have been less likely to cancel the cycle, even if the patient did not meet recommended criteria for oocyte retrieval. Selection bias of this type would tend to bias the results toward no effect, and the effect magnitudes may have been greater if providers did not have knowledge of prior therapy when choosing stimulation protocols.

Furthermore, given the time frame during which this study was carried out, tests of ovarian reserve which may have been more sensitive in identifying poor responders and avoiding cancellations, such as antral follicle count and AMH, were not routinely used. Because these data were not available, gonadotropins may have been underdosed in some cycles, because early follicular FSH was normal in the majority of survivors. This limitation highlights the lack of sensitivity of FSH as a sole marker of ovarian reserve, particularly in a young patient population. AMH may well be the ovarian reserve test of choice for women undergoing ART and we look forward to continued work investigating the utility of AMH levels in cancer survivors.

Another limitation is the relatively small size of the survivor group. Despite our affiliation with a major cancer center, we identified only 53 women undergoing ART in the period of study who had received systemic cancer therapy prior to the first IVF attempt. This potentially indicates that

many cancer survivors were able to conceive spontaneously and did not require ART or had such poor ovarian reserve or amenorrhea that they underwent treatment with donor oocytes, suggesting that the population referred for treatment was a particularly poor-prognosis group of menstruating women. Others had undergone fertility preservation with embryo or oocyte banking before therapy and were not included in this study.

Given the limited sample size and heterogeneity of cancer treatments, we cannot comment on particular cancer types or treatment agents that were associated with the greatest effect on infertility and ART outcomes. Available data from the medical record on cancer survivors universally included cancer diagnosis and agents used, but not dosing information, because many survivors were treated at outside institutions or as pediatric patients. Therefore, we could not correlate cumulative dosing of specific chemotherapeutic agents or radiation with ART outcomes. However, it is interesting to note that none of the nine women with a history of pelvic/abdominal RT that attempted conception in the included fresh cycle had a live birth. Women with this history who have thin endometrial stripe measurements are likely to use a gestational carrier and thus may overcome the effect of RT on the uterus by third-party reproduction. Additionally, the study population was too small to comment on the effect of time between cancer treatment and ART or the effect of age at cancer therapy on ART outcomes.

Conclusion

In conclusion, this study demonstrates that women with infertility that have received chemotherapy or RT for cancer are poor responders in ART. We recommend consideration of aggressive ovarian stimulation protocols, even when ovarian reserve by FSH testing appears to be normal. Furthermore, it may be useful to perform additional tests of ovarian reserve, such as antral follicle count or AMH testing, which may be more sensitive in detecting diminished reserve in young women. Cancer survivors with prior systemic therapy should be counseled that live birth rates from ART in others of similar age may not apply to them. Given the findings of the present study, fertility preservation with cryopreservation of embryos, oocytes, or ovarian tissue, as well as possible use of GnRH agonists in menstruating women, should be offered when possible to all women undergoing systemic treatment for malignancy to optimize future reproduction options, even in those who are receiving therapy not classically thought to be of high risk for ovarian toxicity. Finally, consideration of gestational surrogacy may be required after pelvic/abdominal RT or TBI in some cases.

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