ORIGINAL ARTICLE: FERTILITY PRESERVATION

Long-term outcomes in cancer patients who did or did not pursue fertility preservation

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Objective: To compare long-term outcomes of cancer patients who pursued fertility preservation (FP) with those who did not and compare random-start (RS) and menstrual cycle–specific (CS) protocols for FP.
Design: Retrospective cohort.
Setting: Single urban academic institution.
Patient(s): Oncology patients who contacted the FP patient navigator, 2005–2015.
Intervention(s): None.
Main Outcome Measure(s): Time to cancer treatment, disease-free survival, and reproductive outcomes in FP versus no-FP patients and cycle outcomes for RS versus CS protocols. Data were analyzed by χ^2 and logistic regression.
Result(s): Of 497 patients who met the inclusion criteria, 41% elected FP. The median number of days to cancer treatment was 33 and 19 days in the FP and no-FP groups, respectively. There was no difference in cancer recurrence or mortality. There were no differences in stimulation parameters, outcomes, or days to next cancer treatment in RS versus CS protocols. Twenty-one patients returned to use cryopreserved specimens, resulting in 16 live births. Eight of 21 returning patients used a gestational carrier. Thirteen FP (6.4%) and 16 no-FP (5.5%) patients experienced a spontaneous pregnancy.
Conclusion(s): FP is both safe and efficacious for eligible cancer patients. Only 10% of patients returned to use cryopreserved specimens, and almost half used a gestational carrier, suggesting the need for further research into reproductive decision-making in cancer survivors. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Cancer outcomes, fertility preservation, oncofertility, IVF, recurrence

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In the United States, more than 843,820 new female cancer cases were estimated to be diagnosed in 2016 (1). Fortunately, there has been significant improvement in cancer survival rates because of progress in diagnosing certain cancers at an earlier stage, as well as advancements in treatment. From 2002 to 2012, there was an 83% 5-year survival rate among women younger than 45 years diagnosed with cancer (2). Recent data from the National Cancer Institute indicate that nearly 250,000 cancer survivors are women of reproductive age, ages 20–39 years, with breast cancer being the most common in this age group (3, 4). As a result of the increase in the number of cancer survivors, greater attention has been focused on the delayed effects of cancer treatments on the future quality of life of the survivor, including fertility (5).

Because of the gonadotoxicity of chemotherapy and radiotherapy, 42% of female cancer survivors will develop treatment-induced ovarian failure (6–8). Many cancer survivors are concerned that their reproductive potential will be compromised after cancer treatment (9–15). Doctors and other health care providers have become more aware of and sensitive

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to the fertility needs of cancer patients as indicated by practice guidelines developed by the American Society for Reproductive Medicine and the American Society of Clinical Oncology (16–18). These guidelines state that all health care providers involved in the care of cancer patients need to be able to discuss the effects of cancer treatment on fertility and provide appropriate referrals to reproductive specialists when indicated (17, 18). Despite the recommendation that oncologists refer all patients who are undergoing gonadotoxic therapies, many oncologists do not refer their patients for fertility preservation (FP) (5, 19). Ovarian stimulation for infertility treatment can induce a hyperestrogenic state, which is of particular concern in hormone-sensitive cancers including breast cancer, endometrial cancer, and malignant melanoma. However, at this time there is very limited information about the longer term effects of ovarian stimulation on cancer recurrence and mortality (20).

In 2005, Northwestern Memorial Hospital's Reproductive Endocrinology and Infertility division began providing FP via oocyte or embryo cryopreservation for women with a cancer diagnosis before undergoing cancer treatment (21). Since that time, the division has provided consultation to hundreds of women with a new cancer diagnosis, and a subgroup of these women did undergo ovarian stimulation to cryopreserve their oocytes and/or embryos. The initial appointment with reproductive endocrinology is facilitated by a patient navigator (PN) to ensure that these patients are seen quickly. A significant number of eligible cancer patients decline FP, citing reasons such as trauma from cancer diagnosis, emotional distress, financial constraints, partnered but unmarried, and fear of exacerbating their disease or increasing the likelihood of a recurrence if they underwent ovarian stimulation. Another common concern is that pursuing FP would cause a long delay to initiating cancer therapy (9, 22).

It has been proposed that a random-start (RS) protocol, which does not wait for menses to begin ovarian stimulation, as opposed to the traditional cycle-specific (CS) protocol, may decrease the number of days to next cancer treatment (23–25). While there is no reported difference between RS and CS protocols in ovarian stimulation outcome, the ability to initiate an ovarian stimulation cycle regardless of the menstrual cycle phase presents an opportunity to reduce the number of days until the next cancer treatment is administered (26–28). Studies have not documented the actual time to cancer treatment between CS and RS protocols, which could inform future implementation of an RS protocol for FP patients.

The aim of the current study was to quantify the delay to treatment in patients who elect FP and determine whether there is an association between ovarian stimulation for FP and cancer recurrence and mortality. Furthermore, for patients who underwent ovarian stimulation for FP, we examined whether RS versus CS stimulation starts impacted IVF cycle outcomes and time to cancer treatment. Finally, we explored pregnancy rates and outcomes after cancer treatment.

MATERIALS AND METHODS

Study Population

This was an Institutional Review Board–approved study. Subjects were identified from an FP patient log of women who had been diagnosed with cancer and contacted the FP PN at Northwestern Memorial Hospital from January 2005 through January 2016, regardless of whether they ultimately elected to undergo ovarian stimulation. The initial FP patient list included 1,054 subjects. Subjects were excluded from the initial list if they presented for non-cancer-related FP or for reasons other than FP, were older than 45 years at the time of PN consultation, initially met with the FP PN with a diagnosis of cancer recurrence, or had chemotherapy treatment before PN consultation. We chose to exclude patients with recurrent cancer at presentation because our main end point was cancer recurrence. We excluded both recurrent cancer diagnosis as well as recent chemotherapy from ovarian stimulation outcomes because the history of chemotherapy could directly affect ovarian stimulation outcomes and therefore could be a confounder. We also excluded patients in which PN consultation to next cancer treatment was >100 days from the time to next treatment analysis because we felt that the decision to pursue or to not pursue FP would not have impacted their cancer care. These patients, however, were included in the other analyses, including cancer recurrence, mortality, and stimulation outcomes.

For each patient, cancer diagnosis (breast cancer, hematological cancers, gynecological cancers, and other cancers), treatment history, dates of initial contact with the FP PN, subsequent cancer treatment dates (surgery, chemotherapy, tamoxifen, and/or bone marrow or stem cell transplant), cancer relapse (defined as recurrence of same primary cancer type), and mortality data were collected. Patient mortalities were identified using medical records as well as obituaries. Pregnancy outcomes were also recorded. Cancer recurrence and mortality data were collected from oncology and pathology notes. Pregnancy information, both spontaneous and as a result of using cryopreserved gametes, was also collected.

Patients who underwent an FP cycle were further stratified by whether they underwent a CS or RS protocol. Controlled ovarian hyperstimulation (COH) outcome data were examined, as well as embryo disposition preferences, future pregnancy data, and last encounter with a Northwestern provider.

COH

Our protocol has been documented in previous studies (21, 29). Briefly, COH was started using recombinant FSH with or without urinary menotropins with dosage based on age and ovarian reserve measurements. Over time, our practice has evolved to include more RS protocols, and thus patients who desire to begin stimulation immediately can do so. For a CS protocol, gonadotropins were initiated on the third day of menses, whereas for an RS protocol, gonadotropins were initiated at any point in the menstrual cycle. Response to medication was evaluated with regular