ORIGINAL ARTICLE

The use of fertility preservation services for cancer patients: a single institution experience

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Objective: To analyze the use of services regarding fertility preservation (FP) in cancer patients at a single institution.
Design: A retrospective cohort study.
Setting: Academic medical center.
Patient(s): A total of 208 FP referrals.
Intervention(s): None.
Main Outcome Measure(s): Method of FP; time from referral to FP intervention.
Result(s): A total of 553 patients were referred to a reproductive specialist for FP in the setting of a medical diagnosis from 2011 to 2016. Of these, 208 patients satisfied the inclusion criteria and met with a reproductive specialist. Ninety patients underwent FP services. The average age at referral was 30.9 ± 7.9 years. Breast cancer (n=94, 45%) and leukemia/lymphoma (n=62, 30%) were the most prevalent cancer diagnoses. A 68.9% of patients underwent oocyte cryopreservation (n=62), 26.7% underwent embryo cryopreservation (n=24) and 4.4% underwent ovarian tissue preservation (n=4). The time interval from the referral to the FP intervention ranged from 1 to 810 days, with a median of 17 days.
Conclusion(s): In the setting of a cancer diagnosis, most patients undergoing FP intervention underwent oocyte cryopreservation, were <35 years old, and underwent FP intervention in <30 days from referral. Whereas FP should ideally be initiated at the time of cancer diagnosis, all patients with a cancer diagnosis should be referred to a reproductive specialist and counseled on options for FP to preserve the optionality for the reproductive future they desire. (Fertil Steril Rep® 2022;■:■–■. ©2022 by American Society for Reproductive Medicine.)
Key Words: Fertility preservation, cancer, referral patterns

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Advancements in cancer treatment have led to improved clinical outcomes and survival rates (1). However, many life-saving cancer treatments are gonadotoxic, and young patients are faced with reduced reproductive potential after receiving cancer-directed therapy (2). Over the past decade, assisted reproductive technology advancements have expanded the clinical use of fertility preservation (FP) treatments for personal and medical indications. Oocyte and embryo cryopreservation have become the standard methods for FP (3). Ovarian tissue cryopreservation has also emerged as a recognized method of FP, benefiting those who cannot undergo ovarian stimulation (4). These FP methods can increase the probability of having one's genetic child in the future, improving quality of life after successful cancer treatment, and is a core component of comprehensive cancer care (2).

In 2016, the American Society of Clinical Oncology published the first evidence-based FP practice guidelines (5–7), which urged health care providers to discuss FP with all patients of reproductive age, along with parents or guardians of children and adolescents, when infertility is a potential side effect of the proposed therapy (8). After an initial discussion with their oncologist, patients should be referred to reproductive specialists as soon as possible and ideally before the start of oncologic treatments (9). While around 75% of young cancer

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survivors are interested in their future fertility, the number of patients who access FP services before cancer-directed treatment is significantly lower (10). Studies have shown that future infertility is a major concern of cancer survivors; however, research on resources and options for FP services for cancer patients is lacking (5, 11–14). The lack of proper referral to a reproductive specialist and appropriate counseling are especially problematic, as life-saving cancer treatment must be initiated promptly. The possibility of future reproduction may be lost if proper referrals are not made.

Although many studies have shown that barriers exist, there is limited research documenting how these barriers affect the use of FP services (10, 15, 16). There is also limited research evaluating the type of cancer and FP methods. The objective of this study is to analyze FP referral patterns and the use of services at a tertiary care hospital. We hope that by evaluating FP referral patterns, we can help programs establish more efficient referral services to maximize early FP interventions in reproductive age cancer patients.

MATERIALS AND METHODS

Approval for this study was obtained from the institutional review board of Weill Cornell Medical College. Patients referred to a reproductive specialist from January 2011 to December 2016 at a tertiary care center were assessed for potential inclusion in this retrospective study. Only patients with an active cancer diagnosis or a known high-risk mutation were included. Patients who were followed up at a different reproductive center were excluded. Patient age, cancer diagnosis, time from diagnosis to referral, time from referral to FP intervention, method of FP, cancer treatment, and pregnancy outcomes were obtained from the patient's medical records. FP referrals were made by the oncologist during clinic appointments. After a referral is placed, the patient makes an appointment with a reproductive specialist. At our institution, patients are generally seen within 48 hours of referral. Time from diagnosis to referral is defined as the length of time between the date of initial cancer diagnosis and the date the FP referral was made. Time from referral to FP intervention is defined as the length of time between the date of FP referral and the date of oocyte retrieval or ovarian tissue preservation surgery. Fertility preservation methods included oocyte cryopreservation, embryo cryopreservation, and ovarian tissue cryopreservation or ovarian transposition.

Standard descriptive statistics were used to characterize the study cohort. Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as the number of cases (n) with a percentage of occurrence (%). Statistical comparison of continuous variables was performed using the 2-sample *t*-test and analysis of variance. Statistical significance was set at $P < .05$.

RESULTS

Fertility Preservation Analysis

During the study time period, 553 FP referrals were placed, and 220 patients (39.7%) met with a reproductive specialist. Twelve patients were omitted from the study because of either unknown cancer or noncancer diagnoses such as anorexia nervosa, Turner syndrome, sickle cell disease, or male partner cancer. A total of 208 patients were therefore included in the study. The average age at cancer diagnosis was 30.9 ± 7.9 years, ranging from the age of 6 to 50 years. Fifty percent (n = 104/208) of patients fell within the age range of 25 to 34 years, 30% (n = 64/208) were between 35 and 50 years, and 20% (n = 40/208) were between 6 and 24 years.

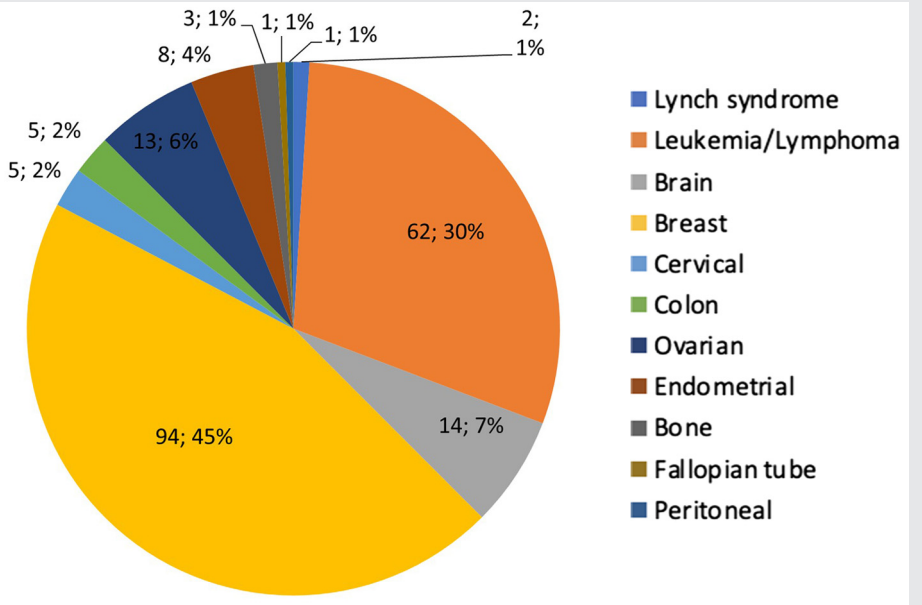
The distribution of fertility cases by diagnosis is presented in Figure 1. Breast cancer (n = 94/208, 45%) and leukemia/lymphoma (n = 62/208, 30%) were the most prevalent diagnoses. Gynecologic cancers accounted for 12.5% of cases (ovarian, n = 13; endometrial, n = 8; cervical, n = 5), and brain cancer accounted for 7% of cases (n = 14). Five patients (2.4%) were referred for colorectal cancer. A total of 7 patients also had known high-risk mutations (4 breast cancer genes and 3 Lynch mutations).

Of the 208 cancer patients who met with a reproductive specialist, 90 patients (43.3%) chose to undergo FP. The remaining 118 patients elected either no FP services after initial counseling visits or failed to follow-up. As shown in Supplemental Figure 1 (available online), of the 90 patients who chose to undergo intervention, 68.9% (n = 62/90) underwent oocyte cryopreservation, 26.7% (n = 24/90) underwent embryo cryopreservation, and 4.4% (n = 4/90) underwent either ovarian tissue cryopreservation 3% (n = 3) or bilateral ovarian transposition 1% (n = 1). The breakdown by age as to who used FP services was 47.5% (n = 19/40) of patients aged <25 years, 46.2% (n = 48/104) of patients 25 to 34 years and 29.7% (n = 19/64) of patients >35 years old. The patients <35 years old were significantly more likely to undergo FP intervention than the patients aged ≥35 (46.5% [n = 67/144] vs 29.7% [n = 19/64], respectively, [$P = .02$]).

Most referrals, 77% (n = 160/208), occurred before beginning cancer-directed treatment. Nineteen percent (n = 39/208) were referred after initial treatment and 3% (n = 6/208) were referred while undergoing treatment. For 1% (n = 3/208) of patients, the timing of the initial cancer intervention could not be determined based on chart review. Of the patients who were referred before cancer treatment, 47.5% (n = 76/160) underwent FP intervention. Of the patients referred during cancer treatment, 30.7% (n = 12/39) underwent FP intervention, and 33.3% (n = 2/6) of those referred after treatment underwent FP intervention. Table 1 demonstrates in vitro fertilization (IVF) demographic data based on the FP treatment timing. The patients who underwent FP before cancer treatment had a more favorable ovarian reserve and IVF outcomes regarding the antimüllerian hormone level, antral follicle count, the number of oocytes harvested, and the number of mature oocytes frozen.

The time from initial cancer diagnosis to referral ranged from 5 to 3,319 days, with a median time lapse of 22 days (Fig. 2). Of the 58 patients who had the date of cancer diagnosis and initial referral recorded, 66% (n = 38/58) presented for initial referral within 30 days of diagnosis, 19% (n = 11/58) presented within 31 to 100 days, and 15% (n = 9/58) presented at least 100 days between diagnosis and referral date. One patient was initially diagnosed with Hodgkin's lymphoma at another institution and did not receive counseling or referral for FP at the time of the initial diagnosis. She

FIGURE 1



Types of cancer diagnoses among patients referred for fertility preservation.

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was then referred to our reproductive center almost 10 years after her initial cancer diagnosis. The time from referral to FP intervention ranged from 1 to 810 days, with a median of 17 days (Fig. 3). Four patients had a delay in FP intervention because they preferred to wait until after chemotherapy. The patients who chose to delay intervention until after chemotherapy were indicated a gonadotropin-releasing hormone agonist while undergoing chemotherapy. Of the 88 patients who had the date of initial referral and intervention recorded, 80% (n = 70/88) underwent intervention within 1 to 30 days from the initial appointment, 8% (n = 7/88) underwent intervention within 31 to 100 days, and 12% (n = 11/88) had a time lapse of >100 days. Most patients in the latter cohort experienced a delay in the FP treatment in the setting of urgent chemotherapy or contraindication to cryopreservation before cancer treatment per their oncologist.

Of the 90 patients who pursued FP treatment, 84% (n = 76/90) had not attempted pregnancy at the time of data collection, and 11% (n = 10/90) had at least one successful live birth either via assisted reproductive technology or spontaneous conception since the time of FP consultation. One patient was currently pregnant at the time of data collection, and 2 were undergoing IVF cycles. Pregnancy information was unavailable for one patient because of failure to follow-up. Of the 10 patients who had a live birth, 7 conceived through IVF, and 3 conceived spontaneously. Four out of the 7 patients had initially undergone embryo cryopreservation, and 3 had undergone oocyte cryopreservation. Of the 7 patients who conceived through IVF, 57% (n = 4 of 7) had undergone an FP intervention before cancer treatment, and 43% of patients (n= 3 of 7) had undergone FP intervention after cancer treatment.

TABLE 1

Ovarian reserve and fertility preservation outcomes in patients undergoing fertility preservation before versus during or after cancer treatment.

Markers of ovarian reserve and FP outcomes	Before cancer treatment	After cancer treatment	During cancer treatment	*P* value
Antimüllerian hormone level (ng/mL)	3.29±3.67	0.67±0.89	0.37±0.18	.04
Antral follicle count (number of follicles)	14.52 ± 6.37	9.83 ± 5.01	9.50 ± 0.41	.046
Number of oocytes harvested	16.59 ± 10.83	12.18 ± 9.60	5.16 ± 2.79	.03
Number of mature oocytes	13.50 ± 7.91	8.33 ± 6.56	2.3 3 ± 1.03	.03
Number of embryos frozen	8.28 ± 5.09	8.2 ± 6.38	—	.98

Note: Values are mean ± standard deviation, unless noted otherwise.
P< .05 is statistically significant.

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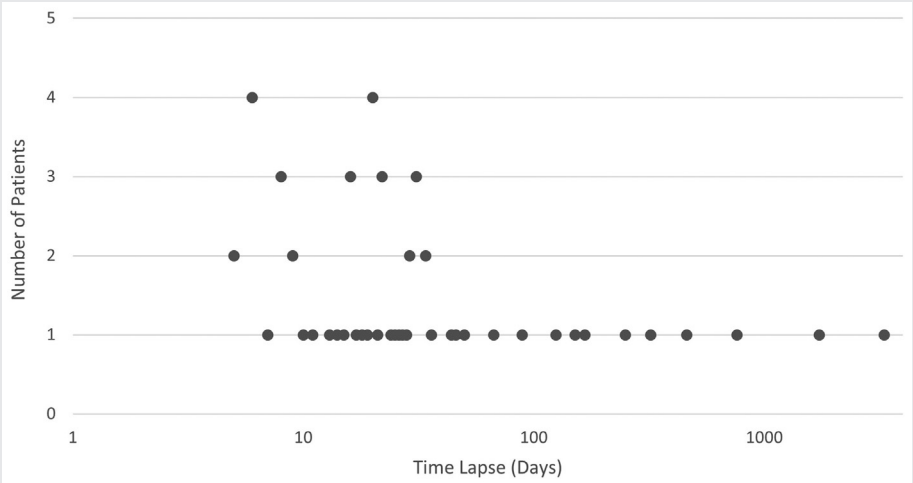
FIGURE 2



Time lapse from the date of cancer diagnosis to the date of referral to a reproductive specialist.

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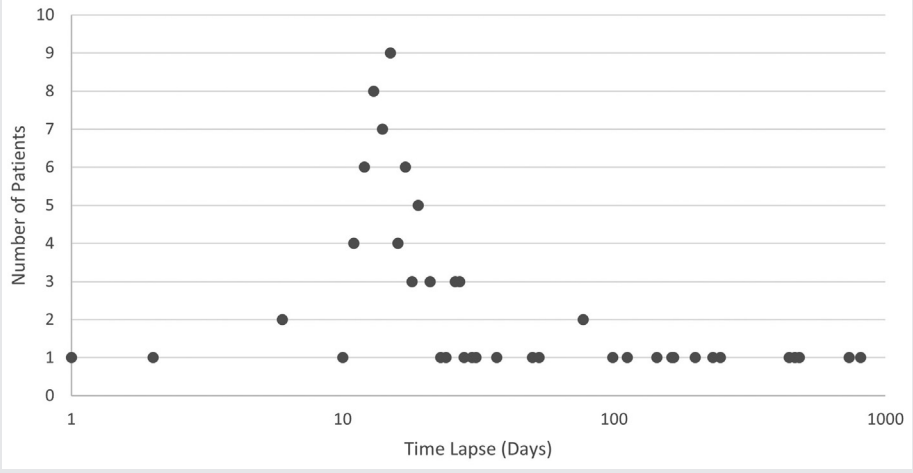
DISCUSSION

Although prior studies have reviewed the use of various methods of FP, there have been few studies evaluating referral patterns and the use of FP services. This study adds to the literature by including data that stratifies FP referrals by cancer diagnosis, evaluating the time from cancer diagnosis to referral, and ultimately FP intervention. In this retrospective study, we found that cancer patients are able to undergo FP intervention in a timely fashion; however, a large percentage of patients are being lost to follow-up after referrals are made.

Because of the improved cancer survival rates, national data from the Centers for Disease Control and Prevention shows a growing number of young cancer survivors (1). More specifically, of the 843,820 women diagnosed with cancer in the United States in 2016, over 89,000 cases were in women $<$45 years old (1). The average age of cancer diagnosis in our study was 30.6 $\pm$ 7.62 years. We found that younger patients were more likely to undergo FP intervention, with 46.5% of patients $<$35 years old undergoing FP intervention compared with 29.7% of patients $\geq$35 years old (P=.02). Our findings demonstrate that women are interested in FP at a

FIGURE 3



Time lapse from the date of referral to reproductive specialist to fertility preservation intervention.

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young age and before childbearing, and maintaining the option of having children in the future using their gametes is extremely important for the quality of life after treatment. Young age should motivate an early conversation about the effects of treatment on fertility to optimize future family planning options for young cancer patients. Additionally, our results demonstrate a smaller number of women over 35 undergoing FP. With the reduced reproductive capacity associated with advanced maternal age, FP in older female cancer patients should still be discussed as early as possible before treatment, even if the probability of future pregnancy is lower. It should be the patient's informed decision about whether to pursue FP. Although FP is not recommended if futile, all reproductive aged women should be appropriately counseled on FP options.

It is imperative to consider FP methods when counseling cancer patients on their cancer treatment options. Embryo cryopreservation is not always an option, especially for young cancer patients, who may lack a partner and are not ready to use donor sperm. Autonomy over the use of the oocytes for the cancer survivor is of paramount importance as relationship status may change. Oocyte and embryo cryopreservation, however, may not be the ideal choice in the setting of acute illness or emergent need for treatment, as time for ovarian stimulation is necessary (17). Ovarian tissue cryopreservation has become a potential option for prepubertal patients who cannot undergo ovarian stimulation and patients who cannot delay cancer treatment for stimulation (17, 18).

In our study, oocyte and embryo cryopreservation were the most common types of FP intervention, with 68.9% (n = 62) undergoing oocyte cryopreservation, 26.7% (n = 24) undergoing embryo cryopreservation, and 4.4% (n = 4) undergoing ovarian tissue cryopreservation or oophoropexy. Interestingly, 75% of patients who underwent ovarian tissue cryopreservation were diagnosed with lymphoma. These patients underwent ovarian tissue harvesting before, during, and after chemotherapy. Chemotherapy was therefore not a hindrance to ovarian tissue cryopreservation as long as the ovary was likely not involved or patients with leukemia were in remission with a negative bone marrow biopsy. Although the timing of ovarian stimulation in oocyte and embryo cryopreservation can delay treatment, random start stimulation protocols have helped expedite time to retrievals by initiating stimulations regardless of the stage in the menstrual cycle (19). Our study found that FP intervention, including oocyte and embryo cryopreservation, can often be initiated within 30 days of initial referral and usually much sooner. At our institution, 80% of the patients underwent an FP intervention within 30 days of referral with a median of 17 days. Our results suggest that the urgent need for cancer treatment should not always be a barrier to referral, as both ovarian tissue preservation and oocyte/embryo cryopreservation may still be options.

Although it should ideally be initiated before cancer treatment, a referral to an infertility specialist for FP should be made regardless of where a patient is in their cancer treatment. Although most patients (79%) were referred before initiation of cancer treatment, 2% were referred while undergoing chemotherapy, and 16% were referred after completing at least one round of chemotherapy. Whereas, 53.5% of the patients who were referred before starting cancer treatment underwent FP, 36.4% of patients referred during treatment were able to undergo some type of FP, and 40% of patients referred after finishing treatment underwent FP. Oncologic treatments included surgery, chemotherapy, nonchemotherapy medication, and radiation. Most patients undergoing chemotherapy at the time of the referral subsequently underwent ovarian tissue harvesting. Those undergoing treatment through nonchemotherapy medication, surgery, or radiation underwent oocyte cryopreservation or ovarian tissue preservation. Our findings demonstrate that patients are still interested in FP regardless of their stage of cancer treatment. However, patients who underwent FP before cancer treatment had a more favorable ovarian reserve and a greater number of mature oocytes cryopreserved. Although our study focused on oocyte/embryo cryopreservation and ovarian tissue cryopreservation, it is important to note that other FP options are available such as gonadal shielding or mobilization during radiation and ovarian suppression with gonadotropin-releasing hormone agonists or antagonists. The use of egg donors or gestational carriers in the future should also be discussed as an alternative method of a family building (11, 18). All these options should be discussed with the patient regardless of cancer diagnosis and treatment. To maximize future fertility options and prompt initiation of cancer treatment, referrals should be made as early as possible after diagnosis (7). History of prior cancer treatment should also not hinder referrals, as FP options are available.

Interestingly, only 39.7% of patients who were referred to infertility specialists followed up with a reproductive specialist, and only 43.3% of patients who saw a specialist underwent FP intervention. Because of the retrospective nature of this study, it is unknown if this lack of follow-up and intervention was due to a lack of interest from the patient or advanced-stage disease at the time of cancer diagnosis. Patients may have also chosen to follow-up at another institution for FP. It is also unknown if proper counseling was performed and the patients were either discouraged from undergoing FP because of cancer treatments being unlikely to affect fertility (i.e., adriamycin, bleomycin sulfate, vinblastine sulfate, and dacarbazine in a young girl with good ovarian reserve) or if the patient was counseled about the poor prognosis of FP measures based on age or other factors. Further investigation needs to be performed to reveal why patients may choose not to pursue FP or see a reproductive specialist. This low rate of follow-up with a reproductive specialist at our institution creates an opportunity for improvement to establish better methods of tracking and ensuring patient follow-up.

The inclusion of institution-wide FP data for cancer patients over an extended time is one of the strengths of this study. As a retrospective study based on chart review, the study is limited in access to data dependent on provider documentation and patient follow-up. Because most patients have not returned to use their frozen eggs or embryos, our study is limited in evaluating pregnancy outcomes. Future research should investigate pregnancy outcomes in this patient population.

CONCLUSION

Our results provide valuable information regarding referral patterns and the use of FP services. Following the current recommendations of the American Society of Clinical Oncology, all health care providers who routinely encounter this population should be educated about referral options to fertility specialists. All patients who are interested in FP, regardless of age and progress in cancer treatment, can undergo FP in a timely manner. Unfortunately, a large percentage of patients are lost to follow-up after referral to a reproductive specialist. Although this study provides the necessary groundwork to evaluate the use of readily available FP services, further research is needed to identify barriers to referral and fertility planning so cancer patients can have the reproductive future they desire.

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