J Assist Reprod Genet (2011) 28:635–641
DOI 10.1007/s10815-011-9559-z

FERTILITY PRESERVATION

Treatment outcomes and quality-of-life assessment in a university-based fertility preservation program: Results of a registry of female cancer patients at 2 years

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Received: 22 December 2010 / Accepted: 7 March 2011 / Published online: 22 March 2011

Abstract
Purpose To explore patient goals and quality of life (QOL) via a prospective registry and compare fertility preservation (FP) outcomes before, during, and after cancer therapy.
Methods Of 35 patients entering the registry from 3/2008 to 3/2010, 29/35 completed the study survey and agreed to follow-up, and 31/35 completed treatment. Survey results and FP outcomes were analyzed.
Results Most patients rated the impact of cancer treatment on fertility of highest importance at baseline and 1-year follow-up. QOL scores were overall positive at both intervals. Patients naïve to any cancer treatment ($n=12$) had more gametes frozen than patients with prior cancer treatment ($n=19$) with no difference in age or gonadotropin dosage. For patients awaiting cancer treatment, the median time from consultation to oocyte retrieval was 25 days. Cancer treatment sequalae posed challenges to optimal FP outcomes.
Conclusions Fertility preservation remains a significant issue for cancer patients. With early reproductive endocrinologist referral, cancer treatment delay is minimized and FP outcomes are optimized.

Capsule Fertility preservation remains a significant issue for cancer patients. With early reproductive endocrinologist referral, cancer treatment delay is minimized and FP outcomes are optimized.

Presented in part at the American Society of Reproductive Medicine 65th Annual Meeting, Atlanta, GA, October 2009.

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Keywords Cancer · Fertility preservation · Infertility · Oocyte cryopreservation

Introduction

Today, at least 85% of young cancer patients survive ≥5 years [1, 2], making long-term quality-of-life (QOL) issues such as fertility and parenthood after cancer paramount in early cancer management. While many women do conceive naturally after cancer therapy, even when menses spontaneously resumes after toxic treatments like chemotherapy, ovarian reserve can show signs of impairment [3]. The greatest risk for fertility compromise results from therapies involving alkylating chemotherapy agents, bone marrow transplantation, or surgical castration [4–11]. Thankfully, fertility preservation (FP) treatment options such as embryo and oocyte cryopreservation have improved dramatically over the past 20 years [12–17]. As a result, FP counseling is integral when a newly diagnosed malignancy requires gonadotoxic therapy in either adults or adolescents [18, 19].

Guidelines issued by the American Society of Clinical Oncology (ASCO) in 2006 advocate that all patients of childbearing age be informed regarding their FP options [20], yet a recent study showed that less than half of American physicians follow these recommendations [21]. More oncologists are now discussing infertility risks with female patients, but referrals to reproductive endocrinologists (RE) remain less common [22]. And while appropriate candidates often decline FP treatment once offered [23], a recent survey reported that about a third of women under age 50 would have liked a fertility consultation before initiating

cancer therapy [24]. Previous studies show that young breast cancer patients have specific fertility and menopause-related concerns that are not adequately addressed prior to commencing adjuvant therapy [25], as well as persistent concerns 2–5 years after diagnosis [26]. Detailed large population studies involving the outcome of ART procedures for this population have yet to be reported, and patients and oncologists alike could benefit from more information on the fertility risks associated with varying cancer treatments.

Our objective was to create a prospective registry with short and long-term follow-up of female cancer patients who presented for initial consultation related to FP and/or fertility treatment. Short-term goals included an analysis of patient motivations, provider referral patterns, and FP treatment outcomes between patients seeking FP before versus after cancer therapy. We also hoped to identify unique challenges in the establishment of a FP program. Long-term goals of the registry included a prospective, observational analysis through periodic follow-up assessments and change over time in responses to the FACT-B QOL survey.

Patients and methods

Female cancer patients aged 15–45 years that presented to the New York University Fertility Center (NYUFC) for fertility counseling and/or treatment were asked to participate in the registry. All patients agreed to be contacted in the future for interval follow-up. Patients completed a medical history intake form, which was cross-referenced for accuracy with physician records through a chart review. Patients also completed a survey about treatment intentions using a 7-point Likert scale (scale 1–7; 7 = most important), developed by the authors. Patients were asked to rate "How important is having a child in your life", and "How concerned are you with the impact of cancer treatment on your fertility". They were also asked to indicate the amount of risk (none/minimal/moderate/whatever it takes/unsure) that they were willing to undertake to their cancer prognosis to pursue fertility treatment. In addition, patients completed the FACT-B QOL survey (http://www.facit.org/qview/qlist.aspx). The FACT-B survey addresses categories of physical, emotional, social, and functional wellbeing, as well as a category of "additional concerns" which asks, among others, about sexual attractiveness, effects of stress on illness, and femininity. Participants agreed to follow-up starting at 1, 5, 10, and 15 years following completion of fertility treatment at NYUFC. Results from patients entering the registry from 3/2008 to 3/2010 are presented.

We analyzed patient characteristics such as age, demographics, fertility and medical history, and noted any previous cancer therapies including surgery, radiation, and/or chemotherapy. FP treatments utilized included oocyte and/or embryo cryopreservation; ovarian tissue freezing was discussed where appropriate but was not first-line management in any of the registry cases. Zygote cryopreservation was encouraged as the sole treatment or in conjunction with oocyte cryopreservation for those patients with a partner; however, if either objected to embryo freezing, only oocyte cryopreservation was recommended. Single patients were offered both oocyte and/or zygote cryopreservation with oocyte cryopreservation encouraged, particularly in women finding donor sperm use and/or embryo creation undesirable.

Treatment used to establish pregnancy included in vitro fertilization (IVF) using autologous or donated oocytes. Outcome parameters for all completed treatments were recorded and assessed. Patient data were then subdivided by whether FP was attempted before any cancer treatment ("Before Treatment" Group), which included patients naïve to either surgery and/or chemotherapy. Patients who had undergone FP after any form of cancer treatment, whether it be surgery and/or chemotherapy, were categorized as the "After Treatment" Group. T-tests were performed as indicated using a p value of <0.05 as significant using SPSS 13.0 for Windows (Chicago, IL). Within-patient change was determined using a paired t-test. IRB approval was obtained through the NYU School of Medicine in conjunction with the NYU Cancer Institute (IRB# 07–746).

Results

Demographics

From March 2008 to March 2010, 37 cancer patients were approached for participation with 35 consenting to registry enrollment. The average age at enrollment was 32±6 (range 21–44) years and the average age at diagnosis for the entire population was 29±5 (range 16–39) years. Of all cancer diagnoses (Table 1), 60% (21/35) were gynecologic, and 71% (25/35) of patients had been referred by their oncologists. The remaining were referred by their Ob/Gyn (2/35); family doctor (1/35) or by family/friend/self (7/35).

Treatment intention/QOL survey results

Twenty-nine of the 35 (83%) patients who agreed to registry participation completed the initial treatment intention/QOL survey (Table 2). From these data, 52% (15/29) of patients felt having a child was "most important" in their life (scale 1–7; mean 6.1; median 7), and 62% (18/29) were "most concerned" with the impact their cancer treatment would have on fertility (mean 6.1; median 7). When asked to compare their preferences regarding the potential need for ART procedures in the future, all patients indicated they

Table 1 Types of cancer in patients seeking fertility preservation

Type of cancer	Number of patients
Cervical	10
Ovarian	6
Breast	4
Endometrial	4
Hodgkin's lymphoma (HL)	3
Acute myeloid leukemia (AML)	2
Nonhodgkin lymphoma (NHL)	1
Chronic myeloid leukemia (CML)	1
Ewing's sarcoma	1
Thymic carcinoma	1
Primary peritoneal	1
Childhood neuroblastoma/renal cell carcinoma (dual primary)	1

were more interested in procedures using autologous rather than donated oocytes, with the exception of one patient already slated to use donor oocytes after oophorectomy. Six patients indicated they would not consider using donor oocytes under any circumstance. Recognizing the limited data on the long-term risks for FP patients, 54% were "unsure" regarding the risk they were willing to undertake to pursue fertility treatment, while 19% were willing to undertake a minimal and 19% a moderate risk. Two patients (8%) indicated they were willing to do "whatever it takes" to conceive a child. Regarding the FACT-B section of the survey, patient scores across the categories were overall positive (Table 2).

A total of 16 patients were approached for 1-year survey follow-up, and 8 follow-up surveys were returned at the time of manuscript submission. Patients' opinions regarding the importance of childbearing or the impact of cancer treatment did not change within each patient between initial consultation and follow-up.

Treatment outcomes

Four (11%) patients chose not to proceed with FP treatment after consultation, of which 3 had already undergone some cancer treatment. Reasons for not proceeding included financial restrictions (n=2), "not ready" (n=1), and having a child already and not willing to undergo fertility therapy (n=1).

Demographics and outcome data for patients who pursued FP treatment are shown in Table 3. Twelve patients pursued FP before completing any cancer therapy ("Before Treatment" Group), and 19 underwent assisted reproductive treatment only after completing some or all cancer treatment ("After Treatment" Group). More than half of the Before Treatment Group was single (n=7; married n=5). In the After Treatment Group, patients were single (n=8); married (n=9), or had a significant other (n=2). No patients in the Before Treatment Group had been diagnosed with infertility, whereas 3 patients in the After Treatment Group had at least one fertility factor.

In the After Treatment Group (n=19), 7 patients had already undergone some form of gynecologic surgery such as an oophorectomy or trachelectomy but were scheduled to undergo additional gynecologic surgery, chemotherapy, and/or radiation. Four additional patients had already received or were receiving chemotherapy and were scheduled to receive additional gonadotoxic treatment, and 8 patients had completed all cancer treatment. For those patients awaiting the start of their cancer treatment (Before Treatment Group), the median time from initial consultation with the RE to the beginning of FP treatment was 12 (range 4–49) days, and 25 (range 15–60) days from consultation to oocyte harvest. For those patients awaiting the completion of cancer treatment, the median time from initial consultation to beginning the fertility cycle was 14 (range 0–176) days, and 31 (range 9–196) days from consultation to oocyte harvest. Over half the patients began and completed their FP cycle within 2–4 weeks of initial consultation.

Table 2 Patient survey and QOL scores at initial and follow-up time points

	Best possible score	Initial survey (Mean±St Dev) (n=29)	1 year follow-up survey (Mean±St Dev) (n=8)	Within patient change (Mean Change±St Dev)	P value (paired t test)
Importance of having a child?	7/7	6.1±1.2	6.3±1.0	−0.1±0.8	NS
Impact of treatment on fertility?	7/7	6.1±1.4	5.5±2.3	+0.9±1.2	NS
FACT-B results: lower scores indicate a better QOL in these categories					
Physical	0/28	4.3±5.1	2.4±2.7	−1.0±2.8	NS
Emotional	0/24	8.5±4.1	8.0±6.7	−1.0±2.2	NS
Additional	0/40	14.4±4.7	11.8±3.2	+1.6±4.7	NS
FACT-B results: higher scores indicate a better QOL in these categories					
Social	28/28	23.6±4.2	25.6±3.0	+3.8±3.3 (better QOL)	0.014
Functional	28/28	20.8±5.6	25.1±3.2	+2.1±3.5	NS

Table 3 Demographics and comparison of treatment outcomes in patients pursuing assisted reproduction before versus after their cancer treatment

	Before treatment group (n=12)	After treatment group (n=19)	P value
Age at cycle start (y)	30±4	33±6	NS
Day 2 serum FSH (IU/L)	5±3	7±4	NS
Day 2 serum estradiol (pg/ml)	46±20	36±15	NS
Partnership status	7 single/5 married	8 single/9 married/2 significant other	–
Time: RE consult to FP treatment (days)	12 (range 4–49)	14 (range 0–176)	–
Time: RE consult to oocyte harvest (days)	25 (range 15–60)	31 (range 9–196)	–
Total gonadotropins used (IU)	3592±828	3572±1355	NS
Maximum serum estradiol (pg/ml)	2634±1277	1875±1752	NS
No. oocytes retrieved	23±10	11±10	0.003
No. frozen gametes (egg/embryo)	17±11	8±9	0.03
Cycles canceled for poor response	0	5	–

In both the Before Treatment and After Treatment Groups, ovarian reserve testing demonstrated baseline serum menstrual-cycle day-2 FSH and estradiol levels to be within normal ranges, as defined as an FSH <13 IU/L and an estradiol <60 pg/ml. Dosages of medication needed to achieve optimal ovarian stimulation as well as maximum serum estradiol levels achieved (a marker of ovarian response) were comparable between the Groups. However, patients naïve to any cancer treatment (Before Treatment Group) had more oocytes retrieved and more gametes frozen than the After Treatment Group, with no difference in the mean age at cycle start.

In the Before Treatment Group (mean age 30±4 y), 6 patients completed 6 oocyte cryopreservation cycles, 4 patients underwent 5 cycles involving both oocyte and embryo cryopreservation, and one patient completed 2 cycles of embryo cryopreservation resulting in a total of 153 cryopreserved oocytes and 38 cryopreserved embryos. Three patients returned after completing cancer treatment in an attempt to achieve pregnancy. One achieved a full-term singleton delivery after thaw and transfer of 2 frozen embryos; one had a sister-gestational carrier who delivered at term after single-embryo transfer of a frozen-thawed embryo, and one had one early pregnancy loss after two thaw cycles using frozen embryos. To date, no patient has returned to use cryopreserved oocytes.

In the After Treatment Group (n=19; mean age 33±6 y), 11 were still undergoing cancer treatment when seeking FP and 8 were seeking immediate pregnancy after completion of cancer therapy. Of those pursuing FP while in treatment (n=11), 9 patients completed 11 cycles of oocyte cryopreservation, 1 patient underwent 3 cycles of embryo cryopreservation, and 1 patient completed a single cycle of both embryo and oocyte cryopreservation for a total of 111 cryopreserved oocytes and 23 cryopreserved embryos. None of these patients have returned to use their frozen gametes. Eight patients seeking pregnancy in the After Treatment Group underwent a total of 18 cycles of IVF (7 patients completed 16 cycles using autologous oocytes, and 1 patient completed 2 cycles using donated oocytes). Of the 8 patients using autologous oocytes, three have become pregnant; one delivered a healthy infant, and two others achieved pregnancies >20 weeks gestation. The one patient who used donor oocytes first suffered a miscarriage and then went on to achieve a healthy twin delivery. One patient who never used her frozen embryos passed away due to pulmonary complications from Hodgkin's lymphoma approximately 1 year after cycling. At the time of manuscript submission, her husband has elected to continue cryostorage of her embryos.

Treatment challenges

Patients with cancer present unique challenges to fertility treatment. In the Before Treatment Group (n=12), no patients were cancelled for poor ovarian response (<3 developing oocytes to ovarian hyperstimulation), but one patient's cycle was cancelled because she required hospitalization by her oncologist for a febrile illness related to her non-Hodgkin lymphoma. In the After Treatment Group (n=19), 5 patients had at least one cycle cancelled for poor ovarian response, and one patient attempting to freeze both oocytes and embryos only produced enough oocytes for embryo cryopreservation (a center specific cutoff of 6 eggs). Another patient's fertility treatment never commenced because of profound pancytopenia after recent chemotherapy. One woman who was recently postoperative from major gynecologic surgery had a resolving intra-abdominal hematoma, making ultrasound visualization more challenging. In addition, one patient who was status-post hysterectomy and oophoropexy required the more difficult transabdominal retrieval, rather than the standard transvaginal approach to oocyte harvest.

Discussion

Our questionnaire found that having a child was of utmost importance to almost all FP patients and that donor oocyte options were least attractive or unacceptable. Moreover, most patients classified themselves as having the highest level of concern regarding the impact of their cancer treatment on their future fertility. We recognize that such concerns may be an overestimation of the general cancer population, given that these patients are actively seeking FP, and that these responses were not part of a validated survey. Given the paucity of data regarding the use of ART after cancer, most patients stated that they were unsure of their risk-tolerance relative to their cancer prognosis. According to oncologists, patients may be willing to sacrifice more in survival than they themselves would, although a recent nationwide survey showed that most oncologists would only be willing to sacrifice a <5% reduction in disease-free survival if a regimen offered better fertility outcomes [22]. In our study population, 89% of consulting patients proceeded to some form of FP.

Assessment of health-related QOL issues in cancer survivors is widely advocated [27], although a standard, validated QOL questionnaire has not been fully developed for this patient group. The FACT-B questionnaire has been reported to be appropriate for use in oncology clinical trials, as well as in clinical practice, as it demonstrates ease of administration, brevity, reliability, validity, and sensitivity to change [28]. Designed for patients with breast cancer, FACT-B was initially chosen because we anticipated large numbers of breast cancer patients entering our registry. However, despite our heterogeneous population, we find the FACT-B to be useful since it addresses specific issues of femininity, self-consciousness, and sexuality identity important to all women regardless of cancer type. As new patients enter the registry, we are reviewing our plan to change to a more generalized QOL assessment for cancer patients such as the Cancer Rehabilitation Evaluation System-Short Form (CARES-SF) or World Health Organization QOL (WHOQOL) [29]. From our short-term QOL assessment, it is apparent that our patients feel supported in their journey as many reported high scores in emotional and social-wellbeing categories with little if any change over our short-term follow-up period. At this time, we are continuing to collect data for long-term assessment.

The majority of our patients were referred by gynecologic oncologists rather than medical or surgical oncologists. This pattern was reflected in a recent survey that also reported that gynecologic oncologists were likely to modify their treatment to better preserve fertility [22]. Reasons for such a referral bias are unclear, and may include their reproductively oriented medical training, or simply colleague familiarity within one's own department.

In our practice, we offer single women, and even partnered individuals, the option to cryopreserve oocytes in addition to embryos as a means to potentially preserve their fertility. Previous studies at our [30] and other [17] centers have shown age-comparable pregnancy rates between patients using cryopreserved vs. fresh oocytes. Thus, we feel our recommendations are appropriate for the patient population we serve.

Previous reports involving cancer patients have shown similar numbers of oocytes retrieved after ovarian hyperstimulation when compared with age-matched infertile controls [31], tubal factor patients [32], and even oocyte donors [33], suggesting that malignancy itself does not adversely affect ovarian response. This has been our [31] experience as well as that of others [32]. In the present study, patients naïve to any cancer treatment had a better ovarian response with more gametes cryopreserved than those completing or currently undergoing cancer treatments, with no difference in mean age, ovarian reserve assessment, or medication dosage. The compromise seen in the After Treatment group is likely a combination of factors including physiologic stress from recent chemotherapy, a history of known gonadotoxic treatment, and possibly some underlying infertility issue. Such is in agreement with previous in vitro studies that showed lower primordial follicle counts and estradiol levels in patients exposed to chemotherapy [34]. While the exact contribution of each factor cannot be determined in this study, it underscores the importance of FP and fertility awareness early in cancer treatment.

Limitations of our study include its small sample size and a significant chance of a sampling bias, since most of our patients chose to undergo treatment at our center, which may have affected the external validity of our survey. In addition, determining the impact of fertility preservation on a patient's quality of life would best be studied by having a larger population of cancer patients for comparison who declined fertility preservation. In addition, while categorizing surgery and chemotherapy patients together emphasized the outcomes of treating naïve patients, it also created a heterogeneous group for comparison.

A patient's success with FP is optimized if FP is performed prior to starting cancer treatment, as has been shown in previous studies [35]. Furthermore, challenges can be minimized or averted if patients seek FP prior to starting cancer treatment, although this is not always practical. For example, all cancer patients are at increased risk of venous thromboembolism and more so following treatment. Clotting risk may be increased in the setting of severe ovarian hyperstimulation, especially in women with underlying coagulopathy [36]. Patients with pulmonary or cardiac compromise, coagulopathy, or any hematologic deficiencies (e.g. anemia, thrombocytopenia and/or leukopenia) resulting

from disease or chemotherapy should undergo preoperative anesthesia consultation to assure that all necessary precautionary steps are addressed prior to and at the time of oocyte harvest. In addition, the disposition of cryopreserved gametes/embryos in the event of death needs to be discussed and documented, particularly since cancer patients may display different attitudes when compared with infertility patients without cancer [23]. Lastly, if a cancer survivor is cleared by her oncologist for pregnancy, she should receive obstetric preconception counseling, particularly if she has suffered prior major-organ compromise. In addition, women status-post cervical trachelectomy should be counseled, given their increased risk for miscarriage and preterm delivery [37, 38].

While it is ideal to refer the patient to a reproductive endocrinologist immediately after cancer diagnosis, often the treatment plan is tentative until pathology reports are finalized, necessitating a flexible and open relationship between oncologist and reproductive endocrinologist. In a previous study on breast cancer patients, the interval from diagnosis to start of adjuvant chemotherapy was not significantly prolonged in those undergoing FP with oocyte retrieval after ovarian stimulation [39]. In our experience, such "emergency" FP is only possible with a multidisciplinary collaboration between the patient's oncology team and a FP-experienced reproductive endocrinologist. In this study, the median time from consult to oocyte retrieval was 25 days, and in many cases was often closer to 15 days.

The education of young patients regarding fertility issues related to their diagnosis and/or treatment is imperative [40]. While FP is optimal prior to cancer treatment, FP at any stage of therapy can offer patients options through embryo, oocyte, (and/or ovarian tissue) cryopreservation. Childbearing and the impact of cancer treatment on fertility are high priorities for reproductive-age women diagnosed with malignancy and QOL remains important among those seeking FP and/or ART after cancer.

Disclosure All authors have nothing to disclose.

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