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Fertility preservation in patients with haematological disorders: a retrospective cohort study☆

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Abstract

This study investigated the factors associated with utilization of fertility preservation and the differences in treatments and outcomes by prior chemotherapy exposure in patients with haematological diseases. This study included all 67 women with haematological diseases seen for fertility preservation consultation at two university hospitals between 2006 and 2011. Of the total, 49% had lymphoma, 33% had leukaemia, 7% had myelodysplastic syndrome and 4% had aplastic anaemia; 46% had prior chemotherapy; and 33% were planning for bone marrow transplantation, 33% pursued ovarian stimulation and 7% used ovarian tissue banking; and 48% of patients did not pursue fertility preservation treatment. All five cycle cancellations were in the post-chemotherapy group: three patients with leukaemia and two with lymphoma. Patients with prior chemotherapy had lower baseline antral follicle count (10 versus 22) and received more gonadotrophins to achieve similar peak oestradiol concentrations, with no difference in oocyte yield (10.5 versus 10) after adjustment for age. Embryo yield was similar between those who had prior chemotherapy and those who had not. Half of the patients with haematological diseases who present for fertility preservation have been exposed to chemotherapy. While ovarian reserve is likely impaired in this group, oocyte yield may be acceptable.

Keywords

cancer; fertility preservation; haematological disease; IVF; ovarian reserve

Introduction

Over 130,000 reproductive-age women are diagnosed with cancer in the USA annually (Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973–2008), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2011, based on the November 2010

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submission), with haematological cancers accounting for 18% of new diagnoses in women under the age of 45 (Kohler et al., 2011). In the paediatric and adolescent populations, US cancer statistics suggest that incidence of leukaemia is increasing 0.5% per year (American Cancer Society, 2011). While various therapeutic protocols for haematological malignancies are available, many include alkylating agents which have been associated with gonadotoxicity and infertility (Meirow and Nugent, 2001). In addition, various non-malignant haematological disorders such as sickle cell disease require gonadotoxic treatment strategies similar to those used for haematological malignancies (Bhatia and Walters, 2008; Walters and Sullivan, 2010). Improvements in treatment regimens have resulted in greater survival in patients with these disorders, thereby increasing the importance of long-term quality of life and future fertility to survivors (Letourneau et al., 2011; Loren et al., 2013). Indeed, studies suggest that the majority of cancer patients are concerned about the risk of infertility associated with treatment, and a third report that concerns about the risk of infertility have an impact on their treatment decisions (Partridge et al., 2004).

Over the past decade, there has been increasing interest in methods to expand the reproductive options of patients facing gonadotoxic therapies. While embryo cryopreservation is the standard option for adult females with a committed partner, oocyte cryopreservation is now widely accepted as well; additionally, ovarian tissue cryopreservation is another experimental option for patients without a committed partner (Lee et al., 2006). However, patients with haematological disorders present unique challenges to fertility preservation counselling and management. These individuals are often too ill at diagnosis to be eligible for fertility preservation treatment, which typically require a delay in therapy for days to weeks and involve minor surgical procedures, which pose increased risks in patients with abnormal haematological parameters. Moreover, even if leukaemia patients are eligible for ovarian tissue cryopreservation, there is concern about reseeding malignant cells with future autologous transplantation of tissue (Dolmans et al., 2010; Greve et al., 2012; Mueller et al., 2005; Salle et al., 2003; Schmidt et al., 2011; Shaw et al., 1996). Leuprolide acetate down-regulation administered prior to chemotherapy is another option, but the long-term benefits with respect to fertility preservation remain unclear (Beck-Fruchter et al., 2008; Chen et al., 2011). While patients with lymphoma are better candidates for fertility preservation treatment, often initial therapies like ABVD (adriamycin, bleomycin, vincristine and doxorubicin) do not have a substantial risk of infertility and, therefore, there is less motivation to pursue fertility preservation (Hodgson et al., 2007). For these reasons, often patients present for fertility preservation consultation only after a relapse in disease has been diagnosed after initial therapy, and sterilizing stem cell transplantation has been recommended. Hence, individuals with haematological malignancies often are seen after having already been exposed to gonadotoxic therapies (Maltaris et al., 2007).

The American Society of Clinical Oncology has recommended that providers discuss the fertility risks and fertility preservation options with patients facing gonadotoxic therapies; however, there are little data on clinical outcomes to guide recommendations for specific populations (Lee et al., 2006). There is a growing body of evidence regarding fertility preservation outcomes in breast cancer patients (Azim et al., 2008; Hill et al., 2012; Letourneau et al., 2011; Oktay et al., 2005, 2006; von Wolff et al., 2011; Westphal and

Wapnir, 2012); however, the natural course of the disease and treatment are very different from haematological conditions, making it difficult to extrapolate data to patients with these disorders. Specifically, there are limited data about the fertility preservation choices and response to ovarian stimulation for women with haematological malignancies, particularly for those who have previously been exposed to chemotherapy (Dolmans et al., 2005; Ginsburg et al., 2001; Klock et al., 2010; Rossi et al., 2011).

The objective of this study was to identify factors that influence the utilization of fertility preservation treatment in patients with haematological disorders who present for fertility preservation consultation and to compare fertility preservation treatment choices and ovarian stimulation parameters between patients who present before or after exposure to chemotherapy.

Materials and methods

This retrospective cohort study identified all female patients with haematological disorders who were referred for fertility preservation consultation at two university centres from 2006 to 2011. Institutional Review Board approval was obtained at both study sites before the start of this study (IRB no. 809406, first approved 16 February 2009, University of Pennsylvania; 4 August 2009, University of North Carolina Chapel Hill). Patients were included if they were post-menarchal, had been recently diagnosed with a haematological disease and had impending chemotherapy treatment.

Medical records were abstracted to obtain detailed demographic and treatment specific data. Recorded data included: patient age at first fertility preservation consultation, race, gravidity, parity, body mass index (BMI) and partner status (by patient self-report). Disease specific information recorded included: haematological diagnosis, treatments prior to presentation for fertility preservation consultation, the time from last treatment, impending treatment plans and fertility preservation strategy pursued. For patients who elected to undergo ovarian stimulation for oocyte or embryo cryopreservation, stimulation parameters including baseline antral follicle count, cycle day 3–5 FSH, total gonadotrophins used during stimulation, duration of stimulation, peak serum oestradiol (pg/ml), oocyte yield (MII), embryo yield and cycle cancellation rates were collected.

Statistical analysis

Baseline characteristics were compared between subjects in different diagnostic categories and between subjects with and without previous exposure to chemotherapy using Pearson Chi-squared, Fisher's Exact and Wilcoxon rank-sum tests for categorical and continuous data as appropriate. Baseline ovarian reserve and ovarian stimulation parameters were compared using linear and Poisson regression models, adjusting for age. All hormone concentrations were transformed using natural log to reduce the influence of a left-skewed distribution of values. Hormone comparisons between groups are presented as risk ratios of geometric mean hormone concentrations. Using bootstrap resampling with 50 replicates drawn from the original samples, 95% confidence intervals (CI) for estimated risk ratios were obtained. Data analysis was performed using STATA Statistical Software version 12.0. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Cohort characteristics

A total of 67 subjects met inclusion criteria for the study: 44 from the University of Pennsylvania and 23 from the University of North Carolina Chapel Hill. The baseline characteristics are presented in Table 1. Haematological diagnoses included: 33 patients with lymphoma (49%), 22 with leukaemia (33%), five with myelodysplastic syndrome (7.5%), three with aplastic anaemia (4.5%), two with sickle cell disease, one with multiple myeloma and pme with Erdheim–Chester disease. Of those with lymphoma, 67% had Hodgkin's lymphoma, while amongst those with leukaemia, 41% had acute lymphoblastic leukaemia, 32% had acute myelogenous leukaemia and 23% had chronic myelogenous leukaemia (no further specification of diagnosis was available for one patient with leukaemia). The median age was 25.9 years (range 14–44 years), median BMI was 23.4 kg/m^2 (range 17–40 kg/m^2) and the majority of the population was Caucasian (79%) with 9% African American, 4.5% Asian and 7.5% representative of other or mixed races. Over half (57%) of the study population had an intimate partner at the time of fertility preservation consultation. The majority (73%) were nulligravid and 88% had no living children. 46% had been exposed to prior chemotherapy and 33% were planning for bone marrow transplantation (BMT) soon after their initial fertility preservation consultation.

For those who had been exposed to prior chemotherapy, the range of time from last treatment was from 32 days to 3 years (median 94 days). Prior chemotherapy regimens included ABVD, R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine and prednisone), BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone), ABV/COP (doxorubicin, bleomycin, vinblastine, cyclophosphamide, vincristine and prednisolone), and ICE (ifosfamide, carboplatin and etoposide) as well as several experimental protocols. There was 26% of patients who had prior chemotherapy regimens that included an alkylating agent, with cumulative alkylator scores ranging from 1 to 3 (Green et al., 2009a). Two patients presented after BMT.

After fertility preservation counselling, 25% of the patients opted for embryo cryopreservation, 7% for oocyte cryopreservation, 3% for ovarian tissue cryopreservation, 6% for some combination of treatments including ovarian stimulation and 9% for leuprolide acetate down-regulation. One patient who had been planning for isolated pelvic radiation opted for oophoropexy and 48% decided against fertility preservation methods after counselling. The median age for opted for fertility preservation management beyond counselling alone was 26 years (range 14–36 years).

Of the 58 patients for whom impending treatment information was available, 22 patients (38%) were anticipating treatment with BMT. Patients planning for BMT were significantly more likely to pursue fertility preservation treatment compared with those who were not anticipating imminent BMT (17/22, 77% versus 11/44, 25%, $P < 0.01$, data unavailable for one patient). Of those who were planning for BMT, 10 patients elected ovarian stimulation to bank embryos, three patients elected ovarian stimulation to bank oocytes, one patient elected to bank both ocytes and embryos and one patient elected to bank oocytes and ovarian tissue. Of note, two patients who attempted ovarian stimulation with the goal of embryo

cryopreservation had cancelled cycles, one of which subsequently had ovarian tissue cryopreservation. There were no differences in any of the ovarian stimulation parameters by diagnosis or planned treatment course.

Fertility preservation choices and outcomes by previous exposure to chemotherapy

Demographic characteristics did not differ between patients who were planning for chemotherapy compared with those who had already been exposed to chemotherapy with respect to age, BMI, race, partner status, gravidity or parity (Table 1). The distribution of cancer diagnoses were similar, and there was no differences in treatment choices overall between the two groups. There was a trend towards more patients in the post-treatment group opting to attempt ovarian stimulation, but this failed reach statistical significance (22% versus 45%).

Of all the women with haematological diseases, 26 patients underwent ovarian stimulation or a combination of ovarian stimulation and ovarian cryopreservation; 62% (16/26) were in the post-chemotherapy group. Most of the patients undergoing ovarian stimulation utilized an antagonist protocol; four patients utilized a protocol with leuprolide acetate down-regulation with even distribution in the pre-chemotherapy and post-chemotherapy groups. Of patients who underwent ovarian stimulation in the post-chemotherapy group, 11 out of 14 (79%) reached oocyte retrieval while all of the patients in the pre-chemotherapy group (n = 10) who attempted stimulation had an oocyte retrieval. All of the cycle cancellations were patients in the post-chemotherapy group, although this rate did not significantly differ between patients presenting before versus after chemotherapy, likely due to small sample size (0% versus 31%). Patients who had cycle cancellation were similar in age compared with those who did not cancel (median age 25.8 versus 25.8 years), but did have lower baseline antral follicle counts (4 versus 13, P = 0.04). Of the five patients with cycle cancellation, three had a diagnosis of leukaemia and two had lymphoma. All underwent stimulation with antagonist protocols. The most common reason for cancellation was poor response (4/5, 80%). One patient was cancelled due to exacerbation of a chronic pulmonary condition on cycle day 2 and cancellation was thus thought to be unrelated to ovarian stimulation. Two of the patients who where cancelled due to poor response repeated ovarian stimulation with variable oocytes yields in the second cycle (2 and 10 oocytes). No patients experienced ovarian hyperstimulation syndrome.

Ovarian reserve and stimulation parameters for cycles in which patients underwent oocyte retrieval are reported in Table 2. Patients who presented after chemotherapy had significantly lower baseline antral follicle counts compared with those presenting prior to chemotherapy (median 10 versus 22, P = 0.01). There was no difference in baseline FSH concentrations between these two groups (median 4.3 versus 6.0 mIU/ml), but several patients were on oral contraceptive pills when the assay was performed. When restricting the analysis to just those patients who were not on ovarian suppression, similar results were seen (median 7.2 versus 7.6 mIU/ml); however, interpretation of ovarian reserve measures in this cohort is limited given the small number of patients in this restricted analysis (n = 8). Linear and Poisson regression modelling with bootstrapping adjusted for age demonstrated that total days of stimulation, number of follicles greater than 14 mm and peak oestradiol

concentrations did not significantly differ between the two groups. Patients who had been exposed to prior chemotherapy required significantly more total gonadotrophins (relative risk 2.26, 95% CI 1.52–3.38, $P < 0.01$) to achieve similar oestradiol concentrations with no difference in oocyte yield between groups (geometric means 9.7 versus 11.3). The post-chemotherapy group had a wider range of oocyte yield (2–24 oocytes) and had lower median embryo yield, although this failed to reach statistical significance in age-adjusted regression modelling. For patients who were post-chemotherapy, time from last treatment was not significantly associated with any ovarian stimulation parameters.

Discussion

This is one of the first studies to examine both fertility preservation choices and stimulation parameters in a multicentre cohort of patients with haematological diseases requiring gonadotoxic therapies. Of patients presenting for fertility preservation consultation, 42% opted for treatments involving assisted reproduction technology (oocyte, embryo or ovarian tissue banking), possibly related to the limitations of their disease status at the time of consultation. This is higher than the use reported in a recent large prospective cohort study, which reported that 23% of lymphoma patients opted for these fertility preservation treatments in a population of women referred to one of 70 European centres for fertility preservation treatment prior to cancer treatment (Lawrenz et al., 2011). Importantly, the use of ovarian suppression with GnRH agonists was much higher in the European cohort (75%) compared with that seen in the current study (9%). Also, in this current study, more patients opted for counselling only (48% versus 16% in the European cohort). These findings may be attributable to differences in prior chemotherapy exposure and current disease status between the two cohorts as well as variations on treatment approach in these regions.

It is also important to highlight the fact that almost half of the patients with haematological diseases who presented for fertility preservation consultation in this study had already been exposed to potentially gonadotoxic therapies. This phenomenon may be explained by the fact that many referrals for patients with haematological diseases occur after relapse when BMT has been recommended. This trend in referral patterns may be due to the narrow window between initial diagnosis and treatment in patients with leukaemia, often on the order of hours to days for patients who may be in acute haematological crises. In addition, while patients with lymphoma have more time available between diagnosis and treatment compared with patients who present in acute crises, there is often less motivation to pursue fertility preservation methods since many initial therapies may not pose a major risk to fertility (Hodgson et al., 2007).

The results of this study indicate that, overall, ovarian reserve is diminished in patients who present after chemotherapy exposure compared with those who present before treatment and that patients previously exposed to chemotherapy will have a higher gonadotrophin requirement but may have similar oocyte yield. The disparate findings between antral follicle count and baseline FSH are likely due to attenuation of baseline FSH concentrations by oral contraceptive use in some patients, and incomplete data regarding baseline FSH concentrations without the influence of ovarian suppression. Serum anti-Müllerian hormone concentrations may be helpful in assessing ovarian reserve in this patient population in order

to determine the optimal stimulation protocol, but these data are not available for the current study. The oocyte yield was quite variable in this group (range 2–24 oocytes), suggesting that stimulation of previously exposed patients can be unpredictable. Our findings suggest that use of higher gonadotrophin doses may be prudent.

A recent meta-analysis suggested that women with malignancy and no previous exposure to chemotherapy should expect a lower number of oocytes retrieved after ovarian stimulation for fertility preservation compared with healthy age-matched patients, but acknowledged that this finding did not account for differences by subsets of malignant diagnoses (Friedler et al., 2012). While the present study did not include a healthy age-matched control group, its findings are consistent with another study evaluating ovarian stimulation parameters before and after chemotherapy exposure, which similarly found that patients with haematological disorders required higher total gonadotrophin doses post-chemotherapy (Dolmans et al., 2005). However, in contrast to the present findings, another study demonstrated lower numbers of oocytes retrieved and embryos cryopreserved overall, but was a heterogeneous population of which haematological malignancies was a small subset (Klock et al., 2010). The differences seen in the current study may be reflective of the relatively younger age of patients in the haematological disease cohort.

While the optimal timing of ovarian stimulation after chemotherapy exposure is unknown and subject to much controversy, the use of fertility preservation treatment in the window after chemotherapy, before haematopoietic stem cell transplantation has been described (Rossi et al., 2011). The current study suggests that ovarian stimulation after chemotherapy may produce acceptable oocyte yields. While data from childhood cancer survivors remote from therapy indicates that pregnancy outcomes are no different compared with healthy controls (Green et al., 2009b), animal studies suggest that miscarriage and rates of birth defects are higher in mice that conceive during chemotherapy exposure (Meirow et al., 2001). Thus, there is clearly a need to follow pregnancy outcomes from gametes and embryos obtained after recent exposure to chemotherapy. Patients should be counselled about the potential risks of ovarian stimulation for oocyte or embryo banking soon after chemotherapy and that outcomes are not known in this population. While ovarian tissue cryopreservation is an alternative option for patients with haematological disorders after exposure to chemotherapy, transplantation is not recommended in patients with leukaemia due to risk of reseeding cancer cells. The development and improvement of in-vitro maturation treatment may allow for ovarian tissue cryopreservation to be a realistic option for having biologic children in the future for these patients.

This study is limited by its relatively small sample size and the heterogeneity of the population both in terms of haematological diagnoses and their treatments. Therefore, it was not able to compare stimulation differences between patients exposed to specific chemotherapeutic regimens. Given that this was retrospective data, it is subject to information bias, as all data were chart abstracted. There may be a degree of selection bias with respect to which patients were referred for consultation and treatment: the current study included all patients who were referred for fertility preservation consultation through infertility practices and it is difficult to know what proportion of patients this represents amongst the total population of reproductive-age women with haematological disorders.

Prospective assessment of multiple centres would be ideal for studying this patient population. In particular, there is a role for looking at time from diagnosis to consultation and improving access to fertility preservation services. Finally, and perhaps most importantly, further studies are needed to assess pregnancy outcomes following the use of the gametes and embryos with respect to live birth rates, neonatal outcomes and childhood outcomes before recommendations regarding the optimal treatment strategy can be made. This study contributes important new data to the growing body of literature regarding the fertility preservation choices and outcomes of female patients with haematological disorders.

Biography

Dr Senapati completed her medical school training at the Ohio State University and residency training at the University of Pennsylvania. She is currently a fellow in the reproductive endocrinology and infertility at the University of Pennsylvania.

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Table 1

Baseline characteristics by total cohort and chemotherapy exposure.

Characteristic	Total cohort	Pre-chemotherapy (*n* = 36)	Post-chemotherapy (*n* = 31)	*P*-value
Age (years)	25.9 (14–44)	25.5 (14–44)	26 (16–36)	NS
Body mass index ((kg/m^2)	23.4 (17–40)	23.6 (19–40)	22.9 (17–40)	NS
Race (Caucasian)[a]	53 (79.1)	28 (77.8)	25 (80.6)	NS
Presence of partner [b]	38 (56.7)	19 (52.8)	19 (61.3)	NS
Nulligravid[a]	49 (73.1)	25 (69.4)	24 (77.4)	NS
Nulliparous[a]	59 (88.1)	30 (83.3)	29 (93.5)	NS
Haematological disorder				
Lymphoma	33 (49.3)	19 (52.8)	14 (45.2)	NS[c]
Leukaemia	22 (32.8)	8 (22.2)	14 (45.2)	NS[c]
Myelodysplastic syndrome	5 (7.5)	5 (13.9)	0 (0)	NS[c]
Aplastic anaemia	3 (4.5)	2 (5.6)	1 (3.2)	NS[c]
Sickle cell disease	2 (3.0)	1 (2.8)	1 (3.2)	NS[c]
Multiple myeloma	1 (1.5)	1 (2.8)	0 (0)	NS[c]
Erdheim–Chester disease[a]	1 (1.5)	0 (0)	1 (3.2)	NS[c]
Fertility preservation treatment				
Embryo/oocyte cryopreservation	22 (32.8)	10 (27.8)	12 (38.7)	NS[c]
Ovarian tissue cryopreservation	2 (3.0)	2 (5.6)	–	NS[c]
Leuprolide acetate	6 (9.0)	5 (13.9)	1 (3.2)	NS[c]
Oophoropexy	1 (1.5)	–	1 (3.2)	NS[c]
Counselling only	32 (47.8)	19 (52.8)	13 (41.9)	NS[c]
Combination[a]	4 (6.0)	–	4 (12.9)	NS[c]
Planning BMT[a]	22 (32.8)	7 (20.0)	15 (48.4)	0.02

Values are median (range) tested by Wilcoxon rank-sum test or *n* (%) tested by [a]Fisher's Exact test or [b]Chi-squared test (data unavailable for one patient).

[c]Fisher's Exact test for distribution of diagnoses/treatment choice overall, by chemotherapy exposure.

Table 2

Ovarian reserve and stimulation parameters by chemotherapy exposure for patients who had oocyte retrieval.

Parameter	Unadjusted analysis			Age-adjusted analysis	
	Pre-chemotherapy (*n* = 8)	Post-chemotherapy (*n* = 11)	*P*-value[a]	Risk ratio (95% CI)[b]	*P*-value
Baseline antral follicle count	22 (13–41)	10 (4–37)	0.01	0.49 (0.25–0.95)	0.02[c]
Baseline FSH (mIU/ml)	4.3 (2.2–8.0)	6.0 (0.6–11.3)	NS	0.98 (0.39–2.43)	NS[d]
Length of stimulation (days)	8.5 (6–14)	10.5 (7–12)	NS	1.04 (0.75–1.44)	NS[d]
Total gonadotrophins (IU)	1331 (900–2775)	4425 (1763–7200)	<0.01	2.26 (1.52–3.38)	<0.01[d]
Peak serum oestradiol (pg/ml)*	1063 (568–2127)	1902 (500–6985)	NS	1.65 (0.76–3.61)	NS[d]
Number of follicles >14 mm	10 (3–13)	9 (2–22)	NS	1.14 (0.57–2.27)	NS[d]
Oocyte yield	10.5 (4–14)	10 (2–24)	NS	1.17 (0.78–1.74)	NS[c]
Embryo yield	6.5 (2–9)	4.5 (1–12)	NS	0.96 (0.57–1.62)	NS[c]

[a] Wilcoxon rank-sum test.

[b] 95% CI for risk ratios reported from bootstrap estimates.

[c] Poisson regression analysis.

[d] Log-transformed for linear regression analysis.