Biol Blood Marrow Transplant 25 (2019) 1232–1239

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Utilization and Outcomes of Fertility Preservation Techniques in Women Undergoing Allogeneic Hematopoietic Cell Transplant

Alexandra Higgins[1], Zaraq Khan[2], Charles C. Coddington[2], Shahrukh K. Hashmi[3], Mehrdad Hefazi[3], Hassan Alkhateeb[3], Mark R. Litzow[3], William J. Hogan[3], Elizabeth Cathcart-Rake[3], Carrie A. Thompson[3], Mrinal M. Patnaik[3,*]

[1] *Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota*
[2] *Division of Reproductive Endocrinology and Infertility, Mayo Clinic, Rochester, Minnesota*
[3] *Division of Hematology, Mayo Clinic, Rochester, Minnesota*

Article history:
Received 19 October 2018
Accepted 9 February 2019

Keywords:
Hematologic malignancy
Fertility preservation
Allogeneic HCT

A B S T R A C T

Iatrogenic menopause with consequent infertility is a major complication in reproductive-age women undergoing hematopoietic cell transplantation (HCT). Recent guidelines recommend a discussion of the possibility of infertility and the options for fertility preservation as part of informed consent before initiation of any cancer-directed therapy, including HCT. Women age 15 to 49 years at the time of allogeneic HCT, between the years 2001 and 2017, were identified from the Mayo Clinic Rochester institutional HCT database. One hundred seventy-seven women were eligible, of whom 49 (28%) were excluded due to documented postmenopausal state or prior hysterectomy. The median age of the cohort was 31 years (range, 15 to 49 years) with median gravidity and parity being G1P1 (range, G0 to G8, P0 to P6). Fifty-four (42%) women were nulligravid at the time of HCT. Eighty-two percent underwent myeloablative conditioning (MAC), whereas 18% underwent reduced-intensity conditioning (RIC). Only 34 women (27%) had documented fertility counseling within 72 hours of diagnosis, and a total of 61 (48%) received fertility counseling prior to HCT. Thirty-eight women (30%) were referred to a reproductive endocrinologist, of whom 13 (10%) underwent assisted reproductive technologies (ART; nine oocyte cryopreservation, four embryo cryopreservation). Of these, nine procedures yielded successful cryopreserved tissue (two completed at outside institutions). The median time to completion of the seven successful ART procedures at Mayo Clinic was 13 days (range, 9 to 15 days). The remainder of women referred to reproductive endocrinology did not undergo ART due to disease severity (68%), financial barriers (20%), and/or low antral follicle count (12%). Ninety-three women (73%) received leuprolide for ovarian suppression prior to conditioning. Three (4%) of 75 women who underwent MAC and were alive >365 days after HCT had spontaneous menstrual recovery after HCT (median time, 14 months; range, 6 to 21 months), in comparison to 10 (50%) of 20 women who underwent RIC and were alive >365 days after HCT ($P < .01$) (median, 21.5 months; range, 5 to 83 months). In the latter cohort, there were two spontaneous pregnancies, occurring at 71 and 72 months after HCT, respectively. Oncofertility is an emerging field due to an increasing number of young cancer survivors. Herein, we document that even at a large tertiary HCT center, the rate of documented fertility counseling and reproductive endocrinology referrals was low and the rate of ART was even lower. Spontaneous menstrual recovery was rare but more likely in the setting of nonmalignant disease and RIC HCT. A concerted multidisciplinary effort is needed to understand parenthood goals and to explore the impact of HCT on decision making about fertility preservation and parenthood. These efforts could improve oncofertility referral, ART utilization, and reproductive outcomes.

INTRODUCTION

More than 10% of new cancer diagnoses occur in reproductive-age women, impacting 87 per 100,000 women each year [1]. Improvement in the management and treatment of these patients is leading to improved survival [2] and greater interest in survivorship outcomes. There is a growing movement to preserve the fullness of cancer patients' future. Satisfactory quality of life in cancer survivors may include the ability to conceive children, and the infertility associated with cancer treatment can contribute to profound distress and depression in survivors [3]. Patients with hematologic malignancies are in a uniquely difficult position in regard to fertility preservation due to the often urgent or emergent need for cytotoxic

Financial disclosure: See Acknowledgments on page 1238.

* Correspondence and reprint requests: Mrinal Patnaik, MBBS, Division of Hematology, Mayo Clinic, 200 First Street SW, Rochester, MN 55902.
E-mail address: Patnaik.Mrinal@mayo.edu (M.M. Patnaik).

https://doi.org/10.1016/j.bbmt.2019.02.013
1083-8791/

chemotherapy, which can be complicated by cytopenias, infections, cardiopulmonary dysfunction, or other clinical instability, with relapse being relatively common and hematopoietic cell transplant (HCT) becoming a more frequently utilized treatment modality [3]. Acute lymphoblastic leukemia (ALL) is a disease primarily of patients under 50 years of age, and about 20% of new acute myelogenous leukemia (AML) cases occur in patients under 50 years of age [3]. Induction chemotherapy for leukemia causes permanent amenorrhea in about 20% of patients, whereas HCT has a documented rate of permanent amenorrhea in >80% of patients [4]. HCT is a life-saving treatment not only in hematologic malignancies including leukemia and lymphoma but also bone marrow failure syndromes, immune deficiency disorders, and some solid organ cancers. In 2009, there were an estimated 108,900 HCT survivors, and that number is estimated to be more than 500,000 by 2030 [5]. Importantly, 45% of allogeneic HCT recipients and 25% of autologous HCT recipients are under 40 years of age [3].

Numerous studies have documented that fertility preservation is one of the most cited unmet needs of cancer survivors [6-8]. To improve quality of life in survivors, the American Society of Clinical Oncology released its first fertility preservation guideline in 2006 recommending discussion of therapy-induced infertility and options for fertility preservation at the earliest opportunity after a new cancer diagnosis [4]. Guidelines in 2013 stressed the importance of documenting the details of this discussion in the medical record [9] with affirmation of these recommendations in a 2018 guideline update [10]. Despite these recommendations, there is increasing evidence in the literature that this counseling is not occurring [11-14]. A recent cross-sectional study found that only 20% of women who had become infertile secondary to cancer treatment had previously attempted fertility preservation, despite more than 90% of the women reporting a desire for pregnancy [15]. A study of four cancer centers found that only 26% of patient records documented discussion of infertility risk, 24% documented discussion of fertility preservation options, and 13% referred to a fertility specialist [12]. *Oncofertility*, a term coined by Dr. Theresa K. Woodruff, is a field of medicine developed to bridge the gap between oncology and reproductive medicine by encouraging increased fertility preservation counseling of young adults with cancer and bolstering research efforts to discover new fertility preservation techniques for young patients with cancer [16]. The objectives of this study were to describe the disease and reproductive variables in a cohort of reproductive-age women undergoing allogeneic HCT, assess the rate of fertility counseling provided, and document the utilization and outcomes of fertility preservation techniques in this medically complex patient population.

METHODS

After obtaining institutional review board approval (#17-001716, approved 7 March 7, 2017, Mayo Clinic Rochester), this retrospective cohort study identified all women 15 to 49 years of age (as per the World Health Organization definition of reproductive age [17]) at the time of allogeneic HCT, between the years 2001 and 2017, using the Mayo Clinic Rochester institutional HCT database. Exclusion criteria included previous hysterectomy or documented postmenopausal state defined as amenorrhea for more than 12 months in women over 40 years old in the absence of other biologic or physiologic causes prior to HCT. Medical records were abstracted to obtain demographic data, treatment details, reproductive variables, and fertility counseling and outcomes. The abstracted disease-specific data included hematologic diagnosis, age at diagnosis, chemotherapy regimens, disease status at HCT, donor type, graft source, age at HCT, HCT conditioning regimen, acute and chronic graft-versus-host disease (GVHD), current disease status, and cause of death. The abstracted reproductive variables included gravidity; parity; menstrual status; documented fertility counseling at diagnosis and at HCT evaluation; desire for future pregnancy; reproductive endocrinology consultation; use of gonadotropin-releasing hormone (GnRH) receptor agonists; assisted reproductive technologies (ART); ovarian reserve markers that included follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH), and antral follicle counts; menstrual recovery; and post-HCT pregnancy. Data were analyzed using descriptive statistics, and the chi-square test was used to compare frequencies using JMP Pro 13.0.0 software (SAS Institute Inc, Cary, NC).

HCT Conditioning Regimens

Several conditioning regimens were used for allogeneic HCT. Myeloablative conditioning (MAC) regimens included cyclophosphamide (CY) 60 mg/kg/day (days -5 and -4) plus 1320 cGy total body irradiation (TBI) over 3 days, busulfan (BU) 0.8 mg/kg (four doses on days -7, -6, -5, and -4) plus CY 60 mg/kg/day (two doses on days -3 and -2) [18], and etoposide 60 mg/kg on day -3 plus 1320 cGy TBI over 3 days as in E2993 conditioning. Reduced-intensity regimens included fludarabine (FLU) 25 mg/m^2 (five doses on days -6, -5, -4, -3, and -2) plus melphalan 70 mg/m^2 (two doses on days -3 and -2) [19], CY 60 mg/kg/day (days -5 and -4) plus 200 to 400 cGy TBI, CY 50 mg/kg/day (days -5, -4, -3, and -2) plus lymphocyte immune globulin, equine (ATGAM) 30 mg/kg/day (days -4, -3, and -2) [20], FLU 30 mg/m^2/day (days -7, -6, -5, -4, -3, and -2) plus BU 0.8 mg/kg/dose (days -4, -3, and -2) [21,22], FLU 30 mg/m^2 (three doses on days -4, -3, and -2) plus TBI 200 to 400 cGy in one or two fractions [23], and CY 60 mg/kg/day (days -7 and -6) plus FLU 25 mg/m^2/day (days -5, -4, -3, -2, and -1) [24].

Definition of Fertility Counseling and Internal Guidelines for Counseling

Fertility preservation counseling should include discussion of both the risk of therapy-induced infertility and options for fertility preservation [9] including ovarian suppression, oocyte cryopreservation, embryo cryopreservation, and experimental options such as ovarian tissue cryopreservation. To be considered for this study, we mandated that both components be documented in the medical record. Documentation of only discussion of therapy-induced infertility risk was not considered fertility preservation counseling. A referral to a reproductive specialist to discuss fertility preservation options in detail did fulfill the second component of counseling. Regarding our institution's internal fertility preservation guidelines, fertility counseling is strongly encouraged within the bone marrow transplant division, as well as the reproductive endocrinology and infertility (REI) department, for all patients of reproductive age undergoing potentially gonadotoxic therapies. Currently, HCT physicians are responsible for initiating this conversation, and there are nurse specialists from REI available during business hours. Additionally, there is a REI fellow available 24/7 for emergency fertility counseling needs. At the time of this study, there is not an internal process for automatically referring patients of reproductive age to REI.

Ovarian Suppression and ART

Four types of fertility preservation techniques were evaluated in this study, including ovarian suppression strategies with GnRH agonists [25,26], oocyte or embryo cryopreservation [8,27], and ovarian tissue cryopreservation [28-35]. The most frequently used GnRH agonist at the study facility is leuprolide acetate, either 3.75 mg i.m. monthly or 11.25 mg i.m. every 3 months. For patients electing to undergo controlled ovarian stimulation for embryo or oocyte cryopreservation, stimulation parameters including protocol used, total gonadotropins used during stimulation, duration of stimulation, peak serum estradiol, oocyte yield, embryo yield, and cycle cancellation rates and reasons were collected.

RESULTS

Patient Characteristics

One hundred and seventy-seven women age 15 to 49 years at the time of allogeneic HCT were identified, between the years 2001 and 2017. Of these 177 women, 49 were excluded due to documented postmenopausal state or hysterectomy prior to HCT, leaving 128 women in the study cohort. The baseline demographics of these patients are included in Table 1, which stratifies the group by MAC versus reduced-intensity conditioning (RIC) regimens. There were 105 (82%) women, median age 32 years, who received MAC and 23 (18%) women, median age 29 years, who received RIC. These regimens are described in Table 2, and protocols are included in the Methods section. The majority of patients in the MAC group (103 of 105) received CY plus 1320 cGy TBI or BU plus CY. Regimens used in the RIC group were more heterogeneous. Reasons for HCT in the cohort included AML 49%, ALL 23%, myelodysplastic syndrome (MDS)/myeloproliferative neoplasm (MPN) 15%,

Table 1
Baseline and Transplant Characteristics Stratified by MAC or RIC

	Total (N = 128)	MAC (n = 105)	RIC (n = 23)	*P* Value
Median age, yr (range)	31 (15-49)	32 (15-49)	29 (18-48)	.05
Diagnosis				
AML	63 (49)	56 (53)	7 (30)	.05
ALL	30 (23)	28 (27)	2 (9)	.07
MDS/MPN	19 (15)	17 (16)	2 (9)	.36
Benign disorders*	14 (11)	3 (3)	11 (48)	<.01
Lymphoma	2 (2)	1 (1)	1 (4)	.23
Prior chemotherapy				
Anthracycline	96 (75)	86 (82)	10 (44)	<.01
Alkylating agents	36 (28)	31 (30)	5 (22)	.45
Hypomethylating agents	4 (3)	4 (4)	0 (0)	.34
Disease status at HCT†				
CR	73 (74)	66 (74)	7 (70)	.78
PR	4 (4)	4 (5)	0 (0.0)	.49
PIF	10 (10)	8 (9)	2 (20)	.27
Relapse	12 (12)	11 (12)	1 (10)	.83
Donor type				
MRD	59 (46)	48 (46)	11 (47.5)	.93
MUD	61 (48)	50 (47)	11 (47.5)	
Double cord blood	8 (6)	7 (7)	1 (4.5)	.68
Graft source‡				
Bone marrow	36 (30)	23 (23)	13 (59)	<.01
Peripheral blood	84 (70)	75 (77)	9 (41)	
Obstetrical status at HCT				
Nulligravida	54 (42)	44 (43)	10 (43.5)	.66
G1-2	49 (38)	39 (37)	10 (43.5)	
G >3	25 (20)	22 (20)	3 (13)	

All data are reported as n (%).
CR indicates complete remission; PR = partial remission; PIF = primary induction failure; MRD = matched related donor; MUD = matched unrelated donor.
* Benign disorders include aplastic anemia (10 of 14), bone marrow failure syndromes, sickle cell anemia, and erythropoietic protoporphyria.
† Includes patients treated with chemotherapy with goal of remission (n = 99).
‡ Excludes double cord blood donor type (n = 120).

nonmalignant hematologic disorders 11%, and lymphoma 2%. Nonmalignant hematologic disorders included aplastic anemia (8 of 14), paroxysmal nocturnal hemoglobinuria with aplastic anemia (2 of 14), other bone marrow failure syndromes (2 of 14), sickle cell anemia (1 of 14), and erythropoietic protoporphyria (1 of 14). Significantly more women with AML underwent MAC (88%), and more women with benign hematologic disorders received RIC (79%, $P < .01$). Anthracycline exposure (75%) was common prior to HCT, with a higher frequency in patients receiving MAC versus RIC ($P < .01$). Donor types included matched related donor (46%), matched unrelated donor (48%), or double cord blood (6%). Graft sources were bone marrow (30%) or peripheral blood stem cells (70%). In the MAC group, peripheral blood stem cell grafts were primarily used, whereas bone marrow graft was more common in the RIC group (largely secondary to the high number of benign hematologic conditions transplanted in the RIC cohort). One hundred three patients (80.5%) were complete HLA matches, 12 (9.4%) were mismatched at 1, and 13 (10.2%) were mismatched at 2 or more alleles. Fifty-four of 128 women (42%) were nulligravid at the time of HCT, whereas 23 (18%) were gravida 1 and 26 (20%) were gravida 2 at the time of HCT. Seven women (6%) were pregnant at the time of diagnosis: 4 with AML, 2 with ALL, and 1 with MDS (RAEB-1). Of these, four pregnancies were carried for more than 32 weeks, two were electively terminated in patients with AML or ALL (at 7 weeks and 14 weeks, respectively), and there was one intrauterine demise at 15 weeks in a patient with AML.

Table 2
Conditioning Regimen

Myeloablative (n = 105)		Reduced Intensity (n = 23)	
CY + TBI	69 (66)	FLU + MEL	7 (30)
BU + CY	34 (32)	CY + TBI (200-400 cGY)	6 (26)
BEAM	1 (1)	CY + ATG	5 (22)
VP16 + TBI	1 (1)	FLU + BU	2 (9)
		FLU + TBI	2 (9)
		CY + FLU	1 (4)

All data are reported as n (%).
MEL indicates melphalan; BEAM = BCNU, etoposide, Ara–C, and melphalan; ATG = antithymocyte globulin; VP16 = etoposide.

Fertility Preservation Counseling

Only 34 (27%) of the 128 women had documented fertility preservation counseling within 72 hours of diagnosis (Table 3). As a large tertiary referral center, 33 (25%) of the women in the study were referred from outside institutions after induction chemotherapy was initiated, and it was unclear whether they received fertility preservation counseling at the time of diagnosis. At the time of HCT consultation, 61 of 128 women (48%) received documented fertility preservation counseling (this counseling was irrespective of counseling at the time of

Table 3
Fertility Preservation Counseling, Intervention, and Fertility Outcomes Stratified by Conditioning Type

	Total (N = 128)	MAC (n = 105)	RIC (n = 23)	*P* Value
Diagnosis				
AML	63 (49)	56 (53)	7 (30)	.05
ALL	30 (23)	28 (27)	2 (9)	.07
MDS/MPN	19 (15)	17 (16)	2 (9)	.36
Benign disorders	14 (11)	3 (3)	11 (48)	<.01
Lymphoma	2 (2)	1 (1)	1 (4)	.23
Fertility counseling at diagnosis	34 (27)	27 (26)	7 (30)	.64
Fertility counseling at HCT consultation	61 (48)	49 (47)	12 (52)	.63
Reproductive endocrinology consult	48 (38)	37 (35)	11 (48)	.26
Fertility preservation intervention				
Leuprolide prior to induction	35 (34) [n = 102]	29 (32) [n = 90]	6 (50) [n = 12]	.22
Leuprolide prior to conditioning	93 (73)	74 (71)	19 (83)	.24
ART*	13 (10)	10 (10)	3 (13)	.61
Menstrual recovery†	13 (14) [n = 95]	3 (4) [n = 75]	10 (50) [n = 20]	<.01
Pregnancies after HCT†	2 (2) [n = 95]	0 (0) [n = 75]	2 (10) [n = 20]	<.01
Died at last follow-up				
0-100 days post-HCT	16 (12.5)	15 (14)	1 (4)	.19
101-365 days post-HCT	17 (13)	15 (14)	2 (9)	.47
>365 days post-HCT	14 (11)	12 (11)	1 (4)	.70

All values are reported as n (%).
* Oocyte or embryo cryopreservation.
† Calculated in the subset of patients alive at 1 year post-HCT follow-up (n = 95).

diagnosis). The fraction of women receiving counseling at HCT consultation increased to 62% when patients 40 to 49 years of age were excluded (Supplementary Table 1). Notably, the frequency of fertility preservation at HCT consultation increased over time, as demonstrated by Figures 1 and 2. From 2001 to 2006, only 20% of women received counseling compared to 71% from 2013 to 2017.

There were 53 patient records of 128 that specifically documented a desire for future pregnancy, and of these 53, there were 41 women (77%) referred to the REI center. Within the entire cohort, only 48 women (38%) were referred to REI prior to HCT. The fraction of women referred to REI prior to HCT increased to 51% if women 40 to 49 years of age were excluded from the analysis. Very few women had reproductive hormones such as FSH, estradiol, and AMH checked prior to HCT, and for most, there was no documentation of the phase of menstrual cycle during which the hormones were checked, which limited the interpretation of FSH and estradiol levels. Only 11 patients (8.6%) had an AMH level checked prior to HCT, which has been documented in the literature as a more

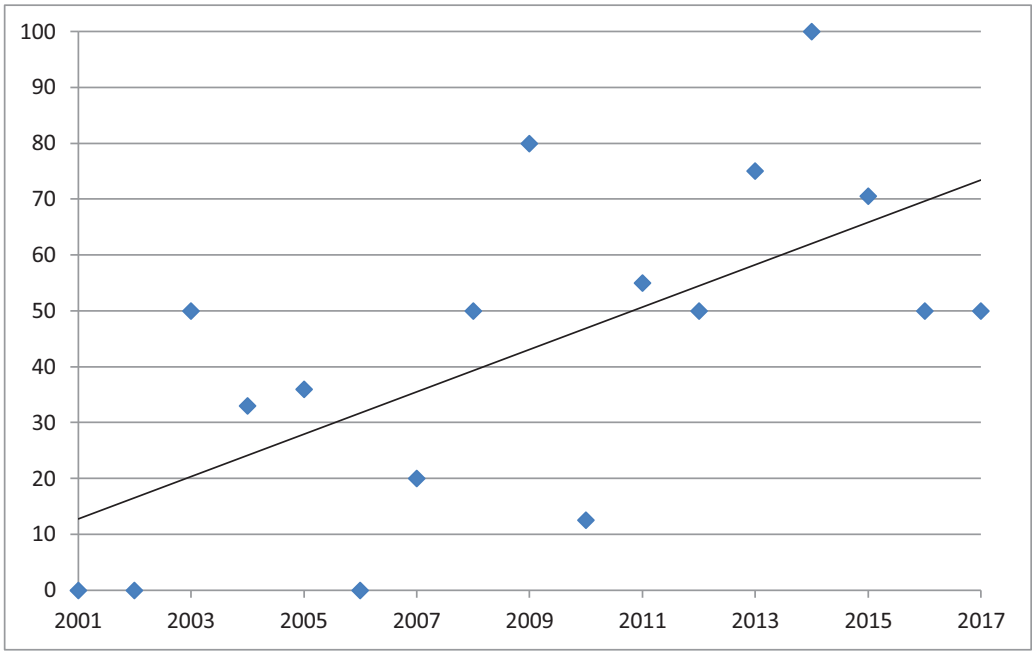

Figure 1. Frequency (%) of women receiving fertility preservation counseling at transplant consultation over time.

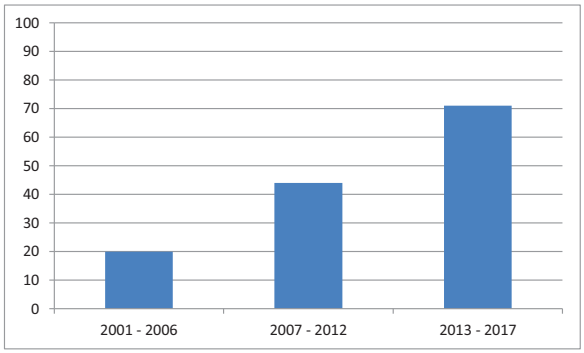

Figure 2. Frequency (%) of women receiving fertility preservation counseling at transplant consultation during three discrete time frames.

reliable indicator of ovarian reserve [36]. The median AMH level prior to HCT was 2.5 ng/mL (range, <0.3 to 6.2 ng/mL,) with 3 patients receiving prior alkylator therapy (AMH levels of 1.5, 5.7, and 6.2 ng/mL).

Assisted Reproductive Technologies

Ten of 48 women referred to REI did not follow through with the consultation for unknown reasons. Of the 38 REI consultations, only 13 women (10% of the cohort) pursued ART with underlying diseases of MDS/MPN (5 of 13), benign hematologic disorders (4 of 13), AML (3 of 13), and ALL (1 of 13). The reasons for not pursing ART after REI consultation among the remaining 25 women were variable but included disease severity (68%) with perceived urgency of therapy or concern for complications from ART due to disease-related cytopenias, financial barriers (20%) secondary to lack of insurance coverage of ART, and low antral follicle count during initial work-up (12%). Of the 13 attempted ART procedures, 9 were oocyte cryopreservation and 4 embryo cryopreservation. Oocyte cryopreservation was chosen when the woman did not have a stable partner and chose not to use a sperm donor. The median age of patients undergoing ART was 22 years (range, 15 to 42 years), and the median time to successful completion of ART was 13 days (range, 9 to 15 days). Overall, 9 of the 13 ART procedures (69%) were successful in yielding cryopreserved tissue, including 3 embryo cryopreservation and 6 oocyte cryopreservation cycles. Of note, 2 of the embryo cryopreservation procedures were performed at outside institution, and thus the parameters of only the remaining 7 successful procedures were available. The successful embryo cryopreservation performed at our institution led to 2 cryopreserved embryos at the pronuclear stage. The median number of cryopreserved oocytes was 10 (range, 5 to 21 oocytes). Among the 4 failed procedures, 3 were in women with AML. Three women did not respond to ovarian stimulation, and 1 woman did not have follicles available for retrieval despite responding to ovarian stimulation. At the last follow-up, no attempts have been made to utilize the cryopreserved oocytes or embryos per documentation in the medical record. Median follow-up of 9 women with cryopreserved tissue is 816 days (range, 147 to 2940 days).

The administration of a GnRH agonist (leuprolide acetate) for ovarian suppression was evaluated. Ninety-three women (73%) received leuprolide acetate (depot formulation 11.25 mg i.m. every 3 months) prior to conditioning, although not all of these women received fertility preservation counseling. The indication for a GnRH agonist was often documented as suppression of heavy menses during periods of thrombocytopenia rather than for protection of fertility. There was not a significant correlation between administration of a GnRH agonist and return of menses (Table 4).

Table 4
Relationship of Leuprolide Prior to Conditioning and Return of Menses

	Menstrual Recovery (n = 13)	No Menstrual Recovery (n = 82)	*P* Value
Leuprolide	12 (92)	65 (79)	.27
No leuprolide	1 (8)	17 (21)	

All values are reported as n (%).

Menstrual Recovery and Fertility

Three (4%) of 75 women who underwent MAC and were alive more than 365 days after HCT had spontaneous menstrual recovery after HCT (median time to recovery, 14 months; range, 6 to 21 months) compared to 10 (50%) of 20 women who underwent RIC and were alive more than 365 days after HCT (median time to recovery, 21.5 months; range, 5 to 83 months; $P < .01$) (Table 3). Ages of women with menstrual recovery ranged from 18 to 45 years (median, 25 years). Eight of the 13 women had benign hematologic conditions. Two patients had been exposed to alkylating agents, and three received myeloablative doses of TBI for conditioning. No women receiving myeloablative doses of BU had return of menses. Twelve of the 13 women with return of menses received leuprolide prior to HCT; however, 81 additional women received leuprolide and have not had menstrual recovery. One woman with return of menses had an AMH checked 6 months after HCT that was 1 ng/mL (range, <0.3 to 6.2 ng/mL). Seven women who did not have return of menses had an AMH level of less than 0.3 ng/mL. There was no significant relationship between occurrence of grade II or greater acute GVHD and menstrual recovery ($P = .67$) and no relationship between chronic GVHD and return of menses ($P = .31$). In this cohort, there were two spontaneous pregnancies (2%) in patients alive more than 365 days after HCT, both occurring after RIC for aplastic anemia (CY + Campath + 400 cGy TBI) and paroxysmal nocturnal hemoglobinuria with aplastic anemia (CY + ATG). Both women received leuprolide prior to the conditioning regimen. The pregnancies occurred at 71 and 72 months after HCT, respectively.

DISCUSSION

This study provides a detailed description of the disease and reproductive variables of reproductive-age women undergoing HCT, an assessment of fertility preservation counseling provided, and an analysis of utilization and outcomes of fertility preservation techniques at a single tertiary transplant center. Nearly half of the women undergoing HCT in this cohort were nulligravid, and 72% of the women had either AML or ALL, with 82% undergoing MAC. Unfortunately, even in a large tertiary transplant center, documented rates of fertility preservation counseling were low (27% at diagnosis, 48% prior to HCT), although it is probable that further counseling had occurred and was not documented [12]. In a subgroup analysis of women age 15 to 39 years, 62% of women received fertility preservation counseling prior to HCT, suggesting a possible provider bias to preferentially counsel younger women. The rate of referral to REI prior to HCT was even lower (38%). Of women age 15 to 39 years, 51% were referred to REI. The reasons for low rates of referral were not specifically evaluated in this retrospective study; however, it was recently reported that the most common barriers to fertility preservation counseling and referral prior to HCT were the perception that

patients were too ill to delay treatment, presumed established infertility from prior chemotherapy exposure, and time constraints [37]. A more detailed look into the trends of the fertility preservation counseling showed that the frequency of counseling increased over time, as seen in Figures 1 and 2. Although this trend is encouraging, we are still falling short of the goal of counseling all reproductive-age women undergoing HCT [10]. Data from women with primary gynecologic tumors have highlighted the importance of counseling for fertility preservation leading to less regret, even if fertility-sparing surgery was not performed [38], suggesting a benefit to counseling even if fertility preservation is not pursued. Furthermore, recent reports have emphasized the critical roles played by oncologists and psychologists in making higher-quality fertility preservation decisions, which lead to better experiences in the decision-making process [39].

This study supports that there is a persistent disconnect between survivors' needs and the counseling and care provided to those patients at the time of disease and treatment. The field of oncofertility [16] attempts to bridge the gap between oncology and reproductive medicine by encouraging increased fertility preservation counseling of young adults with cancer and bolstering research efforts to discover new fertility preservation techniques for young patients with cancer. There are multiple available fertility preservation techniques for women facing the threat of infertility, some techniques well established and others experimental [3,8,25,27,40,41], all of which should be discussed with women who express interest in fertility preservation. Ideally, referral to a reproductive endocrinologist or infertility specialist should be considered part of comprehensive cancer care at diagnosis [25].

Results of three randomized controlled trials studying the role of GnRH agonists during chemotherapy have been mixed [42-44]. A unique benefit to this approach of fertility preservation is preservation of overall gonadal function and thus avoiding other sequelae of decreased ovarian function such as osteoporosis, cardiovascular disease, neurocognitive dysfunction, and sexual dysfunction [26]. GnRH agonists are frequently used because they reduce menstrual bleeding during chemotherapy [25] and conditioning, where resultant thrombocytopenia can lead to menorrhagia, as documented in our study. The use of GnRH agonists in HCT has been studied in a small cohort of patients with lymphoma and leukemia. The study found that administration of a GnRH agonist prior to gonadotoxic conditioning chemotherapy was associated with an increased rate of cyclic ovarian function after HCT in women with lymphoma; however, this association was not seen in women with leukemia [45], consistent with our results that showed no significant correlation between GnRH agonist use and the return of menses.

ART including oocyte and embryo cryopreservation were underutilized in our study, with only 13 procedures performed. This is surprising considering the opportunity available to complete ART after induction chemotherapy and before HCT, as the median time to cryopreserved tissue was only 13 days. Despite the challenges facing this cohort of patients, nearly 70% of the cryopreservation procedures were successful in yielding preserved oocytes or embryos. Overall, menstrual recovery was rare but significantly more likely in patients who underwent RIC ($P < .01$) with age at HCT ranging from 18 to 45 years (median, 25 years). Pregnancy was even more uncommon and only seen post-HCT in two women who underwent RIC for aplastic anemia. Importantly, nearly half of the women who underwent RIC had benign hematologic conditions and were exposed to less chemotherapy prior to HCT, potentially contributing to the observed differences in menstrual recovery and pregnancy.

A particularly challenging patient population includes women who are pregnant at the time of diagnosis. In this cohort, there were seven women (6% of the cohort) pregnant at diagnosis with hematologic malignancy, of whom four delivered between 32 and 36 weeks. Four of these women received ovarian suppression prior to conditioning chemotherapy, and one previously had embryo cryopreservation completed. One woman had menstrual recovery. The patient who underwent previous ART expressed intent to pursue in vitro fertilization with her cryopreserved embryos in the near future. Six of the seven women are still alive and in remission.

Another unique population in this study included 14 women undergoing HCT for benign hematologic conditions including aplastic anemia, bone marrow failure syndromes, and sickle cell anemia. These women comprised 11% of the cohort and 8 of the 13 women with return of menses. All 8 women with return of menses received RIC with CY plus 200 to 400 cGy TBI or CY plus ATG. Three women in this group who did not have return of menses received myeloablative doses of BU in the conditioning regimen. No GVHD was seen in this population, and all received ovarian suppression prior to conditioning.

Although the resultant infertility from HCT is iatrogenic secondary to necessary treatment for life-threatening diseases, ART are rarely subsidized by insurance companies in the United States [46], and thus there are significant financial barriers to pursuing cryopreservation of gonadal tissue for patients. In the United States, insurance benefits for fertility treatments generally come as either a Fortune 500 company or state labor union (i.e., teachers, correctional officers) employee benefits package or through state mandates (15 of 50 U.S. states). The state mandates vary considerably in the coverage of fertility treatments, and oocyte cryopreservation is usually not included in coverage despite U.S. Food and Drug Administration approval and standard of care [46]. Even though states such as Connecticut and Rhode Island (the first states to pass legislation requiring coverage for fertility preservation) have started to lay the foundations, there is still a long way to go [47]. A survey in 2013 found that one third of female cancer survivors recall the cost of fertility preservation to be prohibitive, especially if the household annual income was less than $50,000 [48]. A recent study of women undergoing oocyte cryopreservation found that the average out-of-pocket cost per cycle of in vitro fertilization was $6,966 (range, $1000 to $18,000 per cycle) with heavy reliance on family financial support and community fundraisers to offset this cost [46].

Due to multiple promising developments in fertility preservation in women, there is a strong incentive to counsel all of these women appropriately and maximize the chances of restoring a woman's fertility after gonadotoxic treatments [41]. Techniques currently considered experimental are likely to become the standard of care in the future, and thus awareness of these techniques is necessary. Guidelines currently exist for cancer survivors; however, no such guidelines exist for HCT survivors, and this remains an unmet need in the field of HCT.

We acknowledge that there are several limitations to this study, including the retrospective study design, which relies heavily on accurate and complete documentation within the medical record. Additionally, the study site is a large referral center and thus limits our ability to know the details of fertility counseling that some women received at the time of diagnosis

at outside institutions. The time frame of the study is large, spanning 15 years, over which time there has been evolution of the ART that are available, such as oocyte cryopreservation, which was only offered starting in 2008 and became the standard of care in 2013. Despite these limitations, this study provides granular details regarding the relevant but difficult issue of fertility preservation in women undergoing HCT and provides an opportunity for transplant physicians and allied health staff to reflect on their own knowledge, attitudes, and practices regarding fertility preservation in this challenging patient population.

CONCLUSION

Oncofertility is an emerging field due to an increasing number of young cancer survivors. Herein, we document that even at a large tertiary HCT center, the rate of documented fertility counseling and reproductive endocrinology referrals was low and the utilization of assisted reproductive interventions even lower. Spontaneous menstrual recovery was rare but more likely in the setting of RIC HCT. A concerted multidisciplinary effort is needed to understand decision making in fertility preservation and to improve oncofertility referral and outcomes.

ACKNOWLEDGMENTS

Conflict of interest statement: There are no conflicts of interest to report.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2019.02.013.

REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Statistics Review 1975-2012. 2018. Available at: http://seer.cancer.gov/csr/1975_2012/browse_csr.php. Accessed 8 March 2019.
2. Jemal A, Ward EM, Johnson CJ, et al. Annual Report to the Nation on the Status of Cancer, 1975-2014, Featuring Survival. *J Natl Cancer Inst*. 2017;109.
3. Loren AW. Fertility issues in patients with hematologic malignancies. *Hematology Am Soc Hematol Educ Program*. 2015;2015:138–145.
4. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol*. 2006;24:2917–2931.
5. Majhail NS, Tao L, Bredeson C, et al. Prevalence of hematopoietic cell transplant survivors in the United States. *Biol Blood Marrow Transplant*. 2013;19:1498–1501.
6. Shay LA, Parsons HM, Vernon SW. Survivorship care planning and unmet information and service needs among adolescent and young adult cancer survivors. *J Adolesc Young Adult Oncol*. 2017;6:327–332.
7. Zebrack B. Information and service needs for young adult cancer survivors. *Support Care Cancer*. 2009;17:349–357.
8. Angarita AM, Johnson CA, Fader AN, Christianson MS. Fertility preservation: a key survivorship issue for young women with cancer. *Front Oncol*. 2016;6:102.
9. Loren AW, Mangu PB, Beck LN, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2013;31:2500–2510.
10. Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol*. 2018;36:1994–2001.
11. Quinn GP, Vadaparampil ST, Lee JH, et al. Physician referral for fertility preservation in oncology patients: a national study of practice behaviors. *J Clin Oncol*. 2009;27:5952–5957.
12. Quinn GP, Block RG, Clayman ML, et al. If you did not document it, it did not happen: rates of documentation of discussion of infertility risk in adolescent and young adult oncology patients' medical records. *J Oncol Pract*. 2015;11:137–144.
13. Forman EJ, Anders CK, Behera MA. Pilot survey of oncologists regarding treatment-related infertility and fertility preservation in female cancer patients. *J Reprod Med*. 2009;54:203–207.
14. Niemasik EE, Letourneau J, Dohan D, et al. Patient perceptions of reproductive health counseling at the time of cancer diagnosis: a qualitative study of female California cancer survivors. *J Cancer Surviv*. 2012;6:324–332.
15. Benedict C, Thom B, Friedman D, et al., et al. Young adult female cancer survivors' unmet information needs and reproductive concerns contribute to decisional conflict regarding posttreatment fertility preservation. *Cancer*. 2016;122:2101–2109.
16. Ataman LM, Rodrigues JK, Marinho RM, et al. Creating a global community of practice for oncofertility. *J Glob Oncol*. 2016;2:83–96.
17. World Health Organization. Reproductive Health Indicators: Guidelines for Their Generation, Interpretation and Analysis for Global Monitoring. Geneva, Switzerland: WHO Press; 2006.
18. Andersson BS, Kashyap A, Gian V, et al. Conditioning therapy with intravenous busulfan and cyclophosphamide (IV BuCy2) for hematologic malignancies prior to allogeneic stem cell transplantation: a phase II study. *Biol Blood Marrow Transplant*. 2002;8:145–154.
19. Giralt S, Thall PF, Khouri I, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. *Blood*. 2001;97:631–637.
20. Storb R, Weiden PL, Sullivan KM, et al. Second marrow transplants in patients with aplastic anemia rejecting the first graft: use of a conditioning regimen including cyclophosphamide and antithymocyte globulin. *Blood*. 1987;70:116–121.
21. Kroger N, Zabelina T, Schieder H, et al. Pilot study of reduced-intensity conditioning followed by allogeneic stem cell transplantation from related and unrelated donors in patients with myelofibrosis. *Br J Haematol*. 2005;128:690–697.
22. Kroger N, Holler E, Kobbe G, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Blood*. 2009;114:5264–5270.
23. Sorror ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. *JAMA*. 2011;306:1874–1883.
24. Srinivasan R, Takahashi Y, McCoy JP, et al. Overcoming graft rejection in heavily transfused and allo-immunised patients with bone marrow failure syndromes using fludarabine-based haematopoietic cell transplantation. *Br J Haematol*. 2006;133:305–314.
25. Joshi S, Savani BN, Chow EJ, et al. Clinical guide to fertility preservation in hematopoietic cell transplant recipients. *Bone Marrow Transplant*. 2014;49:477–484.
26. Hickman LC, Valentine LN, Falcone T. Preservation of gonadal function in women undergoing chemotherapy: a review of the potential role for gonadotropin-releasing hormone agonists. *Am J Obstet Gynecol*. 2016;215:415–422.
27. Jensen JR, Morbeck DE, Coddington III CC. Fertility preservation. *Mayo Clin Proc*. 2011;86:45–49.
28. Jensen AK, Kristensen SG, Macklon KT, et al. Outcomes of transplantations of cryopreserved ovarian tissue to 41 women in Denmark. *Hum Reprod*. 2015;30:2838–2845.
29. Shapira M, Raanani H, Barshack I, et al. First delivery in a leukemia survivor after transplantation of cryopreserved ovarian tissue, evaluated for leukemia cells contamination. *Fertil Steril*. 2018;109:48–53.
30. Blumenfeld Z. Ovarian tissue transplantation and leukemia. *Fertil Steril*. 2018;109:69–70.
31. Diaz-Garcia C, Domingo J, Garcia-Velasco JA, et al. Oocyte vitrification versus ovarian cortex transplantation in fertility preservation for adult women undergoing gonadotoxic treatments: a prospective cohort study. *Fertil Steril*. 2018;109. 478-485.e2.
32. Forman EJ. Ovarian tissue cryopreservation: still experimental? *Fertil Steril*. 2018;109:443–444.
33. Greve T, Clasen-Linde E, Andersen MT, et al. Cryopreserved ovarian cortex from patients with leukemia in complete remission contains no apparent viable malignant cells. *Blood*. 2012;120:4311–4316.
34. Zver T, Alvergnas-Vieille M, Garnache-Ottou F, Roux C, Amiot C. A new method for evaluating the risk of transferring leukemic cells with transplanted cryopreserved ovarian tissue. *J Assist Reprod Genet*. 2015;32:1263–1266.
35. Soares M, Saussoy P, Maskens M, et al. Eliminating malignant cells from cryopreserved ovarian tissue is possible in leukaemia patients. *Br J Haematol*. 2017;178:231–239.
36. Lie Fong S, Laven JS, Hakvoort-Cammel FG, et al. Assessment of ovarian reserve in adult childhood cancer survivors using anti-Mullerian hormone. *Hum Reprod*. 2009;24:982–990.
37. Loren AW, Brazauskas R, Chow EJ, et al. Physician perceptions and practice patterns regarding fertility preservation in hematopoietic cell transplant recipients. *Bone Marrow Transplant*. 2013;48:1091–1097.
38. Chan JL, Letourneau J, Salem W, et al. Regret around fertility choices is decreased with pre-treatment counseling in gynecologic cancer patients. *J Cancer Surviv*. 2017;11:58–63.
39. Melo C, Fonseca A, Moura-Ramos M, Almeida-Santos T, Canavarro MC. Female cancer patients' perceptions of the fertility preservation decision-making process: an exploratory prospective study. *J Psychosoc Oncol*. 2018;36:364–381.
40. Jeruss JS, Woodruff TK. Preservation of fertility in patients with cancer. *N Engl J Med*. 2009;360:902–911.

41. De Vos M, Smitz J, Woodruff TK. Fertility preservation in women with cancer. *Lancet*. 2014;384:1302–1310.
42. Demeestere I, Brice P, Peccatori FA, et al. No evidence for the benefit of gonadotropin-releasing hormone agonist in preserving ovarian function and fertility in lymphoma survivors treated with chemotherapy: final long-term report of a prospective randomized trial. *J Clin Oncol*. 2016;34:2568–2574.
43. Moore HC, Unger JM, Phillips KA, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med*. 2015;372:923–932.
44. Del Mastro L, Boni L, Michelotti A, et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. *JAMA*. 2011;306:269–276.
45. Blumenfeld Z, Patel B, Leiba R, Zuckerman T. Gonadotropin-releasing hormone agonist may minimize premature ovarian failure in young women undergoing autologous stem cell transplantation. *Fertil Steril*. 2012;98. 1266-1270.e1.
46. Inhorn MC, Birenbaum-Carmeli D, Westphal LM, et al. Medical egg freezing: how cost and lack of insurance cover impact women and their families. *Reprod Biomed Soc Online*. 2018;5:82–92.
47. Cardozo ER, Huber WJ, Stuckey AR, Alvero RJ. Mandating coverage for fertility preservation—a step in the right direction. *N Engl J Med*. 2017;377:1607–1609.
48. Mersereau JE, Goodman LR, Deal AM, Gorman JR, Whitcomb BW, Su HI. To preserve or not to preserve: how difficult is the decision about fertility preservation? *Cancer*. 2013;119:4044–4050.