Published in final edited form as:
Biol Blood Marrow Transplant. 2011 February ; 17(2): 157–166. doi:10.1016/j.bbmt.2010.07.009.

Pregnancy After Hematopoietic-cell Transplantation: A Report From the Late Effects Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR)

Alison W. Loren, MD, MS[1], **Eric Chow, MD**[2], **David A. Jacobsohn, MD**[3], **Maria Gilleece, MD**[4], **Joerg Halter, MD**[5], **Sarita Joshi, MD**[6], **Zhiwei Wang, MS**[7], **Vikas Gupta, MD**[8], **Gregory A. Hale, MD**[9], **David I. Marks, MD, PhD**[10], **Edward A Stadtmauer, MD**[1], **Jane Apperley, MBChB, MD**[11], **Jean-Yves Cahn, MD**[12], **Harry C. Schouten, MD, PhD**[13], **Hillard M. Lazarus, MD**[14], **Bipin Savani, MD**[15], **Philip L. McCarthy, MD**[16], **Ann A. Jakubowski, MD, PhD**[17], **Naynesh R. Kamani, MD**[18], **Brandon Hayes-Lattin, MD**[19], **Richard T. Maziarz, MD**[19], **Anne B. Warwick, MD**[20], **Mohamed L. Sorror, MD, MSc**[2], **Brian J. Bolwell, MD**[21], **Gerard Socié, MD, PhD**[22], **John R. Wingard, MD**[23], **J Douglas Rizzo, MD, MS**[7], and **Navneet S. Majhail, MD, MS**[24]

[1]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA [3]The Children's Memorial Medical Center, Chicago, IL, USA [4]Leeds Teaching Hospital, Leeds, W. Yorkshire, United Kingdom [5]University Hospital Basel, Basel, Switzerland [6]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA [7]Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI, USA [8]Princess Margaret Hospital, Toronto, ON, Canada [9]All Children's Hospital, St. Petersburg, FL, USA [10]Bristol Children's Hospital, Bristol, United Kingdom [11]Imperial College – Hammersmith Hospital, London, United Kingdom [12]Hospital A Michallon, CHU de Grenoble, Grenoble, France [13]Hospital Maastricht, Maastricht, The Netherlands [14]University Hospitals Case Medical Center, Cleveland, OH [15]Vanderbilt University, Nashville, TN, USA [16]Roswell Park Cancer Institute, Buffalo, NY, USA [17]Memorial Sloan-Kettering Cancer Center, New York, NY, USA [18]Children's National Medical Center, Washington, DC, USA [19]Oregon Health & Science University, Portland, OR, USA [20]Medical College of Wisconsin, Milwaukee, WI, USA [21]Cleveland Clinic Foundation, Cleveland, OH, USA [22]HopitalSaint Louis, Paris, France [23]Shands Hospital at the University of Florida, Gainesville, FL, USA [24]University of Minnesota Medical Center, Minneapolis, MN, USA

Abstract

Preservation of fertility after hematopoietic-cell transplantation (HCT) can have a significant influence on the quality of life of transplant survivors. We describe 178 pregnancies in HCT recipients that were reported to the CIBMTR between 2002 and 2007. There were 83 pregnancies in female HCT recipients and 95 pregnancies in female partners of male HCT recipients. Indications for transplantation included hematologic and other malignancies (N=99) and non-

Address for correspondence: Navneet Majhail, MD, MS, Assistant Professor, Division of Hematology, Oncology and Transplantation, University of Minnesota, 420 Delaware St SE, MMC 480, Minneapolis, MN 55455, Phone: 612 624 6982, Fax: 612 625 6919, majha001@umn.edu.

malignant disorders (N=79, of which 75 patients had severe aplastic anemia). The cohort included recipients of autologous HCT (20 women, 13 men), myeloablative allogeneic HCT (12 women, 50 men) and non-myeloablative allogeneic HCT (2 women, 2 men). Age at HCT was <20 years for 50% of women and 19% of men. Conditioning regimens included total body irradiation (TBI) in 16% of women and 19% of men; doses were myeloablative in 10% of women and in 16% of men. Live births were reported in 86% of pregnancies in partners of male transplant patients and 85% of pregnancies in female transplant patients, with most pregnancies occurring 5-10 years after HCT. We conclude that some HCT recipients can retain fertility, including patients who have received TBI and/or myeloablative conditioning. Young patients undergoing HCT should be counseled both before and after HCT about potential loss of fertility, methods for preserving fertility and planning for future pregnancy. Fertility and outcomes of pregnancy after HCT need prospective evaluation in large transplant cohorts.

Keywords

Allogeneic hematopoietic-cell transplantation; Autologous hematopoietic-cell transplantation; Pregnancy; Fertility Preservation

INTRODUCTION

Long-term survivors of HCT are increasing in number due to improved transplant outcomes and better supportive care. In addition, the expanding indications for transplantation have led to an increase in the number of patients receiving HCT. Hence quality of life after HCT is of greater concern. Among young patients, fertility preservation after transplantation can have a significant influence on quality of life.(1,2) Infertility is a frequently reported “loss” experienced by HCT recipients, especially by women.(3) HCT recipients may already be at high risk for gonadal damage and infertility from previous exposure to chemotherapy and irradiation during pre-transplant therapies. These risks are further increased by most transplant conditioning regimens.(4-9)

Successful pregnancies have been reported in female HCT recipients and in female partners of male HCT recipients.(4,10-15) The two largest studies are from the European Group for Blood and Marrow Transplantation (EBMT) and the Bone Marrow Transplant Survivor Study (BMTSS). Salooja et al addressed this issue in the EBMT by sending questionnaires to 199 centers relating to nearly 38,000 transplants (autologous and allogeneic) inquiring about pregnancy rates in their post-transplant patients.(12) They included data on patients who had conceived via assisted reproductive technologies (ART) as well as those who conceived naturally. They reported 312 pregnancies from 232 patients, for an overall conception rate of 0.6%. Overall, the authors found that the frequency of pregnancy complications was much higher in female allograft recipients compared to the normal population, particularly among those receiving total body irradiation (TBI) containing conditioning regimens. These women had higher rates of Caesarean section, preterm delivery and low birth weight infants compared to the normal population. Partners of male HCT recipients had uncomplicated pregnancies. In 2006, the BMTSS reported on pregnancy outcomes of 619 HCT survivors or their partners.(4) Data was collected via a mailed questionnaire to participants in the study and their siblings. There were 54 pregnancies reported from 34 patients (26 male and 8 female), with 46 live births. Compared to their siblings, HCT survivors had a lower prevalence of conception, but if pregnancy did occur, outcome was likely to be favorable. Risk factors for reporting inability to conceive a pregnancy after transplant included female sex of the HCT recipient, age at HCT >30 years, and use of TBI in conditioning.

We report a large case series of pregnancies after autologous and allogeneic HCT that were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). Our study describes associations of conditioning regimen, age, and disease with pregnancy after HCT.

METHODS

Data for this study were obtained from the CIBMTR, which is a voluntary group of more than 500 transplant centers worldwide. Participating centers register basic information on all consecutive HCT's to a Statistical Center at the Medical College of Wisconsin. Detailed demographic and clinical data are collected on a representative sample of registered patients using a weighted randomization scheme. Patients are followed longitudinally, with yearly follow-up. Observational studies conducted by the CIBMTR during the time period of this study were done with a waiver of informed consent and are compliant with HIPAA regulations as determined by the Institutional Review Board and the Privacy Officer of the Medical College of Wisconsin.

From 2002 to 2007, the CIBMTR requested that centers report whether a transplant recipient or the recipient's partner became pregnant during post-HCT followup. Patients could have received a transplant at any time prior to 2007. Our study describes disease and transplant characteristics of the HCT recipients who reported a pregnancy during this time period. Data for these analyses were limited to the representative sample of patients on whom CIBMTR requests detailed report forms and we did not contact centers for providing supplemental data about reported pregnancies. The date of conception was not collected on CIBMTR forms and was imputed as the median time point between two successive followup reports submitted before and after pregnancy. This is a descriptive case series only and no comparative statistical analyses were planned for this study.

RESULTS

Our cohort included 178 patients for whom a pregnancy was reported to the CIBMTR during the study period. These included 83 female HCT recipients and female partners of 95 male HCT recipients (Tables 1 and 2). In this cohort, 99 patients (34 women and 65 men) were transplanted for a malignant disorder and 79 patients (49 women and 30 men) were transplanted for a non-malignant disorder. The group transplanted for malignancy comprised 97 patients with a hematologic malignancy, primarily acute leukemia (N=35, 10 women and 25 men) and chronic myeloid leukemia (N=25, 3 women and 22 men), as well as 2 patients with solid cancers. The group transplanted for non-malignant disorders included 75 patients with severe aplastic anemia (SAA, 45 women and 30 men) and 4 patients with other conditions (thalassemia, histiocytic disorders, and immune deficiency disorder). Among patients transplanted for malignancy, 33 received an autologous (13 women and 20 men), 62 received a myeloablative allogeneic (12 women and 50 men) and 4 received a non-myeloablative allogeneic (2 women and 2 men) transplant.

Thirty-two patients received TBI, 23 of whom were at myeloablative doses (>800 cGy). Although details regarding dose and duration of radiation treatment prior to HCT were not available, no patient had received craniospinal irradiation. Twelve patients (6 women and 6 men) reported a pregnancy after multiple transplants, including two patients who had received three transplants (one female patient received two autologous HCT followed by a HLA-matched sibling donor HCT for multiple myeloma and a male patient received three HLA-matched sibling donor HCT for CML). For the 6 men whose partners reported pregnancy after multiple transplants, 1 had used cryopreserved sperm to facilitate

conception; information on whether cryopreserved sperm was used was missing for the other 5 patients.

Table 3 describes characteristics of recipients for whom a pregnancy was reported to the CIBMTR. Age at the time of pregnancy ranged from 15-40 years in women and 18-55 years among men whose partners became pregnant. Pregnancies were reported to occur as early as within the first year post-HCT. Fifteen men reported use of cryopreserved sperm, but these data were missing in another 26 of 95 men who fathered a child post-HCT. Information regarding use of cryopreserved embryos or donor oocytes in female transplant recipients was not collected on the CIBMTR follow up forms. Centers reported on whether a pregnancy resulted in a 'live birth' for 169 patients; 67/79 (85%) of pregnancies in female HCT recipients and 78/91 (86%) of pregnancies in female partners of male HCT recipients resulted in live births. We do not have data on the cause or timing of unsuccessful pregnancies or on pre-, peri- or post-natal maternal or fetal complications.

The distribution of age at transplantation of the cohort with dose of TBI, dose of cyclophosphamide in the conditioning regimen, and diagnosis is shown in Table 4. Forty-two women (50%) and 18 men (19%) had received their transplant before the age of 20 years. Overall, although the majority of pregnancies were reported among women and partners of men who had not received TBI as part of conditioning, some pregnancies did occur, even among patients who had received myeloablative doses of TBI and/or cyclophosphamide.

The median time to pregnancy after autologous HCT was 6 years in women and 7 years in partners of men (Table 3). In both women and partners of men receiving myeloablative HCT for malignancy the median time to pregnancy was 7 years after HCT. The median time to pregnancy among non-myeloablative HCT recipients for malignant disorders was 1 year post-HCT for women and 3.5 years for partners of men. The median time to pregnancy among partners of female recipients and male recipients of HCT for non-malignant diseases was 7 and 9 years, respectively. These time periods are consistent with the observation that spermatogenesis recovers in 20-25% of HCT patients after prolonged follow up, even after TBI based regimens,(16,17) and thus longer follow up is important when attempting to fully capture fertility and pregnancy.

Among 34 women who received HCT for a malignant disorder, 3 relapsed between HCT and pregnancy (1 autologous, 1 myeloablative allogeneic and 1 non-myeloablative allogeneic HCT); one was in remission and 2 had persistent disease at the time of pregnancy (Hodgkin's lymphoma and multiple myeloma). No relapse occurred during or after pregnancy in these women. Eight patients (7 men, 1 woman) died following pregnancy. Relapse was the most common cause of death (N=5).

DISCUSSION

Our study provides further evidence that some autologous and allogeneic HCT recipients have preserved fertility, including patients who receive HCT at age <20 years and those receiving myeloablative doses of TBI and/or cyclophosphamide.

Pregnancy after HCT has been reported previously; the relatively large case series that are published in the literature are summarized in Table 5.(4,11-13) Taken together, these previous studies and our present study indicate that fertility is most frequently preserved in patients receiving a transplant in the young adult age group (15-30 years), although some patients who received HCT as young as <5 years of age have become pregnant or fathered a child as adults. Among patients whose fertility was maintained, most received a non-TBI based conditioning regimen. However, there were some pregnancies reported by partners of

men and by women who received very high doses of TBI and/or cyclophosphamide as part of their HCT conditioning regimens. Pregnancy occurred despite the presence of chronic GVHD, indicating that chronic GVHD and its therapies may not always impair fertility. The majority of reported pregnancies occurred within 5-10 years after transplantation, but some occurred within the first year post-transplant. This observation has clear and potentially unrecognized implications for counseling patients about using contraception even in the immediate post-transplant period.

We could not address the risks of maternal or fetal complications in our study, but the literature (as summarized in Table 5) suggests that these complications may occur at an increased rate in female HCT recipients; hence, post-transplant pregnancies should be considered high risk. Nevertheless, pregnancies in this population are very likely to result in a live birth. Importantly, no increase in the risk of congenital malformations has been observed in other published studies.(4,10,12,13) The frequency of preterm births and of low or very low birth weight infants has been reported as increased in some,(12,13) but not all prior series.(4) Our study was not able to address this issue.

The effect of non-myeloablative preparative regimens on fertility preservation is unknown. As these regimens were introduced within the last decade, previous studies did not report on pregnancy outcomes in non-myeloablative HCT recipients. Our study included 4 patients who reported pregnancy after non-myeloablative HCT. Although typically used in patients over the age of 40-50, lesser intensity conditioning regimens have been increasingly used among younger patients, especially for those with low grade lymphoid malignancies and non-malignant disorders. Since the effect of chemotherapy and TBI on gonadal function is dose dependent,(7-9) young patients who undergo HCT using a non-myeloablative conditioning regimen may be expected to have a higher likelihood of preserving fertility compared to recipients of conventional myeloablative regimens. On the other hand, any potential advantages to fertility preservation among young patients receiving a non-myeloablative preparative regimen may be offset by extensive prior therapy that may have adversely impacted fertility. With recent data indicating that HCT outcomes may be similar between reduced intensity and myeloablative transplant regimens for certain disorders, (18-20) the possibility of retaining fertility may be a reason to select non-myeloablative conditioning, even in younger patients who typically can withstand myeloablative therapy. The impact of non-myeloablative conditioning on fertility warrants further prospective investigation.

Another noteworthy feature of our study is the large proportion of patients transplanted with non-malignant diseases, specifically SAA which comprised 42% of reported pregnancies. SAA patients generally have not received cytotoxic agents or radiation prior to HCT, and the conditioning regimens used for SAA commonly utilize lower dose of alkylating agents such as cyclophosphamide. Hence, cyclophosphamide as part of conditioning regimen may be relatively less gonadotoxic if the patient has not received any prior alkylator or other gonadotoxic therapies. Again, this observation has particularly important ramifications for contraceptive counseling post-transplantation in these patients.

Options to preserve fertility are available to patients preparing to undergo HCT. For men, cryopreservation of sperm is standard of care and is readily available in most areas. Barriers may include psychological distress and costs. In women, options are fewer, more invasive and mostly investigational. A commonly utilized option is for the patient to undergo oocyte stimulation and retrieval, a semi-invasive surgical procedure, followed by in vitro fertilization and cryopreservation of embryos. This requires either a male partner or a willingness on the patient’s part to fertilize her eggs with donor sperm. Experimental options include oocyte cryopreservation (without fertilization), or removal of all or part of the ovary

for cryopreservation and reimplantation at a later date. Oncofertility, or the use of reproductive technology for cancer patients, is a new and rapidly growing area due to the efforts of federal and patient advocacy organizations (e.g. NIH-funded Oncofertility Consortium and Fertile Hope, now part of the Lance Armstrong Foundation). Improving access to both standard and investigational fertility preservation techniques before transplant is an important and increasingly necessary part of pre-transplant counseling which can have a long-lasting impact on quality of life after transplantation.

Our report most likely underestimates the true prevalence of conception and pregnancy after HCT partially due to reporting issues, but also due to early first trimester pregnancy losses that may not be recognized or reported. Pregnancies often occur years after transplantation and patients may no longer be followed primarily by the transplant center, thus limiting the capture than the transplant center. Also, patients may not have reported conceptions that were voluntarily terminated or resulted in a spontaneous abortion. We have no information regarding several important factors such as pre-HCT treatment exposures, pre-HCT fertility preservation techniques (e.g. pelvic shielding during prior radiation or TBI), use of assisted reproductive technology, or maternal and fetal complications. Among men whose partners reported pregnancy, information on whether cryopreserved sperm was used to facilitate conception was missing for 26/95 (27%) patients. Finally, because of lack of understanding about which patients are truly of child bearing age and may be interested in conceiving children, the incidence of preserved fertility cannot be estimated using the current observational data. The European Group for Blood and Marrow Transplantation (EBMT) has reported on pregnancy after HCT in 2001 (12); 39 cases from Europe were included in our study and some of these cases may also have been reported in the previous EBMT study.

Notwithstanding these limitations, our large case series of pregnancies after HCT highlights that fertility may be preserved in selected patients; including patients who were very young at the time of transplant, those who received myeloablative TBI or high-dose alkylator based conditioning, and those who have undergone more than one HCT. We recommend that all patients of reproductive age or younger should be counseled about fertility, contraception, and family planning, both before and after HCT, with particular emphasis on fertility preservation strategies available both routinely and on an investigational basis before transplantation. Fertility and outcomes of pregnancy after HCT need prospective evaluation in large transplant cohorts. The CIBMTR is supported by Public Health Service Grant/ Cooperative Agreement U24-CA76518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); a Grant/Cooperative Agreement 5U01HL069294 from NHLBI and NCI; a contract HHSH234200637015C with Health Resources and Services Administration (HRSA/DHHS); two Grants N00014-06-1-0704 and N00014-08-1-0058 from the Office of Naval Research; and grants from AABB; Aetna; American Society for Blood and Marrow Transplantation; Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; Astellas Pharma US, Inc.; Baxter International, Inc.; Bayer HealthCare Pharmaceuticals; Be the Match Foundation; Biogen IDEC; BioMarin Pharmaceutical, Inc.; Biovitrum AB; BloodCenter of Wisconsin; Blue Cross and Blue Shield Association; Bone Marrow Foundation; Buchanan Family Foundation; Canadian Blood and Marrow Transplant Group; CaridianBCT; Celgene Corporation; CellGenix, GmbH; Centers for Disease Control and Prevention; Children’s Leukemia Research Association; ClinImmune Labs; CTI Clinical Trial and Consulting Services; Cubist Pharmaceuticals; Cylex Inc.; CytoTherm; DOR BioPharma, Inc.; Dynal Biotech, an Invitrogen Company; Eisai, Inc.; Enzon Pharmaceuticals, Inc.; European Group for Blood and Marrow Transplantation; Gamida Cell, Ltd.; GE Healthcare; Genentech, Inc.; Genzyme Corporation; Histogenetics, Inc.; HKS Medical Information Systems; Hospira, Inc.; Infectious Diseases Society of America; Kiadis Pharma; Kirin Brewery Co., Ltd.; The

Leukemia & Lymphoma Society; Merck & Company; The Medical College of Wisconsin; MGI Pharma, Inc.; Michigan Community Blood Centers; Millennium Pharmaceuticals, Inc.; Miller Pharmacal Group; Milliman USA, Inc.; Miltenyi Biotec, Inc.; National Marrow Donor Program; Nature Publishing Group; New York Blood Center; Novartis Oncology; Oncology Nursing Society; Osiris Therapeutics, Inc.; Otsuka America Pharmaceutical, Inc.; Pall Life Sciences; Pfizer Inc; Saladax Biomedical, Inc.; Schering Corporation; Society for Healthcare Epidemiology of America; Soligenix, Inc.; StemCyte, Inc.; StemSoft Software, Inc.; Sysmex America, Inc.; THERAKOS, Inc.; Thermogenesis Corporation; Vidacare Corporation; Vion Pharmaceuticals, Inc.; ViraCor Laboratories; ViroPharma, Inc.; and Wellpoint, Inc. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, or any other agency of the U.S. Government.

References

1. Hammond C, Abrams JR, Syrjala KL. Fertility and risk factors for elevated infertility concern in 10-year hematopoietic cell transplant survivors and case-matched controls. J Clin Oncol 2007;25:3511–3517. [PubMed: 17646668]
2. Watson M, Wheatley K, Harrison GA, et al. Severe adverse impact on sexual functioning and fertility of bone marrow transplantation, either allogeneic or autologous, compared with consolidation chemotherapy alone: analysis of the MRC AML 10 trial. Cancer 1999;86:1231–1239. [PubMed: 10506708]
3. Curbow B, Legro MW, Baker F, Wingard JR, Somerfield MR. Loss and recovery themes of long-term survivors of bone marrow transplants. J Psychosocial Oncol 1993;10:1–20.
4. Carter A, Robison LL, Francisco L, et al. Prevalence of conception and pregnancy outcomes after hematopoietic cell transplantation: report from the Bone Marrow Transplant Survivor Study. Bone Marrow Transplant 2006;37:1023–1029. [PubMed: 16604098]
5. 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. [PubMed: 16651642]
6. Sanders JE, Buckner CD, Leonard JM, et al. Late effects on gonadal function of cyclophosphamide, total-body irradiation, and marrow transplantation. Transplantation 1983;36:252–255. [PubMed: 6412404]
7. Sanders JE, Buckner CD, Amos D, et al. Ovarian function following marrow transplantation for aplastic anemia or leukemia. J Clin Oncol 1988;6:813–818. [PubMed: 3130466]
8. Sklar CA, Kim TH, Ramsay NK. Testicular function following bone marrow transplantation performed during or after puberty. Cancer 1984;53:1498–1501. [PubMed: 6421473]
9. Sklar CA, Kim TH, Williamson JF, Ramsay NK. Ovarian function after successful bone marrow transplantation in postmenarcheal females. Medical and pediatric oncology 1983;11:361–364. [PubMed: 6415379]
10. Gulati SC, Van Poznak C. Pregnancy after bone marrow transplantation. J Clin Oncol 1998;16:1978–1985. [PubMed: 9586918]
11. Jackson GH, Wood A, Taylor PR, et al. Early high dose chemotherapy intensification with autologous bone marrow transplantation in lymphoma associated with retention of fertility and normal pregnancies in females. Scotland and Newcastle Lymphoma Group, UK. Leukemia & lymphoma 1997;28:127–132. [PubMed: 9498711]
12. Salooja N, Szydlo RM, Socie G, et al. Pregnancy outcomes after peripheral blood or bone marrow transplantation: a retrospective survey. Lancet 2001;358:271–276. [PubMed: 11498213]
13. Sanders JE, Hawley J, Levy W, et al. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. Blood 1996;87:3045–3052. [PubMed: 8639928]
14. Singhal S, Powles R, Treleaven J, Horton C, Swansbury GJ, Mehta J. Melphalan alone prior to allogeneic bone marrow transplantation from HLA-identical sibling donors for hematologic malignancies: alloengraftment with potential preservation of fertility in women. Bone Marrow Transplant 1996;18:1049–1055. [PubMed: 8971372]

15. Hinterberger-Fischer M, Kier P, Kalhs P, et al. Fertility, pregnancies and offspring complications after bone marrow transplantation. Bone Marrow Transplant 1991;7:5–9. [PubMed: 1904290]
16. Rovo A, Tichelli A, Passweg JR, et al. Spermatogenesis in long-term survivors after allogeneic hematopoietic stem cell transplantation is associated with age, time interval since transplantation, and apparently absence of chronic GvHD. Blood 2006;108:1100–1105. [PubMed: 16543466]
17. Savani BN, Kozanas E, Shenoy A, Barrett AJ. Recovery of spermatogenesis after totalbody irradiation. Blood 2006;108:4292–4293. author reply 4293-4294. [PubMed: 17148595]
18. Sorror ML, Storer BE, Maloney DG, Sandmaier BM, Martin PJ, Storb R. Outcomes after allogeneic hematopoietic cell transplantation with nonmyeloablative or myeloablative conditioning regimens for treatment of lymphoma and chronic lymphocytic leukemia. Blood 2008;111:446–452. [PubMed: 17916744]
19. Alyea EP, Kim HT, Ho V, et al. Impact of conditioning regimen intensity on outcome of allogeneic hematopoietic cell transplantation for advanced acute myelogenous leukemia and myelodysplastic syndrome. Biol Blood Marrow Transplant 2006;12:1047–1055. [PubMed: 17067911]
20. Rodriguez R, Nademanee A, Ruel N, et al. Comparison of reduced-intensity and conventional myeloablative regimens for allogeneic transplantation in non-Hodgkin's lymphoma. Biol Blood Marrow Transplant 2006;12:1326–1334. [PubMed: 17162215]

Table 1

Characteristics of men whose partners reported pregnancy after hematopoietic-cell transplantation

Characteristic	Malignant diseases			Non-Malignant diseases N (%)
	Autologous N (%)	Allogeneic Myeloablative N (%)	Allogeneic Non-Myeloablative N (%)	
Number of patients	13	50	2	30
Median age at HCT (range), years	28 (20-40)	25 (5-53)	(30-49)	22 (4-34)
Age at HCT, years				
<10	0	1 (2)	0	2 (7)
10-19	1 (8)	5 (10)	0	9 (30)
20-29	7 (54)	32 (64)	1	14 (47)
30-39	4 (31)	11 (22)	0	5 (17)
40-49	1 (8)	0	1	0
≥50	0	1 (2)	0	0
Diagnosis				
Acute myeloid leukemia†	2 (15)	17 (34)	1	0
Acute lymphoblastic leukemia†	1 (8)	5 (10)	0	0
Chronic myeloid leukemia	0	22 (44)	0	0
Myelodysplastic syndrome	0	5 (10)	1	0
Lymphoma	7 (53)	1 (2)	0	0
Multiple myeloma	1 (8)	0	0	0
Solid Cancer	2 (15)	0	0	0
Severe aplastic anemia	0	0	0	30 (100)
Chemotherapy prior to conditioning regimen	13 (100)	45 (96)	2	0
Radiation therapy prior to conditioning regimen	3 (23)	0	0	0
Year of HCT				
≤1989	0	6 (12)	0	5 (17)
1990-1994	2 (15)	17 (34)	0	12 (40)
1995-1999	6 (46)	13 (26)	0	5 (17)
≥2000	5 (38)	14 (28)	2	8 (27)
Conditioning regimen				
TBI + Cyclophosphamide ± Other	0	14 (28)	0	0
Busulfan + Cyclophosphamide ± Other‡	2 (15)	32 (64)	0	5 (17)
Cyclophosphamide ± Other (no TBI or Busulfan)	8 (62)	0	1	24 (80)
Other	3 (23)	4 (8)	1	1 (3)
TBI in conditioning				
Median dose (range), cGy	1320	1200 (400-1440)	200	-
TBI dose, cGy				
No TBI	12 (92)	33 (66)	1	30 (100)
<400	0	0	1	-
400-800	0	3 (6)	0	-

Characteristic	Malignant diseases			Non-Malignant diseases N (%)
	Autologous N (%)	Allogeneic Myeloablative N (%)	Allogeneic Non-Myeloablative N (%)	
>800	1 (8)	14 (28)	0	-
Cyclophosphamide dose, mg/kg				
No cyclophosphamide	3 (23)	4 (8)	1	1 (3)
≤120	2 (15)	30 (63)	1	4 (13)
>120	8 (62)	14 (29)	0	25 (83)
Missing	*0*	*2*	*0*	*0*
Donor type				
Autologous	13 (100)	0	0	0
HLA-matched Siblings	0	37 (74)	2	28 (90)
Other related	0	3 (6)	0	1 (3)
Unrelated donor	0	10 (20)	0	1 (3)
Acute GVHD at any time after HCT	-	17 (34)	0	4 (13)
Chronic GVHD at any time after HCT	-	29 (58)	1	11 (37)
Relapse after HCT*	5 (38)	10 (20)	1	-
Median time from HCT to relapse (range), months	7 (<1-62)	17 (<1-144)	1	-
Second transplant or DLI for relapse	2 (15)	3 (6)	1	0
Disease status at last followup				
Continued complete remission	8 (62)	40 (80)	1	0
Complete remission after relapse	1 (8)	9 (18)	0	0
Recurrent disease	4 (31)	1 (2)	1	0
Cured	0	0	0	30 (100)
Median followup (range), years	8 (2-15)	10 (3-19)	(2-5)	11 (2-22)

HCT – hematopoietic-cell transplantation, TBI – total body irradiation, GVHD – graft versus host disease, DLI – donor lymphocyte infusion

*For malignant diseases only

†18/20 patients with acute myeloid leukemia and 5/6 patients with acute lymphoblastic leukemia had received HCT in first complete remission

‡Among 32 men who received myeloablative busulfan + cyclophosphamide +/- other as conditioning, 5 (16%) reported use of cryo-preserved sperm, 17 (53%) fathered a child naturally and information about sperm storage was missing in 10 (31%)

Table 2

Characteristics of women who reported pregnancy after hematopoietic-cell transplantation

Characteristic	Malignant diseases			Non-Malignant diseases N (%)
	Autologous N (%)	Allogeneic Myeloablative N (%)	Allogeneic Non-Myeloablative N (%)	
Number of patients	20	12	2	49
Median age at HCT (range), years	22 (16-33)	21 (9-33)	(24-33)	18 (5-32)
Age at HCT, years				
<10	0	2 (17)	0	3 (6)
10-19	8 (40)	3 (25)	0	26 (53)
20-29	8 (40)	6 (50)	1	19 (39)
30-39	4 (20)	1 (8)	1	1 (2)
Diagnosis				
Acute myeloid leukemia‡	2 (10)	4 (33)	0	0
Acute lymphoblastic leukemia‡	0	4 (33)	0	0
Chronic myeloid leukemia	0	3 (25)	0	0
Myelodysplastic syndrome	0	1 (8)	0	0
Lymphoma	18 (90)	0	0	0
Multiple myeloma	0	0	1	0
Severe aplastic anemia	0	0	0	45 (92)
Immune deficiency disorder	0	0	0	1 (2)
Other†	0	0	1	3 (6)
Chemotherapy pre-HCT	20 (100)	11 (92)	2	45 (92)
Radiation therapy pre-HCT	10 (100)	0	0	0
Year of HCT				
≤1989	0	2 (17)	0	8 (16)
1990-1994	7 (35)	3 (25)	0	9 (18)
1995-1999	7 (35)	6 (50)	0	15 (31)
≥2000	6 (30)	1 (8)	2	17 (35)
Conditioning regimen				
TBI + Cyclophosphamide ± Other	0	9 (75)	0	4 (8)
Busulfan + Cyclophosphamide ± Other	1 (5)	3 (25)	0	1 (2)
Cyclophosphamide ± Other (no TBI or Busulfan)	15 (75)	0	0	43 (88)
Other	4 (20)	0	2	1 (2)
TBI in conditioning				
Median dose (range), cGy	-	1200 (500-1440)	-	200 (200-300)
TBI dose, cGy				
No TBI	20	3 (25)	2	45 (94)
<400	0	0	0	3 (6)
400-800	0	1 (8)	0	0
>800	0	8 (67)	0	0

Characteristic	Malignant diseases			Non-Malignant diseases N (%)
	Autologous N (%)	Allogeneic Myeloablative N (%)	Allogeneic Non-Myeloablative N (%)	
Missing	0	0	0	1
Cyclophosphamide dose, mg/kg				
No cyclophosphamide	4 (20)	0	2	1 (2)
≤120	4 (20)	7 (58)	0	4 (8)
>120	12 (60)	5 (42)	0	43 (90)
Missing	*0*	*0*	*0*	*1*
Donor type				
Autologous	20	0	0	0
HLA-matched Siblings	0	9 (75)	2	42 (86)
Other related	0	1 (8)	0	1 (2)
Unrelated donor	0	2 (17)	0	6 (12)
Acute GVHD at any time after HCT	-	6 (50)	0	6 (12)
Chronic GVHD at any time after HCT	-	5 (42)	0	10 (20)
Relapse after HCT*	1 (5)	1 (8)	1	-
Median time from HCT to relapse, months	36	1	3	
Second transplant or DLI for relapse	0	0	1	5 (10)
Disease status at last followup				
Continued complete remission	19 (95)	11 (92)	1	0
Complete remission after relapse	0	1 (8)	0	0
Recurrent disease	1 (5)	0	1	0
Cured	0	0	0	48 (100)
Missing	*0*	*0*	*0*	*1*
Median followup (range), years	9 (3-15)	10 (5-20)	(3-4)	9 (1-23)

HCT – hematopoietic-cell transplantation, TBI – total body irradiation, GVHD – graft versus host disease, DLI – donor lymphocyte infusion

‡4/6 patients with acute myeloid leukemia and 1/4 patients with acute lymphoblastic leukemia had received HCT in first complete remission

†Includes chronic lymphocytic leukemia (N=1), thalassemia (N=1) and histiocytic disorders (N=2)

*For malignant diseases only

Table 3

Recipient characteristics at the time of pregnancy

Characteristic	Malignant diseases			Non-malignant diseases N (%)
	Autologous N (%)	Allogeneic Myeloablative N (%)	Allogeneic Non-myeloablative N (%)	
Men who fathered a child after HCT				
N	13	50	2	30
Median age at pregnancy (range), years	32 (23-48)	33 (18-55)	(35-51)	31 (19-47)
Age at pregnancy, years				
<20	0	1 (2)	0	1 (3)
20-29	2 (15)	18 (36)	0	12 (40)
30-39	9 (69)	23 (46)	1	15 (50)
40-49	2 (15)	7 (14)	0	2 (7)
≥50	0	1 (2)	1	0
Median time from HCT to pregnancy (range), years	7 (1-12)	7 (1-17)	(2-5)	9 (2-20)
Time from HCT to pregnancy, years				
<3	4 (31)	11 (22)	1	2 (7)
3-5	0	7 (14)	1	6 (20)
5-10	8 (62)	20 (40)	0	9 (30)
>10	1 (8)	12 (24)	0	13 (43)
Fathered a child				
Using cryopreserved sperm	0	14 (28)	0	1 (3)
Naturally	9 (69)	21 (42)	1	23 (77)
Unknown	4 (31)	15 (30)	1	6 (20)
Partner had a live birth				
Yes	12 (92)	38 (76)	1	27 (90)
No	1 (8)	10 (20)	1	1 (3)
Unknown	0	2 (4)	0	2 (7)
Women who reported pregnancy after HCT				
N	20	12	2	49
Median age at pregnancy (range), years	28 (18-40)	29 (18-39)	(25-34)	27 (15-37)
Age at pregnancy, years				
<20	1 (5)	2 (17)	0	8 (16)
20-29	13 (65)	6 (50)	1	26 (53)
30-39	5 (25)	4 (33)	1	15 (31)
40	1 (5)	0	0	0
Median time from HCT to pregnancy (range), years	6 (1-15)	7 (3-18)	1	7 (1-20)
Time from HCT to pregnancy, years				
<3	4 (20)	1 (8)	2	15 (31)
3-5	3 (15)	1 (8)	0	3 (6)
5-10	9 (45)	6 (50)	0	16 (33)

Characteristic	Malignant diseases			Non-malignant diseases N (%)
	Autologous N (%)	Allogeneic Myeloablative N (%)	Allogeneic Non-myeloablative N (%)	
>10	4 (20)	4 (33)	0	15 (31)
Partner fathered a child				
Using cryopreserved sperm	0	0	0	0
Naturally	1 (5)	3 (25)	0	11 (22)
Unknown	19 (95)	9 (75)	2	38 (78)
Had a live birth				
Yes	18 (90)	9 (75)	1	39 (80)
No	0	3 (25)	1	8 (16)
Unknown	2 (10)	0	0	2 (4)

Table 4

Pregnancy after hematopoietic-cell transplantation: distribution of age at transplant with dose of total body irradiation, dose of cyclophosphamide during conditioning and diagnosis

Characteristic	Age at HCT in years, N (%)				
	<10	**10-19**	**20-29**	**30-39**	**≥40**
Men who fathered a child after HCT, N					
N	3	15	54	20	3
Dose of TBI					
No TBI	3 (100)	13 (87)	42 (78)	16 (80)	2 (67)
<400 cGy	0	0	0	0	1 (33)
400-799 cGy	0	1 (7)	2 (4)	0	0
800-1199 cGy	0	1 (7)	8 (15)	4 (20)	0
≥1200 cGy	0	0	2 (4)	0	0
Conditioning regimen cyclophosphamide dose					
No cyclophosphamide	0	0	6 (12)	2 (10)	1 (33)
≤120 mg/kg	1 (33)	5 (33)	23 (44)	6 (30)	2 (67)
121-200 mg/kg	1 (33)	8 (53)	20 (38)	12 (60)	0
>200 mg/kg	1 (33)	2 (13)	3 (6)	0	0
Diagnosis					
Malignant disorder	1 (33)	6 (40)	40 (74)	15 (75)	3 (100)
Non-malignant disorder	2 (66)	9 (60)	14 (26)	5 (25)	0
Women who reported pregnancy after HCT, N					
N	5	36	34	7	0
Dose of TBI					
No TBI	3 (60)	33 (92)	28 (82)	6 (86)	0
<400 cGy	0	0	3 (9)	0	0
400-799 cGy	0	1 (3)	0	0	0
800-1199 cGy	1 (20)	2 (6)	3 (9)	1 (14)	0
≥1200 cGy	1 (20)	0	0	0	0
Conditioning regimen cyclophosphamide dose					
No cyclophosphamide	0	1 (3)	5 (15)	1 (14)	0
≤120 mg/kg	2 (40)	5 (14)	6 (18)	2 (29)	0

Characteristic	Age at HCT in years, N (%)				
	<10	**10-19**	**20-29**	**30-39**	**≥40**
121-200 mg/kg	2 (40)	26 (72)	16 (47)	4 (57)	0
>200 mg/kg	1 (20)	4 (11)	7 (21)	0	0
Diagnosis					
Malignant disorder	2 (40)	11 (30)	15 (44)	6 (86)	0
Non-malignant disorder	3 (60)	26 (70)	19 (56)	1 (14)	0

Table 5

Review of representative large case series of pregnancy after hematopoietic-cell transplantation

Reference	N*	Age at HCT in years, Median (range)	Age at first pregnancy in years, Median (range)	Time between HCT and pregnancy in years, Median (range)	TBI in conditioning, N (%)	Cyclophosphamide in conditioning, N (%)	Remarks
Allogeneic HCT							
Sanders et al (1996)(13)	Women=41	18 (4-34)	24 (16-36)	-- (<1-17)	13 (32%)	41 (100%)	- 115/146 (79%) pregnancies resulted in live births - Rates of abortion and congenital abnormalities no greater than general population rates - Greater than expected rates of preterm deliveries and low birth weight infants in female HCT recipients - TBI increased risk of abortion
	Men=35	22 (11-42)	33 (24-52)	-- (<1-18)	5 (14%)	35 (100%)	
Salooja et al (2001)(12)	Women=74	19 (6-36)	--	6 (<1-13)	32 (43%)	68 (92%)	- 271/312 (87%) pregnancies resulted in live births - Rates of congenital abnormalities no greater than general population rates - TBI increased risk of maternal complications in female recipients of allogeneic HCT
	Men=93	25 (10-45)	--	5 (1-20)	21 (23%)	65 (70%)	
Carter et al (2006)(4)	Women=4	22 (21-30)	26 (23-28)	--	3 (75%)	3 (75%)	- 46/54 (85%) pregnancies resulted in live births - Likelihood of live birth, miscarriage and stillbirth similar to sibling controls - Limited to adult HCT recipients
	Men=18	27 (21-35)	31 (25-43)	--	13 (72%)	14 (78%)	
Autologous HCT							
Jackson et al (1997)(11)	Women=10	25 (23-36)	--	2 (1-6)	0	0	- 13/13 (100%) pregnancies resulted in live births - All patients received melphalan ± etoposide conditioning - No congenital abnormalities observed - Limited to adult HCT recipients

Reference	N*	Age at HCT in years, Median (range)	Age at first pregnancy in years, Median (range)	Time between HCT and pregnancy in years, Median (range)	TBI in conditioning, N (%)	Cyclophosphamide in conditioning, N (%)	Remarks
Salooja et al (2001)(12)	Women=39	24 (18-33)	--	3 (<1-18)	3 (8%)	5 (13%)	- Salooja et al, vide supra
	Men=26	27 (15-33)	--	4 (1-13)	3 (12%)	10 (39%)	
Carter et al (2006)(4)	Women=4	27 (25-30)	31 (29-33)	--	2 (50%)	4 (100%)	- Carter et al, vide supra
	Men=8	30 (23-37)	34 (27-40)	--	2 (25%)	8 (100%)	

HCT – hematopoietic-cell transplantation, TBI – total body irradiation

*Women who reported pregnancy or men who fathered a child