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Pregnancy outcomes in female cancer survivors after hematopoietic stem cell transplantation

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Abstract. – OBJECTIVE: This study was conducted to retrospectively investigate the pregnancy outcomes of patients who underwent stem cell transplantation (SCT). We also aimed at determining the reasons for avoiding pregnancy despite prolonged remission.

PATIENTS AND METHODS: The study population consisted of patients who became pregnant after autologous or allogeneic SCT at Dr. Abdurrahman Yurtarslan Oncology Hospital between 2009 and 2020 for hematologic diseases. Data from 83 patients who had undergone allogeneic or autologous SCT were available for analysis. A total of 18 pregnancies occurred in 14 of these patients. To compare pregnancy outcomes, pregnant patients who received care at Etlik Zübeyde Hanım Maternity Hospital were selected as the control group.

RESULTS: No pregnancy occurred in 69 of the patients whose data were analyzed. Of these 69 patients, 48 (69.6%) did not want to become pregnant. The most common reason for not wanting a pregnancy was due to the fact that the patient was not married [21 patients (30.4%)]. The pregnancy rate was higher in the HL group than in other hematologic malignancies [8 patients (57.1%)]. Twelve (85.7%) of the patients who became pregnant did so after autologous SCT and 2 (14.3%) after allogeneic SCT. The cumulative incidence of obstetric complications was higher in pregnancies after SCT than in the control group, and the prevalence of low birth weight was observed more frequently.

CONCLUSIONS: Patients who became pregnant after SCT have a higher rate of pregnancy complications. However, these patients achieve similar live birth rates as the healthy population. Many patients have concerns about pregnancy and should be counseled appropriately.

Key Words:
Pregnancy complications, Stem cell transplantation, Hematopoietic, Hematological malignancies.

Introduction

Hematopoietic stem cell transplantation (SCT) is an established approach for the treatment of a variety of hematologic disorders[1]. Allogeneic SCT can be curative for fatal hematologic malignancies, such as acute myeloid leukemia and aplastic anemia[2]. Conditioning regimens are administered at SCT to reduce tumor burden and decrease the risk of graft rejection[3,4] . In autologous hematopoietic SCT, the patient's stem cells are harvested and re-infused after conditioning therapy[5]. Autologous hematopoietic SCT is performed in a variety of hematologic malignancies to augment remission[6] . The use of autologous hematologous SCT has increased over the past two decades. More than 45,000 transplants are now performed annually worldwide, and the life expectancy of these patients has increased significantly[7]. On the other hand, the long-term effects of SCT on fertility are a major concern. Most conditioning regimens are gonadotoxic and can impair fertility[8,9]. Alkylating agents and total

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body irradiation (TBI) are often part of many conditioning regimens[8]. These treatments can interfere with every step of reproduction, which is why infertility is common in these patients[10]. With advances in assisted reproductive technologies (ART), the likelihood of pregnancy has increased in patients undergoing SCT[11]. However, pregnancy complications have been shown to be more common in patients who have undergone SCT[12]. These complications were spontaneous abortions, low birth weight infants, preterm births, and stillbirths[13].

This study was conducted to retrospectively examine the pregnancy outcomes of patients who became pregnant after hematopoietic SCT. Our research question was whether pregnancy complications increase in pregnancies after SCT. We also aimed to determine the reasons for avoiding pregnancy despite long-term remission.

Patients and Methods

Study Design, Setting and Participants

This retrospective study was conducted at Abdurrahman Yurtarslan Oncology Hospital and Etlik Zubeyde Hanım Women's Health Training and Research Hospital in Ankara, Turkey. This study followed the Declaration of Helsinki on research involving human subjects[14] and was approved by the Institutional Review Board of Abdurrahman Yurtarslan Oncology Hospital and Etlik Zubeyde Hanım Women's Health Training and Research Hospital. Informed consent was obtained from all participants.

The study population consisted of patients who became pregnant after autologous or allogeneic SCT treatment for hematologic malignancies. Abdurrahman Yurtarslan Oncology Hospital is a tertiary referral center where more than 100 hematopoietic SCTs for hematologic malignancies have been performed annually since 2009. The hospital database was consulted to find female patients who had undergone autologous or allogeneic SCT between 2009 and 2020 and whose transplant age ranged from 18 to 45 years. The exclusion criteria and the number of excluded patients are shown in Figure 1.

Data Collection

Data from 83 patients were available for analysis. Data on patients' hematologic malignancy were obtained from the hospital database. The following data were used for analysis: age of patients at transplantation, type of disease, elapsed time after autologous or allogeneic SCT, disease status according to SCT. All of these patients were contacted by telephone by a single author (Dİ). Patients were asked if they became pregnant after SCT. Patients who became pregnant were asked about the outcome of each pregnancy. The following data were collected: maternal age at pregnancy, gestational age at delivery, sex and birth weight of the newborn. The following pregnancy complications were recorded: miscarriage, stillbirth, preterm birth, intrauterine growth retardation (IUGR) and preeclampsia. Intrauterine fetal death was defined as death of a fetus after 16 weeks of gestation. Preterm birth

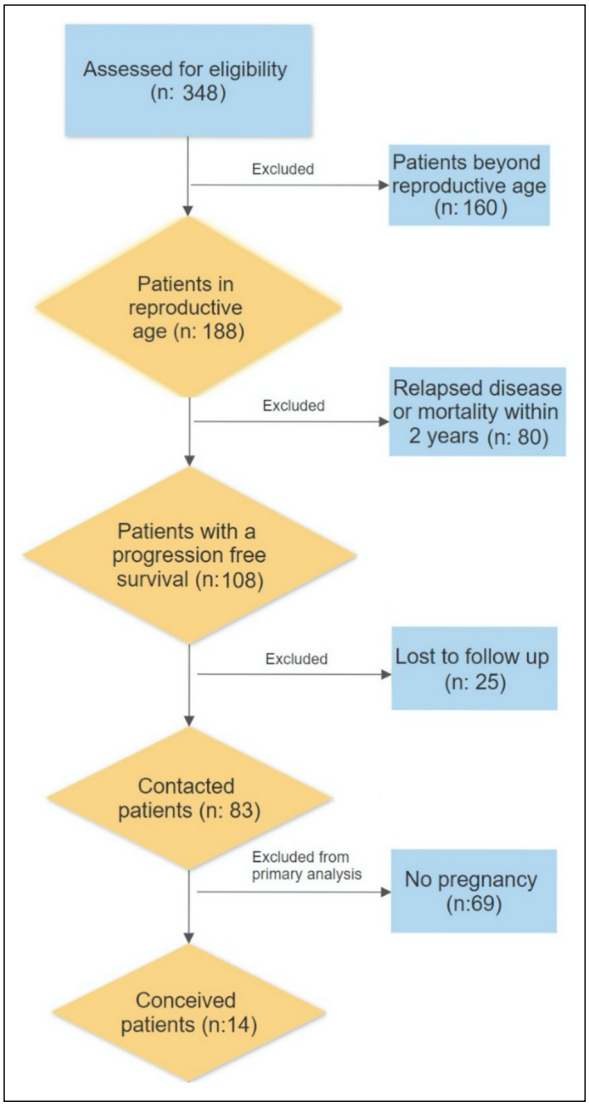

Figure 1. Flow Diagram of the study[17].

was defined as births that occurred before 37 weeks of gestation. Preeclampsia was defined as persistent blood pressure above 140/90 mmHg associated with proteinuria or maternal signs, symptoms or laboratory findings[15]. Previously published criteria were used to define IUGR[16]. To compare pregnancy outcomes, patients who received care at Etlik Zubeyde Hanım Maternity Hospital were selected as the control group. Using a random number table, 10 controls were selected for each pregnancy of patients who had SCT. Data from 180 pregnant women who were followed up between 2016 and 2021 were obtained by reviewing the hospital electronic records.

Patients who did not become pregnant were asked if they wished to become pregnant. Patients who did not want to become pregnant were asked their reasons for avoiding pregnancy.

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) 24 (SPSS Inc., IBM, Armonk, NY, USA). The distribution of parameters was assessed using Shapiro Wilk's normality tests. Descriptive analyzes were performed (using frequency tables for the categorical variables and using means and minimum-maximum values for the normally distributed variables). The students' *t*-test was used for the normally distributed and the Mann Whitney U-test for the non-normally distributed continuous data. Comparison of categorical variables was performed using the chi-square test or Fisher's exact test when appropriate. A *p*-value of less than 0.05 was considered statistically significant.

Results

In this study, 83 patients were contacted after allogeneic or autologous SCT (Figure 1)[17]. A total of 18 pregnancies occurred after SCT in 14 of these patients. No pregnancy occurred in 69 patients. Of these 69 patients, 48 did not want to become pregnant (69.6%) (Table I). The most common reason for not wanting a pregnancy was that the patient was not married [21 patients (30.4%)]. 13 patients (18.8%) stated that they had completed childbearing before SCT. 14 of the patients (20.3%) stated that they did not want to get pregnant due to concerns related to the disease. Three of them (4.3%) stated that they did not want a child because they were afraid of a shortened life expectancy due to the disease. 4 patients (5.8%) stated that they might suffer complications during pregnancy, and 7 patients (10.1%) stated that they did not want to become pregnant because pregnancy might harm their disease. 21 (30.4%) patients stated that they could not get pregnant even though they wanted to. 11 (15.9%) of them stated that they went into menopause shortly after SCT. 6 patients (8.7%) could not get pregnant naturally and 4 patients (5.8%) could not get pregnant with ART.

The clinical and disease characteristics of the patients who achieved pregnancy and the patients who did not or could not become pregnant were compared in Table II. There was no difference between the disease types in the two groups ($p > 0.05$ for all comparisons). Twelve of the patients (85.7%) who achieved pregnancy had an autologous SCT, while 2 (14.3%) had an allogeneic SCT. Of the patients who did not or could not become pregnant, 37

Table I. Reproductive desire in women after stem cell transplantation and reasons for not wishing to conceive.

Patients	Group 1 (n: 69)
No desire to conceive	48 (69.6%)
Not married	21 (30.4%)
Completed childbearing before SCT	13 (18.8%)
SCT/Disease related concerns	14 (20.3%)
Fear of reduced life expectancy due to disease	3 (4.3%)
Concerns about pregnancy complications due to SCT	4 (5.8%)
Concerns about impact of pregnancy on hematological disease	7 (10.1%)
Failed to conceive	21 (30.4%)
Menopause	11 (15.9%)
Failed to conceive after assisted reproduction	4 (5.8%)
Not able to conceive naturally	6 (8.7%)

SCT, stem cell transplantation.

Table II. Comparison of clinical and disease characteristics of patients receiving hematopoietic stem cell transplantation according to post-transplantation reproductive characteristics.

Patients	Patient conceived after SCT (n: 14)	Patients not conceived after SCT (n:69)	p
Age at stem cell transplantation [median (min-max)]	24.6 (19-29)	30.5 (17-45)	**0.041**[a]
Diagnosis (%)			
Acute myeloid leukemia	2 (14.3%)	15 (21.7%)	0.724
Hodgkin lymphoma	8 (57.1%)	23 (33.3%)	0.130
Non-Hodgkin lymphoma	2 (14.3%)	10 (14.5%)	1
Aplastic anemia	2 (14.3%)	5 (7.2%)	0.336
Acute lymphoblastic leukemia	0	6 (8.7%)	0.583
Multiple myeloma	0	7 (10.1%)	0.596
Myelodysplastic syndrome	0	3 (4.3%)	1
Total body irradiation n (%)	1 (7.1%)	8 (11.6%)	1
Stem cell transplantation			**0.026**[a]
Autologous stem cell transplantation	12 (85.7%)	37 (53.6%)	
Allogeneic stem cell transplantation	2 (14.3%)	32 (46.4%)	
Total body irradiation n (%)	1 (7.1%)	8 (11.6 %)	
Conditioning regimen			
Carmustine + Etoposide + Cytarabine + Melphalan	7 (50%)	18 (26.1%)	0.109
Cyclophosphamide + Anti-thymocyte globulin	2 (14.3%)	3 (4.3 %)	0.196
İfosfamide +carboplatin + etoposide	2 (14.3%)	12 (17.4 %)	1
Busulfan + cyclophosphamide + etoposide	1 (7.1%)	0	1
Busulfan + cyclophosphamide	2 (14.3%)	15[a] (21.7%)	0.724
Fludarabine + busulphan	0	6[a] (8.7%)	0.583
Melphalan	0	5 (7.2%)	0.583
Busulfan-fludarabine	0	10[a] (14.5 %)	0.199
Follow up after Stem cell transplantation [(months), mean (min-max)]	64 (18-120)	100 (60-150)	**0.001**[a]
Interval between Stem cell transplantation and pregnancy [(months), mean (min-max)]	39 (13-84)		-
Number of pregnancies per patient (min-max)	(1-3)		-
Total number of pregnancies	18		-

[a]Indicates statistical significance.

patients (53.6%) had an autologous SCT and 32 patients (46.4%) had an allogeneic SCT. The frequency of autologous transplantation was significantly higher in patients who achieved pregnancy than in patients who did not or could not become pregnant (p=0.026). There were no differences in the frequency of conditioning regimens and total body irradiation (TBI) in both groups (Table II). The follow-up time after SCT was 64 months in patients who achieved pregnancy and 100 months in patients who did not or could not become pregnant, and this difference was statistically significant (p-value=0.001).

The results of 18 pregnancies of 14 patients after SCT were compared with 180 patients in the control group (Table III). Gestational age and BMI were similar in both groups. Nulliparity was more common in patients who became pregnant after SCT than in the control group [10 pregnancies (55.7%) *vs.* 68 patients (37.8%), p-value=0.083]. The incidence of ART, twin pregnancies and miscarriages were similar in both groups (Table III). The mean gestational age at delivery was 35.8 weeks in the pregnancies after SCT and 37.5 weeks in the control group (p-value=0.087). Preterm labor occurred in 3 (21.4%), preeclampsia in 2 (14.3%), and IUGR in 2 (14.3%) pregnancies after SCT. All these complications were similar to the control group (p-value > 0.05 for all comparisons). The cumulative incidence of obstetric complications was higher in pregnancies after SCT than in the control group [6 (42.9%) *vs.* 34 (22.2%), p-value=0.015]. The birth weight of the newborns was similar in both groups. A higher prevalence of low birth weight was observed in pregnancies after SCT than in the control group [4 (28.5%) *vs.* 12 (7.8%), p-value=0.031].

Table III. Perinatal and neonatal outcomes of study population and control group.

	Pregnancy after SCT (n:18)	Control Group (n:180)	*p*-value
Age at pregnancy	28.7 ± 5.7	27.5 ± 6.0	0.381
Body mass index	27.4 ± 3.7	26.5 ± 3.9	0.336
Parity			0.083
0	10 (55.6%)	68 (37.8%)	
1-2	8 (44.4%)	97 (53.9%)	
≥ 3		15 (8.3%)	
Assisted reproduction	1 (5.6%)	12 (6.7%)	1.0
Miscarriage	4 (22.2%)	27 (15%)	0.421
Twin Pregnancy	1 (7.1 %)	5 (3.3%)	0.414
Gestational age at delivery weeks			
(mean ± standard deviation)	35.8 ± 4.1	37.5 ± 1.7	0.087
Preterm delivery[a]	3 (21.4%)	17 (11.1%)	0.38
Preeclampsia[a]	2 (14.3%)	11 (7.2%)	0.343
Intrauterine growth restriction[a]	2 (14.3%)	10 (6.5%)	0.265
Stillbirth[a]	1 (7.1%)	1 (0.7%)	0.161
Cesarean delivery[a]	7 (50 %)	64 (41.8%)	0.554
Composite pregnancy morbidity[a,b]	6 (42.9%)	34 (22.2%)	**0.015**[c]
Neonatal birthweight (± standard deviation)	2686 ± 911	3239 ± 393	0.052
Low birthweight infant	4 (28.5 %)	12 (7.8%)	**0.031**[c]
Fetal anomaly	0	5 (3.3 %)	0.353

SCT, stem cell transplantation. [a]Excluding miscarriages. [b]Composite obstetric morbidity defined as presence of any of the following; preterm delivery, preeclampsia, intrauterine growth restriction,stillbirth, cIndicates statistical significance.

Discussion

This study provides perinatal outcomes of patients who became pregnant after hematopoietic SCT. The main finding of the present study is that pregnancy complications are more common in pregnancies after SCT. However, patients who became pregnant after SCT achieved similar live birth rates as the control group.

In the present study, the rate of congenital anomalies was not increased in the infants born to women who delivered after SCT. The rates of preterm birth, preeclampsia, IUGR, and stillbirth were similar in pregnancies after SCT and in the control group. However, the cumulative incidence of obstetric complications was higher in pregnancies after SCT than in the control group [6 (42.9%) *vs.* 34 (22.2%)]. Pregnancy outcomes after autologous or allogeneic SCT are highlighted in Table IV. Previous large-scale studies[13,18,19] have reported increased preterm birth rates in patients who underwent SCT. One of the studies[19] also reported a higher rate of low birth weight infants. However, such an association was not found in other studies[18,20]. In the present study, the rate of low birth weight infants was also increased in pregnancies after SCT. Complications, such as IUGR and preterm birth, were also found to be more common in pregnancies after SCT[13,18].This was attributed to abnormal placentation. We did not find increased rates of preterm birth or IUGR. However, the cumulative risk of pregnancy complications was increased. This may be due to the small number of patients in this study. Previous studies[13,19] have also shown an increased rate of cesarean delivery in pregnancies after SCT. In the present study, cesarean delivery rates were similar in pregnancies after SCT and in the control group. It was reported that pregnancy complications were more common in allogeneic transplant patients than in autologous patients. Moreover, these complications occurred more frequently in women who had received TBI[13,19]. We could neither confirm nor deny this finding as only two patients in the present study received allogeneic SCT. Importantly, in the present study, patients who became pregnant after SCT had similar miscarriage rates as the control group. This is consistent with most previous studies[10,13,18,20-22], as they reported that the number of spontaneous abortions did not increase in patients who became pregnant after SCT. However, Sanders et al[18] reported that the incidence of miscarriage in female TBI recipients before SCT was 38%[19].

Table IV. Clinical characteristics and pregnancy outcomes of women who became pregnant after SCT.

Author	Number of female patients	SCT	Age at SCT (years)	TBI (%)	Total pregnancy	Live birth	ART	Perinatal outcomes
Sanders et al[19]	41	Allogeneic	28	31%	72	44 (56 %)	Not mentioned	• 14% (10/70) spontaneous abortions • High rates of preterm deliveries and low birth weight infants • TBI increased risk of abortion
Jackson et al[20]	10	Autologous	25	0	12	12 (100%)	2	• 100% Live births • No congenital abnormalities observed
Salooja et al[13]	74 39	Allogeneic Autologous	19 24	40% 15%	99 44	78 (78%) 35 (79%)	6	• 79 % Live births • TBI increased risk of maternal complications
Carter et al[10]	170 122	Allogeneic Autologous	22 27	75% 50%	9 5	9 (100%) 4 (80%)	Not mentioned	• 85% Live births • Live birth, miscarriage and stillbirth similar to sibling controls
Pup et al[21]	17	Autologous	23	41%	5	4 (80%)	Not mentioned	• No significant difference between the number of chemotherapy lines before SCT and pregnancy outcome
Lasica et al[22]	17	Autologous	25	Not mentioned	10	14 (100%)	0	• 10 Patients with naturally conceived pregnancies
Current Study	83	Autologous: 12 Allogeneic: 2	24	7%	18	14 (78%)	1	• Obstetric complications was higher in pregnancies after SCT

It is well known that many of the conditioning regimens used in patients undergoing SCT affect fertility. It has been reported that the fertility rate of patients treated with SCT in childhood is lower than that of the normal population. In addition, TBI had a strong negative impact on fertility rates in women who attempted to conceive naturally[18,19,23,24]. ART has been shown to increase pregnancy rates in patients who received TBI as part of their conditioning regimens[18]. However, pregnancy rates remain low. In the present study, only 3 women received TBI, of whom only one became pregnant. Therefore, we were not able to observe the effects of TBI on fertility or pregnancy complications. We were also unable to analyze the effects of SCT on fertility because a substantial proportion of women did not desire pregnancy for various reasons. However, the desire of cancer patients to have a biological family is as strong as in the normal population[25]. For this reason, it is important to inform this group of patients about the risks of infertility before treatment.

Our study has some limitations. First, our study was designed as a retrospective control study with a limited number of patients. This small number of patients is not sufficient for generalization. However, pregnancy outcomes of a limited number of patients have been reported in the literature. Therefore, the data presented in the previous study may be useful in counselling about reproductive outcomes in these patients. In addition, concerns regarding pregnancy in long-term survivors have not been previously addressed.

Conclusions

Infertility rates are increased in patients who have undergone SCT. Patients who became pregnant after SCT have a higher rate of pregnancy complications. However, these patients achieve similar live birth rates as the healthy population. Many patients have concerns about pregnancy and should be counseled accordingly.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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