Human Reproduction, Vol.36, No.11, pp. 2871–2882, 2021
Advance Access Publication on September 16, 2021 doi:10.1093/humrep/deab199

human reproduction

ORIGINAL ARTICLE *Infertility*

Pregnancy and pregnancy outcomes after hematopoietic stem cell transplantation in childhood: a cross-sectional survey of the EBMT Pediatric Diseases Working Party

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Submitted on June 08, 2021; resubmitted on July 30, 2021; editorial decision on August 12, 2021

STUDY QUESTION: What are the characteristics of patients with conceptions transplanted in childhood and adolescence?

SUMMARY ANSWER: Insemination and conception after hematopoietic stem cell transplantation (HCT) in childhood or adolescence was possible, even after myeloablative conditioning regimes, although some patients required reproductive medicine support.

WHAT IS KNOWN ALREADY: Preparative regimens of HCT are highly gonadotoxic, which leads to gonadal failure and pubertal development disorders. There are few population-based studies assessing the risk of future infertility in children after HCT.

STUDY DESIGN, SIZE, DURATION: We conducted a retrospective study to investigate natural or assisted conceptions and their outcomes in patients <18 years old before their first transplantation who received HCT between 1995 and 2016 and were in the European Society for Blood and Marrow Transplantation (EBMT) registry. Adoptions were excluded from the analysis.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Detailed information concerning pregnancy occurrences and outcomes were obtained by a separate questionnaire. Quantitative variables were presented as medians with their interquartile range (IQR) or range, and categorical variables were presented as frequencies and percentages.

MAIN RESULTS AND THE ROLE OF CHANCE: In total, 62 988 pediatric patients received a first HCT in EBMT centers between 1995 and 2016. Pregnancy was reported in 406 patients in the database. The median age at transplantation was 15.7 (range: 0.7–18) years, and the median age at declared conception was 25.0 (range: 16.3–38.8) years. Details concerning the first pregnancy and pregnancy outcome were obtained from 99 patients (24%) from the returned questionnaires. The median age at delivery or pregnancy interruption of the females was 23.0

(IQR: 20.8–27) years, with a median time after transplant of 10.7 (IQR: 6.6–15.4) years. Compared with the mean age of healthy women at their first child's birth (29 years old), the transplanted women delivered 5 years earlier (mean: 24.3 years). In terms of conception modality, 13/25 (52%) females conditioned with total body irradiation (TBI) and 50/52 (96%) of those conditioned without TBI conceived naturally. All seven male patients who had been conditioned with TBI achieved fatherhood but required assisted fertilization or used their cryopreserved sperm. In the females, 63/70 (90%) of all conceptions resulted in a live birth, 49/63 (84.5%) were at term and 43/46 (93%) had normal birthweight. Cesarean delivery was performed in 9/61 (15%) especially in women who had received a myeloablative regimen.

LIMITATIONS, REASONS FOR CAUTION: In the EBMT pediatric dataset, the age at last follow-up or death was <17 years for 75% of the patients, therefore a longer follow-up for all patients would be necessary to calculate the cumulative incidence of conception for patients transplanted during childhood and allow all patients to realize their reproductive willingness/potential.

WIDER IMPLICATIONS OF THE FINDINGS: Reproductive health surveillance and fertility preservation counseling are important in younger transplanted patients. Our results showed that there is a window of opportunity to conceive naturally or with reproductive medicine support.

STUDY FUNDING/COMPETING INTEREST(S): Funding was provided by the 'Stiftung für krebskranke Kinder Regio Basiliensis', Basel, Switzerland. All authors have no conflicts of interest to declare.

TRIAL REGISTRATION NUMBER: N/A.

Key words: pediatric / pregnancy / fertility preservation / hematopoietic stem cell transplantation / counseling / cryopreservation / ovarian reserve

Introduction

The number of hematopoietic stem cell transplantations (HCTs) in children is continuously rising owing to expanding transplant indications (Passweg *et al.*, 2020). Advances in transplantation techniques and supportive care have led to an increased number of long-term survivors (Majhail and Rizzo, 2013). On the other hand, conditioning regimes and transplant-related complications are associated with a variety of organ toxicities. Baker *et al.* (2010) reported a cumulative incidence of late effects of 93% in patients transplanted during childhood at a mean follow-up of 7 years. Infertility is the most frequent late effect after HCT (Mosher *et al.*, 2011) because total body irradiation (TBI) and myeloablative chemotherapy-based conditioning are well-known risk factors for gonadal dysfunction. Infertility in patients transplanted during childhood is high, ranging from 69% to 83%, and significantly lowers survivors' quality of life (Borgmann-Staudt *et al.*, 2012; Lambertini *et al.*, 2016). Pregnancies after HCT in women, as well as in partners of transplanted men, have been documented (Table I) (Salooja *et al.*, 2001; Brice *et al.*, 2002; Carter *et al.*, 2006; Loren *et al.*, 2011; Babb *et al.*, 2012; Naessén *et al.*, 2014; Pup *et al.*, 2014; Chiodi *et al.*, 2016; Lasica *et al.*, 2016; Santarone *et al.*, 2017). The only study that estimated a pregnancy rate after HCT was published in 2001 and reported a pregnancy rate of 0.6% (232/37 362), including patients transplanted at any age. To our knowledge, no study has reported on pregnancy after HCT exclusively performed during childhood. Consequently, there is no information about the characteristics of patients and related complications in patients transplanted during their childhood or adolescence. The study aim was to assess pregnancies and outcomes after HCT in childhood and adolescence.

Materials and methods

Data source

This retrospective study was conducted between July 2017 and June 2018 on behalf of the Pediatric Diseases Working Party of the European Society for Blood and Marrow Transplantation (EBMT) using the EBMT registry. Minimal essential data according to EBMT rules were collected, and patients or legal guardians provided written informed consent for data collection and analysis in accordance with the Declaration of Helsinki.

Selection of patients

In the EBMT database, the centers are asked to fill in patient data at each follow-up regarding pregnancy and its outcome, particularly whether it was followed by a live birth. Therefore, in this population-based study, we sought to identify patients who were transplanted for the first-time during childhood (<18 years old) from 1995 to 2016 in which a pregnancy (or partner pregnancy for males) was reported. A survey was sent to the head physicians of the 203 reporting EBMT centers that transplanted children. The specific data related to the disease that indicated the need for transplant, treatment prior to HCT, conditioning regimen used during HCT, type of transplant, pregnancies (or partner pregnancies for males) and pregnancy outcomes were collected. Specific questions related to pregnancy had the purpose of determining if the pregnancy could be achieved naturally, by artificial insemination, from a partner's cryopreserved sperm, donor sperm or using donor oocytes. Adoptions were not considered for this study.

Definitions

The term myeloablative conditioning (MAC) regimens means administration of TBI in which high doses of alkylating agent are used, which destroys patient bone marrow and does not allow autologous recovery. The term reduced-intensity conditioning regimens refers to regimens with reduced TBI of ≥30% and application of fludarabine with alkylating agents, such as melphalan, busulfan and thiotepa, at reduced doses (Bacigalupo *et al.*, 2009). Conception stands for fertilization of eggs by sperm, which can be achieved naturally or through ART, such as by IVF or ICSI. Pregnancy is defined as implantation of a zygote into the uterus and development into an embryo/fetus. Pregnancy interruption is defined as spontaneous or deliberate termination of pregnancy before the fetus can be expected to survive out of womb.

Table 1 **Overview of the literature on pregnancy after hematopoietic stem cell transplantation.**

Authors	Year of publication	Date of HCT (range)	Underlying disease	Number of patients	Median age at HCT in years (range)	Median time between HCT and pregnancy/delivery in years (range)	TBI in conditioning regimen	Conception (natural/ artificial)	Pregnancy outcome
Santarone *et al*	2017	(1983–2006)	75 non-malignants (β Thal major)	37 females 38 males	14 (2–21) 15 (4–24)	19 (10–26)	0	15 (11/4) 12 (10/2)	42
Chiodi *et al*	2016	(1978–2008)	240 malignants 29 non-malignants	269 females	17	Not reported	217	Not reported	37
Lasica *et al*	2016	(1995–2011)	25 malignants (Lymphoma)	25 females	27 (17–40)	0.3–13	0	10 (10/0)	14
Pup *et al*	2014	(1997–2009)	17 malignants (Lymphoma)	17 females	26 (18–37)	6 (3–11)	0	5	5
Naessén *et al*	2014	(1998–2002)	37 malignants	37 females	27	Not reported	15	8 (4/4)	6
Borgmann-Staudt *et al*	2012	(2000–2005)	296 malignants 48 non-malignants	138 females 206 males	13 (4–27) 13 (4–28)	4 (1–6)	148	Not reported	7
Babb *et al*	2012	(1979–2007)	212 malignants	100 females 112 males	Not reported	14–16 1–10	90 95	6 (6/0) 25 (10/15)	22
Loren *et al*	2011	(2002–2007)	99 malignants 79 non-malignants	83 females 95 males	5–33 5–53	7 (1–20)	32	15 IVF reported	145
Carter *et al*	2006	(1974–1998)	560 malignants 59 non-malignants	292 females 327 males	22 (21–30) 27 (21–35)	5	20	54	46
Brice *et al*	2002	Not reported	109 malignants (NHL)	109 females	Not reported	5.5	0	14 (14/0)	13
Salooja *et al*	2001	(1965–1998)	88 malignants 79 non-malignants	113 females 119 males	19 (6–36) 25 (10–45)	5.8 (0.6–13) 5.4 (1.3–20.1)	58	312	271

HCT, hematopoietic stem cell transplantation; NHL, non-Hodgkin lymphoma; TBI, total body irradiation; Thal, Thalassemia.

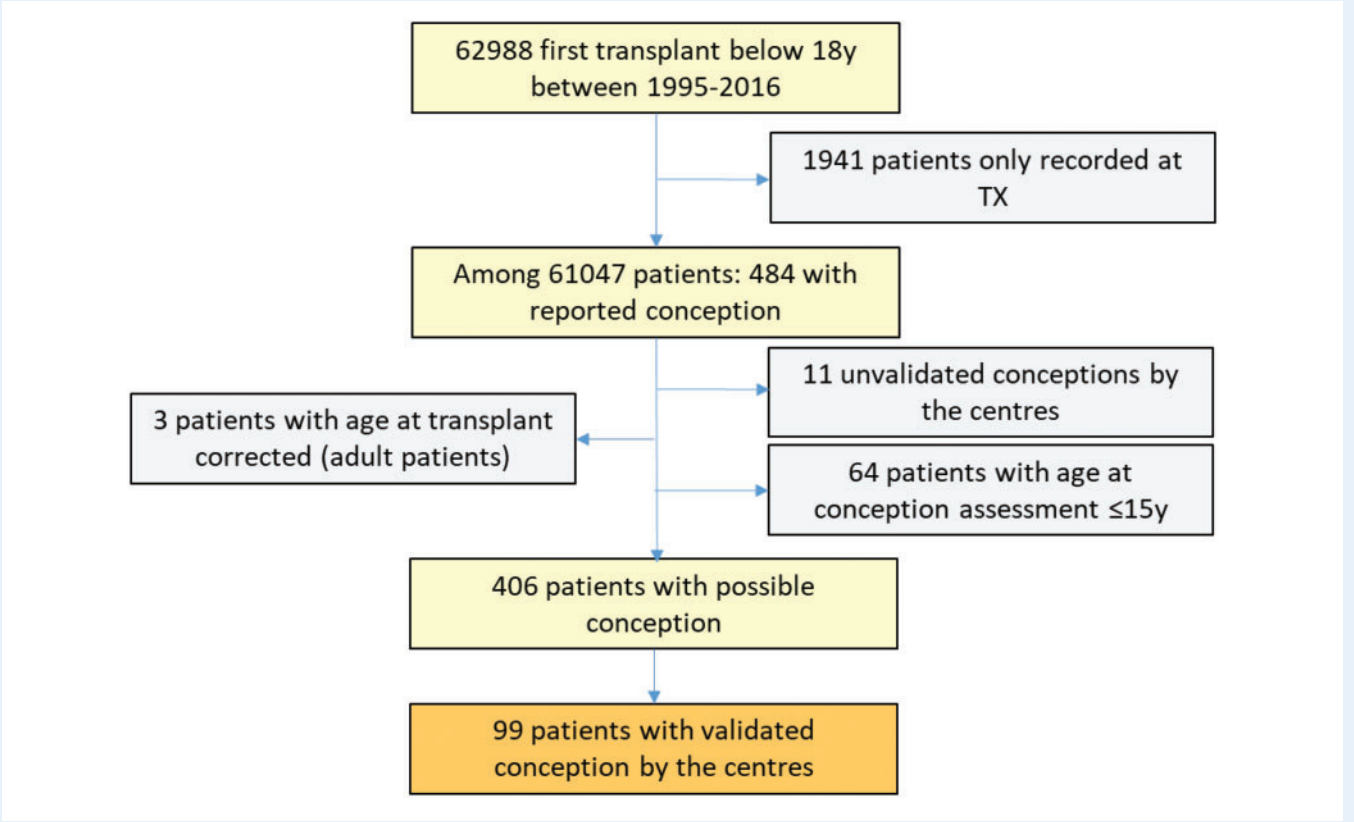

Figure 1. Flow chart of enrolled patients who underwent hematopoietic stem cell transplantation in childhood. TX, transplantation.

Statistical analysis

Quantitative variables are presented as the median and interquartile range (IQR) or range, while categorical variables are presented as frequency and percentage. When the date of birth or pregnancy failure was not reported, the date of assessment of pregnancy in the EBMT registry was used. This was a descriptive study, so no statistical testing was performed. All analyses were performed by using R software version 4.0.2. (R Development Core Team, Vienna, Austria).

Results

Identification of patients with reported pregnancies (or partner pregnancies) in the EBMT registry

In total, 62 988 pediatric patients received a first HCT in EBMT centers between 1995 and 2016. One thousand nine hundred forty-one patients had to be excluded from the 62 988 patients owing to missing follow-up data after transplantation. From the remaining 61 047 patients, the median age at last follow-up or death was 11.9 years (IQR: 6.5–17.1) and 484 had a reported pregnancy (or partner pregnancy) in the EBMT database.

Seventy-eight (16%) pregnancies (or partner pregnancies) were excluded: 11 were invalidated by the centers, 3 had a wrong date of birth recorded (adult patient at first transplant) and 64 were considered to be inconsistent because the patient age at pregnancy assessment was <15 years (median: 8.0; IQR 4.5–12.1), as shown in Fig. 1. The characteristics of the remaining 406 patients are presented in Table II.

The median age at transplantation was 15.7 (range: 0.7–18) years, and the median age at conception was 25.0 (range: 16.3–38.8) years. Pregnancies occurred at a median of 10.7 (IQR: 6.5–15.9) years after the first HCT. Detailed information concerning pregnancy and pregnancy outcomes were obtained by administering a specific questionnaire to 99 (24%) out of 406 patients and partners transplanted in 27 EBMT centers who had 114 pregnancies. The flow chart of the patient selection is shown in Fig. 1.

Results for the 99 patients with pregnancy details

In total, 70 (71%) of the patients with details regarding offspring were females, and their median age at transplantation was 14.3 (IQR 11.4–16.3) years. Underlying conditions for HCT were malignant diseases in 37 (53%) patients. Forty-eight (69%) patients received a MAC regimen, 46 (66%) were conditioned with busulfan or cyclophosphamide and 18 (25%) received TBI. The median age at delivery or pregnancy termination was 23.0 (IQR: 20.8–27) years, with a median time between transplantation and delivery or pregnancy interruption of 10.7

Table II Characteristics of the 406 patients with a reported conception.

Cohort characteristics		All (N = 406)	Allogeneic (N = 284)		Autologous (N = 122)	
			Female (N = 175)	Male (N = 109)	Female (N = 82)	Male (N = 40)
Age at first TX (yrs)	Median [IQR]	15.7 [13.2–17]	15.1 [12–16.8]	15.7 [14.5–17.2]	16.1 [13.8–16.9]	16.8 [15.9–17.6]
	Range	(0.7–18)	(0.7–18)	(1.3–17.9)	(1.5–18)	(3.9–18)
Year at first TX	Median [IQR]	2001 [1998–2005]	2002 [1997–2005]	2002 [1998–2007]	2001 [1999–2003]	2001 [1997–2003]
	Range	(1995–2015)	(1995–2015)	(1995–2014)	(1995–2014)	(1995–2009)
Age at conception assessment (yrs)	Median [IQR]	25.0 [21–29.4]	23.7 [20.5–28.3]	25.8 [19.4–30.3]	25.6 [22.1–28.8]	28.6 [22.5–31.1]
	Range	(16.3–38.8)	(16.3–36.9)	(16.3–38.8)	(17.7–35.7)	(17.6–36.5)
Years between first TX and conception assessment	Median [IQR]	11.2 [6.9–14.5]	10.9 [6.8–14.3]	11 [6.1–15.2]	11.1 [7–13.8]	12.4 [8.8–14.7]
	Range	(0–24.5)	(0.3–21.6)	(0–24.5)	(1.4–19.9)	(0.7–20.1)
Diagnosis (N (%))	Acute leukemia	120 (29.6)	52 (29.7)	43 (39.4)	10 (12.2)	15 (37.5)
	Lymphoma	76 (18.7)	5 (2.9)	5 (4.6)	49 (59.8)	17 (42.5)
	Chronic leukemia	21 (5.2)	12 (6.9)	9 (8.3)	0 (0)	0 (0)
	MDS/MPN	15 (3.7)	11 (6.3)	4 (3.7)	0 (0)	0 (0)
	Solid tumors	29 (7.1)	0 (0)	1 (0.9)	20 (24.4)	8 (20)
	Bone marrow failure	103 (25.4)	71 (40.6)	32 (29.4)	0 (0)	0 (0)
	Hemoglobinopathies	27 (6.7)	19 (10.9)	8 (7.3)	0 (0)	0 (0)
	Inherited disorders	13 (3.2)	5 (2.9)	7 (6.4)	1 (1.2)	0 (0)
	Auto-immune diseases	2 (0.5)	0 (0)	0 (0)	2 (2.4)	0 (0)
Conditioning regimen (N (%))	TBI based	105 (31.1)	59 (37.6)	31 (31.3)	8 (13.8)	7 (29.2)
	Cy alone	61 (18)	36 (22.9)	24 (24.2)	1 (1.7)	0 (0)
	BuCy based	52 (15.4)	26 (16.6)	23 (23.2)	0 (0)	3 (12.5)
	BEAM based	33 (9.8)	0 (0)	0 (0)	27 (46.6)	6 (25)
	FluMel and FluCy based	25 (7.4)	19 (12.1)	5 (5.1)	1 (1.7)	0 (0)
	Treo based	10 (3)	6 (3.8)	4 (4)	0 (0)	0 (0)
	BuMel based	8 (2.4)	0 (0)	1 (1)	3 (5.2)	4 (16.7)
	BuCyFlu based	5 (1.5)	2 (1.3)	3 (3)	0 (0)	0 (0)
	BuCyFluThio based	1 (0.3)	0 (0)	1 (1)	0 (0)	0 (0)
	BuCyMel based	5 (1.5)	2 (1.3)	3 (3)	0 (0)	0 (0)
	BuFlu based	5 (1.5)	2 (1.3)	3 (3)	0 (0)	0 (0)
	BuFluThio based	3 (0.9)	3 (1.9)	0 (0)	0 (0)	0 (0)
	CBV based	3 (0.9)	0 (0)	0 (0)	1 (1.7)	2 (8.3)
	ICE (cis or carbo)	1 (0.3)	0 (0)	0 (0)	1 (1.7)	0 (0)
	Other combinations	21 (6.2)	2 (1.3)	1 (1)	16 (27.6)	2 (8.3)
	missing	68	18	10	24	16

Bu, Busulfan; CBV, Cytoxan; Cy, Cyclophosphamide; Flu, Fludarabine; ICE, Ifosfamide, Carboplatin/Cisplatin, Etoposide; IQR, interquartile range; MDS/MPN, myelodysplastic syndrome/myeloproliferative neoplasm; Mel, Melphalan; TBI, total body irradiation; Thio, Thiotepa; TX, transplant; Yrs, years.

(IQR: 6.6–15.4) years (Fig. 2). The detailed characteristics of the female patients are presented in Table III. Regarding fertilization, 13/18 (72%) who received TBI and 50/52 (96%) of those without TBI conceived naturally (Table V). Among females, 63/70 (90%) of all conceptions resulted in a live birth, 49/63 (84.5%) were at term and 43/46 (93%) had normal birthweights. Cesarean delivery was performed in 9/61 (15%), especially in those who received the MAC regimen.

Of the 99 patients, 29 (29%) were males who reported a pregnancy of their partners (Table IV). Their median age at transplantation was 16 (IQR: 14.9–17.0) years. Fifteen (51%) males had a malignant disease, all received a MAC regimen and seven (24%) received TBI. The median age at partner's delivery or pregnancy termination was 27.3 (IQR: 25.7–30.4) years. The median time between transplant and delivery was 12.3 (IQR: 9.4–14.9) years. The characteristics of the male patients are presented in full in Table IV. All seven patients conditioned with TBI required assisted fertilization or used cryopreserved sperm (Table V).

Discussion

Our study found that fertility was in part preserved and that successful pregnancies after HCT during childhood, although rare, were possible.

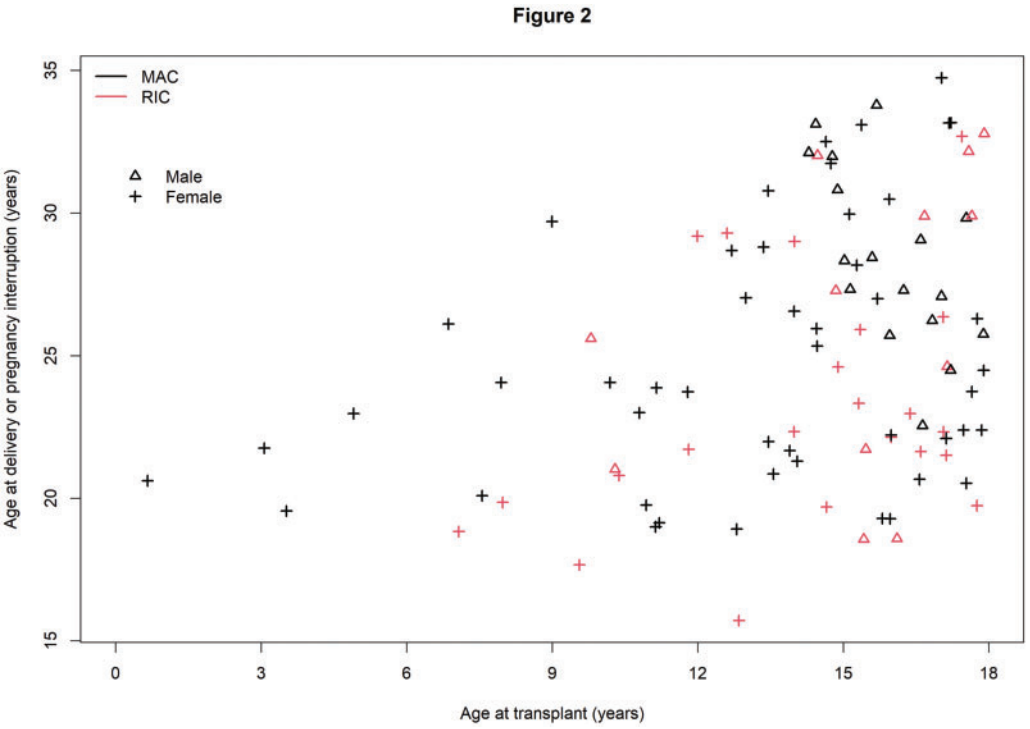

Figure 2. Age at delivery or pregnancy interruption according to age at hematopoietic stem cell transplantation. MAC, myeloablative conditioning; RIC, reduced-intensity conditioning.

Reproductive medicine support (e.g. ART) was more often required by the females in this cohort who received MAC regimens than by the healthy population. To our knowledge, this is the first population-based study to assess pregnancies and pregnancy outcomes exclusively in survivors who received HCT during childhood and adolescence. In this population, the younger the patients are at transplant, the longer they must be followed up to assess whether or not the patients desire and are able to have their own child. Consequently, the cumulative incidence of pregnancy remains unknown in this population. In the EBMT dataset, the age at last follow-up or death was <17 years for 75% of the patients, therefore it was impossible to calculate the cumulative incidence of conception.

The median age at transplantation in our population with offspring was 14.3 years in females and 16 years in males. Santarone *et al.* (2017) and Borgmann-Staudt *et al.* (2012) reported a similar age at transplantation in their population of children and young adults. These very young median ages are because for patients who received prepubertal HCT transplantation, the follow-up was too short to include pregnancies at ages for which family planning is considered. Consequently, for prepubertal transplanted patients, a longer follow-up period is necessary to assess the pregnancy incidence and outcomes.

Transplanted females conceived 5 years earlier on average than the general population for whom the mean age at delivery was 29.3 years (https://ec.europa.eu/eurostat/web/products-eurostat-news/-/ddn-20210224-1). Two other reasons could contribute to this observation: first, awareness of a potentially shorter lifespan after having experienced a life-threatening condition, and second, the fear of possible gonadal insufficiency and inability to conceive a child (Stein *et al.*, 2014). The direct toxicity caused by alkylating agents and radiation on the ovaries dramatically decreases the follicles and induces premature menopause. The cumulative incidence of ovarian failure is known to be associated with pubertal transplantation and is highest in patients transplanted after puberty (Bresters *et al.*, 2014). Recovery of the ovarian function after HCT has been reported within 2.6 years in some cases, especially in women <25 years old, but the incidence is low (Logan *et al.*, 2018). The recovery period often leaves a short window during which fertility is preserved for conceiving naturally or by ART (Socie *et al.*, 2003; Das *et al.*, 2012). A challenge for medical researchers is to identify this group of patients at the right moment.

In discussing the fertility preservation data of our study, it is important to point out that most of the patients were transplanted between 1997 and 2005. During that time, ovarian tissue cryopreservation was not available as a fertility preservation option. Ovarian tissue cryopreservation started around 2004 and has only recently been accepted as an established method for post-pubertal girls (Donnez *et al.*, 2004). Presently, the evolution of ART allows for the different fertility preservation options of ovarian tissue cryopreservation with reimplantation after treatment in pre- and post-pubertal girls, controlled hormonal stimulation for obtaining mature oocytes/embryos, and the cryopreservation of sperm or cryopreservation of testicular tissue in prepubertal boys.

Table III Characteristics of female patients who underwent HCT.

Cohort characteristics		All female (N = 70)	RIC (N = 22)	MAC (N = 48)
Age at first TX (yrs)	Median [IQR]	14.3 [11.4–16.3]	14.8 [12.1–16.5]	14 [11.1–16]
	Range	(0.7–17.9)	(7.1–17.8)	(0.7–17.9)
Age at first TX (yrs)	(0,7]	5 (7.1)	0 (0)	5 (10.4)
	(7,14]	29 (41.4)	10 (45.5)	19 (39.6)
	(14,18)	36 (51.4)	12 (54.5)	24 (50)
Year of TX	Median [IQR]	2002 [1997–2005]	2004 [2002–2006.8]	2001 [1997–2004]
	Range	(1995–2014)	(1995–2014)	(1995–2014)
Disease at first TX (N (%))	Acute leukemia (8 AML, 8 ALL and 1 mixed phenotype)	17 (24.3)	1 (4.5)	16 (33.3)
	Chronic leukemia (2 CML)	2 (2.9)	0 (0)	2 (4.2)
	Myelodisplasic syndrome (1 RA and 1 other)	2 (2.9)	0 (0)	2 (4.2)
	Lymphoma (4 DLBCL, 5 Hodgkins and 1 other)	10 (14.3)	0 (0)	10 (20.8)
	Solid tumors (1 osteosarcoma, 3 Ewing Sarcoma, 1 Ewing sarcoma/PNET and 1 skeletal Teratocarcinoma (yolk sac tumor))	6 (8.6)	1 (4.5)	5 (10.4)
	Bone marrow failure (21 AA and 1 non congenital Pure red cell aplasia)	22 (31.4)	20 (90.9)	2 (4.2)
	Hemoglobinopathies (8 Thalassemia and 3 SCD)	11 (15.7)	0 (0)	11 (22.9)
Chemotherapy before HCT (N (%))	No	32 (45.7)	18 (81.8)	14 (29.2)
	Yes	38 (54.3)	4 (18.2)	34 (70.8)
Radio before HCT (N (%))	No	57 (86.4)	19 (95)	38 (82.6)
	Yes	9 (13.6)	1 (5)	8 (17.4)
	Missing	4	2	2
TBI in regimen (N (%))	No	52 (74.3)	20 (90.9)	32 (66.7)
	Yes	18 (25.7)	2 (9.1)	16 (33.3)
Conditioning regimen (N (%))	Bu based	2 (2.9)	0 (0)	2 (4.3)
	BuCy based	13 (18.8)	0 (0)	13 (27.7)
	Cy based	21 (30.4)	20 (90.9)	1 (2.1)
	Other (without Bu or Cy or TBI)	15 (21.7)	0 (0)	15 (31.9)
	TBI based	8 (11.6)	0 (0)	8 (17)
	TBI+Cy based (<8 gray; <120 mg/kg)	2 (2.9)	2 (9.1)	0 (0)
	TBI+Cy based (≥8 gray; ≥120 mg/kg)	6 (8.7)	0 (0)	6 (12.8)
	TBI+Cy based (≥8 gray; missing dose)	2 (2.9)	0 (0)	2 (4.3)
	Missing	1	0	1
Age at delivery/stopped pregnancy (yrs)	Median [IQR]	23.0 [20.8–27]	22.2 [20.1–25.6]	23.8 [21.2–28.3]
	Range	(15.7–34.7)	(15.7–32.7)	(18.9–34.7)
Time between TX and delivery/ unsuccessful pregnancy (yrs)	Median [IQR]	10.7 [6.6–15.4]	8.8 [5.5–11.5]	12.4 [7.3–16]
	Range	(2–20.7)	(2–17.2)	(3–20.7)
Live birth (N (%))	No	7 (10)	1 (4.5)	6 (12.5)
	Yes	63 (90)	21 (95.5)	42 (87.5)
Reason for 1st conception, not a live child (N (%))	Medically required interruption	1 (16.7)	0 (0)	1 (20)
	Interruption (not specified)	1 (16.7)	0 (0)	1 (20)
	Voluntary interruption	1 (16.7)	0 (0)	1 (20)
	Spontaneous interruption	3 (50)	1 (100)	2 (40)
	Missing	1 on 7	0 on 1	1 on 6
Gestation time for live birth (N (%))	Gestational week <28	1 (1.7)	0 (0)	1 (2.3)
	Gestational week 28–36	8 (13.8)	2 (9.5)	6 (16.2)
	Gestational week >36	49 (84.5)	19 (90.5)	30 (81.1)
	Missing	5 on 63	0 on 21	5 on 42
Birthweight (N (%))	>2.5	43 (93.5)	19 (100)	24 (88.9)
	1.8–2.5	3 (6.5)	0 (0)	3 (11.1)
	Missing	17 on 63	2 on 21	15 on 42

(continued)

Table III Continued

Cohort characteristics		All female (N = 70)	RIC (N = 22)	MAC (N = 48)
Pregnancy complication (N (%))	No	39 (63.9)	17 (85)	22 (53.7)
	Yes	22 (36.1)	3 (15)	19 (46.3)
	Missing	9	2	7
Complication details (N (%))	Cesarean section	9 (40.9)	0 (0)	9 (47.4)
	Miscarriages	6 (27.3)	2 (66.6)	4 (21.1)
	Voluntary interruption of pregnancy	1 (4.5)	0 (0)	1 (5.3)
	Other	6 (27.3)	1 (33.3)	5 (26.3)
	Missing	0 on 22	0 on 3	0 on 19
Total number of live children (N (%))	0	6 (8.6)	0 (0)	6 (12.5)
	1	55 (78.6)	18 (81.8)	37 (77.1)
	2	9 (12.9)	4 (18.2)	5 (10.4)

AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; Bu, busulfan; CML, chronic myeloid leukemia; Cy, cyclophosphamide; DLBCL, diffuse large B-cell lymphoma; HCT, hematopoietic stem cell transplantation; IQR, interquartile range; MAC, myelo-ablative conditioning; mg/kg, milligram/kilogram; PNET, primitive neuro-ectodermal tumor; RA, refractory anemia; RIC, reduce intensity conditioning; SCD, sickle cell disease; TBI, total body irradiation; TX, transplant; Yrs, years.

Patients with malignant disease after TBI-based conditioning regimens rely more often on support of artificial reproduction to achieve conception. At least 51% (36/70) of the females were post-pubertal, a vulnerable period for ovarian reserve. Nevertheless, conception was successful in the 90% (63/70) of the transplanted females. Newborns who were pre-term and small for gestational age occurred more often in patients who received a MAC regimen (van de Loo *et al.*, 2019). In our analyzed population, 18.6% of the patients delivered by cesarean section: in Europe, it ranges from 54.8% in Cyprus to 16.5% in Finland (in the normal population, https://ec.europa.eu/eurostat/web/products-eurostat-news/-/DDN-20191217-1). In addition to a potentially narrow pelvis for younger mothers, other reasons for recommendation of cesarean delivery are the increased risk of uterine rupture, placental anomalies and fetal malpresentation (Chiarelli *et al.*, 2000; Green *et al.*, 2002). Unfortunately, details regarding cesarean indication could not be collected; therefore, obstetric complications, policies implemented for high-risk patients or other causes could not be investigated.

In the male group, all were post-pubertal at time of transplantation, and all of their partners' pregnancies resulted in live births. Ten of the males needed reproductive medicine support. A median of 10.7 years in the females and 12.3 years in the males elapsed between transplantation and delivery, which could be related to the young age of our population at transplantation. Other studies that included young adults have shown that the mean time between transplant and delivery ranged from 4 to 7 years, with a median age at delivery ranging from 20 to 33 years (Loren *et al.*, 2011; Borgmann-Staudt *et al.*, 2012).

Reduced-intensity conditioning regimens were introduced more generally from the year 2000, and a large proportion of our study population, particularly the patients with malignant diseases, received a MAC regimen. Thus, a high percentage of the females (78%) received busulfan and cyclophosphamide alone or combined with TBI as MAC. It is well known that after high-dose busulfan (16 mg/kg), recovery of ovarian function is observed in only 1% of all females, whereas after TBI (12 Gy), ovarian recovery occurs in 10–15% (Sanders *et al.*, 1996; Socie *et al.*, 2003; Okuda *et al.*, 2009). Komori *et al.* (2019) showed that a reduction of the applied TBI dose from 12 Gy to 8 Gy correlated with a lower incidence of premature ovarian failure that affected only 36% of young females (0.8–22.6 years) with a hematological malignancy. In our study, most of the female patients who became pregnant were pubertal when they received HCT, so they had a lower risk for gonadal dysfunction after HCT than adult females. Approximately one-third (21/70) of our female patients with a reported pregnancy received only cyclophosphamide (18/21 with 200 mg/kg) as part of their conditioning regimen, and most of them conceived naturally compared with those who were treated with TBI or busulfan. These results are consistent with those published by Vatanen *et al.* (2014) showing a preservation of ovarian function in the cyclophosphamide group.

One important limitation of our study was that it was impossible to calculate the cumulative incidence of pregnancy. Properly, we would have also needed sufficient follow-up data from patients without conception, which was not the case in this study. An additional difficulty for a study like ours is the long follow-up period needed for patients transplanted during childhood until they reach reproductive age.

In summary, this study showed that conceptions after HCT, even after MAC, are possible, in some cases with the support of reproductive medicine. The outcomes highlight, as supported by international guidelines, that timely discussion and counseling regarding possible late effects of cancer treatment to support patients' decisions regarding future family planning are important (Coccia *et al.*, 2018; Yasmin *et al.*, 2018). Discussions concerning fertility/fertility preservation should be offered to parents of children and adolescents already diagnosed, and the children should be followed up regularly during, and especially after, treatment to allow those without the option of fertility preservation before HCT to take advantage of the 'fertility window' afterwards.

Table IV Characteristics of the male patients who underwent HCT and males who reported a pregnancy of their partners.

Cohort characteristics		All male (N = 29)	RIC (N = 12)	MAC (N = 17)
Age at first TX (yrs)	Median [IQR]	16.0 [14.9–17]	15.8 [14.8–17.2]	16 [15–16.8]
	Range	(9.8–17.9)	(9.8–17.9)	(14.3–17.9)
Age at first TX (yrs)	(7,14]	2 (6.9)	2 (16.7)	0 (0)
	(14, 18)	27 (93.1)	10 (83.3)	17 (100)
Year of TX	Median [IQR]	2002 [1999–2003]	2002 [2000–2003.2]	2001 [1997–2003]
	Range	(1995–2012)	(1995–2012)	(1995–2009)
Disease at first TX (N (%))	Acute leukemia (2 AML CR1 ; 1 ALL CR1 ; 4 ALL CR2)	6 (20.7)	0 (0)	6 (35.3)
	Chronic leukemia (3 CML)	3 (10.3)	0 (0)	3 (17.6)
	Lymphoma (2 DLBCL)	2 (6.9)	0 (0)	2 (11.8)
	Myelodysplastic syndrome (2 RAEB)	2 (6.9)	1 (8.3)	1 (5.9)
	Solid tumors (1 PNET; 1 Ewing Sarcoma)	2 (6.9)	0 (0)	2 (11.8)
	Bone marrow failure (11 AA)	11 (37.9)	11 (91.7)	0 (0)
	Hemoglobinopathies (3 Thalassemia)	3 (10.3)	0 (0)	3 (17.6)
Chemotherapy before HCT (N (%))	No	17 (63)	12 (100)	5 (33.3)
	Yes	10 (37)	0 (0)	10 (66.7)
	Missing	2	0	2
TBI in regimen (N (%))	No	22 (75.9)	12 (100)	10 (58.8)
	Yes	7 (24.1)	0 (0)	7 (41.2)
Conditioning regimen (N (%))	Bu based (without Cy) (≥12 (9.6) mg/kg)	3 (10.3)	0 (0)	3 (17.6)
	BuCy based (<12 (9.6) mg/kg; <120 mg/kg)	2 (6.9)	0 (0)	2 (11.8)
	BuCy based (≥12 (9.6) mg/kg; ≥120 mg/kg)	5 (17.2)	0 (0)	5 (29.4)
	BuFlu (8 mg/kg)	1 (3.4)	1 (8.3)	0 (0)
	Cy based (without Bu) (≥120 mg/kg)	11 (37.9)	11 (91.7)	0 (0)
	TBI based (without Cy) (≥8 gray)	1 (3.4)	0 (0)	1 (5.9)
	TBI+Cy based (≥8 gray; <120 mg/kg)	1 (3.4)	0 (0)	1 (5.9)
	TBI+Cy based (≥8 gray; ≥120 mg/kg)	5 (17.2)	0 (0)	5 (29.4)
Age at delivery/stopped pregnancy (yrs)	Median [IQR]	27.3 [25.6–30.8]	26.4 [21.5–30.4]	28.3 [26.2–30.8]
	Range	(18.6–33.8)	(18.6–32.8)	(22.5–33.8)
Time between TX and delivery/ unsuccessful pregnancy (yrs)	Median [IQR]	12.3 [9.4–14.9]	12.3 [7.2–14.7]	12.3 [9.8–15.9]
	Range	(2.5–18.7)	(2.5–17.6)	(5.9–18.7)
Live birth (N (%))	Yes	28 (100)	12 (100)	16 (100)
	Missing	1	0	1
Birthweight (N (%))	<1.8	1 (5)	0 (0)	1 (10)
	1.8–2.5	2 (10)	0 (0)	2 (20)
	>2.5	17 (85)	10 (100)	7 (70)
	Missing	8 on 28	2 on 12	6 on 16
Pregnancy complication (N (%))	No	20 (95.2)	9 (100)	11 (91.7)
	Yes (cervical complication)	1 (4.8)	0 (0)	1 (8.3)
	Missing	8	3	5
Total number of live children (N (%))	1	22 (78.6)	9 (75)	13 (81.2)
	2	4 (14.3)	1 (8.3)	3 (18.8)
	3	2 (7.1)	2 (16.7)	0 (0)
	Missing	1	0	1

AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; Bu, busulfan; CML, chronic myeloid leukemia; CR, complete remission; Cy, cyclophosphamide; DLBCL, diffuse large B-cell lymphoma; Flu, fludarabine; HCT, hematopoietic stem cell transplantation; IQR, interquartile range; MAC, myeloablative conditioning; mg/kg, milligram/kilogram; PNET, primitive neuro-ectodermal tumor; RAEB, refractory anemia with excess of blasts; RIC, reduced-intensity conditioning; TBI, total body irradiation; TX, transplant; Yrs, years.

Table V Type of fertilization in pregnancies achieved following HCT in childhood.

All the patients (N = 99)	Malignant diseases (N = 52)						Non-malignant diseases (N = 47)		
	No TBI (n = 29) (21f, 8 m)			TBI (n = 23) (16f, 7m)			No TBI (n = 45) (31f, 14m)		TBI (n = 2) (2f)
	Naturally (N = 26)	Artificial reproduction (N = 2)	From partner cryopreserved sperm (N = 1)	Naturally (N = 11)	Artificial reproduction (N = 10)	From partner cryopreserved sperm (N = 2)	Naturally (N = 43)	Artificial reproduction (N = 2)	Naturally (N = 2)
Female (f): N = 70	20	1	0	11	5	0	30	1	2
Male (m): N = 29	6	1	1	0	5	2	13	1	0

HCT, hematopoietic stem cell transplantation; TBI, total body irradiation.

Data availability

The data set from the study are held securely in coded form at the EBMT Study Unit in Paris. The data underlying this article will be shared on reasonable request to the corresponding authors after granting prespecified criteria for confidential access.

Acknowledgements

The authors thank all of the centers that participated in this survey. We also thank Brigit Garwer, Aleksandr Kulagin, Dominique Plantaz, Arjan Lankaster, Herve Tilly, José Maria Fernandez Navarro, Stephen Robinson, Dominiqiue Bron, Rik Schots, Keith M.O. Wilson, Karin Mellgren, Riitta Niityvuopio, Bernd Grugn, Vincenzo Poggi, Simona Sica and Jean Henri Bourthis for their substantial contributions to this research.

We also are grateful to the foundation 'Stiftung für krebskranke Kinde Regio Basiliensis' for their support, which allowed us to conduct the study.

Authors' roles

T.D.-F., A.R. and J.E.G. conceived and designed the study. T.D.-F., A.R., J.E.G. and G.S. were responsible for analysis, interpretation of data and writing of the manuscript. F.G.P., J.H.D., A.B., P.B. and S.C. revised the manuscript critically for important intellectual content. P.S., I.B., V.K.R., B.E.G., X.P., F.F., H.P. and M.F. acquired data. The final version for publication was approved by all authors.

Funding

This study was supported by the foundation 'Stiftung für krebskranke Kinder Regio Basiliensis', Basel, Switzerland.

Conflict of interest

Nothing to declare.

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