Supportive Care in Cancer (2019) 27:4451–4460
https://doi.org/10.1007/s00520-019-05020-8

REVIEW ARTICLE

Reproductive outcomes following a stem cell transplant for a haematological malignancy in female cancer survivors: a systematic review and meta-analysis

Brigitte Gerstl[1,2] · Elizabeth Sullivan[3] · Jana Koch[1] · Handan Wand[1] · Angela Ives[4] · Richard Mitchell[2,5] · Nada Hamad[6] · Antoinette Anazodo[2,5,7]

Received: 28 March 2019 / Accepted: 30 July 2019 / Published online: 21 September 2019

Abstract

Purpose The use of high-dose chemotherapy and radiotherapy combined with haematopoietic stem cell transplantation (HSCT) may negatively affect a woman's reproductive potential. Reproductive outcomes such as infertility are a major concern for women who undergo treatment for a haematological cancer diagnosis.

Objective This systematic review and meta-analysis explores reproductive outcomes following a haematological cancer requiring HSCT.

Methods Electronic databases were searched to identify studies that reported on reproductive outcomes after treatment for a haematological cancer diagnosis. Studies were included that reported on pregnancy and reproductive outcomes following HSCT for a haematological malignancy.

Results The meta-analysis included 14 studies, collectively involving 744 female patients. The subgroup analysis showed an overall pooled estimated pregnancy rate, for autologous or allogeneic HSCT recipients, of 22.7% ($n = 438$). There were 25% ($n = 240$) of women who became pregnant after autologous HSCT compared with 22% ($n = 198$) who subsequently became pregnant following allogeneic HSCT.

Conclusions This meta-analysis reflects low pregnancy rates for cancer survivors desiring a family. However, live births are improving over time with new technology and novel therapies. Hence, female cancer patients should be offered timely discussions, counselling and education around fertility preservation options prior to starting treatment with gonadotoxic therapy.

Keywords Haematological malignancies · Stem cell transplant · Reproductive outcome · Pregnancy · Birth · Oncofertility

Introduction

Over the last decade, multimodality treatment has improved the overall survival for patients with a haematological malignancy globally [1, 2]. Haematological malignancies account for 17% of all cancers diagnosed in women of reproductive age (15–44 years) [3]. Adolescent and young adult (AYA) female patients aged 15–25 years of age (50% Hodgkin's lymphoma (HL), 23% non-Hodgkin's lymphoma (NHL), 11% acute lymphoblastic leukaemia (ALL)) have a different incidence rate for haematological diagnoses compared with adult female patients aged 26–45 years (44% NHL followed

✉ Antoinette Anazodo
Antoinette.anazodo@health.nsw.gov.au

[1] Department of Biostatistics, The Kirby Institute, University of New South Wales, Kensington, NSW, Australia

[2] Kids Cancer Centre, Sydney Children's Hospital, Randwick, Sydney, NSW 2031, Australia

[3] Office of the PVC Health and Medicine, Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW, Australia

[4] Cancer and Palliative Care Research and Evaluation Unit, University of Western Australia, Crawley, WA, Australia

[5] School of Women's and Children's Health, Discipline of Paediatrics, UNSW Medicine, University of New South Wales, Randwick, NSW, Australia

[6] Department of Haematology, The Kinghorn Cancer Centre, St Vincent's Hospital, Darlinghurst, NSW, Australia

[7] Nelune Comprehensive Cancer Centre, Prince of Wales Hospital, Sydney, NSW, Australia

by 28% HL, 13% acute myeloid leukaemia (AML) and 4% ALL) [4–8]. Few new cases of chronic lymphocytic leukaemia (CLL) (2.08%) are diagnosed annually in adult women [9]. Approximately 40% of all cancers diagnosed in pediatric patients (0–14 years) are haematological malignancies [10]; the most common diagnoses include ALL 73%, AML 14%, HL 7% and NHL 5% [4–8].

Haematopoietic stem cell transplantation (HSCT) may involve chemotherapy and radiotherapy and is usually delivered at the end of conventional treatment. The type of HSCT received is dependent on several factors which include disease type, availability of donor source, age of patient, general health of the patient and condition of the patient's marrow.

Abdominal radiotherapy can have adverse effects on ovarian function by depletion of germ cells and a reduction in hormone production in the neuroendocrine system [11]. The extent of damage to the ovaries is correlated with total dose received and patient age at diagnosis [11]. Even if pregnancy is achieved, women receiving radiotherapy to the pelvis may have an increased risk for obstetric complications [12–14].

Additionally, cranial irradiation for malignant central nervous system (CNS) disease [15] has proven to be efficacious, particularly for leukaemia/lymphoma patients with CNS involvement [16]. However, treatment can cause gonadotoxic damage to the hypothalamic–pituitary axis resulting in fertility impairment [17].

Approximately 80% of female patients are at increased risk for primary or secondary amenorrhoea following HSCT resulting in infertility [18, 19]. Reproductive-related complications following HSCT can happen with or without total body irradiation (TBI) and may include uterine dysfunction, premature ovarian failure, graft versus host disease (GVHD) of the genitalia (often under diagnosed) and increased complications during pregnancy [20].

Historically, patients diagnosed with haematological malignancies have not been offered fertility preservation (FP) procedures, except those diagnosed with lymphomas, due to the acute presentation of patient's requiring urgent treatment. For post-pubertal women undergoing FP, time is required for women to proceed with oocyte and/or embryo cryopreservation. This may not always be possible for some patients where urgent start to cancer treatment is required.

Ovarian tissue cryopreservation (OTC) is a technique used to collect and preserve ovarian tissue which is re-implanted when a patient is ready to start a family [21, 22]. In pre- and post-pubertal patients, ovarian tissue may be collected without delay of cancer treatment and preserved for re-implantation when a patient is ready to start a family (OTC). OTC has shown increasing success in AYA and adult patient's diagnosed with haematological malignancies and solid tumors, with over 140 live births having been reported up-to-date. However, ovarian tissue may be contaminated with malignant cells, potentially inducing disease recurrence after autotransplantation. Not only is the use of OTC contraindicated for leukaemia patients, but the risk is also present in various other cancer types (neuroblastoma, bone tumours, etc.) and therefore cannot be ruled out by present technologies due to safety of autotransplantation of thawed ovarian tissue and the possible contamination with malignant cells that may induce disease recurrence [23]. OTC has been used for both pre- and post-pubertal cancer patients who are well enough to undergo surgery and this technique is no longer considered experimental [24]. As of 2018, there have been over 140 live births reported after ovarian tissue transplantation of previously cryopreserved and thawed ovarian tissue [25–35]. Studies by Donnez et al. [36] and Van der Ven and colleagues [37] report pregnancy and birth rates of 29% and 23%, and 33% and 25%, respectively.

In vitro maturation (IVM) of oocytes from surgically obtained ovarian tissue provides haematological patients with an additional opportunity of FP without the risk of reseeding malignant cells. This method can be conducted on a day-to-day basis and therefore does not delay cancer treatment. Implantation rates per embryo transfer are reported to be 15–20% and clinical pregnancy rates range around 30–40%. However, IVM is still considered experimental [38].

Creux and colleagues [39] report clinical pregnancy and live birth rates of 23.5% per embryo transfer and 38.1% per patient respectively using this technique. Generally, clinical pregnancy and implantation rates per embryo transfer are reported to be around 35–40% and 15–20%, respectively, in women with infertility, after IVM of immature oocytes [40].

Ovarian transpositioning, also known as oophoropexy, has been used successfully in reducing the risk of ovarian damage by irradiation in lymphoma patients [41]. Administration of gonadotrophin-releasing hormone (GnRH) is contraindicated in children because the hormonal treatment, in adolescents, shows no clear benefit; therefore, it should not be a sole FP measure [42].

To date, there has not been a meta-analysis published focusing on reproductive outcomes following a haematological cancer diagnosis. The aim of this systematic review and meta-analysis was to report on reproductive outcomes following HSCT for a haematological malignancy in female patients.

Methods

Search

This study was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Statement (Fig. 1) and PROSPERO (CRD42018100337). We performed a detailed electronic search using search engines MEDLINE (OVID) 1995–July 2018 and EMBASE 1995–July 2018 to search for

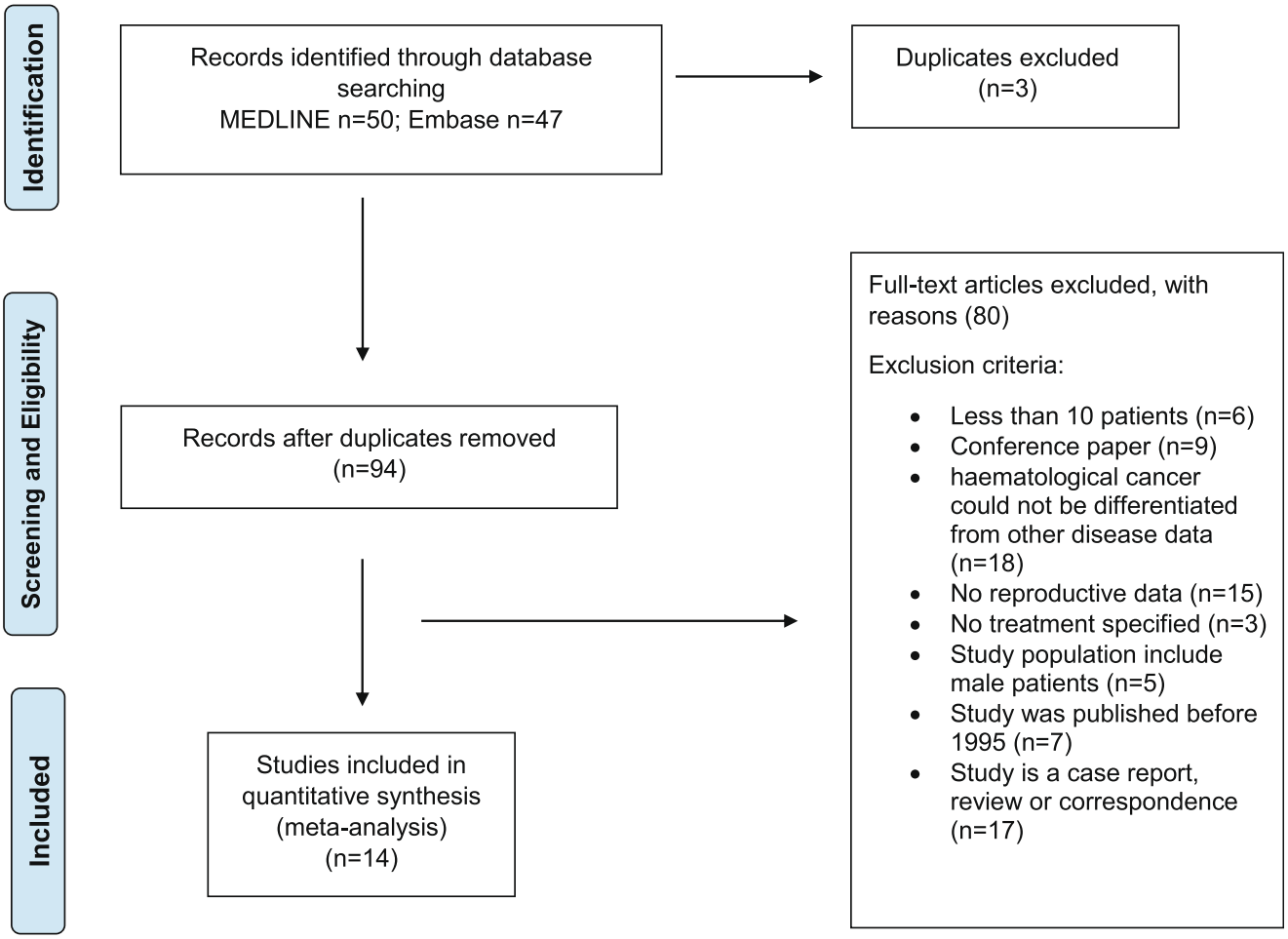

Fig. 1 PRISMA flow diagram of the study selection process

the following terms "haematological neoplasm", "bone marrow transplant", "BMT", "autologous BMT", "allogenic BMT", "haematological cancer", "leukemia", "acute myeloid leukemia", "acute lymphoblastic leukemia", "chronic myeloid leukemia", "chronic lymphocytic leukemia", "lymphoma", "Hodgkin's disease", "non-Hodgkin's disease", "Myelodysplastic syndromes", "fertility", "pregnancy" and "birth". Included papers were also checked for additional references.

Our literature search was limited to the following study designs: retrospective medical-chart review studies, randomized control studies, survey studies, prospective studies, cohort studies and population-based studies.

Data extraction

The data collection tool was designed by 2 researchers (AA, BG) and was used to screen papers for inclusion and exclusion eligibility for the review. Abstracts for inclusion were screened by 2 researchers (BG, JK) and the full text for each included study was independently reviewed by 2 researchers (BG, JK).

Study selection

Study inclusion

Studies were eligible for inclusion based on the following: (1) reported on pregnancy and live birth outcomes following HSCT for a haematological malignancy; (2) published in English; (3) population included only females; (4) published in a peer-reviewed journal; (5) had a sample size ≥ 10 patients; and (6) published between 1 January 1995 and 1 July 2018.

Statistical analysis

Descriptive statistics were used to analyze the frequencies and means of demographic data (age, study design, cancer diagnoses and transplant type). Frequencies were also assessed for type of fertility preservation procedure.

Meta-analyses

The meta-analyses were conducted using a random effects model with weighted inverse variance methods [43].

Higgins' I^2 test was used to estimate the approximate proportion of total variability in point estimates that could be attributed to heterogeneity other than that due to chance. Separate analyses were conducted for autologous and allogeneic HSCT recipients. Studies where the type of HSCT was not defined (autologous vs allogeneic) were excluded from the meta-analysis. Statistical analyses were performed using STATA release 14.2 (Stata Statistical Software, Stata Corporation, College Station, Texas, TX, USA) (Fig. 2).

There were no data reported on preterm births (< 37 weeks), still births or perinatal deaths included in the studies; hence, only pregnancy, terminations, miscarriages and live birth data were reported. Additionally, we conducted pooled (combined data for all included studies) reproductive outcomes following a haematological cancer diagnosis with HSCT (autologous vs allogeneic) with or without systemic therapy (Table 2).

Reproductive outcome rates and 95% confidence intervals (CI) were presented to provide an overall estimate of the effect of treatment for a haematological cancer diagnosis on reproductive outcomes.

Results

Characteristics of included studies

Of the 94 potentially eligible studies, 14 studies [44–57] met the eligibility criteria; seven retrospective medical-chart review studies [47, 49–53, 56], three survey studies [45, 54, 55] and four cohort studies [44, 46, 48, 57]. The studies were conducted in different geographical regions: two were from the Americas (USA and Canada) [47, 56], seven from Europe [44, 45, 48, 49, 52, 53, 57], one from Australasia and four multinational sites [46, 51, 54, 55]. Recruitment of patients occurred via hospital/wards (71%), or from registries (29%).

In the collective papers, 744 female cancer survivors received treatment for a haematological cancer with HSCT (either autologous or allogenic). The mean age for all included female patients at HSCT was 26 years (range 2–60) (mean age for autologous transplant recipients at diagnosis was 25.7 years, range 20–32 years; and for allogeneic transplant recipients the mean age was 22.5 years, range 20–27 years) (Table 1). Treatment details of women from the included studies who reported a pregnancy after HSCT are detailed in Table 1.

Patient characteristics and treatment modalities

The most commonly reported haematological diagnoses for all studies [44–57] were HL or NHL (40%) (these diagnoses were often reported together), CML (21%), AML (15%) and ALL (7%). Of the included studies, 49.3% of patients reported receiving an autologous HSCT; 50.7% of patients received an allogeneic HSCT.

There were 59 of 744 (8%) female patients who underwent a FP procedure. Twenty-one (36%) women had OTC (19 diagnosed with lymphoma, two women without a specified cancer diagnoses). Twelve (20%) women stored embryos (four

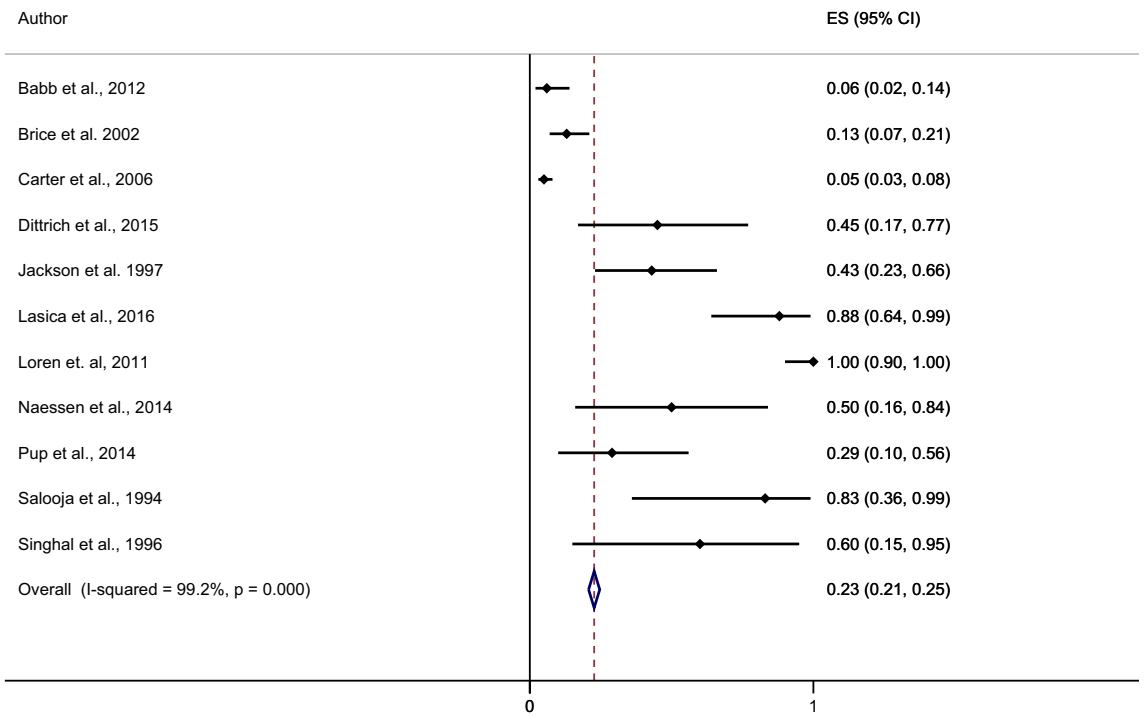

Fig. 2 Pregnancy rates for women in the included studies that received a HSCT for a haematological malignancy [45–57]

Table 1 Treatment characteristics of women who conceived after HSCT

Author	HSCT (*n*)	Autologous transplant (*n*)	Allogeneic transplant (*n*)	Chemotherapy + HSCT (*n*)	Chemotherapy + radiotherapy + HSCT (*n*)	TBI (yes/no)	MAC	RIC	Time of HSCT (day 0) to pregnancy/birth (median months)
Abraham et al., 2018 [44]	101	–	–	–	–	No	–	–	–
Babb et al., 2012 [45]	72	–	72	–	58	Yes	4	4	Median 132 Range 2–29
Brice et al., 2002 [46]	109	109	–	109	–	No	–	–	Median 59
Carter et al., 2006 [47]	292	113	179	–	–	No	–	–	Median 92
Dittrich et al., 2015 [48]	11	–	–	7	4	No	–	–	45
Jackson et al., 1997 [49]	23	23	–	22	–	No	–	–	Range 8–69
Lasica et al., 2016 [50]	25	25	–	25	–	No	–	–	Median 78 Range 3–156
Loren et al., 2011 [51]	34	20	14	25	9	Yes	12	2	Median 10 Range (1–17)
Naessen et al., 2014 [52]	37	11	26	26	11	Yes	19	7	–
Pup et al., 2014 [53]	17	17	–	5	12	No	–	–	Median 37 Range (17–74)
Sanders et al., 1996 [56]	41	–	–	28	13	Yes	*	*	–
Salooja et al., 1994 [54]	10	10	–	10	–	No	–	–	Range 4–40
Salooja et al., 2001 [55]	113	39	74	77	30	Yes	*	*	50
Singhal et al., 1996 [57]	12	–	12	12	–	No	–	–	Range 36–60

* not specified, *RT* radiotherapy, *TBI* total body irradiation, *RIC* reduced intensity conditioning, *MAC* myeloablative conditioning

women with lymphoma, eight women without a specified cancer diagnoses). Six women (10%) underwent oocyte cryopreservation (no cancer diagnoses specified), 18 (31%) women received GnRH (all 18 women were diagnosed with lymphoma) and two women (3%) received donor eggs (no cancer diagnoses specified).

Meta-analysis of reproductive outcomes following HSCT

Table 2 highlights the reproductive outcomes following treatment for either autologous or allogeneic HSCT for the combined studies ($n = 744$) [44–57]. Of those who received a transplant, 22.7% ($n = 438$) (95%CI 0.21, 0.25; $I^2 = 99.2\%$) [45–54, 57] subsequently conceived, of which 7.5% ($n = 25$) (95%CI 0.03, 0.12; $I^2 = 64.2\%$) [45, 48, 49, 55] were achieved with the use of assisted reproductive technologies (ART). The miscarriage rate (< 14 weeks) for all pregnancies was 10.4% ($n = 30$) (95%CI 0.06, 0.15; I^2 9.6%) [45, 49, 50, 55, 56] with a medical termination rate of 9% ($n = 29$) (95%CI 0.05, 0.13; I^2 9.6%) [46, 52, 54, 55].

Of those women who successfully conceived, 78% ($n = 361$) (95%CI 0.74, 0.83; I^2 47.1%) [45, 47–56] experienced a live birth. No preterm birth data were reported for the included studies.

Of the 367 female patients who received autologous HSCT [46, 47, 49–55], 25% ($n = 240$) (95%CI 0.22, 0.27; I^2 =

Table 2 Meta-analyses for each reproductive outcome following HSCT for a haematological malignancy

	Total	Autologous HSCT	Allogeneic HSCT
Total number of patients *n* (%)	744 [45–57]	367 (49.3%) [46, 47, 49–55]	377 (50.7%) [45, 47, 51, 52, 55, 57]
Pregnancy	438 (22.7%) (95%CI 0.21, 0.25; $I^2 = 99.2\%$) [45–54, 57]	240 (25%) (95%CI 0.22, 0.27; $I^2 = 99.4\%$) [46, 47, 49–54]	198 (22%) (95%CI 0.20, 0.24; $I^2 = 99.7\%$) [45, 47, 51, 52, 57]
ART pregnancy	25 (7.5%) (95%CI 0.03, 0.12; $I^2 = 64.2\%$) [45, 48, 49, 55]	11 (6.6%) (95%CI 0.02, 0.11; $I^2 = 0\%$) [45, 55]	14 (8%) (95%CI 0.03, 0.12; $I^2 = 86.3\%$) [45, 55]
Miscarriage	30 (10.4%) (95%CI 0.06, 0.15; I^2 9.6%) [45, 49, 50, 55, 56]	15 (9%) (95%CI 0.04, 0.14; $I^2 = 0\%$) [49, 50, 55]	15 (10%) (95%CI 0.05, 0.15; $I^2 = 71\%$) [45, 55]
Termination	29 (9%) (95%CI 0.05, 0.13; I^2 9.6%) [46, 52, 54, 55]	16 (9%) (95%CI 0.04, 0.13; $I^2 = 31.1\%$) [46, 52, 54, 55]	13 (8%) (95%CI 0.03, 0.14; $I^2 = 72.3\%$) [52, 55]
Live birth rates	361 (78%) (95%CI 0.74, 0.83; I^2 47.1%) [45, 47–56]	203 (81%) (95%CI 0.75, 0.86; $I^2 = 51.6\%$) [47, 49–55]	158 (82%) (95%CI 0.76, 0.87; $I^2 = 33.5\%$) [45, 47, 51, 52, 55]

99.4%) [46, 47, 49–54] became pregnant. Of those women who became pregnant, 6.6% ($n = 11$) (95%CI 0.02, 0.11; $I^2 = 0\%$) [45, 55] successfully conceived with the use of ART. There were 9% ($n = 15$) (95%CI 0.04, 0.14; $I^2 = 0\%$) [49, 50, 55] of pregnancies that resulted in a miscarriage and similar findings were reported for women who terminated a pregnancy ($n = 16$) (9%, 95%CI 0.04, 0.13; $I^2 = 31.1\%$) [46, 52, 54, 55]. The live birth rate was 81% ($n = 203$) (95%CI 0.75, 0.86; $I^2 = 51.6\%$) [47, 49–55].

Women who received allogeneic HSCT ($n = 377$) (either a matched related or matched unrelated donor) [45, 47, 51, 52, 55, 57] reported a pregnancy rate of 22% ($n = 198$) (95%CI 0.20, 0.24; $I^2 = 99.7\%$) [45, 47, 51, 52, 57]. There were 8% ($n = 14$) (95%CI 0.03, 0.12; $I^2 = 86.3\%$) [45, 55] of pregnancies that were successful with the use of ART. The miscarriage rate was 10% ($n = 15$) (95%CI 0.05, 0.15; $I^2 = 71\%$) [45, 55] with a medical termination rate of 8% ($n = 13$) (95%CI 0.03, 0.14; $I^2 = 72.3\%$) [52, 55]. There were 82% ($n = 158$) (95%CI 0.76, 0.87; $I^2 = 33.5\%$) [45, 47, 51, 52, 55] live births experienced.

Discussion

This is the first meta-analysis on reproductive outcomes following HSCT for haematological malignancies. For autologous transplant recipients, the reported pregnancy rate was 25% [46, 47, 49–54] with a slightly lower pregnancy rate (22%) [45, 47, 51, 52, 57] presented for those who received allogeneic HSCT. We performed a sub-analysis using pooled data from included studies and found that 7.5% [45, 48, 49, 55] of conceptions were successful through uptake and utilization of ART with the highest number of ART pregnancies achieved in women who underwent an allogeneic transplant (8%) [45, 55]. It is important to highlight that ART was not considered a reproductive endpoint as part of this study; hence, this figure may not provide a true account of the number of women who utilized ART strategies to become pregnant.

We present findings comparable with those highlighted in other studies, with one study reporting that HSCT recipients were 48% more likely to report infertility compared with women from the general population [58]. Infertility rates may reach up to 83% following allogeneic HSCT in childhood and adolescent cancer patients [58]. This can be explained by a reduced fertile window in these patients, as infertility on average occurs approximately around 2.6 years (range 0.1–12.0) following HSCT [59]. This emphasizes the importance of timely referral of these patients to a fertility specialist for comprehensive counselling.

Generally, childhood, adolescent and adult female cancer patients are reported to have an elevated risk for infertility compared with the general population, as well as age-matched controls without a cancer diagnosis. Adult female cancer patients are 39% less likely to become pregnant compared with women from the general population as reported in a large population-based study conducted by Stensheim and colleagues [60]. A recent Scottish study reported lower conception rates for patients (aged < 39 years) diagnosed with Hodgkin's (46%), non-Hodgkin's (34%) and leukaemia (31%) following cancer treatment compared with age-matched controls (non-cancer) [61]. For childhood and adolescent leukaemia patients, pregnancy rates were diminished compared with infertility rates of 25% and 18% of the general population, as reported by Balcerek et al. [62] and Zynda et al. [63], respectively. However, a cancer patient's desire for a biological family was reported to be strong, similar to those feelings expressed by the general population. The importance of young patients being counselled effectively, prior to cancer treatment, regarding the risks for infertility has been previously emphasized [12, 62].

A study by Sanders and colleagues [64] reported subsequently low pregnancy rates for women (median age of 25 years, range of between 13 and 49), who received high-dose cyclophosphamide in combination with TBI as part of the patient's HSCT conditioning regimen. Similar outcomes were reported from the Childhood Cancer Study where pregnancy rates were 20% lower than those of a closest-aged sibling and reported that 82% of patients were less likely to become pregnant following radiotherapy to the pelvic region [65].

TBI or cranial radiation can have detrimental effects on the neuroendocrine pathway causing disruption to a patient's fertility or may damage the ovaries leading to infertility; hence, there are limited options. However, if a patient has only received cranial irradiation, neuroendocrine disruption can be treated by hormone replacement therapy (hypogonadotropic hypogonadism), which can lead to reversibility of fertility impairment, which may allow these women to conceive naturally [55].

However, cancer patients may present with infertility concerns unrelated to their cancer diagnosis (ovulation problems, endometriosis, polycystic ovary syndrome, etc.) [66] prior to commencing treatment and these women may be at the greatest risk for infertility. It is therefore important that these women are offered an opportunity to have discussions prior to starting treatment, regarding the late effects of cancer treatment on their fertility [66].

Data presented in this paper should be interpreted with caution. Not all cancer patients may desire to become pregnant for many personal reasons or may have unsuccessfully attempted to become pregnant and this data may not have been captured. However, research indicates that cancer survivor's desire to have children and that an unfulfilled desire for a child and interrupted childbearing increases the risk for poorer mental health, more fertility-related trauma symptoms, higher reproductive concerns, greater cancer distress and lower psychological well-being [67].

For this study, we report a pooled estimated miscarriage rate post-HSCT (< 14 weeks) of 10.4% [45, 49, 50, 55, 56]. However, miscarriage data is often underreported [55] or not captured at a patient's consultation [68]. Overall pooled estimated medical termination rate for all included studies was 9% [46, 52, 54, 55]. Women who decide to terminate a pregnancy following cancer treatment may have additional psychological concerns and fears. These fears and concerns may be associated with disease relapse or the effects that cancer treatment may have on their unborn offspring; clinician uncertainty with recommending family planning following cancer treatment; cancer treatment may not have ceased; not being in a committed relationship; and a patient may have already completed their family [69, 70].

The pooled estimated live birth rate was 78% [45, 47–56]. High birth rates presented in this study may be attributed to the timing of pregnancy or the age of cancer patients who may have had a window of opportunity for pregnancy while their reproductive reserve may have been high, in addition to improvements in assisted reproductive technologies. Routine follow-up in the survivorship period may also provide improvement in uptake and utilization of FP, as well as timely referral of patients to consult with a reproductive specialist and providing psychological support to this cohort of patients.

Limitations

There are several limitations that need to be addressed when interpreting reproductive outcomes from these studies. There were often inconsistencies and underreporting in relation to specific gonadotoxic treatments such as chemotherapeutic agents and dose of radiotherapy administered in relation to each reproductive outcome. Additionally, studies did not report on individual reproductive outcomes according to a specific haematological malignancy. Malignant diagnoses were generally viewed collectively in relation to a specific reproductive outcome or with regard to a specific multimodality treatment in conjunction with HSCT in relation to a reproductive endpoint. Having data available on parity would have been useful to understand a woman's proven reproductive potential before starting cancer treatment.

These limitations highlight the importance for bone marrow transplant registries to collect reproductive fertility parameters. This is especially important given that women are choosing to become pregnant later in life in addition to the improvement in transplant survival outcomes and an increase in overall transplant numbers.

Conclusion

In summary, this study reports low pregnancy rates for female patients diagnosed with a haematological malignancy who underwent HSCT. These outcomes support current international guidelines which highlight offering patient timely discussions, education and counselling regarding the late effects of cancer treatment on a patient's fertility in order to support patients in making well-informed decisions regarding future family planning [71–73]. Discussions centred on fertility protection should also be extended to parents of children and adolescents with cancer at the time of the patient's diagnosis, and patients should be followed up for further discussions around their reproduction health and FP in the survivorship period [74].

While FP options may not be possible for all haematology patients, close follow-up and monitoring after completion of cancer treatment will provide female cancer survivors with an opportunity to have FP following treatment to support future pregnancies after the successful completion of cancer treatment.

Author contributions BG and AA made substantial contributions to the conception and design. BG and JK were accountable for collection and assembly of data. NG, AA, HW and JK were responsible for data analysis. BG, AA, ES, NH, RM and AI were major contributors in drafting and writing the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. de Bree E, Makrigiannakis A, Askoxylakis J, Melissas J, Tsiftsis DD (2010) Pregnancy after breast cancer. A comprehensive review. J Surg Oncol 101(6):534–542
2. Azim HA Jr, Santoro L, Pavlidis N, Gelber S, Kroman N, Azim H, Peccatori FA (2011) Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. Eur J Cancer 47(1):74–83
3. Landis SH et al (1999) Cancer statistics, 1999. CA Cancer J Clin 49(1):8–31
4. Huyghe E, Matsuda T, Thonneau P (2003) Increasing incidence of testicular cancer worldwide: a review. J Urol 170(1):5–11
5. Botchan A, Karpol S, Lehavi O, Paz G, Kleiman SE, Yogev L, Yavetz H, Hauser R (2013) Preservation of sperm of cancer patients: extent of use and pregnancy outcome in a tertiary infertility center. Asian journal of andrology 15(3):382–386
6. Ferrari S, Paffoni A, Filippi F, Busnelli A, Vegetti W, Somigliana E (2016) Sperm cryopreservation and reproductive outcome in male cancer patients: a systematic review. Reprod BioMed Online 33(1): 29–38
7. Meirow D, Schenker J (1995) Infertility: Cancer and male infertility. Hum Reprod 10(8):2017–2022

8. Australian Institute of Health and Welfare (AIHW) (2017) Australian Cancer Incidence and Mortality (ACIM) books: acute myeloid leukemia. AIHW, Canberra [cited 2018, 6th December]; Available from: http://www.aihw.gov.au/acim-books
9. Zaidi A, Johnson LM, Church CL, Gomez-Garcia WC, Popescu MI, Margolin JF, Ribeiro RC (2014) Management of concurrent pregnancy and acute lymphoblastic malignancy in teenaged patients: two illustrative cases and review of the literature. J Adolesc Young Adult Oncol 3(4):160–175
10. Youlden D et al (2009) Childhood cancer incidence in Australia, 1983–2006. Viertel Centre for Research in Cancer Control, Cancer Council Queensland and the Australian Paediatric Cancer Registry: Brisbane, Queensland
11. Hyman JH, Tulandi T (2013) Fertility preservation options after gonadotoxic chemotherapy. Clin Med Insights. Reprod Health 7: 61–69
12. Green DM, Whitton JA, Stovall M, Mertens AC, Donaldson SS, Ruymann FB, Pendergrass TW, Robison LL (2002) Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Am J Obstet Gynecol 187(4): 1070–1080
13. Marhhom E, Cohen I (2007) Fertility preservation options for women with malignancies. Obstetrical & Gynecological Survey 62(1): 58–72
14. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, Beck LN, Brennan LV, Oktay K, American Society of Clinical Oncology (2006) American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 24(18):2917–2931
15. Gunther JR, Rahman AR, Dong W, Yehia ZA, Kebriaei P, Rondon G, Pinnix CC, Milgrom SA, Allen PK, Dabaja BS, Smith GL (2017) Craniospinal irradiation prior to stem cell transplant for hematologic malignancies with CNS involvement: effectiveness and toxicity after photon or proton treatment. Practical radiation oncology 7(6):e401–e408
16. Bath LE, Anderson RA, Critchley HOD, Kelnar CJH, Wallace WHB (2001) Hypothalamic-pituitary-ovarian dysfunction after prepubertal chemotherapy and cranial irradiation for acute leukaemia. Hum Reprod 16(9):1838–1844
17. Wo JY, Viswanathan AN (2009) Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. Int J Radiat Oncol Biol Phys 73(5):1304–1312
18. Lambertini M et al (2016) Cancer and fertility preservation: international recommendations from an expert meeting. BMC Med 14(1):1–16
19. Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, Quinn G, Wallace WH, Oktay K, American Society of Clinical Oncology (2013) Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 31(19):2500–2510
20. Shanis D, Merideth M, Pulanic TK, Savani BN, Battiwalla M, Stratton P (2012) Female long-term survivors after allogeneic hematopoietic stem cell transplantation: evaluation and management. Semin Hematol 49(1):83–93
21. Donnez J et al (2011) Pregnancy and live birth after autotransplantation of frozen-thawed ovarian tissue in a patient with metastatic disease undergoing chemotherapy and hematopoietic stem cell transplantation. Fertil Steril 95(5):1787.e1–1787.e4
22. Demeestere I, Simon P, Emiliani S, Delbaere A, Englert Y (2007) Fertility preservation: successful transplantation of cryopreserved ovarian tissue in a young patient previously treated for Hodgkin's disease. Oncologist 12(12):1437–1442
23. Rosendahl M, Greve T, Andersen CY (2013) The safety of transplanting cryopreserved ovarian tissue in cancer patients: a review of the literature. J Assist Reprod Genet 30(1):11–24
24. 2013 Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril 100(5): 1214–23
25. Silber S, Kagawa N, Kuwayama M, Gosden R (2010) Duration of fertility after fresh and frozen ovary transplantation. Fertil Steril 94(6):2191–2196
26. Silber SJ, Gosden RG (2007) Ovarian transplantation in a series of monozygotic twins discordant for ovarian failure. N Engl J Med 356(13):1382–1384
27. Donnez J, Jadoul P, Squifflet J, van Langendonckt A, Donnez O, van Eyck AS, Marinescu C, Dolmans MM (2010) Ovarian tissue cryopreservation and transplantation in cancer patients. Best practice & research Clinical obstetrics & gynaecology 24(1):87–100
28. Donnez J, Silber S, Andersen CY, Demeestere I, Piver P, Meirow D, Pellicer A, Dolmans MM (2011) Children born after autotransplantation of cryopreserved ovarian tissue. A review of 13 live births. Ann Med 43(6):437–450
29. Andersen CY, Rosendahl M, Byskov AG, Loft A, Ottosen C, Dueholm M, Schmidt KLT, Andersen AN, Ernst E (2008) Two successful pregnancies following autotransplantation of frozen/thawed ovarian tissue. Hum Reprod 23(10):2266–2272
30. Donnez J, Dolmans MM (2017) Fertility preservation in women. N Engl J Med 377(17):1657–1665
31. Ernst E, Bergholdt S, Jorgensen JS, Andersen CY (2010) The first woman to give birth to two children following transplantation of frozen/thawed ovarian tissue. Hum Reprod 25(5):1280–1281
32. Meirow D, Levron J, Eldar-Geva T, Hardan I, Fridman E, Zalel Y, Schiff E, Dor J (2005) Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. N Engl J Med 353(3):318–321
33. Sánchez-Serrano M et al (2010) Twins born after transplantation of ovarian cortical tissue and oocyte vitrification. Fertil Steril 93(1): 268 e11–268. e13
34. Dittrich R, Lotz L, Keck G, Hoffmann I, Mueller A, Beckmann MW, van der Ven H, Montag M (2012) Live birth after ovarian tissue autotransplantation following overnight transportation before cryopreservation. Fertil Steril 97(2):387–390
35. Roux C et al (2010) Live birth after ovarian tissue autograft in a patient with sickle cell disease treated by allogeneic bone marrow transplantation. Fertil Steril 93(7):2413.e15–2413.e19
36. Donnez J, Dolmans MM, Diaz C, Pellicer A (2015) Ovarian cortex transplantation: time to move on from experimental studies to open clinical application. Fertil Steril 104(5):1097–1098
37. Van der Ven H et al (2016) Ninety-five orthotopic transplantations in 74 women of ovarian tissue after cytotoxic treatment in a fertility preservation network: tissue activity, pregnancy and delivery rates. Hum Reprod 31(9):2031–2041
38. Berwanger AL, Finet A, Hachem HE, Parco S, Hesters L, Grynberg M (2012) New trends in female fertility preservation: in vitro maturation of oocytes. Future Oncol 8(12):1567–1573
39. Creux H, Monnier P, Son WY, Buckett W (2018) Thirteen years' experience in fertility preservation for cancer patients after in vitro fertilization and in vitro maturation treatments. J Assist Reprod Genet 35(4):583–592
40. Chian R-C, Uzelac PS, Nargund G (2013) In vitro maturation of human immature oocytes for fertility preservation. Fertil Steril 99(5):1173–1181
41. Meirow D, Nugent D (2001) The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update 7(6):535–543

42. Clowse ME et al (2009) Ovarian preservation by GnRH agonists during chemotherapy: a meta-analysis. J Women's Health 18(3): 311–319
43. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188
44. Abraham A, et al (2018) Oocyte donation in women cured from cancer provide similar live birth rates compared to women without previous history of cancer. Geburtshilfe und Frauenheilkunde. Conference: Jahrestagung der Osterreichischen Gesellschaft fur Gynakologie und Geburtshilfe, OEGGG. 78(5)
45. Babb A, Farah N, Lyons C, Lindsay K, Reddy N, Goldman J, Apperley JF, Salooja N (2012) Uptake and outcome of assisted reproductive techniques in long-term survivors of SCT. Bone Marrow Transplant 47(4):568–573
46. Brice P et al (2002) Pregnancies after high-dose chemotherapy and autologous stem cell transplantation in aggressive lymphomas. Blood 100(2):736
47. Carter A, Robison LL, Francisco L, Smith D, Grant M, Baker KS, Gurney JG, McGlave PB, Weisdorf DJ, Forman SJ, Bhatia S (2006) Prevalence of conception and pregnancy outcomes after hematopoietic cell transplantation: report from the Bone Marrow Transplant Survivor Study. Bone Marrow Transplant 37(11): 1023–1029
48. Dittrich R, Hackl J, Lotz L, Hoffmann I, Beckmann MW (2015) Pregnancies and live births after 20 transplantations of cryopreserved ovarian tissue in a single center. Fertil Steril 103(2):462–468
49. Jackson GH, et al (1997) 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 28, 1–2: 127–32
50. Lasica M, Taylor E, Bhattacharyya P, Bennett A, Cooke RE, Stern C, Agresta F, Ayton R, Grigg A (2016) Fertility in premenopausal women post autologous stem cell transplant with BEAM conditioning. Eur J Haematol 97(4):348–352
51. Loren AW, Chow E, Jacobsohn DA, Gilleece M, Halter J, Joshi S, Wang Z, Sobocinski KA, Gupta V, Hale GA, Marks DI, Stadtmauer EA, Apperley J, Cahn JY, Schouten HC, Lazarus HM, Savani BN, McCarthy PL, Jakubowski AA, Kamani NR, Hayes-Lattin B, Maziarz RT, Warwick AB, Sorror ML, Bolwell BJ, Socié G, Wingard JR, Rizzo JD, Majhail NS (2011) Pregnancy after hematopoietic cell transplantation: a report from the late effects working committee of the Center for International Blood and Marrow Transplant Research (CIBMTR). Biol Blood Marrow Transplant 17(2):157–166
52. Naessén S, Bergström I, Ljungman P, Landgren BM (2014) Long-term follow-up of bone density, general and reproductive health in female survivors after treatment for haematological malignancies. Eur J Haematol 93(2):137–142
53. Pup LD, Zanet E, Rupolo M, Talamini R, Tirelli U, Mazzucato M, Steffan A, Zanussi S, Doretto P, Michieli M (2014) Which tools may help physicians in female fertility prediction after autologous bone marrow transplantation for lymphoma? A pilot study. J Chemother 26(5):293–299
54. Salooja N, Chatterjee R, McMillan A, Kelsey SM, Newland AC, Milligan DW, Franklin IM, Hutchinson RM, Linch DC, Goldstone AH (1994) Successful pregnancies in women following single autotransplant for acute myeloid leukemia with a chemotherapy ablation protocol. Bone Marrow Transplant 13(4):431–435
55. Salooja N, Szydlo RM, Socie G, Rio B, Chatterjee R, Ljungman P, Lint MTV, Powles R, Jackson G, Hinterberger-Fischer M, Kolb HJ, Apperley JF (2001) Pregnancy outcomes after peripheral blood or bone marrow transplantation: a retrospective survey. Lancet 358(9278):271–276
56. Sanders JE et al (1996) Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. Blood 87(7):3045–3052
57. Singhal S et al (1996) 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 18(6):1049–1055
58. Borgmann-Staudt A, Rendtorff R, Reinmuth S, Hohmann C, Keil T, Schuster FR, Holter W, Ehlert K, Keslova P, Lawitschka A, Jarisch A, Strauss G (2012) Fertility after allogeneic haematopoietic stem cell transplantation in childhood and adolescence. Bone Marrow Transplant 47(2):271–276
59. Pfitzer C, Orawa H, Balcerek M, Langer T, Dirksen U, Keslova P, Zubarovskaya N, Schuster FR, Jarisch A, Strauss G, Borgmann-Staudt A (2015) Dynamics of fertility impairment and recovery after allogeneic haematopoietic stem cell transplantation in childhood and adolescence: results from a longitudinal study. J Cancer Res Clin Oncol 141(1):135–142
60. Stensheim H, Cvancarova M, Møller B, Fosså SD (2011) Pregnancy after adolescent and adult cancer: a population-based matched cohort study. Int J Cancer 129(5):1225–1236
61. Anderson RA, Brewster DH, Wood R, Nowell S, Fischbacher C, Kelsey TW, Wallace WHB (2018) The impact of cancer on subsequent chance of pregnancy: a population-based analysis. Hum Reprod 33(7):1281–1290
62. Balcerek M, Reinmuth S, Hohmann C, Keil T, Borgmann-Staudt A (2012) Suspected infertility after treatment for leukemia and solid tumors in childhood and adolescence. Dtsch Arztebl Int 109(7): 126–131
63. Zynda A, Reinmuth S, Pfitzer C, Hohmann C, Keil T, Borgmann-Staudt A (2012) Childhood leukemia and its impact on graduation and having children: results from a national survey. Leukemia & Lymphoma 53(12):2419–2422
64. Sanders JE, Buckner CD, Amos D, Levy W, Appelbaum FR, Doney K, Storb R, Sullivan KM, Witherspoon RP, Thomas ED (1988) Ovarian function following marrow transplantation for aplastic anemia or leukemia. J Clin Oncol 6(5):813–818
65. Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, Donaldson SS, Byrne J, Robison LL (2009) Fertility of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 27(16):2677–2685
66. Wallace WH, Anderson RA, Irvine DS (2005) Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol 6(4):209–218
67. Logan S, Perz J, Ussher JM, Peate M, Anazodo A (2019) Systematic review of fertility-related psychological distress in cancer patients: informing on an improved model of care. Psycho-Oncology 28(1):22–30
68. Gerstl B, Sullivan E, Ives A, Saunders C, Wand H, Anazodo A (2018) Pregnancy outcomes after a breast cancer diagnosis: a systematic review and meta-analysis. Clin Breast Cancer 18(1):e79–e88
69. Logan S, Perz J, Ussher JM, Peate M, Anazodo A (2018) A systematic review of patient oncofertility support needs in reproductive cancer patients aged 14 to 45 years of age. Psychooncology 27(2): 401–409
70. Winther JF, Boice JD, Svendsen AL, Frederiksen K, Olsen JH (2009) Induced abortions in Danish cancer survivors: a population-based cohort study. J Natl Cancer Inst 101(9):687–689

71. Yasmin E, et al (2018) Fertility preservation for medical reasons in girls and women: British fertility society policy and practice guideline. Hum Fertil (Camb) 1–24
72. Coccia PF, Pappo AS, Beaupin L, Borges VF, Borinstein SC, Chugh R, Dinner S, Folbrecht J, Frazier AL, Goldsby R, Gubin A, Hayashi R, Huang MS, Link MP, Livingston JA, Matloub Y, Millard F, Oeffinger KC, Puccetti D, Reed D, Robinson S, Rosenberg AR, Sanft T, Spraker-Perlman HL, von Mehren M, Wechsler DS, Whelan KF, Yeager N, Gurski LA, Shead DA (2018) Adolescent and young adult oncology, version 2.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 16(1):66–97
73. (2007) Report of a Working Party of the Royal College of Physicians Royal College of Radiologists and Royal College of Obstetricians and Gynaecologists. The effects of cancer treatment on reproductive functions: guidance on management. Royal College of Physicians, London
74. Levine JM (2014) Preserving fertility in children and adolescents with cancer. Children (Basel) 1(2):166–185