A Short Review on Growth and Endocrine Long-term Complications in Children and Adolescents with β-Thalassemia Major: Conventional Treatment versus Hematopoietic Stem Cell Transplantation

Shayma Ahmed[1], *Ashraf Soliman*[1], *Vincenzo De Sanctis*[2], *Fawzia Alyafei*[1], *Nada Alaaraj*[1], *Noor Hamed*[1], *Mohamed Yassin*[3]

[1]Department of Pediatrics, Hamad General Hospital, Doha, Qatar; [2]Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy; [3] Department of Hematology, Cancer Research Center, Hamad Medical Center, Doha, Qatar

Abstract. The conventional treatment of β-thalassemia (β-TM) patients is based on the correction of anemia through regular blood transfusions and iron chelation therapy. However, allogeneic hematopoietic stem cell transplantation (HSCT) remains the only currently available technique which has the curative potential. Variable frequency and severity of long-term growth and endocrine changes after conventional treatment as well as after HSCT have been reported by different centers. The goal of this mini review is to summarize and update knowledge about long-term growth and endocrine changes after HSCT in patients with β-TM in comparison to those occurring in β-TM patients on conventional treatment. A regular surveillance, early diagnosis, treatment, and follow-up in a multi-disciplinary specialized setting are suggested to optimize the patient's quality of life (www.actabiomedica.it).

Key words: Allogeneic hematopoietic stem cell transplantation (HCT), β-thalassemia major, growth, endocrinopathies, fertility

Introduction

Thalassemias are inherited hemoglobinopathies characterized by impaired or absent production of one of the globin chains of adult hemoglobin (Hb). The most common form is β-thalassemia related to a defective production of the β-globin chains causing an unbalanced ratio of α-globin to β-globin.

As a consequence, the unbound free α-globin chains precipitate in erythroid precursors, leading to ineffective erythropoiesis, chronic hemolytic anemia, and compensatory hemopoietic expansion (1,2). More than 50,000 children with this disease are born worldwide each year, adding to the disease burden of this condition (3).

Historically, β-thalassemia has been divided into three main subgroups based on severity of the clinical phenotype: major (β-TM), intermedia, and minor. Distinction of the various phenotypes of thalassemia is mostly based on clinical parameters, although a genotype-phenotype association is established in both α- and β-thalassemia syndromes. Nowadays, β-thalassemia patients are classified as either transfusion-dependent (TDT) or non–transfusion-dependent (NTDT) according to the severity of phenotype. This classification embraces all other forms of thalassemia syndromes such as α-thalassemia, hemoglobin E/β-thalassemia and combined α- and β-thalassemias (4). Diagnosis and management of these disorders both in the neonatal period or later using appropri-

ate approaches and uniform technology are extremely important.

Definitive diagnosis of thalassemia requires a comprehensive workup from complete blood count, Hb analysis, and molecular studies to identify mutations of globin genes (1,2). The most common mutations that cause β-thalassemia are single nucleotide substitutions, small deletions, or insertions within the β-globin gene. To date, more 400 identified mutations of the β-globin gene (HBB) or promoter region that reduce or prevent the expression of the β-globin subunit of hemoglobin (Hb) in erythroid precursors (1,2,4).

After birth, HbF synthesis which is composed of two α-globin and two γ-globin chains ($^{\alpha 2\gamma 2}$) rapidly declines and HbF is gradually substituted by the major and minor adult hemoglobin forms, HbA and HbA2, respectively. As postnatal red blood cells (RBCs) HbF levels drop (less than 1%), children with β-TM experience severe microcytic, hypochromic anemia and become dependent on lifelong periodic blood transfusions (1,2,5,6). Unfortunately, chronic transfusions result in an increasing iron load (IOL) that lead to iron toxicity in vulnerable organs such as the heart, liver and endocrine glands, and necessitates daily iron chelation therapy (ICT), an expensive and sometimes uncomfortable treatment (7,8).

Deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX) are used to treat IOL in an attempt to reduce morbidity and mortality related to organs siderosis (5-8). Moreover, the advances in the understanding the mechanism of iron toxicity and overloading, and the availability of noninvasive methods to monitor iron loading in the liver, heart, and pancreas, the life expectancy of β-TM patients has improved significantly in high-income countries.

Combined oral chelation with DFO and DFP (9) in 39/52 β-TM patients with abnormal glucose metabolism, 44% normalized. In 18/52 requiring thyroxine supplementation for hypothyroidism, 10 were able to discontinue, and four reduced their thyroxine dose. In 14/52 hypogonadal males on testosterone therapy, seven stopped treatments. Of the 19/52 females, who were hypogonadal on DFO monotherapy, six were able to conceive. Moreover, no patients developed de novo endocrine complications (9). Combined oral chelation with DFP and DFX significantly decreased serum ferritin level in children with severe IOL (10). A 40-year-old male with β-TM, with refractory severe iron overload, was successfully and safely chelated with a combination of DFO with DFX (11).

Nevertheless, in clinical practice, endocrine complications are still observed and have been mainly attributed to the poor compliance to ICT, chronic liver disease (9) and cost of medication The latter figure is even higher in patients of developing countries. The proportion of non-compliance to ICT was 24.7% amongst patients with TDT aged 9 years old and above, attending three tertiary hospitals in Malaysia (12). Moreover, a meta-analysis showed that the non-adherence to DFO ranged from 3.9% to 29.4%, non-adherence to DFP ranged from 5.1% to 17.6%, and non-adherence to DFX ranged from 1% to 14.7% (13).

In the recent decades, with the improvements of transfusion and ICT, the advances in the understanding the mechanism of iron toxicity and overloading, and the availability of noninvasive methods to monitor iron loading in the liver, heart, and pancreas, the life expectancy of β-TM patients has improved significantly in high-income countries (14). Nevertheless, the occurrence of endocrine disorders still persist and have been attributed to poor compliance to iron-chelating agents and cost of medication The latter figure is even higher for patients in developing countries.

Unlike supportive blood transfusions, hematopoietic stem cell transplantation (HSCT) offers the hope of a definitive cure for patients with β-TM (15). Advances in transplantation techniques and supportive care strategies have resulted in a significant improvement in survival of those who have undergone treatment. However, HSCT survivors are at risk of developing long-term complications, such as endocrinopathies. The risk of these complications is influenced by pre-HSCT therapeutic exposures, transplantation-related conditioning, and post-transplantation management of graft-versus-host disease (GVHD) (16).

Gene therapy with globin lentiviral vectors and genome editing to inhibit the *BCL11A* gene are currently under investigation (17). Gene therapy and HSCT, however, have limitations, are feasible in a

small subset of patients and require pre- transplantation conditioning.

Moreover, the recent approval of luspatercept, an erythroid maturation agent that binds select TGF-β superfamily ligands to diminish Smad 2/3 signaling and enhance late-stage erythropoiesis, offers a new long-term therapeutic option for adult patients with β-TM to reduce red blood cell transfusion burden, anemia, and iron overload (17).

The goal of this short review is to summarize and update knowledges about long-term growth and endocrine changes after HSCT in patients with β-TM in comparison to those conventionally treated with packed RBC transfusions and iron chelating agents.

Methods

Search Strategy

The search identified articles, published in the last 30 years, retrieved from PubMed, Google Scholar and Research Gate. As keywords, we used Medical Subject Headings such as "allogeneic bone marrow transplantation", "stem cells transplantation", "conditioning regimens ", "β-thalassemia major","transfusion-dependent thalassemia", "children", "adolescents","young adults", "growth", "endocrine abnormalities", "hypogonadism", "growth hormone deficiency", "hypothyroidism", "diabetes mellitus", "fertility ","cyclophosphamide", and "busulfan". Exclusion criteria: all articles included publication dates prior to 1990 and related topics not listed in the inclusion criteria.

Inclusion and exclusion article selection

Studies were included if they were published in peer-reviewed journals, in English, described

the protocols of conditioning regimens utilized in HSCT and were not abstracts or reviews. Titles were first screened to eliminate irrelevant articles. Abstracts were then reviewed to confirm eligibility, and selected articles were processed for full-text analysis. The search also included studies cited in relevant articles.

Results

Hemopoietic stem cell transplantation in patients with β-TM

In 1980, allogeneic HSCT was introduced as a treatment option (18). In the 1980s and early 1990s, more than 1,000 β-TM patients were transplanted in Pesaro (Italy) and in 900 consecutive unselected patients transplanted from an HLA-identical sibling donor a 20-year probability of thalassemia- free survival was reported in 73% of patients, who were divided into three classes based on presence of hepatomegaly, portal fibrosis, and a history of inadequate iron chelation (19).

Initial experiences with thalassemia patients undergoing allogeneic HSCT were limited to matched sibling donors (20). Later, various centers using modern improved transplantation approaches, and careful patient selection, reported a significant reduction of transplantation-related mortality (TRM) in young low-risk β- TM transplanted children (21). Nowadays, the availability of an international network of voluntary stem cell donor registries and cord blood banks has significantly increased the odds of finding a suitable HLA matched donor. Although acute and chronic GvHD remains the most important complication in unrelated HSCT in thalassemia, leading to significant rates of morbidity and mortality for a chronic non-malignant disease (22). For several decades little progress has been made in treating GvHD, with corticosteroids being the mainstay of first-line therapy. Over the past years, intensive pre-clinical research has led to an improved understanding of the pathophysiology of acute and to a lesser extend chronic GvHD. This has translated into the approval of several new agents for the treatment of both forms of GvHD (21-23).

Conditioning regimens for hematopoietic stem cell transplantation in patients with β-TM

The purpose of the preparative regimen is twofold: to provide adequate immunosuppression to prevent rejection of the transplanted graft and to eradicate the disease for which the transplant is being performed. The biological aspects of allogeneic

HSCT in β-TM are different from those for hematologic malignancies. For many years, the most common conditioning regimen reported in literature included oral busulfan (Bu) at 14 mg/kg followed by cyclophosphamide (Cy) given intravenously at 120-200 mg/kg. The addition of azathioprine, hydroxyurea and fludarabine to the Bu-Cy regimen have made an important contribution to improving the results in high-risk patients (24).

In the last decade, new conditioning regimens for β-TM patients have been introduced with improved results, such as intravenous Bu, or treosulfan associated with thiotepa and fludarabine (25-27), and the preferred graft-versus-host disease (GVHD) prophylaxis in the majority of published studies of HSCT from matched sibling donors consisted of cyclosporine and methotrexate (28).

In conclusion, HSCT has been well established for several decades and now offers very high rates of cure for β-TM patients who have access to this therapy. Outcomes have improved over the last decade, even in high-risk patients. This has been possible due to better risk stratification, more effective targeted dose adjustment of intravenous Bu during conditioning, a modified conditioning regimen and continually improving supportive care. Systematic follow-up is needed to measure long term outcomes and an adequate management needs to be provided post-HSCT for all pre-existing complications particularly iron chelation to prevent further organ dysfunction (29-33).

Pharmacology of alkylating agents

Alkylating agents are an important component of many conditioning protocols for HSCT in both children and adults. With increasing survival rates after HSCT, long-term effects represent a major concern especially in pediatric HSCT recipients. Toxicity profiles of the two major alkylating agents (Cy and Bu), are briefly reviewed.

Cyclophosphamide (Cy)

Cy is a synthetic nitrogen mustard alkylating agent, with antineoplastic and immunosuppressive activities. In the liver, Cy is converted to active metabolites including phosphoramide mustard, which binds to and crosslinks DNA and RNA, thereby inhibiting DNA replication and protein synthesis. This agent, at low doses, is also a potent immunosuppressant primarily by depleting T-regulatory cells (34).

Busulfan (Bu)

Busulfan is a bifunctional alkylating agent of the alkylsulfonate type; it hydrolyzes in aqueous environment and releases methanesulfonate groups, leading to a reactive carbonium ion that alkylates DNA. Its metabolism is complex and not yet completely understood. It is primarily metabolized by the liver through conjugation with glutathione, mainly by glutathione-S-transferase A1 (GSTA1) (35).

Treosulfan (Treo)

Treo is a water-soluble bifunctional alkylating agent and a structural analogue of busulfan. Although Treo has structural similarities with Bu, its mechanism of alkylation is different. As a pro-drug, it undergoes non-enzymatic and pH-dependent conversion into active mono and diepoxide derivatives under physiological conditions. Interpatient variability of clearance in children is high; between 30 and 68% have been reported in population pharmacokinetic studies (36). Treo has a strong myeloablative potential and is considered less toxic than Bu; therefore, it has been considered in children with malignant and non-malignant disorders an appealing alternative to Bu as part of conditioning of HSCT (37,38).

Thiotepa is often combined with Treo and Fludarabine (Flu) or Bu and Flu in a myeloablative regimen. Thiotepa is primarily metabolized by the hepatic system, where it is rapidly bio transformed by CYP3A4 and CYP2B6 to its key metabolite, TEPA, which is also an alkylating agent (39,40). Thiotepa and TEPA are eliminated in urine, but also dermally via sweat (39,40). Thiotepa is approved by the European Medicines Agency in adults and children, in combination with other chemotherapeutic agents, as both autologous and allogeneic HSCT therapy in hematological diseases and solid tumors (40).

Effects of alkylating agents on growth, bone formation and gonads in animal studies

Cyclophosphamide

In rats, Cy chemotherapy altered survival or proliferation of growth plate chondrocytes and metaphyseal osteoblastic cells and reduced heights of metaphyseal spongiosa trabecular bone, which may contribute to chemotherapy side effects of this drug on bone lengthening and bone mass accumulation (41). In addition, mice treated with Cy for 6 weeks had impaired bone formation as evidenced by significant reduction of bone mineral density (BMD) and decrease in alkaline phosphatase levels compared to mice without chemotherapy. Besides its direct effect of inhibiting bone formation it also inhibits bone removal, making the resulting bone loss particularly difficult to treat with antiresorptive therapy (42).

In mice, Cy treatment (100 mg/kg/day) for 7 days led to osteoporosis through inhibition of osteoblastogenesis as shown by decreasing the number and differentiation of bone mesenchymal stem cells (MSCs) and reducing the formation and activity of osteoblasts. In addition, Cy suppressed the osteoclastogenesis by reducing the maturation and activity of osteoclasts. Authors suggested that the effect of Cy on bone formation might play a dominant role in its detrimental effects on bone remodeling (43).

The negative effects on the gonads of mice consist of irreversible follicle loss and permanent impairment of oocyte quality (44) and high gonadotoxic effects when administered before the initiation of spermatogenesis (45, 46). Multidose regimens of Cy did not eliminate the stem spermatogonia but resulted in cell loss and residual damage (47).

Decapeptyl ameliorates cyclophosphamide-induced reproductive toxicity in male Balb/C mice (48). In addition, when GH-deficient rats were treated with GH, it was demonstrated to have a protective effect on the count and motility of spermatids following treatment with Cy (49).

Busulfan

In animals, Bu is known to have a detrimental effect on differentiating spermatogonia (50). In mice, Bu disrupts spermatogenesis by interrupting meiosis that decreases the percentage of cells in late phases. In addition, it disrupts the expression of genes/proteins important for spermatogenesis and increases intracellular oxidative stress (51).

In male mice, following single injections of Bu at 15, 30 or 45 mg/kg, regardless of Bu doses, fertility was lost within 4 weeks after treatment, while more than 95% spermatogonial stem cells (SSCs) were lost within 3 days. Fertility and SSC numbers gradually recovered with time, but the recoveries were delayed at higher busulfan doses. The loss and restoration of fertility after busulfan treatment are direct consequences of SSC loss and expansion (52).

Effects of alkylating agents on growth, bone formation and gonads in human

Cyclophosphamide

In human, Cy has a significant reproductive toxicity in both males and females. It interferes with spermatogenesis and oogenesis. Sterility, sometimes reversible, can occur in both men and women treated with Cy. This toxic effect depends on the dose and duration of therapy. Cy causes premature ovarian insufficiency by inducing death and/or accelerated activation of primordial follicles and increased atresia of growing follicles. It also causes an increase in damage to blood vessels and the stromal compartment and increment inflammation (52).

In males, spermatogenesis is much more likely to be disrupted than is testosterone production because the germinal epithelium of the testis is more sensitive to damage from cytotoxic drugs than the Leydig cells. The degree of damage to the germinal epithelium is influenced by the stage of sexual maturation of the testis. In general, the post pubertal testis appears to be more susceptible to damage than the prepubertal testis (53).

Busulfan

It is generally assumed that Bu/Cy-based conditioning regimens for HSCT do not affect growth, although Bakker et al. (54) found in 4/10 non β-TM children, without a history of irradiation, an insufficient secretion of growth hormone (GH). They suggested that Bu crosses blood brain barrier and accordingly might have negative outcome on growth.

In human, the preparative regimen including Bu is associated with damage to the testicular function in as much as 83% of patients. In prepubertal children, Sanders et al. (55) and Thibaud et al. (56) reported that Bu induced a complete ovarian failure with extremely rare spontaneous recovery. Moreover, Sanders et al.(55) demonstrated that Bu administered at myeloablative doses was associated with increased levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) as well as ovarian failure (57).

Comparing ovarian function in two groups of girls who received Bu versus those who did not receive Bu in the conditioning regimen showed that those treated with Bu had a significantly higher incidence of ovarian failure (100% vs 27%; P= 0.002). Among the 11 girls who did not receive Bu eight were prepubertal compared to five out of 10 in the Bu-treated group. In addition, ovarian toxicity of Bu was also severe and permanent and displayed irreversible reduction of reserve primordial follicles in the ovaries (58,59).

In males, Bu administration resulted in a permanent, more severe atrophy of the testicles that included detrimental effect on testicular histology, manifested by obliteration of the typical morphology of the seminiferous tubules and spermatogenic milieu. Zini et al. (60), reported that Bu interrupt DNA synthesis in sperm cells and lead to reduced sperm motility.

Growth and endocrine changes in patients with β-TM: conventional therapy versus after HSCT

Growth and endocrinopathies in patients with β-TM on conventional therapy:

The prevalence and severity of hypogonadism and short stature in β-TM varies among studies, depending on patients' age, genotype, transfusion frequency and starting age, compliance, and efficiency of iron chelation therapy. Intensive combined chelation has been shown to improve patients' iron load and consequently prevent, decrease or reverse multiple endocrine complications associated with transfusion iron overload including abnormal glucose metabolism, hypothyroidism, and hypogonadism. However, there is progressive increase of endocrinopathies in these patients related to age (longevity) and with increased hepatic iron overload. Therefore, in assessment of the prevalence of endocrine complications these important factors shall be conjointly interpreted (7,8).

Soliman et al. (61), described the prevalence of growth and endocrine abnormalities in adolescents and young adults with β-TM reported, after 2020, from 10 countries (Figure 1). Growth impairment and growth hormone deficiency (GHD) occurred from 31% to 49 %, hypogonadism and delayed or absent puberty from 35% to 57 %, primary hypothyroidism from 4% to 29 %, dysglycemia (impaired glucose tolerance and diabetes mellitus) from 5% to 17% and hypoparathyroidism from 1.2% to 10.5% of patients.

Recently, a meta-analysis of 74 studies, published from 1978 to 2019, on the prevalence of growth impairment was reported in patients with β-TM treated with conventional protocols (blood transfusion and iron chelation therapy). Studies from the following countries were included: Asia (71.6%), Europe (16.2%), Africa (6.7%), America (2.7%), Oceania (1.3%), and Multicenter (2.7%) (62). The overall mean age of the participants was about 14 years. The pooled prevalence of short stature was 48.9% and was higher in males (61.9%) compared to females (50.9%). The pooled prevalence of growth retardation was 41.1% and was higher in males (51.6%) versus females (33.1%). The pooled prevalence of GHD was 26.6% (62).

Short stature was defined when the patient height is more than two standard deviations below the mean for age, gender, and ethnicity, growth retardation was when the height of the subject was lower than the mid-parental-height (MPH) and GHD was defined when the peak of GH after provocative test was below 5 ng/mL (62).

In another meta-analysis of 44 studies, conducted by He et al. (63) including 16,605 patients, aged from 2 to 28 years, was reported that the prevalence of impaired fasting glucose, impaired glucose tolerance and diabetes mellitus were 17.2%, 12.4%, and 6.5%, respectively

In general, it was highly recognized that the high prevalence of growth retardation and endocrinopathies in patients with β-TM was primarily due to iron overload which induce oxidative damage to different organs including endocrine glands (pituitary, thyroid, pancreas and parathyroid) and the liver (leading to insulin resistance and low IGF1 secretion) (61-69).

Various combination schemes have been developed in order to maximize treatment efficacy, tolera-

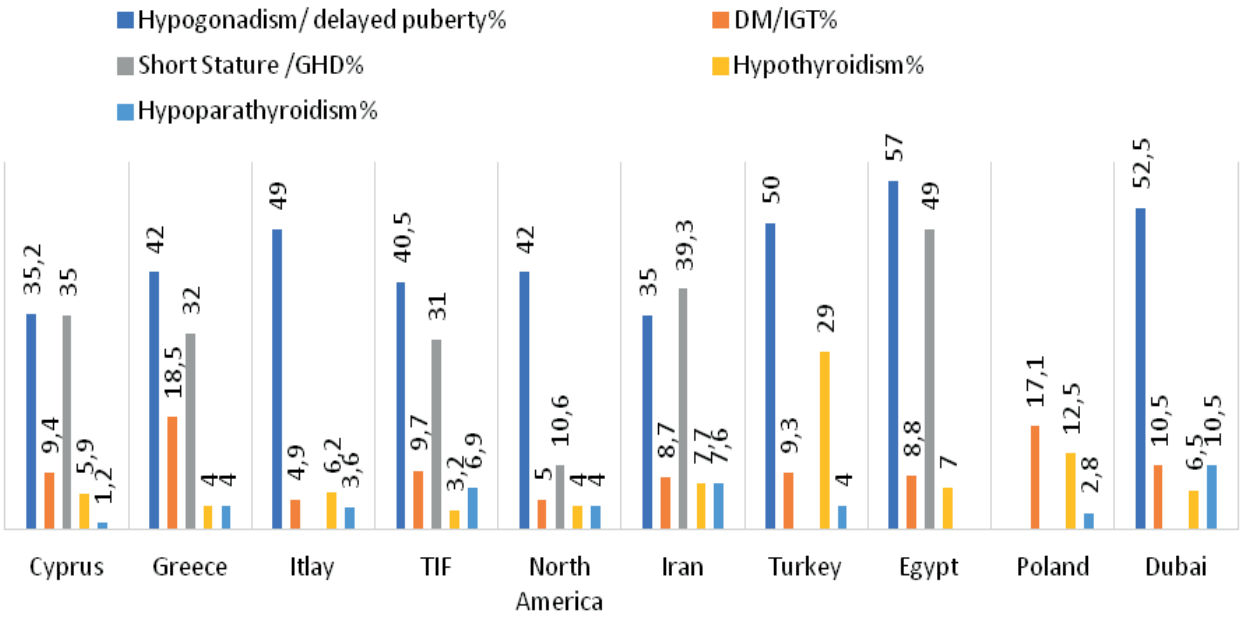

Figure 1. Prevalence (%) of short stature and endocrine complications, reported in 10 different countries after year 2000, in patients with β-TM.

bility and compliance and to prevent the development of iron-load complications (7,8, 61-69). Irregular use of chelating drugs was associated with a higher risk of iron tissue damage, regardless of the type of chelating agent. Additionally, combined chelating iron agents significantly decreased the prevalence of endocrine disorders when compared with monotherapy (65-68).

Growth and endocrinopathies after HSCT in patients with β-TM:

After HSCT a variable occurrence of growth and endocrine long-term consequences very reported from different centers (Table 1). In one study (73), a strict correlation was observed between age at time of transplant and final adult height. The patients whose age at transplant was <7 years had a less impaired growth rate than did patients who were >7 years. Moreover, greatest loss in height was observed in subjects who had higher serum levels of transaminases and ferritin and these biochemical parameters were strictly correlated to the final adult height. The mean final adult height, in subjects who received HSCT after 7 years of age, failed to achieve their full genetic potential.

Gonadal damage has been commonly reported in both sexes. Rahal et al. (85) evaluated long-term complications in 99 β-TM patients who successfully received HSCT. The median duration of clinical follow up was 12 years. After transplantation, 11% of patients developed thyroid dysfunction, 5% diabetes, and 2% heart failure. Hypogonadism was present in 56% of females and 14% of males. Female patients who reached a spontaneous puberty after HSCT were significantly younger at transplantation than those who experienced delayed puberty (median age 2.5 *vs* 8.7 years). Fertility was preserved in 9/27 females, aged 20 years or older, and 2 other patients became pregnant following oocyte donation. Moreover, male β-TM patients who underwent allogeneic HSCT had lower fertility potential, mainly in sperm parameters compared with patients treated with blood transfusion and chelation (82).

Health-related quality of life (HRQoL) measurements in β-TM patients have shown that HSCT was associated with improved health, activity, and emotional well-being compared to patients on conventional treatment chronic (80,89,90). The improvements were not as robust when HSCTs were performed in older β-TM patients with advanced disease or in the presence of chronic GVHD (83).

However, it must be kept in mind that when we interpreted the data of all these studies, there were

Table 1. Growth and endocrine disorders in patients with β-TM who underwent HSCT (Ref.70-88)

Author name, Ref. and Patients's age	Study design and Sample size	Growth retardation	Gonadal dysfunction	Thyroid disorder	Comments
Ponte et al., 1991 (70). 1.9 -18 yrs at HSCT.	Longitudinal-8	7/8 children had decreased growth velocity after HSCT.	-	-	1/8 patient (with normal ferritin) had normal growth after HSCT.
De Sanctis et al., 1991 (71). 9.3 -17.2 yrs.	Prospective - 30 (15 boys and 15 girls)	-	12 girls and 15 boys presented hypogonadotropic hypogonadism.	-	-
De Simone et al., 1995 (72). N.A.	Longitudinal - N.A.	Worsening of growth in patients > 7 yrs.	-	-	16 had impaired GH secretion.
De Simone et al., 2001 (73). N.A.	Longitudinal - 47	Subjects who received HSCT< 7 yrs did not reach the genetic target height.	-	-	-
De Sanctis et al., 2002 (74). N.A.	Retrospective-68 (30 males)	In all but 3 ex-thalassaemic females an improvement of standing height was observed.	66% females and 38% of males had abnormal puberty. 68% had gonadal dysfunction.	-	-
Li et al., 2004 (75). N.A.	Longitudinal - 32	40% had Ht-SDS < -2 before HSCT 15% had Ht-SDS <-2 after HSCT.	Gonadal failure was universal in girls, but boys were less affected.	-	1/10 developed GH deficiency. One patient developed diabetes mellitus.
Valchopapadopoulou et al., 2005 (76). N.A.	Prospective-25 (12 males)	-	14 (1 male and 13 females).	-	100% of the post-menarcheal females exhibited amenorrhea.
Di Bartolomeo et al., 2008 (77). Median age 9 yrs (range: 11 months to 28 yrs).	Prospective - 115	-	-	-	Ten spontaneous pregnancies were recorded (4 women - age at HSCT: 14, 14,13.17 yrs and 2 partners of male patients- age at HSCT:17 and 24 yrs). The births resulted in 10 normal babies.
Khalil et al., 2012 (78). 1.1-32 yrs at HSCT.	Retrospective-47	52% had final Ht-SDS < -2 after HSCT.	Gonadal failure in 80% of females and 36% of males.	11% HT.	9% DM.
Poomthavorn et al., 2013 (79). Median age13.2 yrs (range:5.9-25.8yrs).	Prospective-47	-	29 patients (62%) presented gonadal dysfunction.	-	-
La Nasa et al., 2013 (80). Mean age 34 yrs (range 21-48 yrs).	Cross sectional-109	-	-	-	Pregnancy: 14% women (n=6), 17% partners of male patients (n=11).
Aldemir-Kocabaş et al., 2014 (81). Mean age 12.4 ± 5.4 yrs.	Longitudinal-41	The height SDS were better in patients whose age was < 7 yrs at HSCT.	14.6% low FSH, LH, testosterone or estradiol.	10% HT	The risk of gonadal insufficiency was significantly lower in patients who underwent HSCT <7 years of age.

Table 1. Growth and endocrine disorders in patients with β-TM who underwent HSCT (Ref.70-88)

Author name, Ref. and Patients's age	Study design and Sample size	Growth retardation	Gonadal dysfunction	Thyroid disorder	Comments
Chaudhury et al., 2017 (82). Median age at HSCT 5.5 yrs.	Retrospective-176	Mean SDS for height and weight were low at baseline and remained low after HSCT. (79%).	Hypogonadism occurred most frequently in older transplanted patients.	-	Hypogonadism was significantly higher in recipients ≥ 7 years at the time of HSCT and in those with pre-existing morbidity.
Caocci et al., 2017 (83). Median age at HSCT 12 yrs (range: 1-45 yrs).	Multicentric -258	-	-	-	Pregnancy: 6 women and 6 partners of male patients.
Hamidieh et al., 2018 (84). 10.8 ± 3.9 yrs.	Prospective-20 (6 females)	8 low IGF-1.	-	-	HSCT did not appear to have an overall positive or negative effect after 3 months of observation.
Rahal et al., 2018 (85). Age range:3.1-11.2 yrs at HSCT.	Retrospective multicenter-99 (54 females)	The median Ht-SDS for final height was of −1.4 in males and −1.1 in females.	Hypogonadism was present in 56% of females and 14% of males.	11% HT	5% had diabetes and 36% of adults was overweight
See et al., 2018 (86) Age range:1-30 yrs	Retrospective-40	Mean height decreased of -0.84 SDS	55% gonadal dysfunction.	7.5% HT	Diabetes: 2 cases Pregnancy: 1 patient
Ntali et al., 2018 (87). Median age at HSCT 13 yrs (range:3–17 yrs).	Retrospective-11(5 males)	-	18.18% HH.	45.5% HT	72% had osteopenia/ osteoporosis. Two women conceived spontaneously while on HRT and their pregnancies were both uneventful.
Rostami et al., 2020 (88). Age range :16 -41 yrs.	Cross sectional - 43 males	-	Hypogonadism was documented in 36.6% patients.	-	Lower fertility potential.

Legend= HT: primary hypothyroidism; Ht-SDS: height -standard deviation score; GH: growth hormone; HH: hypogonadotropic hypogonadism; DM: diabetes mellitus; HRT: hormone replacement therapy.

some limitations, such as: (a) endocrine complications were not systematically investigated indicating the need for systematic tracking; (b) some studies only reported small patient numbers, which makes it difficult to assess the possible influence of transplantation; (c) different combinations of conditioning agents may have influenced the patient's outcome; and (d) due to the constantly evolving field and improvement of the transplant procedures over time, some of the regimens and procedures in the reported studies are already amended or revised/renewed.

Conclusions

HSCT technologies have improved substantially during recent years, and their outcome is likely to be much better today than it was at first. Various approaches have been developed for HSCT preparation and conditioning: intravenous busulfan, targeted intravenous busulfan, treosulfan, thiotepa, and fludarabine, as well as intensive pre-transplant transfusion-chelation regimens (91). Nevertheless, with increasing numbers of long-term survivors, delayed complications, often presenting years after HSCT, are becoming a concern. Late sequala may arise as a result of the disease for which transplantation was performed or from toxicity associated with the wide variety of conditioning regimens (70-88).

Considerable growth and endocrine abnormalities have been detected in β-TM patients after HSCT. Growth retardation and short final stature occurred to a greater extent in patients transplanted after the age of 7 years (72,73). Similar results were reported, recently, by Rahal et al. (85).

These data support the set-up of simple universal measures that allow early identification and proper and timely management of these consequences. Therefore, patients with β-TM should be recruited and evaluated for transplantation in early stage of the disease, especially before the age of seven years.

Primary gonadal failure was observed in both sexes (in males: germ cell failure with compensated Leydig cell failure; in females: ovarian failure with elevated gonadotropins in 80% of recipients) (71).

Most but not all of these endocrine problems were a consequence of conditioning regimens because etiology is multifactorial and is also correlated to previous iron overload, class risk factors before HSCT, patient's age, chronic GVHD, and corticosteroid treatment. The normal-low LH and FSH levels and reduced testosterone responses, after gonadotrophin releasing hormone and human chorionic gonadotrophin, noted in 15 prepubertal boys after HSCT were likely due to the association of iron deposition in the pituitary and Bu/Cy gonadal toxicity (71).

In the light of fertility impairment and uncommon recovery of gonadal damage after HSCT, (De Sanctis V, personal observation in 750 β-TM patients - unpublished data) these patients should receive comprehensive counselling regarding measures for fertility preservation. However. there is no doubt that, this must be taken into account when discussing the pros and cons of HSCT with the patient and parents. it must be also remembered that when a β-TM patient is treated with a conventional treatment traditional manner, delayed puberty or absence of puberty is the most common endocrine disorder and many girls even though they start to menstruate may develop secondary amenorrhoea or secondary hypogonadism (8, 92-98).

Today there are good possibilities for fertility preservation. Cryopreservation of spermatozoa is the first line treatment for fertility preservation in adolescent and adult male patients. Where sperm retrieval is impossible, such as in prepubertal boys, or it is unfeasible in adolescents prior to the onset of HSCT, alternative experimental treatments such as testicular tissue cryopreservation and the harvesting and banking of isolated spermatogonial stem cells can now be proposed as viable means of preserving fertility (99).

In females, egg or embryo cryopreservation are established approaches but are not achievable for many children and adolescents. Recently, the harvesting and cryopreservation of ovarian tissue represents a novel surgical option that allows for the possibility of fertility preservation to be extended to children of all ages. These procedures appear to be safe and do not add to transplant-related morbidity (100-102).

In conclusion, the growing data on these disorders in the post-transplant setting highlight the need for more research and evidence-based guidelines. After HSCT we recommend an annual assessment of growth, pubertal development, endocrine, sexual, and reproductive functions is recommended. Additionally, a regular surveillance, early diagnosis, treatment, and follow-up in a multi-disciplinary specialized setting are suggested to optimize the patient's quality of life.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Thein SL. Genetic Basis and Genetic Modifiers of β-Thalassemia and Sickle Cell Disease. Adv Exp Med Biol 2017;1013:27-57.
2. Jaing TH, Chang TY, Chen SH, Lin CW, Wen YC, Chiu CC. Molecular genetics of β-thalassemia: A narrative review. Medicine (Baltimore) 2021;100(45):e27522.
3. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ 2008;86:480–7
4. Viprakasit V, Ekwattanakit S. Clinical Classification, Screening and Diagnosis for Thalassemia. Hematol Oncol Clin North Am 2018;32:193-211.
5. Taher AT, Cappellini MD. How I manage medical complications of beta-thalassemia in adults. Blood 2018;132:1781–91.
6. Cappellini MD, Farmakis D, Porter J, Taher A. 2021 Guidelines for the Management of Non Transfusion Dependent Thalassaemia (NTDT). 4rd ed. Nicosia, Cyprus: Thalassaemia International Federation; 2021.
7. Vogiatzi MG, Macklin EA, Trachtenberg FL, et al. Differences in the prevalence of growth, endocrine and vitamin D abnormalities among the various thalassaemia syndromes in North America. Br J Haematol 2009; 146:546-56.
8. De Sanctis V, Elsedfy H, Soliman AT, et al . Endocrine profile of β-thalassemia major patients followed from childhood to advanced adulthood in a tertiary care center. Indian J Endocrinol Metab 2016;20:451-9.

9. Farmaki K, Tzoumari I, Pappa C, Chouliaras G, Berdoukas V. Normalisation of total body iron load with very intensive combined chelation reverses cardiac and endocrine complications of thalassaemia major. Br J Haematol 2010;148:466-75.
10. DivakarJose RR, Delhikumar CG, Ram Kumar G. Efficacy and Safety of Combined Oral Chelation with Deferiprone and Deferasirox on Iron Overload in Transfusion Dependent Children with Thalassemia - A Prospective Observational Study. Indian J Pediatr 2021;88:330-5.
11. Voskaridou E, Komninaka V, Karavas A, Terpos E, Akianidis V, Christoulas D. Combination therapy of deferasirox and deferoxamine shows significant improvements in markers of iron overload in a patient with β-thalassemia major and severe iron burden. Transfusion 2014;54:646-9.
12. Chai CAS, Nani Draman N, Yusoff SSM, et al. Non-compliance to iron chelation therapy in patients with transfusion-dependent thalassaemia. Ped Hematol Oncol J 2021;6:207-15
13. Fortin PM, Fisher SA, Madgwick KV, et al. Interventions for improving adherence to iron chelation therapy in people with sickle cell disease or thalassaemia. Cochrane Database Syst Rev 2018;5: CD012349.
14. Wood JC, Ghugre N. Magnetic resonance imaging assessment of excess iron in thalassemia, sickle cell disease and other iron overload diseases. Hemoglobin 2008;32:85-96.
15. Baronciani D, Angelucci E, Potschger U, et al. Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000-2010. Bone Marrow Transplant 2016; 51:536-41.
16. Bhatia S. Long-term health impacts of hematopoietic stem cell transplantation inform recommendations for follow-up. Expert Rev Hematol 2011; 4: 437–54.
17. Cappellini MD, Motta I. New therapeutic targets in transfusion-dependent and -independent thalassemia. Hematology Am Soc Hematol Educ Program 2017;2017:278-83.
18. Thomas ED, Buckner CD, Sanders JE, et al. Marrow transplantation for Thalessemia. Lancet 1982; 2: 227-9.
19. Angelucci E, Baronciani D. Allogeneic stem cell transplantation for thalassemia major. Haematologica 2008;93:1780-4.
20. Jaing TH, Chang TY, Chen SH, Lin CW, Wen YC, Chiu CC. Molecular genetics of β-thalassemia: A narrative review. Medicine (Baltimore) 2021;100(45):e27522.
21. Mulas O, Mola B, Caocci G, La Nasa G. Conditioning Regimens in Patients with β-Thalassemia Who Underwent Hematopoietic Stem Cell Transplantation: A Scoping Review. J Clin Med 2022;11(4):907.
22. La Nasa G, Vacca A, Littera R,et al. What Unrelated Hematopoietic Stem Cell Transplantation in Thalassemia Taught us about Transplant Immunogenetics. Mediterr J Hematol Infect Dis 2016;8(1): e2016048.
23. Link-Rachner CS, Sockel K, Schuetz C. Established and Emerging Treatments of Skin GvHD. Front Immunol 2022;13:838494.
24. Sodani P, Gaziev D, Polchi P, et al. New approach for bone marrow transplantation in patients with class 3 thalassemia aged younger than 17 years. Blood 2004;104:1201-3.
25. Li C, Wu X, Feng X, et al. A novel conditioning regimen improves outcomes in beta-thalassemia major patients using unrelated donor peripheral blood stem cell transplantation. Blood 2012;120:3875-81.
26. Tan W, He Y, Feng X, et al. Thiotepa-Based Conditioning Regimen Compared to Non-Thiotepa Conditioning Regimen Prior to Allogeneic Stem Cell Transplantation in β Thalassemia Major: Impact on Survival. Blood 2018; 132 (Supplement 1): 2082.
27. 27.King AA, Kamani N, Bunin N, Sahdev I,et al. Successful matched sibling donor marrow transplantation following reduced intensity conditioning in children with hemoglobinopathies. Am J Hematol 2015; 90: 1093–8.
28. Angelucci E, Matthes-Martin S, Baronciani D, et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. Haematologica 2014;99:811-20.
29. Khalil A, Zaidman I, Elhasid R, et al. Factors influencing outcome and incidence of late complications in children who underwent allogeneic hematopoietic stem cell transplantation for hemoglobinopathy. Pediatr Hematol Oncol 2012;29:694-703.
30. La Nasa G, Caocci G, Efficace F, et al. Longterm health-related quality of life evaluated more than 20 years after hematopoietic stem cell transplantation for thalassemia. Blood 2013;122:2262-70.
31. Angelucci E, Muretto P, Lucarelli G, et al. Phlebotomy to reduce iron overload in patients cured of thalassemia by bone marrow transplantation. Italian Cooperative Group for Phlebotomy Treatment of ransplanted Thalassemia Patients. Blood 1997;90:994-8.
32. Giardini C, Galimberti M, Lucarelli G, et al. Desferrioxamine therapy accelerates clearance of iron deposits after bone marrow transplantation for thalassaemia. Br J Haematol 1995;89:868-73.
33. 33, Yesilipek MA, Karasu G, Kazik M, Uygun V, Ozturk Z. Posttransplant oral iron-chelating therapy in patients with beta-thalassemia major. Pediatr Hematol Oncol 2010; 27:374-9.
34. Dix SP, Yee GC. Pharmacologic and biologic agents. In: Whedon MK, Wujcik D, Edts . Blood and Marrow Stem Cell Transplantation: Principle, Practice and Nursing Insights. 2nd ed. Sudbury, MA: Jones and Barrlett Publishers; 1997; pp.100–150
35. Krivoy N, Hoffer E, Lurie Y, Bentur Y, Rowe JM. Busulfan use in hematopoietic stem cell transplantation: pharmacology, dose adjustment, safety and efficacy in adults and children. Curr Drug Saf 2008;3:60-6.
36. ten Brink MH, Zwaveling J, Swen JJ, Bredius RG, Lankester AC, Guchelaar HJ. Personalized busulfan and treosulfan conditioning for pediatric stem cell transplantation: the role of pharmacogenetics and pharmacokinetics. Drug Discov Today 2014;19:1572-86.
37. Slatter MA, Rao K, Abd Hamid IJ, et al . Treosulfan and

Fludarabine Conditioning for Hematopoietic Stem Cell Transplantation in Children with Primary Immunodeficiency: UK Experience. Biol Blood Marrow Transplant 2018;24:529-36.
38. 38.Slatter M, Boztug H, Pötschger U, et al. Treosulfan-based conditioning regimens for allogeneic haematopoietic stem cell transplantation in children with non-malignant diseases. Bone Marrow Transplant 2015;50:1536-41.
39. Jacobson PA, Green K, Birnbaum A, Remmel RP. Cytochrome P450 isozymes 3A4 and 2B6 are involved in the in vitro human metabolism of thiotepa to TEPA. Cancer Chemother Pharmacol 2002; 49:461–7.
40. Kondo E, Ikeda T, Goto H, et al. Pharmacokinetics of thiotepa in high-dose regimens for autologous hematopoietic stem cell transplant in Japanese patients with pediatric tumors or adult lymphoma. Cancer Chemother Pharmacol 2019;84:849-60.
41. Xian CJ, Cool JC, van Gangelen J, Foster BK, Howarth GS. Effects of etoposide and cyclophosphamide acute chemotherapy on growth plate and metaphyseal bone in rats. Cancer Biol Ther 2007;6:170-7.
42. Ponnapakkam T, Katikaneni R, Nichols T, et al. Prevention of chemotherapy-induced osteoporosis by cyclophosphamide with a long-acting form of parathyroid hormone. J Endocrinol Invest 2011;34:e392-7.
43. Zhao D, Wang C, Zhao Y, et al . Cyclophosphamide causes osteoporosis in C57BL/6 male mice: suppressive effects of cyclophosphamide on osteoblastogenesis and osteoclastogenesis. Oncotarget 2017; 8:98163-83.
44. Kim J, You S. Extended adverse effects of cyclophosphamide on mouse ovarian function. BMC Pharmacol Toxicol. 2021;22(1):3.
45. McGee EA, Hsueh AJ. Initial and cyclic recruitment of ovarian follicles. Endocr Rev 2000;21:200–14.
46. Drumond AL, Weng CC, Wang G, Chiarini-Garcia H, Eras-Garcia L, Meistrich ML. Effects of multiple doses of cyclophosphamide on mouse testes: accessing the germ cells lost, and the functional damage of stem cells. Reprod Toxicol 2011;32:395-406.
47. Kanno TYN., Sensiate L A, de Paula NA, Salles MJS. Toxic effects of different doses of cyclophosphamide on the reproductive parameters of male mice . Bras J Pharm Sc 2009; 45:313-9.
48. Niakani A, Farrokhi F, Hasanzadeh. Decapeptyl ameliorates cyclophosphamide-induced reproductive toxicity in male Balb/C mice: histomorphometric, stereologic and hormonal evidences. Iran J Reprod Med 2013;11:791-800.
49. Satoh K, Ohyama K, Nakagomi Y, et al. Effects of growth hormone on testicular dysfunction induced by cyclophosphamide (CP) in GH-deficient rats. Endocr J 2002; 49:611–9.
50. Bucci LR, Meistrich ML. Effects of busulfan on murine spermatogenesis: cytotoxicity, sterility, sperm abnormalities, and dominant lethal mutations. Mutat Res 1987;176:259-68.
51. Ma D, Han P, Song M, et al. β-carotene Rescues Busulfan Disrupted Spermatogenesis Through Elevation in Testicular Antioxidant Capability. Front Pharmacol 2021;12:593953.
52. Spears N, Lopes F, Stefansdottir A, et al. Ovarian damage from chemotherapy and current approaches to its protection. Hum Reprod Update 2019;25:673-93.
53. Rivkees SA, Crawford JD. The relationship of gonadal activity and chemotherapy-induced gonadal damage. JAMA1988;259:2123-5.
54. Bakker B, Oostdijk W, Bresters D, et al. Disturbances of growth and endocrine function after busulphan-based conditioning for haematopoietic stem cell transplantation during infancy and childhood. Bone Marrow Transplant 2004;33:1049-56.
55. Sanders JE, Hawley J, Levy W, et al. Pregnancies following high-dose cyclophosphamide with or without high-dose busulphan or total-body irradiation and bone marrow transplantation. Blood 1996; 87:3045–52.
56. Thibaud E, Rodriguez-Macias K, Trivin C, et al. Ovarian function after bone marrow transplantation during childhood. Bone Marrow Transplant 1998;21:287–90.
57. Teinturier C, Hartmann O, Valteau-Couanet D, Benhamou E, Bougneres PF. Ovarian function after autologous bone marrow transplantation in childhood: high-dose busulfan is a major cause of ovarian failure. Bone Marrow Transplant 1998;22:989-94.
58. Teinturier C, Hartmann O, Valteau-Couanet D, Benhamou E, Bougneres PF. Ovarian function after autologous bone marrow transplantation in childhood: high-dose busulfan is a major cause of ovarian failure. Bone Marrow Transplant 1998;22:989-94.
59. Levi M, Stemmer SM, Stein J, Shalgi R, Ben-Aharon I. Treosulfan induces distinctive gonadal toxicity compared with busulfan. Oncotarget 2018;9:19317-27.
60. Zini A, Phillips S, Lefebvre J, Baazeem A, Bissonnette F, Kadoch IJ, et al. Anti-sperm antibodies are not associated with sperm DNA damage: a prospective study of infertile men. J Reprod Immunol 2010;85:205–8
61. Soliman AT, De Sanctis V, Yassin M. Focus on prevalence of endocrinopathies in β-thalassemia major (TDT), intermedia (NTDT) and sickle cell disease (SCD). Riv Ital Med Adolesc (EndoThal) 2020; 18:104-8.
62. Arab-Zozani M, Kheyrandish S, Rastgar A, Miri-Moghaddam E. A Systematic Review and Meta-Analysis of Stature Growth Complications in β-thalassemia Major Patients. Ann Glob Health 2021;87:1-17.
63. He LN, Chen W, Yang Y, et al. Elevated prevalence of abnormal glucose metabolism and other endocrine disorders in patients with thalassemia major: a meta-analysis. Biomed Res Int. 2019; 2019: 6573497.
64. De Sanctis V, Eleftheriou A, Malaventura C; Thalassaemia International Federation Study Group on Growth and Endocrine Complications in Thalassaemia. Prevalence of endocrine complications and short stature in patients with thalassaemia major: a multicenter study by the Thalassaemia International Federation (TIF). Pediatr Endocrinol Rev 2004;2 Suppl 2:249-55.

65. Christoforidis A, Perifanis V, Athanassiou-Metaxa M. Combined chelation therapy improves glucose metabolism in patients with beta-thalassaemia major. Br J Haematol 2006;135:271– 2.
66. De Sanctis V, Soliman AT, Canatan D, et al. Thyroid Disorders in Homozygous β-Thalassemia: Current Knowledge, Emerging Issues and Open Problems. Mediterr J Hematol Infect Dis 2019;11(1):e2019029.
67. Farmaki K, Tzoumari I, Pappa C. Oral chelators in transfusion-dependent thalassemia major patients may prevent or reverse iron overload complications. Blood Cells Mol Dis 2011;47:33-40.
68. Sobhani S, Rahmani F, Rahmani M, Askari M, Kompani F. Serum ferritin levels and irregular use of iron chelators predict liver iron load in patients with major beta thalassemia: a cross-sectional study. Croat Med J 2019; 60:405–13.
69. Singer ST, Fischer R, Allen I, et al. Pituitary iron and factors predictive of fertility status in transfusion dependent thalassemia. Haematologica 2021;106:1740-4.
70. Ponte G, Ferrara M, Esposito L. Growth in homozygous beta-thalassemia after bone marrow transplantation. Bone Marrow Transplant 1991;8 Suppl 1:68-9.
71. De Sanctis V, Galimberti M, Lucarelli G, Polchi P, Ruggiero L, Vullo C. Gonadal function after allogenic bone marrow transplantation for thalassaemia. Arch Dis Child1 1991;66:517-20.
72. De Simone M, Olioso P, Di Bartolomeo P, et al. Growth and endocrine function following bone marrow transplantation for thalassemia. Bone Marrow Transplant 1995;15:227-33.
73. De Simone M, Verrotti A, Iughetti L, et al. Final height of thalassemic patients who underwent bone marrow transplantation during childhood. Bone Marrow Transplant 2001;28:201-5.
74. De Sanctis V. Growth and Puberty and Its Management in Thalassaemia. Horm Res. 2002;58 Suppl 1:72–9.
75. Li CK, Chik KW, Wong GW, Cheng PS, Lee V, Shing MM. Growth and endocrine function following bone marrow transplantation for thalassemia major. Pediatr Hematol Oncol 2004;21:411-9.
76. Vlachopapadopoulou E, Kitra V, Peristeri J, et al. Gonadal function of young patients with beta-thalassemia following bone marrow transplantation. J Pediatr Endocrinol Metab 2005;18:477-84.
77. Di Bartolomeo P, Santarone S, Di Bartolomeo E, et al. Long-Term Results of Survival in Patients with Thalassemia Major Treated with Bone Marrow Transplantation. Am J Hematol 2008;83:528-30.
78. Khalil A, Zaidman I, Elhasid R, Peretz-Nahum M, Futerman B, Ben-Arush M. Factors influencing outcome and incidence of late complications in children who underwent allogeneic hematopoietic stem cell transplantation for hemoglobinopathy. Pediatr Hematol Oncol 2012;29:694-703.
79. Poomthavorn P, Chawalitdamrong P, Hongeng S, et al. Gonadal function of beta-thalassemics following stem cell transplantation conditioned with myeloablative and reduced intensity regimens. J Pediatr Endocrinol Metab 2013;26:925-32.
80. La Nasa G, Caocci G, Efficace F, et al. Long- Term Health-Related Quality of Life Evaluated More than 20 Years after Hematopoietic Stem Cell Transplantation for Thalassemia. Blood 2013;122:2262-70.
81. Aldemir-KocabaşB, Tezcan-Karasu G, Bircan I, Bircan O, Aktaş-Samur A, Yeşilipek MA. Evaluating the patients with thalassemia major for long-term endocrinological complications after bone marrow transplantation. Pediatr Hematol Oncol 2014;31:616-23.
82. Chaudhury S, Ayas M, Rosen C, et al. A Multicenter Retrospective Analysis Stressing the Importance of Long-Term Follow-Up after Hematopoietic Cell Transplantation for β-Thalassemia. Biol Blood Marrow Transplant 2017;23:1695-700.
83. Caocci G, Orofino MG, Vacca A, et al. Long-term survival of beta thalassemia major patients treated with hematopoietic stem cell transplantation compared with survival with conventional treatment. Am J Hematol 2017;92:1303-10.
84. Hamidieh AA, Mohseni F, Behfar M, et al. Short-term Assessment of HSCT Effects on the Hypothalamus-Pituitary Axis in Pediatric Thalassemic Patients. Arch Iran Med 2018;21:56-60.
85. Rahal I, Galambrun C, Bertrand Y, et al. Late effects after hematopoietic stem cell transplantation for β-thalassemia major: the French national experience. Haematologica 2018;103:1143-9.
86. See WQ, Tung JY, Cheuk DK, et al. Endocrine complications in patients with transfusiondependent thalassaemia after haematopoietic stem cell transplantation. Bone Marrow Transplantat 2018;53:356-60.
87. Ntali G, Stella Roidi R, Stavroula Michala S, et al. Long-term endocrine sequelae of patients with beta-thalassemia following bone marrow transplantation in childhood/adolescence. Endocrine Abs 2018; 56;P678.
88. Rostami T, Mohammadifard MA, Ansari S, et al. Indicators of male fertility potential in adult patients with beta-thalassemia major: a comparative study between patients undergone allogeneic stem cell transplantation and transfusion-dependent patients. Fertil Res Pract 2020;6:4.
89. Cheuk DK, Mok AS, Lee AC, et al. Quality of life in patients with transfusion-dependent thalassemia after hematopoietic SCT. Bone Marrow Transplant 2008;42:319-27.
90. Uygun V, Tayfun F, Akcan M, et al . Quality of life assessment in hematopoietic stem cell transplantation performed on thalassemia major patients. Pediatr Hematol Oncol 2012;29:461-71.
91. Angelucci E. Hematopoietic stem cell transplantation in thalassemia. Hematology Am Soc Hematol Educ Program 2010;2010:456-62.
92. 92.De Sanctis V, Soliman AT, Yassin MA, et al. Hypogonadism in male thalassemia major patients: pathophysiology, diagnosis and treatment. Acta Biomed 2018;89:6-15.
93. De Sanctis V, Elsedfy H, Soliman AT, et al. Acquired Hypogonadotropic Hypogonadism (AHH) in Thalassaemia

Major Patients: An Underdiagnosed Condition? Mediterr J Hematol Infect Dis 2016;8(1): e2016001.
94. De Sanctis V, Soliman AT, El-Hakim I, et al . Marital status and paternity in patients with Transfusion- Dependent Thalassemia (TDT) and Non Transfusion-Dependent Thalassemia (NTDT): an ICET - A survey in different countries. Acta Biomed 2019;90:225-37.
95. De Sanctis V, Soliman AT, Elsedfy H, Di Maio S, Canatan D, Soliman N, Karimi M, Kattamis C. Gonadal dysfunction in adult male patients with thalassemia major: an update for clinicians caring for thalassemia. Expert Rev Hematol 2017;10:1095-1106.
96. Chen MJ, Peng SS, Lu MY, Yang YL, Jou ST, Chang HH, Chen SU, Lin DT, Lin KH. Effect of iron overload on impaired fertility in male patients with transfusion-dependent beta-thalassemia. Pediatr Res 2018;83:655-61.
97. Bajoria R, Chatterjee R. Hypogonadotrophic hypogonadism and diminished gonadal reserve accounts for dysfunctional gametogenesis in thalassaemia patients with iron overload presenting with infertility. Hemoglobin 2011;35:636-42.
98. Perera D, Pizzey A, Campbell A, Katz M, Porter J, Petrou M, Irvine DS, Chatterjee R. Sperm DNA damage in potentially fertile homozygous beta-thalassaemia patients with iron overload. Hum Reprod 2002;17:1820-5.
99. Picton HM, Wyns C, Anderson RA, et al.; ESHRE Task Force On Fertility Preservation In Severe Diseases. A European perspective on testicular tissue cryopreservation for fertility preservation in prepubertal and adolescent boys. Hum Reprod 2015;30:2463-75.
100. Brodigan K, Kapadia M, Frazier AL, et al. Safety of Surgical Fertility Preservation Procedures in Children Prior to Hematopoietic Stem Cell Transplant.Transplant Cell Ther 2021;27:696.e1-696.
101. Tichelli A, Rovó A. Fertility issues following hematopoietic stem cell transplantation. Expert Rev Hematol 2013;6:375-88.
102. ESHRE Guideline Group on Female Fertility Preservation, Anderson RA, Amant F, Braat D, et al. ESHRE guideline: female fertility preservation. Hum Reprod Open. 2020;2020(4),52.

Received: 10 July 2022
Accepted: 10 August 2022
Correspondence:
Shayma Ahmed, MD
Department of Pediatrics
Hamad General Hospital
Doha, Qatar
Phone: 00974 33300367
E-mail: SMohammed5@hamad.qa