Chapter 5

Hypogonadism in Female Patients with Beta Thalassemia Major

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Additional information is available at the end of the chapter

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Abstract

Beta thalassemia is the most frequent hemoglobinopathy worldwide. In patients with beta thalassemia major (BTM), the consequence of long-term life-saving transfusions is iron overload in liver, heart and endocrine glands. Hypogonadotropic hypogonadism is the most frequent endocrine complication. Recent progresses in the treatment of BTM dramatically improved life expectancy and quality of life of these patients, making the concern for fertility and pregnancy to gain importance. Therefore, we performed a review of the available data regarding hypogonadism in female patients with BTM. We found that hypogonadotropic hypogonadism is still frequently found in female patients with BTM. Pituitary iron overload seems to be the main factor contributing to hypogonadism occurrence, although iron-related damage of the ovaries and the genital tract cannot be excluded. The increased oxidative stress observed in BTM patients was hypothesized as a contributor to pituitary-gonadal dysfunction. Hypogonadism has significant consequences on quality of life, final height, bone health and fertility of the patients. Estroprogestative administration is essential in order to minimize consequences, although the best treatment regimen should be carefully weighted in each patient. Although spontaneous fertility is reduced by the presence of hypogonadism, it seems that ovulation-induction treatment with gonadotropins is effective in achieving pregnancies in majority of patients.

Keywords: beta thalassemia, fertility, infertility, hypogonadism, pregnancy, short stature, osteoporosis

1. Introduction

Beta thalassemia major (BTM) is a severe medical condition that requires long-term life-saving transfusions. As a consequence, secondary hemosiderosis results in significant morbidity due

to organ injury produced by excessive iron. Most frequently affected organs are heart, liver and endocrine glands. While iron-induced cardiomyopathy is the most common cause of death in BTM patients, endocrinopathies are among the most frequent complications, leading to a low quality of life. In the last decades, increase of iron chelating agents' availability and better compliance to treatment with oral agents was followed by an increase in life expectancy and a decrease of morbidity in BTM patients. However, the prevalence of endocrine complications remained high enough to significantly impact their quality of life. Hypogonadism is the most prevalent endocrine complication in BTM patients and affects patients from various age groups. The early forms of hypogonadism have a clinical impact starting at age of 10–11 years as decreased growth velocity, short stature and delayed pubertal development. In pubertal patients, the appearance of hypogonadism results in arrested pubertal development and lack of sexual maturation. In adult patients with full pubertal development, the occurrence of hypogonadism causes regression of secondary sexual characteristics, sexual dysfunction and infertility. Therefore, hypogonadism has a significant psychological impact and is associated with complications as infertility, osteoporosis and short stature which lead to additional morbidity and medical care requirements. Early diagnosis and treatment of hypogonadism has a particular importance for future fertility in female BTM in order to maintain the normal genital tract and to avoid complications as short stature and osteoporosis which will interfere with normal evolution of a future pregnancy.

Therefore, the aim of the present chapter was to perform a review of the available data regarding the prevalence, physiopathology, consequences and treatment of hypogonadism in female patients with BTM. We searched in PubMed and Google Scholar using the following key words: beta thalassemia, fertility, infertility, hypogonadism, pregnancy, short stature and osteoporosis. Only articles written in English were selected.

2. The prevalence of hypogonadism in BTM patients

Hypogonadism is the most frequent endocrine complication in BTM patients, the prevalence being as high as 50–100% in various populations [1–4]. The high variability in the proportion of patients affected by hypogonadism could be explained by ethnic factors, different availability of therapeutic agents, economic status and genetic susceptibility. For example, in the study by Gulati et al. [4], 10 of 11 BTM young patients (90%) from a developing country were presented with early form of hypogonadism. In turn, a study on 382 BTM patients treated with desferrioxamine at the **Thalassemia** Centre in Dubai showed a significantly lower prevalence of hypogonadism of only 25% [5]. However, most studies reported a prevalence of hypogonadism of approximately 50% [6].

In spite of significant progresses on the therapeutic regimens of thalassemia major aiming to correct most of the factors considered responsible for BTM complications, hypogonadism continues to be frequently found in these patients. Moreover, it seems that the prevalence was not significantly reduced along with hematologic treatment improvement [7]. Gamberini et al.

followed a cohort of 273 patients with BTM from diagnosis for 30 years in Ferrara Centre and observed that, although the incidence of the other endocrine complications (hypothyroidism, hypoparathyroidism and diabetes mellitus) has decreased over time, the proportion of patients with primary and secondary amenorrhoea was similar in the three cohorts according to the year of birth [7]. Moreover, the hypogonadism prevalence did not decrease along with the decrease in serum ferritin over time, suggesting irreversible iron-induced lesions or an increased susceptibility of pituitary cells to damages produced by excessive iron.

3. Etiopathogenesis of hypogonadism in BTM patients

3.1. Etiology of hypogonadism in BTM

Hypogonadism is defined as low levels of sex hormones as a consequence of decreased production by the gonads. There are two types of hypogonadism: hypogonadotropic hypogonadism (or secondary gonadal insufficiency) due to a pituitary defect in gonadotropins production and hypergonadotropic hypogonadism (or primary gonadal insufficiency) due to a defect in gonadal steroidogenesis. In both forms of hypogonadism, the clinical picture is the same with amenorrhoea, regression of secondary sexual characteristics (breast, uterus and vaginal atrophy) and hot flushes. In hypogonadal patients, the gametogenesis is also affected, the consequence being anovulation and infertility. In BTM, most patients with hypogonadism are presented with low gonadotropins levels indicating the presence of hypogonadotropic hypogonadism [2]. Although these data support the existence of a pituitary defect, the coexistence of an ovarian lesion cannot be excluded. However, the success of ovulation induction with gonadotropins in hypogonadic female BTM patients shows that, if ovarian lesions coexist, these are mild or reversible with a proper iron chelation as part of preconceptional care.

Iron overload is considered as the main factor involved in pathogenesis of hypogonadism in BTM patients. This hypothesis is supported by several types of observations. For instance, most studies reported an association of high serum ferritin levels with the presence of hypogonadism [5, 8] or with a faster evolution to hypogonadism [8]. Serum ferritin level is considered an accurate marker of tissue iron deposits, being correlated with T2* magnetic resonance imaging of the heart, liver [8] and pituitary [9]. Moreover, magnetic resonance imaging showed that pituitary iron and volume loss predict the presence of hypogonadism [10].

Whether the hypogonadism is reversible with a better chelation therapy is incompletely clarified. In some of the studies, the recent serum ferritin was poorly correlated to the presence of hypogonadism, suggesting that a previous deleterious effect of iron overload could not be reversed by decreasing glandular iron [6]. However, the study by Chatterjee and Katz [11] found that BTM patients with less severe iron overload and organ damage in the hypothalamic-pituitary axis could present with potentially reversible hypogonadotropic hypogonadism. In turn, patients with severe iron overloaded had an irreversible form of hypogonadism [11].

It was also suggested that the anterior pituitary has a high susceptibility to iron accumulation that could be explained by the increased number of transferrin receptors in this tissue [12].

Other factors were observed to be associated with the presence of hypogonadism, being possible contributors to its etiology. For instance, the study by Belhoul et al. demonstrated that splenectomy is related to the presence of hypogonadism independently of ferritin levels [5], the mechanism behind this association being unknown. It was also reported that the development of hypogonadotropic hypogonadism is associated with the severity of the underlying genetic defect in beta-globin synthesis gene [13, 14]. The most probable explanation is that the patients with severe defects in hemoglobin synthesis require higher quantities of transfused blood, followed by a more severe iron overload. Liver dysfunction, diabetes, hypothyroidism [15] and lower hemoglobin levels [16] were also reported as possible contributors to hypogonadism.

3.2. Mechanisms involved in hypogonadism occurrence in BTM

In patients with BTM, the excessive iron deposition in tissues, following chronic life-saving transfusion regimens, generates an increase in non-transferrin bound iron. This form of iron has high tissue toxicity due to the excessive production of the reactive oxygen species (ROS) [17]. Because ROS have a pro-oxidant activity, the excessive production of ROS disrupts the oxidants/antioxidants balance of the cells generating chronic oxidative stress [18]. Moreover, the antioxidant mechanisms in BTM patients could be decreased, contributing to oxidative stress. The antioxidative defense is performed by enzymic (superoxide dismutase, catalase, and glutathione peroxidase) and nonenzymic systems (scavenging molecules endogenously produced like GSH, ubiquinols and uric acid or derived from the diet, such as vitamins C and E). In patients with BTM, the level of vitamin E, glutathione peroxidase and superoxide dismutase [19], total antioxidant capacity [20], ascorbate, vitamin A, beta-carotene and lycopene [20] were found to be significantly lower in comparison to controls [19, 21, 22], supporting the existence of a decreased antioxidant defense. Microelements essential for the function of the antioxidative enzymes were also reported to be decreased in BTM patients [20]. Moreover, HCV infection and hepatic dysfunction, frequently found in BTM patients, might be involved in the depletion of antioxidant mechanisms [23, 24]. Growth hormone deficiency, another common complication in BTM patients, is a condition recognized for its association with increased oxidative stress [25], being a possible contributor to redox imbalance in BTM (**Figure 1**).

As a consequence of chronic oxidative stress, the fatty acids in membranes of cells suffer a peroxidation process, resulting cytotoxic products will impair cell function, protein synthesis and DNA structure [26].

Although no direct evidence exists linking oxidative stress with gonadal dysfunction in BTM patients, oxidative stress is a reasonable putative factor based on data demonstrating their involvement in female fertility in general population. For example, in the study by Appasamy et al. was showed that, in patients performing assisted reproduction, total antioxidant capacity

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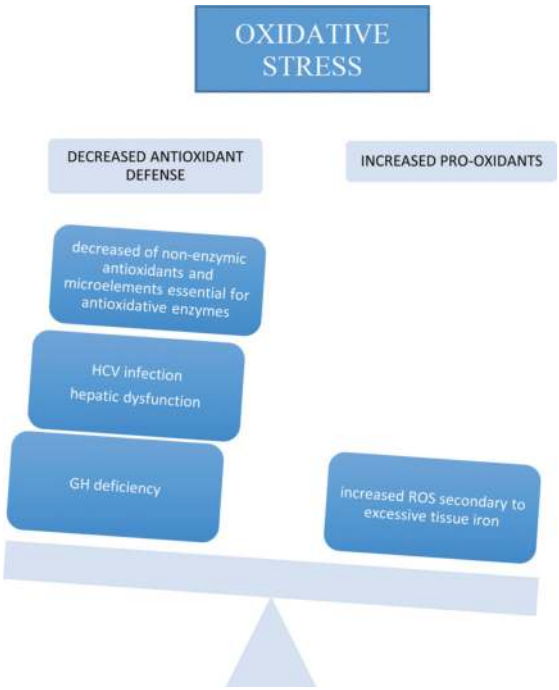

Figure 1. The mechanisms hypothesized to be involved in the appearance of oxidative stress in beta thalassemia major.

was positively associated with follicular fluid estradiol levels [27], indirectly supporting that oxidative stress might have a negative impact on follicular development. It was also suggested that oxidative stress contribute to the decrease of fertility related to age [18] and that non-heme iron deposits in ovarian stromal tissue is associated to oxidative stress-induced ovarian aging [28]. Moreover, low level of antioxidants was found to be related to anovulation in women [29].

The indirect evidence that oxidative stress is involved in iron overload-related complications is provided by interventional studies showing the supplementation of antioxidants as vitamin C and E in children with BTM is followed by improved liver function [30]. However, similar evidence regarding the improvement of female fertility in BTM following antioxidants administration does not exist.

The link between oxidative stress and iron overload in BTM is suggested by reports showing that iron chelation agents desferrioxamine (DFO) and deferasirox are effective in decreasing iron overload along with oxidative stress [31]. Similarly, the study by Kuppusamy et al. found that chelating treatment is associated with lower oxidative stress in BTM patients [32].

Other mechanisms were also proposed to be involved in hypogonadism occurrence in BTM. For example, some authors suggested that adipose tissue dysfunction due to iron toxicity could contribute to hypogonadotropic hypogonadism occurrence through a perturbed leptin

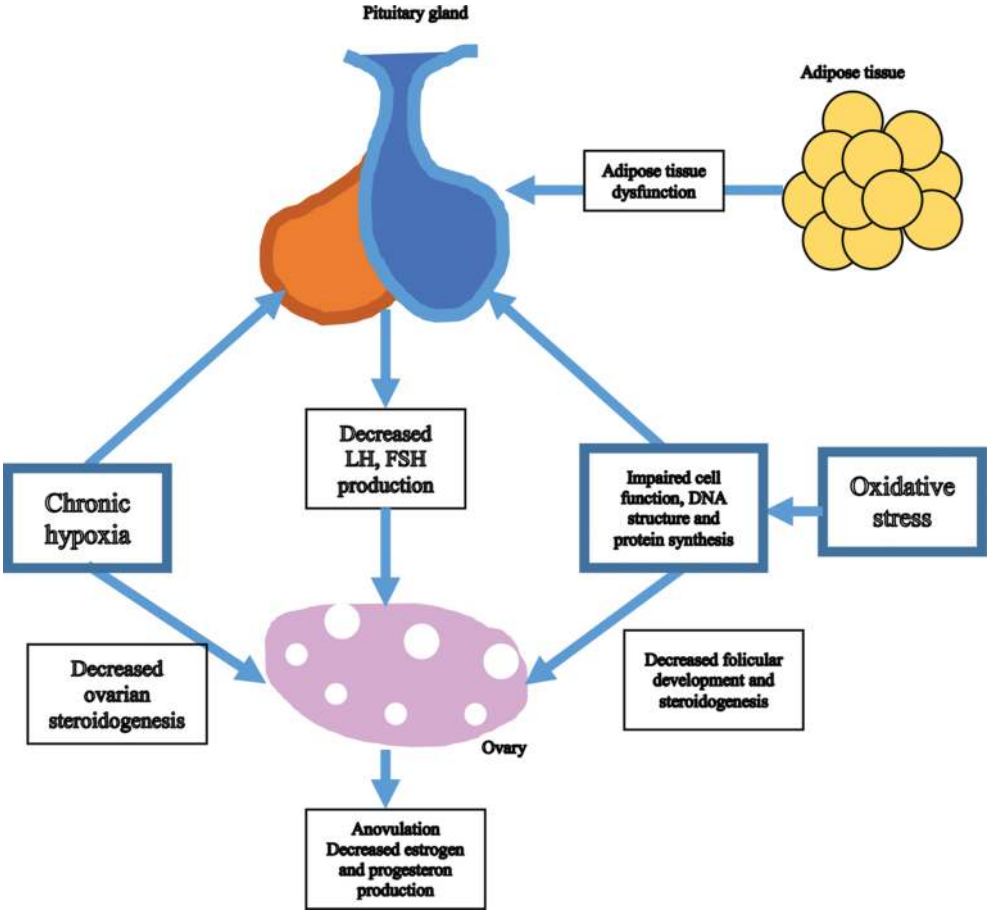

Figure 2. The etiopathogenesis of hypogonadism in beta thalassemia major.

production [33, 34]. Liver dysfunction, diabetes and hypothyroidism were found to be associated to hypogonadism [15], probably contributing to its occurrence by perturbed hormone metabolism [35].

Chronic hypoxia due to anemia could be another mechanism involved in pituitary-gonadal dysfunction in BTM. In support of this hypothesis are the studies showing decreased gonadotropin secretion few days after arriving at moderate altitude [36]. Moreover, it was observed that the fertility rate is lower in high altitude population in comparison to low altitude, probably as a consequence of a different reproductive hormones profile [37]. Animal studies show that exposure to high altitude hypoxia affects the development and function of corpus luteum [38]. Moreover, in men hypoxemia due to obstructive pulmonary disease was associated with hypogonadism and low testosterone levels [39], probably by downregulation of

androgen biosynthesizing genes in the testis as demonstrated by studies in rats [40]. However, similar effects of hypoxemia on ovary were not demonstrated (**Figure 2**).

4. Consequences of hypogonadism

4.1. Osteoporosis

Osteoporosis in BTM patients is one of the most frequent complications, multiple factors contributing to their appearance, being a major cause of morbidity in these patients as well. Hypogonadism is a widely recognized risk factor for secondary osteoporosis. However, in patients with BTM, the contribution of hypogonadism to osteoporosis pathogenesis was reported variable in different populations. The study by Anapliotou et al. showed that patients with hypogonadism had the lowest bone mineral density (BMD) and the sex steroids serum level was the only parameter related to BMD measurements [41]. Moreover, the patients who received continuous sex steroid replacement therapy had a better increase of their BMD in comparison to those with intermittent treatment [41].

Although genetic factors play a role in other types of osteoporosis, the study by Origa et al. found no association of osteoporosis with specific polymorphisms in candidate genes (vitamin D receptor, estrogen receptor, calcitonin receptor and collagen type 1 alpha 1) [42]. Instead, in female patients, osteoporosis was strongly associated with primary amenorrhea [42].

Similar findings are reported by Tzoulis et al. who find no relationship of low bone mass with vitamin D status, the only significant association observed in the multivariate analysis being between hypogonadism and low BMD at the lumbar spine [43].

However, the study by Chatterjee et al. reported that, in comparison to premature ovarian failure patients, those with BTM increased, but did not normalized their BMD following hormone replacement therapy. The authors concluded that other factors contribute to osteoporosis in patients with BTM [44]. Skordis et al. summarized the current knowledge about osteoporosis in BTM, highlighting the fact that GH-IGF 1 axis dysfunction, hypoparathyroidism, hypothyroidism, diabetes and vitamin D deficiency are important contributors as well [45]. Therefore, osteoporosis in BTM should be considered a multifactorial condition, hypogonadism being probably an important contributor to its appearance. All the contributors to osteoporosis should be addressed in order to reduce the incidence and to optimize the effect of treatment.

4.2. Infertility

Although spontaneous pregnancy can be obtained by the female patients with BTM, most of them are infertile. However, in most of the studies, pregnancies were obtained after ovulation induction with gonadotrophins or assisted reproduction. Skordis et al. reported spontaneous pregnancies among 34 patients with regular menstrual cycles and induced pregnancies in patients with primary or secondary amenorrhoea [46]. In the study by Origa et al., pregnancy was achieved with gonadotropins stimulation in 33 of 46 women with BTM [47]. Bajoria et al.

reported their experience with 11 BTM patients undergoing assisted reproductive technology (ART). They found that 60% of infertile female patients with BTM present with hypogonadotropic hypogonadism and respond favorably to gonadotropins administration [48], suggesting that central hypogonadism is the main cause of infertility in these patients. Moreover, in patients with regular menstrual cycles, fertility is usually preserved [46]. All these data suggest that pituitary dysfunction is the main cause of infertility and that the ovaries are usually intact in BTM female patients. In the light of these data, although few other factors were suggested as contributors to infertility, they do not seem to play a major role. Decreased endometrial receptivity due to iron deposition [49] is one of the factors possibly involved in infertility, although the evidences are limited. Only one study evaluated this aspect and demonstrated the presence of hemosiderin deposits in the endometrial epithelium of three patients with BTM [49]. The desferrioxamine administration resulted in reduction or disappearance of hemosiderin depositions [49].

The integrity of the ovarian tissue in patients with BTM is a matter of debate. Singer et al. [50] found that the ovarian reserve is preserved in most thalassemic patients younger than 30–35 years old. In the same study, the circulating levels of anti-Müllerian hormone (AMH), an accurate marker of ovarian reserve, were correlated with non-transferrin-bound iron, suggesting the involvement of labile iron in the regulation of ovarian reserve [50]. In turn, the study by Chang et al. demonstrated that the serum levels of AMH are lower in women with transfusion-dependent β thalassemia than in age-matched normal controls, suggesting a reduced ovarian reserve in the former [51]. Moreover, the serum AMH level in BTM patients was significantly inversely related to the ferritin level. Therefore, both studies suggest that iron overload can affect directly the ovaries, although the extent of the damage could vary depending on the severity of iron excess.

Although the presence of oxidative stress in BTM is widely recognized, its deleterious effect on oocyte maturation, fertilization, embryo development and implantation described in general population [52, 53] is not clearly linked to fertility in BTM patients. The success of ovulation induction with gonadotropins in hypogonadal patients suggests deleterious effect of iron depositions and oxidative stress on ovaries is not severe enough to impair the response to treatment. However, the hypothesis that preconceptional care of patients undergoing fertility treatment, including intensive chelation therapy prior to pregnancy, could reverse mild ovarian hemosiderosis and ovarian oxidative stress-related injuries should not be neglected. Moreover, patients referred for infertility treatment are selected in order to lower the risk of complications during pregnancy and those with severe iron-related complications are excluded. Therefore, the population of women treated for infertility is not completely relevant for the general population of female BTM patients and definitive conclusions regarding involvement of ovarian iron deposits in infertility should not be drawn.

4.3. Quality of life

The quality of life in patients with BTM was widely reported to be decreased due to affected physical, emotional and social functioning. Hypogonadism seems to be an early and significant contributor to decreased quality of life in BTM as suggested by a recent study which

evaluated the quality of life in adolescent BTM patients [54]. The authors observed that BTM adolescents had poor perception of their general health and scored significantly lower in all the subscales compared with the controls [54]. The high prevalence of short stature and pubertal delay was associated with lowest scores for physical and psychological domains [54], suggesting the important contribution of these endocrine complications to decreased quality of life of BTM patients. The siblings of BTM patients also scored significantly less in environment domain, probably reflecting the impact of BTM within families [54].

4.4. Short stature

Short stature is frequently found in patients with BTM, being variably reported in different populations, with prevalence as high as 30% in female patients [55]. Skordis et al. reviewed the growth disturbances in BTM patients [45]. They concluded that the etiology is multifactorial, causative factors including hemosiderosis, hypoxia secondary to chronic anemia, chronic liver disease, nutritional deficiencies, intensive iron chelating therapy, emotional factors, endocrinopathies (hypogonadism, delayed puberty, hypothyroidism, disturbed calcium homeostasis and bone disease) and dysregulation of the GH-IGF-1 axis [45]. The authors also describe three phases of growth in BTM children: a first phase in which growth disturbance is due to hypoxia, anemia, ineffective erythropoiesis and nutritional factors; a second phase during late childhood during which growth retardation is mainly due to GH-IGF-1 axis dysfunction probably secondary to iron overload; a third phase that starts after the age of 10–11 years when delayed or arrested puberty contribute significantly to growth failure [45].

A multicenter international study performed by Thalassaemia International Federation (TIF) in 2004 including 29 Centers and 3817 patients reported that short stature is present in 31.1% of males and 30.5% of females. However, the prevalence of growth hormone deficiency was only 7.9% in males and 8.8% in females, suggesting that other causes contributes significantly to height deficit [55]. In turn, delayed puberty was the most common endocrine complication (40.5%) [55].

Delvecchio et al. reviewed 123 papers and concluded that disproportionate short stature is frequent and aggravates at puberty because of the lack of growth spurt. Later on, partial height recovery may occur. Long-term treatment with recombinant human growth hormone seems ineffective to improve final height [56]. Therefore, short stature is associated with early forms of hypogonadism rather than with growth hormone deficiency, supporting of involvement of the former in the etiology of height deficit.

5. Treatment of hypogonadism

5.1. Hormone replacement treatment

The aim of the treatment of hypogonadism in female BTM patients is to maintain secondary sexual characteristics, to increase the quality of life and to counteract the negative impact on bone health. However, due to the complexity of conditions accompanying BTM, some

particularity should be taken into account when treating hypogonadic BTM patients. The sequential estrogen-progestogen regimens are the cornerstones of treatment in women with hypogonadism. These can be administrated as combined oral contraceptives (COC) or hormone replacement treatment (HRT). Depending on the preparation used the doses of estrogens vary, being higher in COC than in HRT, and the type of progestogen differs. The routes of hormones administration might be also different, the estrogens being administrated orally, vaginally or transdermally in most of the preparation. Progestogens can be administrated as oral tables, transdermal patch or intrauterine devices. Natural progesterone is available for oral, vaginal and transdermal routes. The major concern regarding the use of estro-progestative in BTM patients is the risk of thromboembolic events which is a well-known complication in COC and HRT users [57]. BTM is a condition characterized by an increased risk for thromboembolism [58, 59], mainly due to thrombocytosis secondary to splenectomy and to decreased production of anticoagulants due to chronic liver dysfunction. Therefore, the risk of thrombosis associated to COC or HRT administration can be even higher in BTM patients, although no study addressed this aspect. It was suggested that BTM patients with cardiomyopathy, diabetes, liver function anomalies and hypothyroidism [59], splenectomy and inadequate transfusion regimen [60] could have an increased risk of thromboembolic events, representing potential categories of patients in which COC administration should be avoided. However, among COC those containing newer progestin compounds (desogestrel, gestodene, drospirenone and cyproterone acetate) were reported to be more thrombogenic in comparison to older ones [61–63] and this aspect should be taken into account in BTM patients. Moreover, estrogens administered transdermally seem to have no prothrombotic effect [63], probably because the high estrogens concentrations in portal system generated by the oral administration of estrogens are avoided. In turn, vaginal ring has a similar venous thromboembolism (VTE) risk to third and fourth COC generation [63]. All these factors should be weighted when the decision to administer estro-progestative preparation for hypogonadism in a female BTM patient should be taken. Although a combined regimen with transdermal estrogen and natural progesterone may seem advantageous in BTM patients due to an assumed decreased risk of thrombosis, no data proving that hypothesis are published. Moreover, strict recommendations (COC versus HRT) in other categories of patients requiring hormonal replacement like those with premature ovarian failure are not available. Meanwhile, a recently published paper in International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine (ICET-A) [64] recommend that the clinician should take into consideration the United States Medical Eligibility Criteria (US MEC) for Contraceptive Use [65]. According to these criteria, no restriction exists for women with BTM, chronic hepatitis or with non-complicated insulin-dependent or non-insulin-dependent diabetes. However, in women with past VTE and known thrombogenic mutations (e.g., factor V Leiden; prothrombin mutation; and protein S, protein C and antithrombin deficiencies) and in women with diabetes associated with nephropathy, retinopathy or neuropathy, the risk is considered unacceptable if the contraceptive method is used [64, 65]. In patients with cholelitiasis COC administration represents a contraindication only in the presence of symptoms requiring medical treatment [65].

Some specific recommendations are made by ICET-A for patients with BTM [64]. They recommend that the physician should take into account the risk and benefits of estro-progestative administration in each particular patient and thoroughly discuss with the patients before

starting the treatment. Splenectomized patients should receive antiagregant or anticoagulant therapy during estro-progestative administration. In acute liver disease, estro-progestative is contraindicated, but their administration should be reinitiated after the acute episode has passed. They also consider the transdermal estradiol in association with micronized progesterone 'the most physiologic regimen with the best safety profile', being an option in women with risk factors for venous thromboembolism [64].

In order to reduce the risk of treatment, it is recommended that the serum estradiol level maintained approximately 100 pg/mL [66]. This level could be obtained with 25–50 μg 17β estradiol administered transdermally [67].

In patients with delayed puberty, the treatment should be started with low doses of transdermal, oral or parenteral estrogens. No particular regimen was reported for BTM patients and data from other populations can be used. The doses should be gradually increased (with 25–100% every 6 months) over 2–3 years to mimic normal puberty and progesterone should be added when vaginal bleeding occur or after 2 years of estrogen administration [68]. The initial proposed estrogens doses are: transdermal estradiol 3–7 μg/day, oral ethinyl estradiol 2 μg/day, micronized oral 17β estradiol 0.25 mg/day and depot estradiol 0.2 mg/month [68]. The adult doses that should be reached are: transdermal estradiol 25–100 μg/day, oral ethinyl estradiol 10–20 μg/day, micronized oral 17β estradiol 1–4 mg/day and depot estradiol 2 mg/month [68].

5.2. Infertility treatment

As a consequence of improved care of BTM patients and increased quality of life and life expectancy, an increasing number of women with BTM desire pregnancy. The existing reports show that in BTM women with normal gonadal function, the pregnancy can be obtained spontaneously, while in hypogonadal patients fertility is usually retrievable [47, 48]. Patients with BTM contemplating pregnancy should be addressed to a BTM-specialized preconception care department. During evaluation, the fertility potential and the woman's fitness for pregnancy should be assessed and the risks of pregnancy should be discussed. The iron overload consequences and especially liver and heart involvement is the main target of preconception evaluation, ensuring that associated conditions are stabilized and the potential of decompensation during pregnancy is minimized. The associated medications should be reviewed in order to exclude those with teratogenic risk and genetic screening of the partner should be provided in order to reduce the risk of a hemoglobinopathy in the baby.

Although the hypogonadotropic hypogonadism is the cause of infertility in most of the patients, a full evaluation is necessary in all the patients in order to identify associated causes (tubal obstruction and male factor). The first line of treatment in infertile BTM female patients with hypogonadism without other causes of infertility is ovulation induction with gonadotropins. Although some studies raised the question whether ovaries are injured by iron overload, most of the patients respond to this treatment [47]. There are no specific stimulation protocols for BTM patients, standard regimens being usually effective. In case of repeated failure of ovulation induction with gonadotropins or in couples with oligo/azoospermia or tubal infertility, in vitro fertilization is indicated. Growth hormone deficiency is not infrequent among adult BTM patients and can be involved in fertility treatment success in selected cases as

suggested by Surbek et al. [69] in their study. Although in patients with BTM data are limited, numerous experimental studies suggest that growth hormone acts on oocytes competence and ovarian steroidogenesis. Moreover, in patients with poor response to assisted reproduction growth hormone administration can improve the outcome of infertility treatment. In the light of these data, future studies should clarify the utility of growth hormone administration in infertile BTM female patients.

In conclusion, hypogonadism is still a frequent complication in BTM female patients having a significant impact on their health and quality of life. Early diagnosis and treatment is essential in order to prevent complications, although a careful evaluation of the risks and benefits is necessary in every patient. Fertility is usually retrievable with treatment. However, the evaluation of fitness for pregnancy and preconceptional improvement of health are of paramount importance for optimal results.

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