Mediterranean Journal of Hematology and Infectious Diseases

Review article

Review and Recommendations on Management of Adult Female Thalassemia Patients with Hypogonadism based on Literature Review and Experience of ICET-A Network Specialists

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Competing interests: The authors have declared that no competing interests exist.

Abstract. ***Background:*** **Multi-transfused thalassemia major (TM) patients frequently develop severe endocrine complications, mainly due to iron overload, anemia, and chronic liver disease, which require prompt diagnosis, treatment and follow-up by specialists.**

The most common endocrine complication documented is hypogonadotropic hypogonadism which increases with age and associated comorbidities. It is thus important for physicians to have a clear understanding of the pathophysiology and management of this disorder. Also to be aware of the side effects, contraindications and monitoring of sex steroid therapy. In this paper, practical ICET-A recommendations for the management of hypogonadism in adult females with TM are addressed.

Methods: **In March 2015, the Coordinator of the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine (ICET-A) conducted a two-step survey to assess the attitudes and practices of doctors in the ICET-A network taking care of adult female TM patients with hypogonadism. They were clinically characterized by the absence of pubertal development or discontinuation or regression of the maturation of secondary sex characteristics, and biochemically by persistent low FSH, LH and estradiol levels. Recently a supplementary survey on adult female hypogonadism in TM was undertaken within the ICET-A network.**

Results: **The completed questionnaires were returned by 16 of 27 specialists (59.2%) following 590 female TM patients over the age of 18 years; 315 patients (53.3%) had hypogonadism, and only 245 (74.6%) were on hormone replacement therapy (HRT). Contraceptive oral pills (COC) were the first treatment choice in 11 centers (68.7%). A wide range of COCs was used with different progestin contents. In general, the patients' compliance to treatment was reported as good in 81.2 % of centers. The frequency of required tests for follow-up HRT, in addition to the regular check-up for thalassemia, was variable in the participating centers.**

Conclusions: **Doctors taking care of TM patients should have sound knowledge of the pathophysiology of hypogonadism in adult females with TM. They should know the potential effects of HRT including advantages and disadvantages of estrogen and progestins. Moreover, they should keep in consideration the emotional needs of these patients dreaming of attaining a full pubertal development.**

Keywords: Thalassemia, hypogonadism, hormone replacement therapy, benefits and disadvantages.

Citation: De Sanctis V., Soliman A.T., Elsedfy H., Albu A., Al Jaouni S., Anastasi S., Bisconte M.G., Canatan D., Christou S., Daar S., Di Maio S., El Kholy M., Khater D., Elshinawy M., Kilinc Y., Mattei R., Mosli H.H., Quota A., Roberti M.G. , Sobti P., AL Yaarubi S., Canpisi S., Kattamis C. Review and recommendations on management of adult female thalassemia patients with hypogonadism based on literature review and experience of ICET-A network specialists. Mediterr J Hematol Infect Dis 2017, 9(1): e2017001, DOI: http://dx.doi.org/10.4084/MJHID.2017.001

Published: January 1, 2017 **Received: August 20, 2016** **Accepted: November 14, 2016**

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Introduction. Multi-transfused thalassemia major (TM) patients frequently develop severe endocrine complications mainly due to iron overload, anemia, and chronic liver disease, which require prompt diagnosis, treatment and close follow-up by specialists.[1-3]

The most common endocrine complication documented in adult TM patients is hypogonadotropic hypogonadism which increases with age and the associated comorbidities.[3] In adult females TM patients, hypogonadism is clinically diagnosed by the absence of pubertal development, or discontinuation or regression of the maturation of secondary sex characteristics due to pituitary dysfunction and/or gonadal damage, secondary to iron overload.[4] The incidence rate of hypogonadism, in both sexes, varies considerably between countries and much more between specialized centers, ranging from around 50% and may even approach 100%.[1-4]

Evidence suggests that more severe defects are related to a higher rate of iron loading possibly due to increased vulnerability to free radical toxicity.[1-4]

Hormone replacement therapy (HRT) in females with hypogonadism aims to alleviate symptoms of estrogen deficiency and prevent long-term complications such as osteoporosis.[5] However, HRT has been linked to various risks and the debate regarding its risk-benefit ratio continues. The principal risks of HRT are thromboembolic disease, stroke, cardiovascular events, gallbladder disease, breast cancer and endometrial hyperplasia or endometrial cancer.[6]

In March 2015, the Coordinator (VDS) of the International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine (ICET-A) conducted a two-step survey to assess the attitudes and practices of doctors taking care of adult TM with hypogonadism. In

this report, we present the results of the study and the practical recommendations for hypogonadism in adult females with TM based on literature review and the experience of specialists of ICET-A network. Where possible, the recommendations are based on and linked to, the evidence that supports them, unless good-quality evidence is absent.

Methods. The ***first step***- survey was held on the 19th and 20th of March 2015, in Rome, during the 10th International Workshop of ICET-A. A questionnaire was distributed before the beginning of sessions to participants with relevant experience in thalassemia care. The answers were collected and discussed at the end of the session. The aim of the study was to investigate the attitudes and prescription habits of doctors concerning HRT in TM patients. Exclusion survey criteria included patients with thalassemia intermedia.

The ***second step*** survey was administered online to the ICET-A members on July 4th, 2016. An introductory letter explained the purpose of the study. The questionnaire consisted of 23 questions, namely: personal doctors' data, place of work, specialization, number of female patients with TM followed over the age of 18 years, number of TM patients on HRT, type/s of HRT used, the patients' compliance to treatment, the speciality of the physician recommending HRT, opinions on indications and contraindications for HRT use among doctors and types and number of tests used during patients' follow-up.

After collection and analysis of data, the ICET-A Steering Committee (VDS, ATS, HE, MEK, SDM, CK) prepared (***third step***) practical recommendations for the management of these patients. In making these recommendations, experts considered the differences in countries' facilities, general cost of tests and recommended management of hypogonadism. The ICET- A members were asked to provide comments on the accuracy, feasibility, and approval of the recommendations.

Results

First step: Twenty-five questionnaires were distributed, and 24 (96%) were answered. The participants included ten pediatricians, four endocrinologists, and ten hematologists.They were following a total of 2326 females and males with TM.

Twelve different formulations and three routes of administration for HRT were used. The majority of respondents (33.3%) used ethinyl estradiol 30 µg/drospirenone 3 mg as first-line treatment choice, (25%) ethinyl estradiol 20 µg/drospirenone 3 mg. Ethinyl estradiol 35 µg/cyproterone acetate 2 mg (41.6 %) and ethinyl estradiol 20 µg/drospirenone 3 mg (29.1%) were reported as second-line treatment choice. Transdermal patch, estradiol transdermal plus progesterone, and etonogestrel/ethinyl estradiol vaginal ring were used and recommended by 16.6%, 4.1%, and 4.1%, respectively.[7]

Second step: The questionnaires were returned by 16 of 27 specialists: 6 pediatric endocrinologists, 2 endocrinologists; 3 pediatric hematologists, 3 hematologists, 1 pediatrician and 1 general practitioner [the majority (75%) were female doctors] following 590 female TM patients over the age of 18 years; 315 (53.3 %) had hypogonadism, and 245 (74.6 %) were on HRT.

The reported most common contraindications to treatment were: elevation of liver enzymes - from 3 to 6 times the normal values (62.5%), thrombophilia (43.7 %), insulin dependent diabetes (25%), insulin dependent diabetes associated with vascular complications (6.2 %), patient non-compliance to treatment (25%). HRT was recommended by endocrinologists in 9 thalassemia centers, by endocrinologists and gynecologists in 6, and by endocrinologist and hematologist in 1 center. Responders were asked to select the three commonest compounds used as HRT. Contraceptive oral pills (COC) were the first choice of treatment in 11 centers. A wide range of COCs was used with different progestin contents, such as drospirenone, dydrogesterone, norgestrel, norethisterone, gestodene, desogestrel, medroxyprogesterone acetate, micronized progesterone soft gelatin capsules. In 6 Centres transdermal estrogen patch in combination with oral progesterone was given as the first choice of treatment. In general, patients' compliance to treatment was reported as good in 81.2 % of Centres.

The frequency and number of required tests during follow-up, in addition to the regular check-up for thalassemia, varied in the participating Centres (even in centers within the same country). The results for each Centre participating in the survey are reported in **Table 1**.

Table 1. Frequency of required tests during follow-up of TM patients with hypogonadism on HRT.

	Liver enzymes	Serum glucose	OGTT	Clotting factors	Lipids	Renal function	BMD	Pelvic ultrasound	Other tests
Cyprus	3 months	3 months	12 months	12 months	12 months	3 Months	12 Months	12 months	NR
Egypt	3 months	3 months	12 months	when indicated	when indicated	3 Months	Research basis	when indicated	FSH, LH and Estradiol
Egypt	NR	6 months	nil	Nil	nil	Nil	2 Years	NR	NR
India	3-6 months	12 months	nil	Nil	24 months	12 Months	Nil	NR	NR
Italy	monthly	monthly	24 months	6 months	3 months	monthly	12-24 Months	12 months	EcoCG ECG
Italy	3 months	6 months	24-36 months	12 months	12 months	6 Months	24 Months	12 months	NR
Italy	monthly	2 months	12 months	6 months	3 months	12 Months	12 Months	12 months	Cardiac T2*
Italy	monthly	3 months	12-24 months	6-12 months	6-12 months	6-12 Months	12-24 Months	12 months	Cardiac T2* HOMA-IR § A-US every 12 months
Italy	2 months	3 months	when indicated	3 months	3 months	2 Months	12-18 Months	12 months	NR
Italy	3 months	3 months	3 months	3 months	6 months	3 Months	12 Months	12 months	NR
Italy	6 months	6 months	24 months	6 months	12 months	6 Months	24 Months	12 months	NR
Kingdom of Saudi Arabia	3-4 months	3-4 months	12 months	6 months	12 months	3-4 Months	12 months	when indicated	Cardiac T2* if needed
Oman	1-6 months	6 months	12 months	Nil	12 months	1-6 Months	24-36 months	12 months	FSH, LH, and estradiol. Liver T2* at least yearly, A-US yearly
Romania	12 months	nil	12 months	Nil	12 months	2 Months	12 months	12 months	NR
Turkey	1-3 months	3 months	6 months	12 months	12 months	monthly	12 months	when indicated	FSH, LH and Estradiol
Turkey	3 months	3 months	12 months	12 months	12 months	3 months	12 months	12 months	NR
UK	2 months	6 months	12 months	4 months	6 months	2 Months	24-36 months	nil	NR

Abbreviations. TM - thalassemia major; OGTT- Oral Glucose Tolerance Test; NR- Not reported; HOMA-IR Homeostatic Model Assessment of Insulin Resistance- § every 6-12 months; Abdominal A-US- abdominal ultrasound; EcoCG-Echocardiogram; ECG-Electrocardiogram; BMD -Bone Mineral Density

Third step: The ICET-A recommendations for hypogonadism in adult females with TM were based on published, peer-reviewed scientific evidence, expert opinion, and accumulated professional knowledge and experience of ICET-A network specialists. Recommendations from published guidelines were used when available and appropriate. Original articles for the evidence-based recommendations were obtained following a computer search for 'hormone replacement' as a keyword and also in combination with 'venous thrombosis' (VTE) or 'deep venous thrombosis' (DVT) or 'pulmonary embolism' or 'thrombophilia' or "chronic liver disease" or "diabetes" applied to Medline.

The ICET-A Network also issued expert consensus opinions on topics for which limited or low-level evidence was available in the literature. Since not all published references were based on randomized controlled trials, the recommendations have been scored according to the following criteria:

A. High confidence indicates that further research is unlikely to change the confidence in the estimate of effect (●●●)

B. Moderate confidence indicates that further research may change the confidence in the estimate of effect (●●○)

C. Low confidence indicates that further research would likely have a significant impact on the confidence in the estimate of effect (●○○)

D. Insufficient indicates that the evidence is unavailable or does not permit a conclusion (○○○)

Discussion. The goals of substitutive therapy in adult female patients with hypogonadism are to maintain secondary sexual characteristics, to optimize the accrual of bone mineral content and to promote physical and social well-being.

Few trials of the effects and complications of estrogen therapy in primary and secondary hypogonadism of women at premenopausal age have been published and none of TM patients. As a consequence of the scanty evidence, recommendations for HRT in thalassemia are based on publications on the effects and complications of COC used for contraception and postmenopausal hormone replacement in healthy women.

The three forms of estrogen produced in the human body are estrone (E1), estradiol (E2) and estriol (E3). The estrogen composition in the female body is approximately 3% estrone, 7% estradiol, and 90% estriol. The potencies of these hormones vary, with estradiol being the most potent followed by estrone and estriol.[6,8]

Sequential estrogen-progestogen replacement therapy is the mainstay of treatment for women with hypogonadism. Estrogen may be replaced using oral, micronized, vaginal, or transdermal preparations. Subcutaneous implants and more recently, nasal sprays and injectable estrogen preparations are also available.

There are three types of estrogen available for hormone replacement: estradiol, ethinylestradiol (a synthetic estrogen, EE) and conjugated equine estrogens (derived from pregnant mare urine, CEE). Major characteristics that differentiate one formulation from another include the form of estrogen used and its dosage, and the generation of the progestin.

The formulations of COC have changed over the past 50 years. The dose of the EE component has decreased from the original 100-150 μg to 15 to 30 μg. These changes were made to lower the risk of thromboembolic complications associated with the use of oral contraceptive pills.[6]

In the absence of a consensus regarding the ideal hormonal replacement regimen for women facing a premature cessation of ovarian function, the estroprogestative substitution commonly involves either HRT or COC prescription.

Several studies compared estrogen preparations in adult females, but the adolescent and young adult population are relatively understudied.[9-12] A recent report in girls with Turner syndrome demonstrated more physiologic estrogen concentrations with the use of the transdermal estrogen preparation versus oral preparations. [13] Ninety percent of the EE is absorbed from the upper gastrointestinal tract in 1 to 2 hours, then exposed to oxidation. Following absorption, EE is metabolized during passage through the enterohepatic circulation. EE has a strong hepatic impact related to its 17a-ethinyl group. This group prevents the inactivation of the EE and results in a slow metabolism and prolonged tissue retention. EE is much more potent than the naturally secreted estrogens because it remains in the blood for a longer time after administration and has a greater effect on the liver.[8]

In our survey, the majority of specialists (11 centers) preferred COCs as the first line of treatment COCs of convenience, efficacy and patients' preference and availability.

COC are classified into different generations (first, second, third and fourth), depending on the time of introduction into the market. They vary regarding the dose of estrogen and the type of progestin. Progestins are needed to avoid an unopposed estrogen effect and maintain endometrial health. Progestins can be administered via the oral, transdermal (as a patch), or intra-uterine routes. Micronized progestogens are available to use orally, vaginally and as transdermal (cream) preparations.

Progestins have no selectivity for the various steroid receptors. The first progestins developed were medroxyprogesterone acetate (MPA) and norethisterone enanthate (NET-EN). Shortly after, these were followed by its first derivative norethisterone acetate (NET-A). Many more synthetic progestins have been developed in the following years. We now have second, third and fourth-generation progestins. Examples are levonorgestrel (LNG, 2nd generation), gestodene (GES, 3rd generation), and drospirenone (DRSP), dienogest (DNG) and trimegestone (TMG), all fourth generation. The third-generation progestins have minimal impact on blood glucose levels, plasma insulin concentrations, and the lipid

profile. Thus, they are suitable for use in patients with lipid disorders or diabetes.[9-11]

Contrary to menopausal women, adolescents and young female adults with hypogonadism due to other pathologic mechanisms as in TM patients, the HRT treatment is extremely complex because of associated comorbidity (iron overload, the presence of thrombophilic status, chronic liver disease, impaired glucose tolerance or diabetes and cardiovascular disease). In addition, the long-term duration of chelation treatment and psychosocial patients' needs enhance the difficulty of the management.[1- 4,14-18]

Taher et al.[17] reported in a retrospective multicentre study, that thromboembolic events (TE) occurred in a clinically relevant proportion (1.65%) of 8,860 thalassemia patients (75.3% with TM). Thromboembolic events were 4.38 times more frequent in thalassemia intermedia (TI) than in TM patients ($p < 0.001$). More venous events occurred in TI and more arterial events took place in TM.

A survey, done in 9 Italian thalassemia Centres, disclosed that 32 patients out of a total of 735 (683 with TM and 52 TI), had VTE episodes corresponding to an incidence of 3.95% and 9.61%, respectively. Localization of TE varied; the main one (16/32) involved the central nervous system.[15]

Patients with TE events presented a higher incidence of associated organ dysfunction, such as cardiomyopathy, diabetes, liver function anomalies, and hypothyroidism than those without TE events (50 vs. 13.8%, $p < 0.05$).[15]

Haghpanah and Karimi conducted an electronic search on PUBMED (MEDLINE), SCOPUS, and Google Scholar databases up to January 2011. Out of 152 thalassemic patients with cerebral thromboembolic events; 48% were splenectomized. Nine TM patients had diabetes. Activated protein C resistance, decreased protein C or protein S or plasminogen level were detected in 8 patients.[18] Inadequate transfusion was reported to increase the risk of thrombosis secondary to increased release of pro-coagulant red cell particles.

Oral administration of EE leads to pharmacologic concentration of the hormone in the portal vein before it is metabolized by the liver. This first-pass reaction results in an increased hepatic production of several hormone binding globulins, clotting factors, lipoproteins and angiotensinogen. This increase in VTE risk is highest during the first year of use. It may vary according to the different characteristics of COCs, such as estrogen dose, molecule, and type of progestins. Whether the type of estrogen molecule is associated with different degree of risk for venous thrombosis remains controversial.[19,20]

Based on the Women's Health Initiative (WHI) trials, oral conjugated equine estrogen and 2.5 mg MPA increased VTE compared with placebo (RR, 2.06; CI, 1.57–2.70). These findings, however, require confirmation.[21,22]

Newer generation formulations of hormonal contraceptives seem to be more thrombogenic than those of second-generation.[19,20,22] Using LNG as the reference , VTE rate ratios for other progestins were: NET-EN0.98, desogestrel 1.82, GES 1.86, DRSP 1.64 and cypropterone (CPA) 1.88.[19,20,22]

Some observational studies assessed the risk of VTE associated with transdermal estrogen therapy in non-thalassemic population. The pro-thrombotic effects seem to be circumvented by transdermal administration of estrogen and, therefore, have significant clinical implications.[22]

The VTE risk for vaginal ring or patch is as high as for COCs of third or fourth generation. [22]

Liver dysfunction in thalassemics is mainly attributable to liver siderosis and chronic HCV infection (chronic hepatitis C).[23,24] Furthermore, chronic hemolysis in TM favours the development of bilirubin gallstones. The incidence of gallstones varies considerably in clinical studies and is related to age and the efficiency of transfusion treatment of studied cohorts. Thirty percent of 858 consecutive Italian TM patients had chololithiasis diagnosed by abdominal ultrasonography or a history of cholecystectomy.[25] In addition, chronic application of third generation progestogens as contraceptives or HRT could influence the serum lipid profile, and consequently increase the risk of biliary lithogenicity.[26]

Although elevation of liver enzymes - from 3 to 6 times the normal values was the commonest contraindication to hormonal treatment reported by 10/16 Centres, further studies including liver imaging and LIC assessment are needed to clarify the role of HRT on liver enzyme levels, metabolic variables and liver fat content.

Insulin dependent diabetes (IDDM) and impaired glucose tolerance (IGT) are relatively common complications in thalassaemia major (TM) patients with iron overload and sub-optimal

chelation therapy. The prevalence of IDDM and IGT in adolescents and young adults with TM mainly treated with desferrioxamine mesylate (DFO) varies considerably in 2 studies ranging from 0 to 21% and from 9.3 to 24.3 %, respectively.[27,28] Even higher differences exist in other studies depending on the age composition and on the efficiency of chelation of the studied TM cohorts.

Currently, there appear to be wide variations in the way that professionals evaluate the risk-benefit equation in subjects with IDDM, and significant differences in prescribing practice have been identified. In women with insulin-dependent or non–insulin-dependent diabetes COCs use have limited effect on daily insulin requirements and no effect on long-term diabetes control or progression to retinopathy, if clinical and metabolic monitoring can be ensured. COCs must be avoided in case of, cardiovascular disease or severe microvascular complications such as nephropathy with proteinuria or active proliferative retinopathy.[29-33]

The safety of prescription of COCs to women with type II diabetes is unclear, but a supervised program similar to that of IDDM patients is recommended.

Conclusions and Recommendations. Despite the large number of patients for whom HRT is prescribed, there are no prospective studies of treatment and/or recommendations to guide clinicians in the application of the optimal treatment regimens in patients with TM presenting with hypogonadism and complications influenced by HRT. Therefore, there is an urgent need to develop guidelines based on solid research in order to optimize the care of this group of women.

The United States Medical Eligibility Criteria (US MEC) for Contraceptive Use, in July 2016,[33] recommended the following medical eligibility criteria categories for estrogen/progestin pill, hormonal patch and combined vaginal ring:

1 = A condition for which there is no restriction for the use of the contraceptive method.

2 = A condition for which the advantages of using the method generally outweigh the theoretical or proven risks.

3 = A condition for which the theoretical or proven risks usually outweigh the advantages of using the method.

4 = A condition that represents an unacceptable health risk if the contraceptive method is used.

No restrictions are reported for estrogen/progestin pill, patch or vaginal ring in TM patients ***(category 1***). Regarding some other pathologies, the US MEC for the contraceptive use, reported the following risk categories: an increased risk in the presence of family history (1st-degree relatives) for venous thrombosis (***category 2***) and a high risk in presence of past TE and known thrombogenic mutations (e.g., factor V Leiden; prothrombin mutation; and protein S, protein C, and antithrombin deficiencies) (***category 4***); in women with chronic hepatitis, COC use does not increase the rate or severity of cirrhotic fibrosis, nor does it increase the risk for hepatocellular carcinoma (***category 1***); a small increased risk for asymptomatic gallbladder disease (***category 2***), in subjects with gallbladder disease treated medically the risk is higher (***category 3)***; in women with insulin-dependent or non–insulin-dependent diabetes COC use have limited effect on daily insulin requirements and no effect on long-term diabetes control or progression to retinopathy ***(category 1)***, in presence of associated nephropathy, retinopathy, or neuropathy the risk is high **(*category 4*)**; for atherosclerotic cardiovascular diseases (e.g. smoking, diabetes, hypertension, low HDL, high LDL, or high triglyceride levels) the risk is high ***(category 3/4);*** in subjects with migraine without aura or with aura the risk ***category*** is ***2 and 4,*** respectively.

On deciding to treat a hypogonadal TM woman with estrogen and progestin, consideration must be given to the general condition of the patient, current chelation therapy and the presence of associated complications.[34-36]

To minimise the potential risks of treatment, excessively high sex hormonal concentrations should be avoided.[36] The aim is to achieve, in regularly menstruating women the typical mean serum estradiol levels of approximately 100 pg/ml (400 pmol/l).[37] Transdermal administration of 25-50 μg 17β estradiol generally produces in TM patients a plasma E2 value in the early to mid-follicular phase range (100-300 pmol/l).[36] Progesterone is usually given at for 12-14 days each month to bring on a menstrual withdrawal bleed. Micronized progesterone is composed of smaller particles that may aid in absorption. It was proposed as first-line progestin because there are

reasons to believe that natural progesterone might be safer for the cardiovascular system (no adverse lipid effects) and possibly the breast, although the strongest evidence for endometrial protection is for oral cyclical combined treatment.[34,35,37-39]

The potential effects of HRT demand that doctors taking care of TM patients have a sound knowledge of the benefits and disadvantages of estrogens and progesterone. They must also possess comprehensive knowledge of female reproductive biology and particular sensitivity to the emotional needs of these patients. Current guidelines in patients with premature ovarian failure suggest that therapy should be continued until the average age of menopause (age 50 to 51 years) to prevent premature bone loss, coronary heart disease, and stroke.[40,41]

Because HRT in patients with chronic diseases is a complex task, the ICET-A prepared some relative recommendations for HRT in TM patients and its monitoring (**Tables 2** and **3**), based on the data reported in the literature for adolescent and young women without TM, for HRT with sex steroids. Further research consortia are needed to investigate these important questions, and to assist clinicians in making the best possible health care approach for the adolescents and young women with TM and hypogonadism.

Acknowledgements. We wish to express our sincere thanks to dr. Ploutarchos Tzoulis, Department of Endocrinology, Whittington Hospital, University College London, London, UK for taking part in the second step survey promoted by ICET-A.

Table 2. The ICET-A recommendations for female TM patients with hypogonadism.

- Iron status (including LIC and cardiac T2*) should be assessed before treatment in order to evaluate its clinical relevance, the need for treatment, and the timing and monitoring of chelation therapy (●●●).
- Intensive iron chelation therapy is recommended in iron overloaded patients before treatment (●●●).
- Doctors should weigh the risks against the benefits when prescribing combination estrogen plus progestin hormone therapy and counsel the patient accordingly (●●●).
- Before starting HRT, each patient should be carefully screened by a physician who should identify an increased risk of thrombophilia and tailor the laboratory testing (●●●).
- In TM patients with a known thrombophilic defect (such as deficiency of antithrombin, protein C or protein S) that has been identified through screening the pros and cons of HRT treatment should be discussed with a specialist (●●○). In TM patients with a history of VTE, HRT must be avoided (●●○).
- Transdermal estradiol and micronized progesterone seem to be the most "physiologic regimen" with the best safety profile, particularly in women with risk factors for VTE (●●○). Natural progesterone may have a more favorable cardiovascular profile and possibly a reduced risk of breast cancer, although the strongest evidence for endometrial protection is for oral cyclical combined treatment (●●○).
- Transdermal patches may result in local skin irritation, and some find them difficult to keep in place (●●○). Advice on correct positioning and rotation of application sites may help. However, if compliance is not fit or if contraception is required, the use of the COC is a reasonable choice (●○○).
- Splenectomized TM patients with hypogonadism on HRT should receive antiplatelet or anticoagulant therapy with aspirin or low dose warfarin (●●○).
- There are no studies on the effect of HRT on lipids, and little information on bone densitometry in hypogonadal TM women on HRT (●○○).
- HRT is contraindicated in acute liver disease. However, once the episode of acute illness has entirely passed, HRT may be initiated (●●○).
- Treatment of chronic hepatitis C with new antiviral drugs, and intensive chelation in those with severe liver siderosis (LIC > 7 mg/dry weight) prior to HRT is recommended (●●●).
- Limited data from studies on chronic hepatitis or its sequelae in non-TM patients suggest that COC use does not influence the progression or severity of liver fibrosis or development of hepatocellular carcinoma (●○○).
- If the serum liver enzymes after one month of HRT rise by more than 100 %, or if baseline serum bilirubin is elevated, liver biochemistry should be repeated monthly for at least three months, and treatment needs to be reconsidered (●○○).
- Chronic use of third generation contraceptives or HRT could influence the serum lipid profile, and consequently cause an increase in bile lithogenicity (●○○).
- In women with insulin-dependent or non–insulin-dependent diabetes COCs use has a limited effect on daily insulin requirements and no effect on long-term diabetes control or progression to retinopathy. COCs must be avoided in case of severe microvascular complications such as nephropathy with proteinuria or active proliferative retinopathy (●●○).
- Young and adult women with hypogonadism should be counseled as to alcohol and tobacco avoidance, daily exercise for obesity prevention, and an appropriate diet to achieve optimal cardiovascular health (●●○).

Table 3. The ICET-A guidelines for the monitoring of HRT in female TM patients with hypogonadism.

	Start of treatment (baseline)	Each visit	3-6 Months	Yearly	1–2 years
Physical examination and compliance	√	√			
Blood pressure and Tanner's stage assessment	√		√		
Pelvic exam in sexually active patients	√			√	
Assessment of iron overload (*)	√		√		
Basal FSH, LH and 17β estradiol levels and thyroid status Pelvic and abdominal US	√			√	
Renal and liver function	√			√	
Fasting lipids	√			√	
Family and personal history of VTE and Thrombophilia screening	√			√	
Basal glucose and insulin glucose and HOMA-IR assessment	√		√		
Oral glucose tolerance test (OGTT)	In selected cases			√	
BMD of lumbar spine/femoral neck	√				√

Abbreviations. HOMA-IR Homeostatic Model Assessment of Insulin Resistance; BMD- bone mineral density; US-ultrasound; *Serum ferritin levels every three months, Magnetic Resonance Imaging (Liver iron concentration -LIC) at baseline and in one year if LIC >7mg/ and in two years if LIC < 7mg).

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