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Review Article

Hormone Replacement Therapy in Adolecents with Turner Syndrome

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Abstract

Turner Syndrome (TS) is a common chromosome disorder in clinical practice occuring in approximately 1/2500 births. This syndrome is characterized by short stature, gonadal dygenesis (streak ovaries), somatic alterations, multisystemic involvement and infertility. Most patients present delayed or even absent puberty. Premature ovarian failure can be expected even if spontaneous menarche occurs. Laboratory markers of gonadal dysgenesis are a markedly rise in plasma gonadotropins, especially FSH levels. The choice of optimal Hormone Replacement Therapy (HRT) in adolescents remains controversial, particularly regarding the age at which therapy should be initiated, as well as the dose and route of estrogen administration. Protocols for HRT are based on a risk-benefit assement. The aim of this manucript is based on a review of literature and the author's experience.

Keywords: Induction of puberty; Hormone Replacement Therapy (HRT); Turner syndrome

Abbreviations

TS: Turner Syndrome; HRT: Hormone Replacement Therapy; ERT: Estrogen Replacement Therapy; GH: Growth Hormone; E2: Estradiol; CEE: Conjugated Equine Estrogen; MPA: Medroxyprogesterone

Introduction

Turner Syndrome (TS) is a genetic disease caused by complete or partial absence of the X chromosome with or without mosacism, affecting approximately 1/2500 new-borns with female phenotype [1]. This syndrome may occur in the presence of multiple cells line with varying chromosomal composition (moisacism) [2]. The patients with moisacism may have functional ovarian tissue and in some cases, normal puberty (incluiding menses) occurs and only 2-5% of TS patients achieved spontaneous pregnancy. The prevalence of spontaneous puberty is 6% for 45, X and 54% for miscellaneous karyotypes. These patients frequently experience premature menopause [3,4].

In any case with "Y" chromosome material (or SRY presence) gonadectomy is indicated to reduce the risk of germ-cell tumors. These patients should be followed like other patients [5].

TS is the most prevalent example of hypergonadotropic hypogonadism. However, even when an ultrasensitive assay was used, spontaneous gonadotrophin levels in TS had a diphasic pattern: highest in childhood, declining at 6-10 years of age and then increasing again.The biphasic age pattern of gonadotrophins is preserved in all patients and spontaneous FSH and LH are not useful as a diagnostic marker of hypogonadism for TS girls aged 6-10 years [6].

The Anti-Mullerian Hormone (AMH) seems a promising marker of ovarian function in girls with TS and it seems potentially useful in counselling TS patients with regard to their fertility potential. Generally, the AMH concentration reflects the total number of non-growing follicles and becomes undetectable following ovarian failure [7].

The past few years have seen significant advances in our understanding of Tuner's syndrome and the ways in which quality of life of affected adolescents can be improved. Growth failure has been reported in 95-100% of patients and the majorities have no pubertal development due to gonadal dysgenesis [8].

A variety of disorders are associated with this syndrome including: obesity, dyslipidemia, osteoporosis, diabetes, insulin resistance, Hashimoto's thyroiditis, cardiovascular disease, renal malformations, ear and ophthalmological problems, certain phenotypic traits, biscupid aortic valve, coarctacion and rupture of the aorta [9]. *SHOX* deficiency is thought to cause the skeletal abnormalities (cubitus valgus, shortening of forearms, lower legs, the Madelung deformity and the shortened metacarpals) seen in TS [10].

The Role of Estrogen and Ovarian Failure in Turner Syndrome

The main role of estrogen

The goals of estrogen replacement in adolescence include: developing secondary sexual characteristics, maximizing final height; improving the quality of life and optimize peak bone mass. However, there is no consensus in the doses and ideal forms of administration of estrogen to induce puberty and its use in adulthood [6]. Potential spontaneous pubertal development in girls with TS must be monitored by physical examination, assessment of follicle-stimulating hormone levels beginning and performing a pelvic ultrasonography at about age 10 years [3,6].

The literature shows that treatment with Growth Hormone (GH) and the recommended dose for girls between two and twelve years is 0.05 mg/kg/day (0,15 IU/kg/day). The interruption of treatment will depend on the growth rate (less than 2.0 cm for year and the bone

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Table 1: Protocols of induce puberty in adolescentes with turner syndrome.

Type of Estradiol	*First 6 m	6-12 m	12-18 m	After 18 m
E_2	2,5 mcg/day	5 mcg/day	7,5-10 mcg/day	10 mcg
CEE	0,15 mg/day	0,3 mg/day	0,3-0,625 mg/ day	0,625-1,125 mg 1ª to 25ª day
17 β estradiol (percutaneous)	0,5 mg/day	1,0 mg/day	1,5 mg/day	1,5 a 2,0 mg 1ª to 25ª day
17 β estradiol transdermally	25 mcg/day or 0.05-0.07 µg/kg	50 mcg/day	100 mcg/day	100 mcg 1ª to 25ª day

M: Months; E2: Estradiol; CEE: Conjugated Equine Estrogens; MPA: Medroxyprogesterone
*Induction Pubertal- first 6 monthlys
**MPA 5 to 10 mg - 15ª to 25ª day

Table 2: Associated problems in turner syndrome: Birth to young adulthood.

Birth and neonatal period	Growth: often borderline small for gestational age
	Lymphoedema
	Cardiac abnormalities: e.g. coarctation of aorta, aortic stenosis, bicuspid aortic valve
Infancy	Growth: length-usually close to and parallel to the 3rd percentile
	Feeding difficulties with weight faltering
	Poor sleeping pattern
Preschool	Short stature: growth velocity usually low/normal
	Behavioral difficulties with exaggerated fearfulness
	Recurrent middle ear infections; otitis media; variable conductive hearing loss
Adolescence	Growth: impaired pubertal growth spurt even with estrogen induction
	Ovarian failure: absent/incomplete puberty
	Obesity
	Hypertension
	Increased prevalence of immune disorders
	Autoimmune thyroiditis
	Celiac disease
	Inflammatory bowel disease
	Specific learning difficulties
	Social vulnerability
	Foot problems
Young adulthood	Long term estrogen replacement
	Fertility
	Obesity
	Hypertension
	Cardiovascular diseases
	Hyperlipidemia
	Aortic dilation/dissection
	Autoimmune thyroiditis
	Osteoporosis
	Visuospatial difficulties
	Sensorineural deafness

[Adapted from Donaldson and cols [47]].

age up to 14 years) [11]. The GH is essential to improve short stature and patients with ovarian insufficiency require estrogen therapy to induce puberty at 12 ou 13 years of age, in accordance with the consent of the patient and their parents. Estrogen Replacement Therapy (ERT) allows for a normal pubertal development without interfering with the positive effect of GH on final adult stature. The use of estrogen may be delayed in patients who used growth hormone. Delaying estrogen therapy until 15 years of age to optimize potential stature, as previously recommended, appears inadvisable because it underestimates the psychosocial importance of normal pubertal maturation [11-14].

Bone mass gain and prevention of fractures

Although data on impairment of bone density and geometry and

Table 3: Suggested guideline in turner syndrome.

Yearly	Height, weight, blood pressure and complete physical examination
Special attention to pubertal staging	Pelvic ultrasound-after puberty
	Mammography-after 40 years
	Laboratory tests: Blood cell count, fasting glucose, renal and liver function tests, lipid profile and thyroid function
	At 10 years of age until the end of puberty: LH, FSH and estradiol
2 in 2 years	Audiometry
	Ophthalmological examination
5 to 5 years	Echocardiography
	Bone densitometry
When necessary: refer to gynecologist, cardiologist, otolaryngologist and orthopedist	

[Adapted from: Collett-Solberg and cols [49] and Lucaccioni and cols].

fracture risk are often controversial, bone fragilityis recognized as one of the major lifelong comorbidities in TS subjects. The pathogenetic mechanisms responsible of bone impairment remain to be well clarified, although estrogen deficiency (reduced bone formation), high FSH serum levels (FSH enhances osteoclastogenesis and bone resorption directly by binding to FSH receptor expressed on osteoclasts) and X chromosomal abnormalities (SHOX deficiency) represent important factors [10,13-17].

GH is effective in stimulating linear growth and bone formation and estrogen treatment reduced the bone turnover and levels of FSH, retarding the development of osteopenia in such patients [13-16].

There is a cortical bone deficit in girls with TS characterized by low cortical area, thin cortex and probably decreased cortical volume Bone Mineral Density (vBMD) [18]. This ovarian estrogen independent selective reduction in cortical BMD would primarily be ascribed to SHOX deficiency. In addition, although SHOX expression is primarily identified in the growth plate and is absent from osteoblasts and osteoclasts, SHOX are known to interact with multiple factor relevant for skeletogenesis [10].

Achieving optimal bone density is of critical importance for fracture prevention in TS and should be pursued by timely introduction of hormone replacement therapy, adequate dose of estrogens during young adult life, optimal calcium and vitamin D intake and regular physical exercise [15-17].

Glucose homeastase, lipidis and cardiovascular disesase

Glucose homoeostasis is altered in TS. Glucose intolerance has been reported in both TS girls and women and type 2 diabetes is four times more common (relative risk: 4.4) [9]. TS patients' present central obesity and a more sedentary lifestyle and these factors may contribute to the risk of developing diabetes. Most of the patients with TS present estrogen deficiency, which results in the loss of the cardio-protector effect of estrogen observed in menacme. Estradiol deficiency can influence several conditions related to glucose homeostasis, like endothelial dysfunction, decreased insulin production, an abnormal lipid pattern, increased central adiposity and early atherosclerosis. However, there is no consensus regarding the ideal dosage, route of administration, type of estrogen, type of gestagen and forms of administration of these hormones for the induction of puberty and for their use in adolescence and adult life in TS patients [19].

Hepatic enzymes

Elevated liver enzymes are a common feature in Turner syndrome, with a prevalence of 58.3%, compared to reference ranges. The most frequently elevated enzyme was Gamma-Glutamyl Transferase (GGT) in 55.8%, followed by Aminotransferase De Alanine (ALT) and Aspartate Aminotransferase (ALP) in 17.9% and 21.4% of cases, respectively. Compared to the control population, almost 91% of women with TS demonstrated liver enzyme elevation. Clinical studies show positive effects of HRT on liver function. Elevated ALT, GGT and ALP decreased after a 2-month HRT [20].

Role of Ovaries: Physiology and Hormone Replacement Therapy

Estrogens

Ovaries serve two main roles: germ cell development and steroid production. Estradiol (E2) is classified as the main estrogen, which regulates gonadotropin secretion and promotes the development of female secondary sexual characteristics, uterine growth, thickening of vaginal mucosa, thinning of the cervical mucus and a linear growth of the ductal system of the breast. Estrone, produced by the ovaries and estriol, produced by the metabolism of estrone and estradiol in extraovarian tissues are only weakly estrogenic and must be converted to estradiol to show full estrogenic action [19].

There are many different types of sex hormones used in HRT, including partially synthetic, semisynthetic, derived from animal sources and bioidentical. Therefore, bioidentical human estrogen (E2: Estradiol) is preferred instead of non-bioidentical (ethinylestradiol and conjugated equine estrogens) [21].

The formulations with most commonly used oral estrogen are: estradiol valerate, ethinyl estradiol and most often a mixture of several conjugates (CEE: Conjugated Equine Estrogens) which are predominantly converted to estrone [21-24].

The administration of estrogen transdermally (17β estradiol-patches or gel) provides a more stable plasma concentrations E2 and reduces its conversion to estrone when compared the use of formulations oral, by not making a first pass through the liver. The use of estrogen in this way prevents the deleterious effects on hepatic enzymes, coagulation and levels of triglycerides; although not favor cholesterol levels (reduction in LDL and increase in HDL) [21-26]. The adhesives are available in two systems: the reservoir system

(ethanol) and the matrix (propylene glycol), the latter being preferred, to cause less allergic reaction [27].

Progesterone

Progesterone, together with pregnenolone and 17-hydroxyprogesterone, belongs to progestagens. This hormone is responsible for the progestational effects: cell differentiation and induction of secretory activity in the endometrium, implantation of the fertilized ovum and maintenance of pregnancy and promotes lateral development of the breast glands. If a uterus is present, progesterone must be added, due to the risk of endometrial cancer associated with unopposed estrogen. Progestins, synthetic progestagens are most frequently used. Progesterone is the only bioidentical progestagen. Both estrogens and progestagens can be used orally, transdermally, intranasally or intramuscularly [19,21].

Puberty Induction

The aim of pubertal induction with estrogen in TS is to achieve physical and psychological development and establish adequate peak bone mass in the first two decades of life. However, girls with TS are usually introduced to the estrogens late in their lives to prevent stunting of growth [12,13].

The international consensus is to initiate HRT at the age 12 or 13 years old, if there is no spontaneous puberty and FSH levels are elevated. It permits relatively appropriate feminization without interfering in growth [22,23]. For pubertal induction in girls without spontaneous puberty, the preferred regimen is low-dose and should be increased gradually over a period of 2-4 years. The HRT is adjusted at regular time intervals to stimulate the progression of the development of secondary sexual characters (Table 1) [3,15].

The optimal route of estrogen replacement in TS is controversial. Nevertheless, according to a various authors the oral replacement with estrogenic steroids is traditionally most used. This route is the most used due to low cost, long accumulated experience and the convenience of the patient. However, the intestinal absorption and hepatic first-pass inhibiting the generation of IGF-I and IGF-II. After the hepatical metabolism observed an increased synthesis of coagulation factors, angiotensinogen and SHBG. This effect reducing the growth velocity in puberty and increased risk of hypertension and cardiovascular events [19-21,27-30].

There are many options for HRT. However, systemic administration of estradiol, usually by transdermal application in a patch or gel, is the only form of therapy to achieve natural levels of estradiol in blood [31].

In practice, the most useful method of administration is the transdermal route of estrogen replacement therapy. Theoretical advantages of transdermal over oral estrogen include a more physiologic mode of delivery, without first-pass mechanism in the liver and avoidance of unphysiological changes and action of the hormones. Moreover, transdermal E2 results in faster bone accrual at the spine, increased uterine growth and better final height [31,32]. Compared with oral E2, transdermal E2 results in E2, E1 and bioestrogen concentrations closer to normal; it also achieves greater suppression of LH/FSH in lower doses [33,34]. The use of percutaneous estrogen gel/patches leads to a gradual developmentof secondary sexual characteristics and uterine growth, mimicking natural puberty [33,34].

The adhesive can be used for the induction of puberty; it also permits titration of dose (release presentations with 25-100 mcg/day) and monitoring by means of serial dosages of estradiol [26-28]. Additionally, the possibility to cut a transdermal patch in four pieces and use only its part, facilitates mimicking the spontaneous levels as well as the diurnal pattern of serum E2 in early puberty [31]. Commercially available patches releasing 25 or 50 mcg of estradiol per 24 h can be cut (the matrix patches) and 1/2 to 1/4 (12.5 mcg/24 h), respectively or even less (6.25 mcg/24 h) may be may be used as an initial dose [35].

The percutaneously (gel) can be used in the form of sachets and bottles with metering valve to release the gel (0.50 mg to 0.75 mg 17-β-estradiol per dose). The advantage of this presentation is the convenience for the patient, with minimal side effects [33,34]. We observed in our patients a great acceptance to treatment, with positive effects on bone mass, insulin resistance quality of life. The main disadvantage of long-term use was the higher cost and noncompliance with the omission of prescribed doses [14,24].

Progesterone should be added to Estrogen (E2) when the first menstrual bleeding or after 24 months of use of estrogen in order to enable normal breast, uterine development and establishing regular menstrual cycles [6,24,35, 36]. The most presentations used are: Medroxyprogesterone (MPA) and compounds present in an ovulatory pills as norethindrone, gestodene, levonosgestrel, desogestrel, among others. Ideally, use natural micronized progesterone, however, due to high cost; it is used in selected cases [37].

About 90% of TS patients require or will require HRT to initiate progress and maintain puberty. Estrogen administration should be advised as continuous therapy. Despite the known advantages of HRT in hypogonadism, a rather high percentage of adult TS patients discontinue their estrogen therapy. It is recommended that women with TS should receive estrogen and progestin, which have a longterm [37,38].

To control HRT in adolescence, the access to sensitive estradiol determination methods (RIA or mass spectrometry) are very desirable, nevertheless, unavailable in most countries [12,21]. Practically, the decision concerning the modification of HRT is based on puberty assessment (Tanner stage), uterus development and growth velocity in the context of bone age [34-39].

In most cases, earlier diagnosis of TS allows for early HRT induction. Nevertheless, further research is warranted, establishing the optimal time, dose and route of HRT, not only in TS, but also in other types of female hypogonadism [40].

Protocols of Puberty Induction

Several Protocols for pubertal induction are used in literature to induce puberty. The ERT should be started with low dose (1/4 of the adult woman maintenance dose) and increased gradually (every 3/6 months), according to stage pubertal, bone age and uterus growth [37-40]. The protocols of induce puberty with low dose of estrogens are demostrated in (Table 1).

Estrogens

- Ethinyl estradiol was used at a dose of 0.01 to 0.02 mg for/ day [39].

- The Conjugated Estrogen Equine (CEE): can be started in the dose that may vary from 0.15 to 0.3 mg. The final dose may vary from 0.625 to 1.250 mg [40-42].

- Estadiol percutaneously-initial dose 0.1 mg to 1.5 mg in the end, suggesting that this type of administration E2 safe and provides the individualized induction, it is easy to use and well accepted by patients [33,34,38,40,42].

- Adhesive E2: initial dose ¼ of the adhesive. The application of a dose of 50 to 100 mg of estradiol adhesive twice a week or 1.5 g of gel is equivalent the oral ingestion of 0.625 to 1.25 mg of CEE [26,28,29,31,35,39,40].

- Valerate micronized Estradiol: 1 to 2 mg/day [37,39].

Progestagens

- Medroxyprogesterone (MPA): 2,5 to 10 mg- Example: 15th to 25th day / month.

- Micronized progesterone: 100 to 200mg / day) [24,35,37,40].

- Gestodene (0.75 mg/dose): is androgenically neutral, meaning that contraceptive pills containing gestodene do not exhibit the androgenic side effects (e.g. acne, hirsutism and eight gain) often associated with second-generation contraceptive pills, such as those containing levonorgestrel [37].

- Levonorgestrel-is used in monophasic and triphasic formulations of combined oral contraceptive pills, with available monophasic doses ranging from 100-250 μg and triphasic doses of 50 μg/75 μg/125 μg [35,38].

Estrogen is used cyclically with progesterone during the first 21 or 25-day cycle associated with progesterone for seven to ten days of the month and interval of five or seven days without replacement to mimic the menstrual cycle. The most used type of estrogen in our clinicwas CEE 24. The optimal protocolol of induce puberty is demostrated in (Table 1).

Hormone replacement therapy after puberty induction

The dose and route of administration should be individualized. The recommended treatment plan includes 1 to 2 mg valerate micronized estradiol or 0.625 to 1.25 mg of CEE or 0.01 to 0.02 mg for ethinyl estradiol. In generally, these dosages determine serum levels of estradiol from 30 and 50 pg/ml, which correspond to the beginning of folicular phase [38-40,43]. The ideal hormone replacement therapy should be based on the use of a more natural estrogen as 17-β-estradiol as well as more neutral progesterone like natural micronized progesterone.

Because in the literature are described higher prevalence of elevated liver enzymes, heart disease, hypertension and obesity [1,19,20]. The ideal way to use estrogen in ST would probably be the transdermal or percutaneous because oral estrogens present bioavailability variable that depends on the intestinal absorption and the first pass the liver, which may promote high levels of estrogens the portal circulation, stimulate liver protein synthesis and consequently, elevated hepatic enzymes [24,29,32,44]. The use of oral contraceptive pillsin ST appears to be not appropriate, it may worsen the hepatic function and cause undesirable changes in the lipid profile and insulin resistance [44,45]. Recent study has shown a two-fold higher risk of vein thrombosis and possibly of myocardial infarction in users of oral conjugated equine estrogens [40].

The HRT must be maintained at least until 50 years of age. However, most patients interrupt the treatment irregularly, increasing the risk of cardiovascular disease, hypertension, diabetes, reduction in bone mass and fractures [1,6,14,24,44-46]. HRT should be monitored regularly with evaluation clinical, especially in hypertensive, dyslipidemic and patients with congenital disease [47,48]. In (Table 2) we described the associated problems in Turner syndrome [47].

In this group of patients is essential to educate patients on the importance of continuing HRT until the normal age of menopause to maintain feminization, reduce cardiovascular disease and prevent osteoporosis. In (Table 3) we suggested a guideline for the management of Turner syndrome: at the time of diagnosis to adult life [49].

Conclusion

In most TS cases, premature ovarian failure can be expected, even if the patient presents some symptoms of puberty.

Estrogen therapy should be initiated around the age of 12-14, at a low-dose and gradually increased over two to four years.

The use of progesterone derivatives can be started two years after use of estrogen aimed to mimic the menstrual cycles, avoid undesirable uterine bleeding and prevent endometrial hipeplasia and endometrial carcinoma.

Ideally, use both a more natural estrogen as 17-β-estradiol as well as more neutral progesterone. The ideal way for the use of estrogen is the transdermal or percutaneous.

Is recommended that patient with TS should receive estrogen and progestin, which have a longterm impact on puberty, in metabolism, in psychological functioning and support normal bone maturation and calcification.

The HRT in the ST should be regularly monitored with close clinical evaluation. Irrespective of the form of estrogen therapy, liver function is improved; HDL-cholesterolincreases and it may also be cardioprotective.

Decisions, concerning sex steroid replacement therapy, should be made individually.

Sex steroid replacement for girls with TS remains an area of active investigationand there is no consensus regarding optimal approaches in terms of dosage, type and route of administration.

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