Endocrine diseases, perspectives and care in Turner syndrome

Doenças endócrinas, perspectivas e cuidados na síndrome de Turner

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SUMMARY

Turner syndrome is a frequent chromosome disorder in clinical practice. It is characterized by short stature, gonadal dysgenesia and multisystemic involvement, responsible for a high morbidity and reduced life expectancy. The aim of the present paper is to describe the endocrinopathies and major problems at different ages, and to present suggestion for follow-up care in these patients. Arq Bras Endocrinol Metab. 2011;55(8):550-8

Keywords

Turner syndrome; endocrinopathies; rhGH treatment; estrogen HTR

SUMÁRIO

A síndrome de Turner é uma doença cromossômica frequente na prática clínica. É caracterizada pela baixa estatura, disgenesia gonadal e alterações em diversos sistemas, o que leva a uma alta morbidade e diminuição da expectativa de vida. O objetivo do presente estudo é descrever as endocrinopatias e outros problemas em cada idade e apresentar uma sugestão de cuidados e segmentos dessas pacientes. Arq Bras Endocrinol Metab. 2011;55(8):550-8

Descritores

Síndrome de Turner; endocrinopatias; tratamento com GH; terapia de reposição hormonal estrogênica

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INTRODUCTION

Turner syndrome (TS) is characterized by a female phenotype and loss of the second sexual chromosome. It occurs in about 1:2,500 to 4,000 live female births. The features vary widely, and are associated with short stature, and ovarian failure with sexual infantilism and infertility. Dysmorphisms like cubitus valgus, low hairline, small mandible, multiple pigmented nevi, characteristic face, short fourth toe, high-arched palate, nuchal folds, edema of hands or feet, left-sided cardiac and renal anomalies are commonly observed in the syndrome. The diagnosis is performed by karyotyping, and requires a standard 30-cell karyotype. In routine TS practice, roughly half of the patients have a 45,X karyotype, 20%-30% have mosaicism (45,X plus at least another cell line), and the remainder have structural abnormalities (1). Females with short stature and deletion of the distal region of Xp including the *SHOX* (short stature homeobox gene) gene are generally not diagnosed with TS. Likewise, individuals with deletions of Xq24, with primary or secondary amenorrhea and without short stature are typically diagnosed with premature ovarian failure (2). The main endocrine problems are short stature, ovarian failure, immune diseases and disturbances of the lipid glucose and bone metabolism (1).

SHORT STATURE

TS patient adult height is in average 20 cm shorter than the mean height of women of the same population (3). This short stature reflects the sum of a normal but small size at birth, decreased growth velocity starting at an early age, and a poor growth spurt during puberty. Several techniques were used to assess the growth hormone (GH) – Insulin-like growth factor (IGF) axis, from stimulation tests (4), to evaluation of the levels of different isoforms, and investigation of IGF-I and IGFBP-3

generation tests (5,6). All of them show normal values. Presently, the short stature in girls with Turner syndrome is thought to be related to the haploinsufficiency of the *SHOX* gene, a pseudoautosomal gene (7). Even though the production of growth hormone is normal, treatment with rhGH was approved in the United States in 1996, and is now routine in several countries.

Girls with TS are born with normal but small size, and present slow growth during the first three years of life (8). Davenport and cols. investigated the use of rhGH in this population before 4 years of age, and demonstrated that two years after initiating treatment, patients who received rhGH had an average height of -0.3 SD of the normal population, while patients who did not receive rhGH had a height of -2.2 SD (9).

The gain in height, using expected values prior to initiation of treatment, may be of 8.5 cm above expected height (10). There are few studies comparing treated and control groups. Stephure and the Canadian Growth Hormone Advisory Committee compared adult height of children treated with rhGH to the adult height of a control group who did not receive rhGH, and showed an increment of 7.2 cm in adult height (confidence interval 6.0, 8.4) (11). One important aspect of treatment with rhGH is the quality of life with the treatment (benefits of being taller versus the effects of medicalization – rhGH injection for many years), and two different studies did not find benefits or adverse effects (12). Other aspects of adult height in girls with Turner syndrome is when to start estrogen replacement to optimize growth, and which dose to use. A recently published study compared the effects of rhGH treatment associated with the use of very low doses of estrogen during childhood. Even though the use of ethinyl estradiol alone decreased adult height, when compared with a control group, the use of rhGH alone increased adult height by 5.0 cm, and the association with low doses of estrogen increased adult height by other 2.1 cm (13).

One study published in 1992 reported that the use of oxandrolone, a non-aromatizable androgen, in girls with TS, improved growth (14). Based on the knowledge that estrogen is the hormone responsible for the closure of the epiphysis, the idea of using oxandrolone and rhGH became popular again, and several recently published studies investigated this topic, with increased adult height of about 4.5 cm, using doses of about 0.05 mg/kg/day (15). Breast development was slower in both studies, and there was no sign of virilization. Menke and cols. had different results. They compared the use of 0.03 mg with 0.06 mg/kg/day or placebo, and found a gain between 2 and 3 cm with the low dose, and no benefits with the use of 0.06 mg when compared with control patients. More patients receiving the higher dose reported virilization (16).

Growth hormone used in patients with TS, probably starting at a very young age, will improve adult height even further, but this has not been shown yet. The use of low dose estrogen during childhood and the use of oxandrolone are still topics of debate.

OVARIAN FAILURE

Gonadal function of patients with TS is variable. The ovaries may degenerate during fetal life, in childhood or in early adulthood. Approximately 20% of patients with TS show spontaneous menarche, primary amenorrhea (85%), infertility (98%), and the non-assisted pregnancy rate is 2% to 5% (17).

In most prepubertal TS patients, ovarian failure and reduced ovarian feedback result in significantly elevated FSH and LH levels during early childhood (0-5 years) and adolescence (around 10 years), whereas gonadotropin levels are not significantly elevated at age 5-10 years, compared with healthy girls (18). However, in adulthood FSH and LH increase to menopause levels in gonadal dysgenesis girls (19). Potential spontaneous pubertal development in girls with TS must be monitored by physical examination and assessment of follicle-stimulating hormone levels beginning at about age 10 (20). Inhibin B is secreted by developing follicles, and FSH and inhibin B are markers of remaining ovarian function in girls with TS. However, inhibin B evaluation is not a routine analysis in the follow-up of TS; this analysis is only indicated when testing the possibility of fertility.

When FSH and LH are clearly elevated, and clinical signs of puberty are absent, pubertal induction should be started. The aim of pubertal induction with estrogen in TS is to achieve physical and psychological development similar to that of natural puberty, and to establish adequate peak bone mass in the first two decades of life. However, girls with TS are often introduced to the estrogens late in their lives to prevent stunting of growth. Recent evidence shows that the regimens initiating estrogen treatment at age 12 enable the evolution of puberty without interfering with final height (21). The optimal route of estrogen replacement in TS is unknown. For pubertal induction in girls without spontaneous puberty, the preferred regimen is low-do-

se, transdermal estrogen treatment, with gradual dose increases over approximately 2-3 years until feminization. In these cases, there is a direct correlation between breast stage and gonadotropin levels (22). Optimal estrogen administration seems to be important in preserving bone mass and enhancing trabecular bone volume. Hormone replacement therapy should begin at a normal pubertal age, and be continued until the age of 50. Transdermal estradiol provides the most physiological form of replacement (1). If spontaneous pubertal development occurs, in most cases it is followed by progressive premature ovarian failure (23).

AUTOIMMUNE DISORDERS

Patients with TS are prone to develop autoimmune conditions such as thyroiditis, celiac disease, inflammatory bowel disease, type 1 diabetes, Grave's hyperthyroidism, ulcerative colitis, Crohn's disease, juvenile rheumatoid arthritis, psoriasis, alopecia and vitiligo (23). These patients frequently exhibit transient, recurrent and asymptomatic variations in TSH and/or thyroid hormones (24).

The prevalence of Hashimoto's thyroiditis in these patients ranges from 13.3% to 55%, according to the criteria used for diagnosis, the age range covered, and the technique used to measure antibodies (25).

Morbidity secondary to autoimmunity ranks among the most prominent syndrome-associated characteristics, and studies estimated that 50% of the middle-aged patients suffer from thyroiditis, and prevalence increases with age (26).

Mortensen and cols. (23) showed positive results for anti-TPO in 94% of TS patients with hypothyroidism, and this fact indicated a relationship between autoimmune reactivity and hypothyroidism in this syndrome. However, the authors were not able to say that there was an increase in the number of cases with age, because of the relatively low number of pediatric TS patients in the study (27).

Although the study by Wilson and cols. described the presence of antibody-positive among both patients with TS and their mothers, other study pointed to the opposite direction, and the presence of autoimmune hypothyroidism was associated with the syndrome itself, not the presence of family history (27).

The higher risk of autoimmune diseases in women with TS has been suggested to be due to haploinsufficiency of the X-chromosome (28). However, proinflamatory cytokines, interleukin-6, interleukin-8 and tumor necrosis factor α may be partly responsible for that (29,30). Su and cols. studied the expression of the X-linked FOXP3 gene and the prevalence of autoimmunity in patients with TS, but did not find a positive correlation (30).

In the general population of women, the diagnosis of thyroiditis is based on clinical evidence of thyroid dysfunction, whereas in patients with TS, functional evaluation is done periodically, regardless the clinical picture, which allows the detection of subclinical changes that cannot always be correlated with disorders of the hypothalamic-pituitary-thyroid axis (25).

The incidence of celiac disease in patients with TS is increased when compared with the general population. Mortensen and cols. found a prevalence of 5% in a cohort of Turner syndrome individuals with 18% of autoantibodies, and revealed a considerable number of silent cases and delayed diagnoses (23).

In Brazil, a 3.6% prevalence of biopsy-proven celiac disease was observed in a group of females with TS, which is 10 times the prevalence among females of the general population in the same geographical area. This result provides additional support to an association between these two disorders, and restates that girls and women with Turner syndrome represent a high risk population for developing celiac disease (31).

CARBOHYDRATE METABOLISM IN TURNER SYNDROME

Glucose homoeostasis is altered in TS, and early reports of diabetes and glucose intolerance have been found. Glucose intolerance has been reported in both TS girls and women, and type 2 diabetes is four times more common (relative risk: 4.4) (32), in addition to increased mortality due diabetes (33), and earlier onset than general population. TS patients present central obesity (34) and a more sedentary lifestyle, and these factors may contribute to the risk of developing diabetes. Additionally, women with TS were at significantly increased risk of certain specific autoimmune diseases, including Hashimoto thyroiditis and type 1 *diabetes mellitus* (23). Fasting glucose and insulin levels were frequently normal despite the fact that, in adults, glucose intolerance (GI) has been found in 25%-78% during an oral glucose tolerance test (OGTT) (35,36). Glucose homeostasis is not completely understood. There are controversies surrounding insulin sensitivity in TS, and the exact mechanism behind the elevated occurrence of type 2 diabetes and GI remains unclear.

Reduced insulin sensitivity was demonstrated, but not in all patients, and in some of them, impaired insulin secretion was found (37).

Glucose homoeostasis during hormone replacement therapy (HRT)

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 (37). For example, when the route of estrogen administration is considered, existing data have not demonstrated important advantages of any form of estrogen administration in TS (38). There is a great probability that the dose, rather than route of administration, is more important in these patients.

Glucose homoeostasis during rhGH treatment

Insulin levels increase during rhGH use. Insulin levels decrease after the end of the treatment, but do not return to levels as low as before treatment. GH generally reduces insulin sensitivity in the first 6-12 months of treatment, when it becomes stable. This stabilization could be due to increased lean body mass (LBM) and decreased fat mass (FM). The number of TS patients with GI do not seem to increase significantly during treatment, and HbA1c remains unchanged or even decreases during rhGH therapy. However, the long-term effects of the GH-induced hyperinsulinism and insulin resistance are not known (37).

Finally, adult women with TS require careful medical follow-up. Early medical intervention may decrease the substantially increased morbidity, mortality, and improve the quality of life (39). Many of the problems of adult life in patients with TS are related to obesity (34), partly because of low physical fitness and a sedentary lifestyle. Women with TS should aim at having a body mass index lower than 25 kg/m^2 and a waist/hip ratio lower than 0.80. Lifestyle education with advice on diet and exercise must be included in a diabetes prevention program. However, exercise programs should be individualized.

There is a need to pay attention to the increased risk of type 1 and type 2 diabetes in TS. Focus on diabetes symptoms and yearly screening of fasting glucose. OGTT is recommended when there is a suspicion of the disorder. Diabetes is often relatively mild and responsive to weight loss or oral monotherapy (37). Recommendations for diagnosis and treatment of diabetes are the same for the general population.

CARDIOVASCULAR RISK

The population with Turner syndrome has an increased risk for cardiovascular and cerebrovascular disease of ischemic origin (40). The existence of dyslipidemia in patients with TS is controversial. In some studies, the levels of cholesterol and triglycerides are comparable to controls, as well as the numerical superiority of HDL (41). However, most studies demonstrate that there is abnormal lipid profile with increased LDL cholesterol, decreased HDL cholesterol, and high triglycerides, especially because of altered body composition, leading to insulin resistance. Low-density lipoprotein cholesterol and triglycerides are elevated, and lipid particle size is reduced in women with TS compared with women with normal karyotype and ovarian failure matched by age and body mass index, suggesting that the X chromosome deletion *per se*, apart from the effects of premature ovarian failure, is associated with dyslipidemia (42). Our group, in a recent, unpublished study, noted that patients with TS have higher postprandial triglycerides than controls, and this fact was not influenced by the route of estrogen replacement.

There is no consensus on the treatment of dyslipidemia in patients with TS. Some studies have reported the improvement of some lipid profile parameters, such as decrease in lipoprotein A, apoprotein A-I and increase in HDL cholesterol after the beginning of estrogen replacement. The administration of rhGH also improves the lipid profile by reducing total cholesterol and LDL cholesterol and increasing HDL (41,43). Androgen replacement therapy presents controversial effects on lipid metabolism in patients with TS. Zuckerman-Levin and cols. have shown that the administration of methyl-testosterone had improved the lipid profile, not only with a reduction in total cholesterol, LDL cholesterol and triglycerides, but also with a decrease in HDL cholesterol (44). However, Wilson and cols. did not observed any change on lipid profile after administration of oxandrolone (45).

BONE MASS GAIN AND PREVENTION OF FRACTURES IN TURNER SYNDROME

Estrogens and gestagens play a crucial role, and several reports suggest that during puberty and late adolescence normal gonadal function is required in TS girls for adequate skeletal mineralization, as well as attainment and posterior maintenance of normal bone mass peak (46). Genetic factors are important determinants of adult bone mass, but no inheritable variables, including body mass, calcium nutrition, vitamin D, sex steroids, and activity may strongly influence whether maximal bone mineral is achieved. These risk factors contribute to the osteopenia associated with delayed puberty, TS, and growth hormone deficiency (47).

Osteopenia is a common complication among adult patients and may be related to the delayed pubertal development and hypoestrogenism. In addition, prepubertal estradiol secretion may also play a role in bone mass acquisition during this period. Adolescents girls with TS and spontaneous puberty have bone mineral density (BMD) in the normal range, while in TS girls who underwent induced puberty (48) and young TS patients do not attain peak BMD despite proper HRT and growth hormone therapy (49).

In girls with TS, transdermal E2 resulted in faster bone accrual at the spine, and increased uterine growth compared with conjugated oral estrogen. Neither BMI, nor calcium intake, karyotype, nor concomitant rhGH therapy appear to be significant factors accounting for these differences. Inadequate availability of estrogens to bone tissue from infancy to adulthood, caused by early prepubertal ovarian dysfunction, delayed puberty, therapeutic estrogen/gestagen regimens, and treatment compliance, should be considered as major factors responsible for the low BMD values observed in our puberty-induced patients. However, unknown genetic factors related to bone mineralization, or disturbances in other calcium-regulating hormones cannot be ruled out. In addition, it has been reported that rhGH therapy increases bone calcium availability, and enables adequate bone mass peak in adolescent Turner syndrome patients (50).

Several studies have shown decreased BMD in girls, as well as in younger and middle-aged women with TS (51,52). This finding may be largely due to the two--dimensional nature of dual energy x-ray absorptiometry (DEXA) scans (53), which fails to account for the reduced height in TS, leading to lower BMD *a priori*. Studies of volumetric BMD, taking actual body height into account, have shown largely similar volumetric BMD in TS and controls (54).

Increased fracture risk is a feature of TS. However, the reasons for this finding are unclear. It is not entirely clear whether a primary bone defect exists in TS (55), perhaps due to skeletal dysmorphogenesis caused by haploinsufficiency of the *SHOX* gene (7). In addition, deletions of the Xp11.2-p22.1 region of the X chromosome have been identified in non-mosaic TS patients, and were related to the presence of phenotypical traits such as short stature, ovarian failure, high-arched palate, and autoimmune thyroid disease. Whether the presence of functional mutations in unidentified genes related either to factors that regulated bone mass acquisition, or to intrinsic bone defects in TS patients, play a role in the differences observed in BMD values in our patients, is something that should also be considered. Some authors observed reduced BMD at the femoral neck; QCT data suggests that cortical density is reduced with sparing of trabecular bone. This differential of cortical and trabecular BMD may predispose to fracture (56). There is an approximately 25% increase in fracture risk, most of which is related to medium or high-impact trauma. Longer bones, especially of the forearm, are predominantly affected. This fact may be due to a selective cortical bone deficiency in TS, which is unrelated to hypogonadism. In addition, lack of adequate estrogen replacement can lead to trabecular bone deficiency, and increase vertebral compression fractures after the age of 45.

Although DEXA evaluation is important, it should be used judiciously in TS in view of its inherent tendency to underestimate the bone density of people with short stature. Bone size-independent methods, such as QCT or volumetric transformation of DEXA data, should be used in individuals shorter than 150 cm. 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 (57).

Assays on bone turnover markers show evidence of increased bone turnover. Bone deficiency is most marked at the femoral neck and seems correlated with serum testosterone and estradiol levels (58).

On the whole, bone health represents a main clinical issue for the management of persons with disorders of sex differentiation, and well-designed longitudinal studies should be developed to improve their bone

health and well-being. In addition, early detection of osteopenia in prepubertal age and early instauration of preventive measures, such as adequate calcium intake and optimal physical activity, should be considered mandatory in the health care of TS patients. Bone health can be maintained in most women with TS when appropriate information is given, and proper HRT, as well as vitamin D and calcium supplementation, is recommended (21).

PERSPECTIVES IN TURNER SYNDROME

The main perspective in TS is related to the fertility problem. Pregnancy is an exceptional event, but is possible in 2% of cases. It can occur in patients with structural anomalies of the X chromosomes in which the Xq13--q26 region, containing the genes that are thought to control ovarian function, is spared; or in patients with a mosaic karyotype containing a 46, XX cell line, which preserves ovarian function (59). *In vitro* fertilization with donor oocytes and subsequent embryo transfer has been the predominant fertility option for such patients (60). Women with Turner mosaicism (46XX/45XO) and normal FSH levels may have an adequate ovarian reserve and undergo attempts at traditional assisted reproduction. At the time of retrieval, an ovarian biopsy may be performed in order to directly evaluate the ovarian karyotype. A successful pregnancy results from oocytes retrieved from the gonad demonstrating a normal karyotype (61). The combination of ovarian tissue cryobanking and immature oocyte collection from the tissue, followed by *in vitro* maturation and vitrification of matured oocytes represent promising approaches to fertility preservation for young women with mosaic Turner syndrome (62,63).

CARE OF TURNER SYNDROME

The presence of Y-chromosome material in patients with dysgenetic gonads increases the risk of gonadal tumors and/or nontumoral androgen-producing lesions, and the risk increases with age (64). The gonads should, therefore, be removed, even if they appear inconspicuous on ultrasound.

Otherwise, adults with TS have a 4- to 5-fold increased rate of premature mortality, which is attributed mainly to complications of congenital heart disease (CHD) and premature coronary artery disease. TS patients with congenital anomalies indicating involvement of the cardiovascular system should be followed up by a cardiology specialist. In young girls, transthoracic echocardiogram is sufficient, if it enables clear visualization of the cardiac anatomy. If not, or if otherwise indicated, cardiac magnetic resonance (CMR), with sedation if necessary, may be advised. In addition to echocardiogram, CMR is recommended as a screening test for older girls and for all adults, ideally, adults with TS (20). Similarly, TS patients should be followed up by other specialists, such as nephrologists, gastroenterologists, gynecologists and others, besides the endocrinologist. Table 1 summarizes the problems, and table 2, the care at different ages of TS patients.

Table 1. The natural history of Turner syndrome and its associated problems

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
High activity levels
Behavioral difficulties with exaggerated fearfulness
Recurrent middle ear infections; otitis media with effusion (glue ear); variable conductive hearing loss; sensorineural deafness in a minority
School
Growth: height — gradually falling away from 3rd percentile
Middle ear disease (see above)
Obesity
Specific learning difficulties: e.g. mathematics, visuospatial tasks
Social vulnerability
Foot problems: e.g. toenail involution, cellulitis
Renal anomalies: e.g. horseshoe, duplex, unusually shaped kidneys
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
Need for counseling in relation to:
Long term estrogen replacement
Fertility
Obesity
Hypertension
Aortic dilation/dissection
Autoimmune thyroiditis
Osteoporosis
Visuospatial difficulties
Sensorineural deafness

[Adapted from Donaldson and cols. (65)].

Table 2. Guideline of care for the management of Turner syndrome

At the time of diagnosis
Height, weight, blood pressure and complete physical examination
Bone age
Blood cell count, fasting glucose, renal and liver function tests, lipid profile, TSH, T4, antithyroid antibodies, estradiol, LH, FSH.
Renal and pelvic ultrasound; echocardiogram
Audiometry
Bone mineral density (prepubertal and after ages)
Refer to cardiologist, ENT, ophthalmologist and orthopedist
Annual evaluation until 10 years of age
Height, weight, blood pressure and complete physical examination
Thyroid function tests
At the ages of 4, 6, and 8 years, the following should be added to routine annual evaluation
Bone age
Blood cell count, fasting glucose, renal and hepatic function tests, lipid profile, and antithyroid antibodies
At 5 years of age, the following should be added to routine annual evaluation:
Echocardiogram and audiometry
Refer to cardiologist, ENT, ophthalmologist and orthopedist
At 10 years of age, the following should be added to routine annual evaluation
Special attention to pubertal staging
Careful exam of Nevi
Bone age
Blood cell count, fasting glucose, renal and liver function tests, lipid profile, TSH, T4, antithyroid antibodies, estradiol, LH, FSH
Renal and pelvic ultrasound; echocardiogram
Audiometry
Bone mineral density
Refer to cardiologist, ENT, ophthalmologist, orthopedist and orthodontist
Annually, between 11 and 14 years of age
Height, weight, blood pressure and a complete physical examination
Special attention to pubertal staging
Careful exam of Nevi
Bone age
Blood cell count, fasting glucose, renal and liver function tests, lipid profile, TSH, T4, antithyroid antibodies, estradiol, LH, FSH
Pelvic ultrasound
At 15 years of age
Height, weight, blood pressure and a complete physical examination
Special attention to pubertal staging
Careful exam of Nevi
Bone age
Blood cell count, fasting glucose, renal and liver function tests, lipid profile, TSH, T4, antithyroid antibodies, estradiol, LH, FSH.
Pelvic ultrasound
Bone mineral density
Refer to gynecologist
Annual evaluation after 16 years of age
Weight, blood pressure and a complete physical examination
Careful exam of Nevi
Blood cell count, fasting glucose, renal and liver function tests, lipid profile, TSH, T4, antithyroid antibodies, estradiol, LH, FSH
Refer to gynecologist
Evaluation every 2 years after 16 years of age, to be added to routine annual evaluation
Bone density and body composition if previous exam was abnormal
Evaluation every 5 years after 15 years of age, to be added to routine annual evaluation
Echocardiogram
Audiometry
Bone density and body composition if previous exams were normal
Refer to cardiologist, ENT, ophthalmologist

ENT: Ear, nose and throat specialist.

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REFERENCES

1. Davenport ML. Approach to the patient with Turner syndrome. J Clin Endocrinol Metab. 2010;95(4):1487-95.
2. Wolff DJ, Van Dyke DL, Powell CM. Working Group of the ACMG Laboratory Quality Assurance Committee. Laboratory guideline for Turner syndrome. Genet Med. 2010;12(1):52-5.
3. Guimarães MM, Guerra CTG, Alves STF, Cunha MCSA, Marins LA, Barreto LFM, et al. Intercorrências clínicas na síndrome de Turner. Arq Bras Endocrinol Metab. 2001;45(4):331-8.
4. Cuttler L, Vliet GV, Conte FA, Kaplan SL, Grumbach MM. Somatomedin-C levels in children and adolescents with gonadal dysgenesis: differences from age-matched normal females and effect of chronic estrogen replacement therapy. J Clin Endocrinol Metab. 2001;60:1087-92.
5. Pessoa de Queiroz AN, Collett-Solberg PF, Cardoso ME, Jusan RC, Vaisman M, Guimarães MM. IGF-I, IGFBP-3 and ALS generation test in Turner syndrome. Growth Horm IGF Res. 2007;17(3):254-60.
6. Collett-Solberg PF, Pessoa de Queiroz AN, Cardoso ME, Jusan RC, Vaisman M, Guimarães MM. The correlation of the IGF-I, IGFBP-3, and ALS generation test to height velocity after 6 months of recombinant growth hormone therapy in girls with Turner syndrome. Growth Horm IGF Res. 2006;16(4):240-6.
7. Clement-Jones M, Schiller S, Rao E, Blaschke RJ, Zuniga A, Zeller R, et al. The short stature homeobox gene SHOX is involved in skeletal abnormalities in Turner syndrome. Hum Mol Genet. 2000;9(5):695-702.
8. Even L, Cohen A, Marbach N, Brand M, Kauli R, Sippell W, et al. Longitudinal analysis of growth over the first 3 years of life in Turner's syndrome. J Pediatr. 2000;137(4):460-4.
9. Davenport ML, Crowe BJ, Travers SH, Rubin K, Ross JL, Fechner PY, et al. Growth hormone treatment of early growth failure in toddlers with Turner syndrome: a randomized, controlled, multicenter trial. J Clin Endocrinol Metab. 2007;92(9):3406-16.
10. Soriano-Guillen L, Coste J, Ecosse E, Léger J, Tauber M, Cabrol S, et al. Adult height and pubertal growth in Turner syndrome after treatment with recombinant growth hormone. J Clin Endocrinol Metab. 2005;90(9):5197-204.
11. Stephure DK. Canadian Growth Hormone Advisory Committee. Impact of growth hormone supplementation on adult height in turner syndrome: results of the Canadian randomized controlled trial. J Clin Endocrinol Metab. 2005;90(6):3360-6.
12. Amundson E, Boman UW, Barrenäs ML, Bryman I, Landin-Wilhelmsen K. Impact of growth hormone therapy on quality of life in adults with turner syndrome. J Clin Endocrinol Metab. 2010;95(3):1355-9.
13. Ross JL, Quigley CA, Cao D, Feuillan P, Kowal K, Chipman JJ, et al. Growth hormone plus childhood low-dose estrogen in Turner's syndrome. N Engl J Med. 2011;364(13):1230-42.
14. Rosenfeld RG, Frane J, Attie KM, Brasel JA, Burstein S, Cara JF, et al. Six-year results of a randomized, prospective trial of human growth hormone and oxandrolone in Turner syndrome. J Pediatr. 1992;121(1):49-55.
15. Zeger MP, Shah K, Kowal K, Cutler GB Jr, Kushner H, Ross JL. Prospective study confirms oxandrolone-associated improvement in height in growth hormone-treated adolescent girls with Turner syndrome. Horm Res Paediatr. 2011;75(1):38-46.
16. Menke LA, Sas TC, de Muinck Keizer-Schrama SM, Zandwijken GR, de Ridder MA, Odink RJ, et al. Efficacy and safety of oxandrolone in growth hormone-treated girls with turner syndrome. J Clin Endocrinol Metab. 2010;95(3):1151-60.

17. Gravholt CH. Clinical practice in Turner syndrome. Nat Clin Pract Endocrinol Metab. 2005;1:41-52.
18. Fechner PY, Davenport ML, Qualy RL, Ross JL, Gunther DF, Eugster EA, et al. Toddler Turner Study Group Differences in follicle--stimulating hormone secretion between 45,X monosomy Turner syndrome and 45,X/46,XX mosaicism are evident at an early age. J Clin Endocrinol Metab. 2006;91(12):4896-902.
19. Bondy CA. Care of girls and women with Turner syndrome: a guideline of the Turner syndrome study group. J Clin Endocrinol Metab. 2007;92:10-25.
20. Bondy CA. Turner syndrome 2008. Horm Res. 2009;71(Suppl 1):52-6.
21. Cleemann L, Hjerrild BE, Lauridsen AL, Heickendorff L, Christiansen JS, Mosekilde L, et al. Long-term hormone replacement therapy preserves bone mineral density in Turner syndrome. Eur J Endocrinol. 2009;161(2):251-7.
22. Alves ST, Gallicchio CT, Guimarães MM, Santos M. Gonadotropin levels in Turner's syndrome: correlation with breast development and hormone replacement therapy. Gynecol Endocrinol. 2003;17(4):295-301.
23. Mortensen KH, Cleeman L, Hjerrild BE, Nexo E, Loc H, Jeppesen EM, et al. Increased prevalence of autoimmunity in Turner syndrome--influence of age. Clin Exp Immunol. 2009;156:205-10.
24. Medeiros CCM, Marini SHVL, Filho MB, Camargo EE, Santos AO, Magna LA, et al. Evidências de doença tireoidiana auto-imune crônica subclínica em portadoras da síndrome de Turner. Arq Bras Endocrinol Metab. 2007;51:401-9.
25. Medeiros CCM, Marini SHVL, Baptista MTM, Guerra Jr G, Maciel--Guerra AT. Turner's syndrome and thyroid disease: a transverse study of pediatric patients in Brazil. J Pediatr Endocrinol Metabol. 2000;13:357-62.
26. El-Mansoury M, Bryman I, Berntorp K, Hanson C, Wilhelmsen L, Landin-Wilhelmsen K. Hypothyroidism is common in Turner syndrome: results of a five-year follow-up. J Clin Endocrinol Metab. 2005;90:2131-5.
27. Wilson R, Chu CE, Donaldson MD, Thompson JA, McKillop JH, Connor JM. An increased incidence of thyroid antibodies in patients with Turner's syndrome and their first degree relatives. Autoimmunity. 1996;25:47-52.
28. Invernizzi P, Miozzo M, Selmi C, Persani L, Battezzati PM, Zuin M, et al. X chromosome monosomy: a common mechanism for autoimmune diseases. J Immunol. 2005;175:575-8.
29. Gravholt CH, Hjerrild BE, Mosekilde L, Hansen TK, Rasmussen LM, Frystyk J, et al. Body composition is distinctly altered in Turner syndrome: relations to glucose metabolism, circulating adipokines, and endothelial adhesion molecules. Eur J Endocrinol. 2006;155:583-92.
30. Su MA, Stenerson M, Liu W, Putnam A, Conte F, Bluestone JA, et al. The role of X-linked FOXP3 in the autoimmune susceptibility of Turner Syndrome patients. Clin Immunol. 2009;131:139-44.
31. Dias Mdo C, Castro LC, Gandolfi L, Almeida RC, Córdoba MS, Pratesi R. Screening for celiac disease among patients with Turner syndrome in Brasília, DF, midwest region of Brazil. Arq Gastroenterol. 2010;47:246-9.
32. Gravholt CH, Juul S, Naeraa RW, Hansen J. Morbidity in Turner syndrome. J Clin Epidemiol. 1998,51:147-58.
33. Stochholm K, Juul S, Juel K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. J Clin Endocrinol Metab. 2006;91:3897-902.
34. Elsheikh M, Conway GS. The impact of obesity on cardiovascular risk factors in Turner's syndrome. Clin Endocrinol. 1998;49:447-5.
35. Bakalov VK, Cooley MM, Quon MJ, Luo ML, Yanovski JA, Nelson LM, et al. Impaired insulin secretion in the Turner metabolic syndrome. J Clin Endocrinol Metab. 2004;89:3516-20.
36. Gravholt CH, Naeraa RW, Nyholm B, Gerdes LU, Christiansen E, Schmitz O, et al. Glucose metabolism, lipid metabolism, and cardiovascular risk factors in adult Turner's syndrome. The impact of sex hormone replacement. Diabetes Care. 1998;21:1062-70.
37. Hjerrild BE, Mortensen KH, Gravholt CH. Turner syndrome and clinical treatment. Br Med Bull. 2008;86(1):77-93.
38. Alves ST, Gallichio CT, Guimarães MM. Insulin resistance and body composition in Turner syndrome: effect of sequential change in the route of estrogen administration. Gynecol Endocrinol. 2006;22(10):590-4.
39. Price WH, Clayton JF, Collyer S, De Mey R, Wilson J. Mortality ratios, life expectancy, and causes of death in patients with Turner's syndrome. J Epidemiol Community Health. 1986;40:97-102.
40. Gravholt CH. Turner syndrome and the heart: cardiovascular complications and treatment strategies. Am J Cardiovasc Drugs. 2002;2:401-13.
41. Lanes R, Gunczler P, Palacios A, Villaroel O. Serum lipids, lipoprotein lp(a), and plasminogen activator inhibitor-1 in patients with Turner's syndrome before and during growth hormone and estrogen therapy. Fertil Steril. 1997;68(3):473-7.
42. Van PL, Bakalov VK, Bondy CA. Monosomy for the X chromosome is associated with an atherogenic lipid profile. J Clin Endocrinol Metab. 2006;91:2867-70.
43. Bannink EM, van der Palen RL, Mulder PG, de Muinck Keizer--Schrama SM. Long-term follow-up of GH-treated girls with Turner syndrome: metabolic consequences. Horm Res. 2009;71(6):343-9.
44. Zuckerman-Levin N, Frolova-Bishara T, Militianu D, Levin M, Aharon-Peretz J, Hochberg Z. Androgen replacement therapy in Turner syndrome: a pilot study. J Clin Endocrinol Metab. 2009;94(12):4820-7.
45. Wilson DM, Frane JW, Sherman B, Johanson AJ, Hintz RL, Rosenfeld RG. Carbohydrate and lipid metabolism in Turner syndrome: effect of therapy with growth hormone, oxandrolone, and a combination of both. J Pediatr. 1988;112(2):210-7.
46. Baron J, Manolagas SC, Shaw NJ, Rappold GA, Donaldson MD, Gault EJ, et al. Hormones and genes of importance in bone physiology and their influence on bone mineralization and growth in Turner syndrome. Horm Res Paediatric. 2010;73(3):161-5.
47. Bacharach LK. Bone mineralization in childhood and adolescence. Curr Opin Pediatr. 1993;5:467-73.
48. Gallicchio CT, Figueiredo-Alves ST, Tórtora RP, Mendonça LM, Farias MLF, Guimarães MM. Effect of puberty on the relationship between bone markers of turnover and bone mineral density in Turner's syndrome. Horm Res. 2004;61:193-9.
49. Gallicchio CT, Alves STFG, Guimarães MM. Indução da puberdade e terapia de reposição hormonal na síndrome de Turner. Femina. 2008;36(11):677-81.
50. Neely EK, Marcus R, Rosenfeld RG, Bacharach LK. Turner syndrome adolescents receiving growth hormone are not osteopenic. J Clin Endocrinol Metab. 1993;76:861-7.
51. Landin-Wilhelmsen K, Bryman I, Windh M, Wilhelmsen L. Osteoporosis and fractures in Turner syndrome-importance of growth promoting and oestrogen therapy. Clin Endocrinol (Oxf). 1999;51:497-502.
52. Bakalov VK, Lauren A, Jefrey B, Antón Lori, Nelson LM, Reynolds JC, et al. Selective reduction in cortical bone mineral density in Turner syndrome independent of ovarian hormone deficiency. J Clin endocrinol Metab. 2003;88:5717-22.
53. Lage AZ, Brandão CA, Mendes JR, Huayllas MK, Liberman B, Mendonça BB, et al. High degree of discordance between three--dimensional and two-dimensional lumbar spine bone mineral density in Turner's syndrome. J Clin Densitom. 2005;8(4):461-6.
54. Gussinyé M, Terrades P, Yeste D, Vicens-Calvet E, Carrascosa A. Low areal bone mineral density values in adolescents and young adult Turner syndrome patients increase after long-term transdermal estradiol therapy. Horm Res. 2000;54:131-5.
55. Bakalov VK, Chen ML, Baron J, Hanton LB, Reynolds JC, Stratakis CA, et al. Bone mineral density and fractures in Turner syndrome. Am J Med. 2003;115:259-64.

56. Holroyd CR, Davies JH, Taylor P, Jameson K, Rivett C, Cooper C, et al. Reduced cortical bone density with normal trabecular bone density in girls with Turner syndrome. Osteoporos Int. 2010;21(12):2093-9.
57. Zuckerman-Levin N, Yaniv I, Schwartz T, Guttmann H, Hochberg Z. Normal DXA bone mineral density but frail cortical bone in Turner's syndrome. Clin Endocrinol (Oxf). 2007;67(1):60-4.
58. Gallicchio CT, Figueiredo-Alves ST, Tórtora RP, Mendonça LM, Farias MLF, Guimarães MM. Effect of puberty on the relationship between bone markers of turnover and bone mineral density in Turner's syndrome. Horm Res. 2004;61:193-9.
59. Tarani L, Lampariello S, Raguso G, Colloridi F, Pucarelli I, Pasquino AM, et al. Pregnancy in patients with Turner's syndrome: six new cases and review of literature. Gynecol Endocrinol. 1998;12:83-7.
60. Kavoussi SK, Fisseha S, Smith YR, Smith GD, Christman GM, Gago LA. Oocyte cryopreservation in a woman with mosaic Turner syndrome: a case report. J Reprod Med. 2008;53:223-2.
61. Ditkoff EC, Vidali A, Sauer MV. Pregnancy in a woman with Turner mosaicism following ovarian stimulation and in vitro fertilization. J Assist Reprod Genet. 1996;13:447-8.
62. Huang JY, Tulandi T, Holzer H, Lau NM, Macdonald S, Tan SL, et al. Cryopreservation of ovarian tissue and in vitro matured oocytes in a female with mosaic Turner syndrome: case report. Hum Reprod. 2008;23:336-9.
63. Lau NM, Huang JY, MacDonald S, Elizur S, Gidoni Y, Holzer H, et al. Feasibility of fertility preservation in young females with Turner syndrome Reprod Biomed Online. 2009;18(2):290-5.
64. Bianco B, Lipay M, Guedes A, Oliveira K, Verreschi IT. SRY gene increases the risk of developing gonadoblastoma and/or nontumoral gonadal lesions in Turner syndrome. Int J Gynecol Pathol. 2009;28(2):197-202.
65. Donaldson MDC, Gault EJ, Tan KW, Dunger DB. Optimising management in Turner syndrome: from infancy to adult transfer. Arch Dis Child. 2006;91(6):513-20.