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The Patient with Turner Syndrome: Puberty and Medical Management Concerns

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Abstract

Turner Syndrome (TS) affects approximately 1 in 2500 liveborn females and is characterized by loss or structural anomalies of an X chromosome. Clinical features vary among patients; multiple organ systems can be affected. Endocrinologists are involved in the management of short stature, delayed puberty, and infertility. Endocrine therapies can include growth hormone, estrogen, and progesterone to promote linear growth and pubertal development. The duration of estrogen and progesterone treatment (HRT) is generally more than 40 years.

There is not one standard HRT protocol that is suitable for all women. Thus, general guidelines are provided for HRT to induce pubertal development. Additional considerations regarding choice of HRT include thrombotic risk and disorders associated with thrombophilia. Involvement of cardiologists is important because approximately 50% of patients with TS have congenital structural cardiac anomalies linked to an increased risk for aortic dissection and rupture. Although oocyte donation offers the chance to carry a pregnancy, accumulating information has highlighted the potential dangers associated with pregnancy.

Advances in the care of infants, girls, and women with TS have been achieved. Management of infants, girls, and women with TS involves coordinated care from a multi-disciplinary team including endocrinologists, cardiologists, geneticists, otolaryngologists, behavioral health experts, nurse educators, and social workers.

Introduction

Turner's syndrome (TS) is a common chromosomal disorder affecting approximately 1:2500 live-born females (1). The diagnosis of "Turner syndrome" denotes females with a broad constellation of characteristic findings. The clinical features include growth failure, ovarian failure secondary to gonadal dysgenesis, cardiac anomalies, renal anomalies, and autoimmune disorders. Manifestations affect multiple organ systems and tissues (2). As a consequence of these associated disorders, morbidity and mortality are increased in individuals with TS. (Stochholm) This review focuses on particular aspects of endocrine and cardiac management of patients with TS. Several comprehensive reviews provide additional helpful information (3,4).

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TS is characterized by the loss of an entire X chromosome, loss of a portion of the X chromosome, or complex rearrangements affecting the X chromosome (5). Structural abnormalities can include deletions of the short or long arms of the X chromosome, duplications (isochromosomes), or ring chromosomes. Some individuals are mosaic and carry one or more additional cell lines. Clinical features are highly variable; individuals with a 45,X karyotype tend to have more clinical features than those who are mosaic with a normal cell line (45,X/46,XX or 45,X/46,XY). Potential explanations for the phenotypic variability include parental origin of the X, cell line mosaicism, imprinting, and X-linked mutations.

Normally, random X chromosome inactivation occurs in females after fertilization. Hence, females with TS are haploinsufficient for genes that are normally expressed from both X chromosomes. One such gene is the short-stature homeobox-containing gene on the X chromosome (*SHOX*). Haploinsufficiency for *SHOX* may contribute to the short stature and other skeletal manifestations associated with TS (6).

Diagnosis of TS

The diagnosis of TS is often delayed particularly for individuals with minimal stigmata. Clinicians need to be alert to the signs and symptoms associated with TS especially short stature, subnormal growth velocity, delayed puberty, primary amenorrhea, or premature ovarian failure. Earlier diagnosis facilitates management especially regarding growth hormone therapy.

The diagnosis of TS can be suspected prenatally due to the presence of specific ultrasound findings such as fetal edema, increased nuchal translucency, and cystic hygroma. Additional ultrasound findings suggestive of TS include coarctation of the aorta, left-sided cardiac anomalies, brachycephaly, renal anomalies, polyhydramnios, oligohydramnios, and growth retardation. The results of the maternal triple or quadruple screening (α -fetoprotein, hCG, inhibin A, and unconjugated estriol) may arouse suspicion regarding the diagnosis. Since none of these findings are diagnostic, a confirmatory karyotype obtained from the liveborn infant is essential.

Postnatally, approximately 20–30% of affected girls are identified in the neonatal period due to lymphedema and/or webbed neck. The diagnosis of TS should be considered in newborn girls with hypoplastic left heart or coarctation of the aorta because both conditions occur more frequently among girls with Turner's syndrome. Other typical clinical features include low hairline, low set ears, and small mandible. Approximately 35% of girls are diagnosed in childhood during an evaluation for short stature. TS should be considered for all girls with declining growth velocity or growth velocity <10th percentile for age. During the adolescent years, findings such as markedly elevated FSH concentrations, absence of breast development by 13 years of age, pubertal arrest, or primary/secondary amenorrhea warrant consideration of TS especially in the short female. Other findings associated with TS include multiple pigmented nevi, cubitus valgus, nail hypoplasia, hyperconvex uplifted nails, characteristic facies, shortening of the fourth metacarpal, high arched palate, recurrent otitis media, and neurosensory hearing loss. Intelligence is generally normal, but TS is associated with specific patterns of cognitive abilities (7).

All individuals with suspected TS should have a standard 30-cell karyotype performed. In approximately 5%, the karyotype analysis reveals the presence of Y-chromosomal material. Evaluation for Y chromosome material should be performed in any TS patient with evidence of virilization, or when a marker chromosome is present. Females with mosaicism for a cell line carrying a Y chromosome are at increased risk for gonadoblastoma arising within their streak gonads and may benefit from gonadectomy (8).

Growth hormone in TS

Short stature is one of the most common features of TS. Approximately 95% of all individuals with TS have short stature. In the past, girls with TS who did not receive growth hormone (GH) therapy achieved an average adult stature approximately 20 cm shorter than normal. Although growth failure begins in utero, the mean birth length and birth weight of infants with TS typically fall within the low normal range. Further deceleration in linear growth velocity may occur as early as 18 months of age.

Growth hormone (GH) therapy has become the standard of care for girls with TS and should be considered as soon as decreased linear growth velocity is apparent (4,9). Several studies have shown that GH therapy accelerates growth velocity and improves final adult stature. Final adult height is maximized if GH therapy is begun at a young age; and is positively associated with the duration of treatment. Recent studies have suggested that treatment initiated prior to 4 years of age significantly improved height outcome (10,11). Dosing should be individualized and adjusted according to the patient's growth velocity. Monitoring of IGF-1 may be used to further adjust dosing. Therapy is generally continued until a satisfactory height has been attained or the patient's growth velocity has decreased to less than 2.0 cm per year. Although generally considered to be beneficial, the efficacy of GH to improve adult height varies between individuals (12).

Overall, GH treatment has a favorable safety profile in TS. Nevertheless, careful surveillance for side effects of GH therapy including benign intracranial hypertension, scoliosis, slipped capital femoral epiphysis (SCFE), and abnormal glucose metabolism during GH therapy is recommended. Importantly, GH treatment of girls with TS increases stature but does not disproportionately affect cardiac dimensions (see below) (13).

One concern regarding the introduction of estrogen therapy is the opposing effects of GH and estrogen on bone maturation. It was believed that estrogen, when used for induction of puberty, stimulated fusion of the epiphyses and limited longitudinal bone growth. However, most studies show no significant deleterious effect of estradiol treatment on final height with low dose ethinyl estradiol. On the other hand, Chernauskas et al. reported a negative effect with early use of oral conjugated estrogens in a non-placebo controlled randomized study (14). Yet, another study showed a modest growth benefit and improved final height outcome with the combination of ultra-low-dose childhood estrogen replacement and growth hormone (15).

The use of oxandrolone, a non-aromatizable anabolic testosterone-derived androgenic steroid, remains controversial. Oxandrolone has been used for its anabolic effects to promote linear growth in girls with TS. Virilization and lack of efficacy are the major reported deleterious consequences of oxandrolone. A recent randomized placebo controlled trial involving 106 girls with TS (and on GH therapy) reported positive effect on height outcome which was comparable to delaying onset of puberty (initiation of estrogen therapy) until 14 years of age (16). Additional data from randomized placebo controlled studies are necessary to determine the role, if any, of oxandrolone.

Puberty and Hormone Replacement Therapy

Gonadal dysgenesis associated with gonadal failure is a cardinal feature of TS. Initially, the process of ovarian differentiation proceeds normally in fetuses with TS. Beginning during the 4th week of gestation, the primitive germ cells migrate from their extra-gonadal site of origin to the genital ridge. By 18 weeks of gestation, premature degeneration of ovarian follicles begins. Ovarian follicles are replaced by abundant connective tissue (streak gonad).

This germ cell attrition has been attributed to faulty pairing of homologues during meiosis in the developing oocytes (17).

The follicular atresia results in ovarian failure in most females with TS. As expected with ovarian failure, LH and FSH concentrations show a biphasic pattern with elevated concentrations during the first year of life and again at the expected age of puberty (18,19). For this reason, gonadotropin concentrations obtained between ages 5–9 years cannot be used to assess ovarian function. As many as 20–30% of affected females show some spontaneous pubertal development. Spontaneous menarche and unassisted pregnancy have been reported to occur in 2–5% of women with TS (20,21).

Spontaneous pubertal development is more common among girls with mosaic karyotypes. Anti-Müllerian hormone (AMH) concentrations showed correlation with specific karyotypes and ovarian function. Although the specific cutoff value depends on the AMH assay, AMH values less than 8 pmol/L have a high sensitivity for predicting ovarian failure. AMH concentrations may prove to be a valuable marker of ovarian function in girls, adolescents, and adult women with TS (22). Consistently undetectable inhibin B concentrations may be another indication of ovarian failure (23).

Most girls with TS require hormone replacement therapy for breast development, uterine growth, and bone health. The consensus is to initiate hormone replacement therapy at a time that coincides with normal female pubertal development (4). Prior to initiation of hormone replacement therapy, LH and FSH concentrations should be measured to confirm presumed ovarian failure.

The optimal estrogen formulation, dosage, method of administration, and time to initiate progestagen treatment are controversial (Table 1). The overall goal is to replicate a tempo of pubertal development comparable to the young woman's peers. In other words, hormone replacement therapy should be initiated such that girls with TS experience the physical changes of puberty and experience menarche with their peers around 12–14 years of age. Initial hormone replacement involves low dose estrogen monotherapy. Progestagen replacement is generally added 1–2 years after starting estrogen or upon breakthrough bleeding.

Estrogen can be provided by oral or transdermal routes. Oral ethinyl estradiol is no longer commercially available as a single agent in the United States. Conjugated equine estrogen has been utilized, but this formulation contains multiple estrogenic substances with varying biologic potencies and is best avoided in this population. Patients receiving oral estrogens have higher estrone concentrations than those using transdermal estradiol because oral estrogens undergo first pass metabolism in the liver. Transdermal estrogen is often preferred for the initial stages of pubertal development. Beginning doses can be as low as 6–7 mcg estradiol daily; transdermal estradiol patches can be cut into halves and quarters. The dose can be gradually increased over several years.

In a short term pharmacokinetics study, transdermal estradiol (Vivelle TD System, Novartis Pharmaceuticals) and oral micronized estradiol (Estrace, Bristol-Myers Squibb) were compared in girls with TS. For comparison, estradiol concentrations were measured in 20 healthy regularly cycling adolescent girls; mean follicular phase estradiol concentration was 51 ± 6 pg/ml and mean luteal phase estradiol concentration was 142 ± 17 pg/ml. Among girls with TS, transdermal estradiol resulted in estradiol, estrone, and bioestrogen concentrations closer to those of the normal adolescent girls along with greater suppression of LH and FSH concentrations (24). Mean estradiol concentration for the higher transdermal estradiol dosage was 114 ± 31 pg/ml. While this concentration is close to the mean luteal phase

estradiol concentration among the healthy girls, the long term consequences of sustained estradiol concentrations at this level are unclear.

Progestagen can be added in several ways. Switching the patient to oral contraceptives may be the easiest because the regimen involves taking a single daily pill. Some girls prefer to continue transdermal estradiol and add progesterone. The most common synthetic progestagens are derived from testosterone or progesterone; more recent formulations have been designed to bind to the progesterone receptor with greater specificity (25). Although not directly comparable, a pilot study comparing oral dydrogesterone and vaginal micronized progesterone in women with premature ovarian failure reported that vaginal micronized progesterone was more effective to stimulate an 'in-phase' secretory endometrium and resulted in higher progesterone and lower LH and FSH serum concentrations on day 21 of the cycle (26). The specific hormone replacement regimen should be individualized for each individual particularly because progestagens may have variable effects (27). Further, each girl's regimen should be reassessed with her on a regular basis along with review of alternative approaches (28).

Uterine size is smaller in girls with Turner syndrome at Tanner stage 5 breast development (29). Thus, despite adequate estrogen for breast development, the currently recommended doses may be insufficient for uterine growth and development.

Estrogens, Progestagens, and Venous Thromboembolism

Hormone replacement therapy for women with TS begins in adolescence and ends 40–50 years later. Since women receiving estrogen-containing hormone therapy have an increased risk to develop venous thromboembolism, understanding risk factors for thromboembolic events is relevant. Manifestations of venous thromboembolism events (VTEs) include deep vein thrombosis (DVT), pulmonary embolism, upper extremity and intra-abdominal DVT, cerebral sinus thrombosis, and superficial venous thrombophlebitis (30). Although VTEs can occur at any time, the risk is highest in the first year of oral contraceptive use.

One likely etiologic factor is hepatic metabolism of oral estrogen which triggers an imbalance between anti-thrombotic mechanisms and procoagulant factors (31). Specific findings include increased hepatic synthesis of Factor VII, Factor X, and fibrinogen. Increased plasma levels of Factors II and VII and acquired resistance to activated protein C have been reported (32). Estrogen use also favors fibrinolysis through decreased plasminogen activator inhibitor-1 (PAI-1) and increased plasminogen levels (33).

Not only do estrogens affect thrombosis, but certain progestagens influence thrombotic risk. Desogestrel, gestodene, and cyproterone acetate have been particularly associated with increased thrombotic risk. Inherited and acquired forms of thrombophilia can also influence risks for thrombosis (Table 2). Inherited factors include point mutations in Factor V (Factor V Leiden) and Factor II (prothrombin G20210A). Protein C, protein S, and antithrombin deficiencies are rare inherited causes of thrombophilia. Acquired causes include antiphospholipid antibodies, prolonged immobilization, smoking, obesity, and malignancies.

Case reports suggest that the frequency of VTEs may be increased among women with TS (34). A survey of 60 women with TS (age range 21–66 years) reported higher levels of procoagulant factor and inflammatory markers (35). At this time, screening for disorders associated with thrombophilia is not cost effective. The most useful tool is to obtain a thorough history regarding the patient and family history of VTEs prior to initiation of hormone replacement therapy (Table 2) (36). Risks for VTE and education regarding thrombosis prevention should be discussed with the patient and her family. Transdermal

estradiol and micronized progesterone are preferable for girls with TS who have an increased risk of VTE (37).

Bone Health

Bone mineral density (BMD) reflects many factors including genetic background, physical activity, diet, environment, and hormones. The estrogen deficiency in girls with Turner syndrome interferes with achievement of bone mass accrual during adolescence and increases the risk for osteoporosis. Since dual X-ray absorptiometry (DXA) scanning is based on two-dimensional area, this technique leads to an underestimation of bone mineral density in short individuals. Rather, a three-dimensional volumetric BMD (vBMD) is preferable (38). Different methods for assessing BMD confound comparison of available published data.

The relative risk for fractures, especially involving the forearm, is increased for girls with TS at all ages. This risk for fracture occurs in pre-pubertal girls suggesting that additional factors influence BMD. These additional factors include abnormal bone geometry, *SHOX* gene haploinsufficiency, and PTH, osteoprotegerin, and vitamin D concentrations (39). Girls with TS who undergo spontaneous puberty have higher BMD than girls who require HRT for pubertal changes. Optimal HRT beginning during the adolescent years is important to maintain BMD. In addition, regular exercise and supplementation of both vitamin D and calcium are beneficial to attain maximal bone mass acquisition and mineralization (39,40).

Developmental and Behavioral Considerations

Most patients with TS have normal intelligence and identify as females. However, 10% of patients have substantial developmental delays irrespective of the karyotype. The risk of mental retardation is highest in patients with ring chromosome (33%) or with a marker chromosome (66%). Many girls and women with TS have difficulties with visual-motor skills (i.e., writing and copying designs), visual-spatial skills (i.e., visual imagery, directional sense, map reading), visual attention, executive functioning, planning, and problem solving. Some individuals have difficulty interpreting non-verbal communication resulting in difficulties with socialization and coping with new situations. These findings tend to be more common among patients with 45,X karyotype. Typical strengths include verbal memory, receptive and expressive language abilities, and word knowledge (41). Self-esteem is often poor and may be confounded by immaturity, social isolation and anxiety during the adolescent years. Potential etiologies of this neurodevelopmental phenotype include haploinsufficiency, imprinting, or mutations involving specific genes on the X chromosome or sex steroid hormone deficiency (42).

Cardiac Features

Congenital structural anomalies of the cardiovascular system occur in approximately 50% of women with TS (43). Characteristic cardiovascular anomalies (Figure 1) include bicuspid aortic valve, coarctation of the aorta, partial anomalous pulmonary venous connection, and hypoplastic left heart syndrome (44). In addition, thickness of carotid intima-media was found to be increased and the internal diameters of the ascending aorta, internal carotid, and brachial arteries were increased in women with TS (45,46).

Women with TS have an increased risk for aortic dilatation and aortic dissection. Histology of the aorta shows cystic medial necrosis (CMN). However, the molecular mechanism responsible for CMN is unclear and may differ from the CMN observed in connective tissue disorders such as Marfan syndrome. Aortic dissection is generally an acute event associated with sudden onset of chest, neck, or back pain and is often associated with fatal outcome.

Median age at dissection was reported as 35 years in a review of 85 cases; yet 20 cases occurred in girls less than 20 years of age. All younger girls had structural cardiac anomalies (47). The presence of a bicuspid aortic valve accelerated the rate of aortic dilatation (48). Women with TS often develop hypertension. However, the role of hypertension in the pathogenesis and progression of aortic dissection is unclear (49). Nevertheless, the threshold to initiate anti-hypertensive therapy in hypertensive women with TS should be low. One major safety concern for this population is the occurrence of aortic dissection during or after pregnancy (21,50). The diagnosis of TS should be viewed as a relative contra-indication to pregnancy (51).

All girls diagnosed with TS require comprehensive cardiovascular evaluation. Recent recommendations advocate that cardiac MRI should be performed beginning during the teenage years and periodically repeated. Although echocardiology may be sufficient for some, MRI with gadolinium provides better visualization of the entire aortic arch (52). Finding a body-surface area-adjusted aortic size index greater than 2.0 cm/m² warrants a prompt referral to an experienced cardiologist and close follow-up (48,52).

With these data, the discussion regarding oocyte donation and pregnancy in women with TS has changed. In the past, adolescent girls were informed that reproductive options included adoption and oocyte donation. Counseling requires frank and brutally honest discussions of the risk for aortic dissection during or years after pregnancy. As noted by the Practice Committee of ASRM, “Turner syndrome is a relative contraindication for pregnancy, and patients should be encouraged to consider alternatives, such as gestational surrogacy or adoption (50).” Women with TS who wish to proceed with pregnancy need to be carefully evaluated and monitored by cardiologists and fetal-maternal specialists.

Auto-immune Disorders

The incidence of auto-immune disorders is increased among females with TS. Specific manifestations include auto-immune thyroid disease (both Hashimoto’s thyroiditis and Grave’s disease), celiac disease, inflammatory bowel disease, alopecia areata, and diabetes mellitus (53). Of 107 Danish patients with TS, 58% were positive for one or more auto-antibodies and 45% were positive for anti-thyroperoxidase (TPO) antibodies (54).

Kidneys

Approximately 30–40% of females with TS have congenital malformations of the urinary system. By ultrasound imaging, collecting-system malformations are the most common anomaly followed by horseshoe kidneys, malrotation, and other positional abnormalities. Structural malformations of the kidney occur more frequently in 45,X monosomy whereas collecting-system malformations occur more frequently in those with karyotypes showing mosaicism or structural X anomalies (55). All girls with TS should have a renal ultrasound study performed at diagnosis (4). Long term concerns for the girls with renal anomalies include urinary tract infections and hypertension.

Conclusions

Numerous advances in the care of infants, girls, and women with TS have been achieved. Questions remain regarding optimal hormone replacement regimens (sex steroids and GH) and optimal medical management to recognize under-diagnosed complications. Management of infants, girls, and women with TS involves long term care from a multi-disciplinary team comprised of pediatric endocrinologists, reproductive endocrinologists, cardiologists, geneticists, otolaryngologists, behavioral health experts, nurse educators, and social workers (28). A coordinated and consistent transition process from pediatric to ongoing adult care is

beneficial to ensure appropriate treatment especially regarding the important concerns regarding hormone replacement therapy, bone health, and cardiovascular issues (56).

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Figure 1. MRI and MRA images of cardiac anomalies found in females with TS. A. Coarctation of the aorta; B. Dilation of the aorta; C. Bicuspid aortic valve; D. Elongation of the transverse aortic arch. [reproduced with permission from the Journal of Clinical Endocrinology & Metabolism from Freriks K, Timmermans J, Beerendonk CC, et al. Standardized multidisciplinary evaluation yields significant previously undiagnosed morbidity in adult women with Turner syndrome. *J Clin Endocrinol Metab* 2011;96:E1517–26.]

Table 1

Guidelines for Hormone Replacement Therapy in Turner Syndrome.

Age	Proposed Treatment
Childhood	Consider GH treatment when linear growth velocity declines. Begin to monitor for auto-immune thyroid disease
8–10 years	Anticipatory guidance regarding induction of puberty. Obtain family history regarding disorders associated with thrombophilia
9–11 years	Obtain LH and FSH concentrations to assess for ovarian failure. Consider obtaining AMH and inhibin B concentrations. Obtain bone age X-ray to assure that bone age is > 8yrs of age (to accurately interpret LH and FSH concentrations)
12–14 years	Begin low dose estrogen monotherapy preferably using transdermal route Begin the discussion regarding fertility and reproductive options Encourage parents to initiate and continue this discussion at home
Next 1–2 years	Gradually increase estrogen dose
13–16 years	Add progestagen therapy
17–50 years	Continue cyclic hormone replacement therapy Monitor glycemic status (earlier if clinically indicated)
50 years	Consider continuation of hormone replacement therapy with consideration of risk factors (similar to normal women undergoing menopause)

Table 2

Factors associated with increased risk of VTE.

Inherited	Factor V Leiden Anti-thrombin deficiency Protein C deficiency Protein S deficiency Factor II (prothrombin G20210A) Increased Factors II, VIII, IX, or XI Increased fibrinogen Resistance to activated protein C (APC) Hyperhomocystinuria
Acquired	Antiphospholipid antibodies Surgery Obesity Malignancies
Environmental	Prolonged immobilization Smoking