

**Care of Girls and Women with Turner Syndrome: A Guideline of the  
Turner Syndrome Study Group.**

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The Turner Syndrome Consensus Study Group\***

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**Disclosure**

CAB has nothing to disclose

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**Abstract***Objectives*

To provide updated guidelines for the evaluation and treatment of girls and women with Turner syndrome (TS)

*Participants*

The Turner Syndrome Consensus Study Group is a multi-disciplinary panel of experts with relevant clinical and research experience with TS that met in Bethesda, April, 2006. The meeting was supported by the National Institute of Child Health and unrestricted educational grants from pharmaceutical companies.

*Evidence* The Study Group used peer-reviewed published information to form its principle recommendations. Expert opinion was used where good evidence was lacking.

*Consensus* The study group met for three days to discuss key issues. Breakout groups focused on genetic, cardiological, auxological, psychological, gynecological and general medical concerns and drafted recommendations for presentation to the whole group. Draft reports were available for further comment on the meeting website. Synthesis of the section reports and final revisions were reviewed by email and approved by whole group consensus.

*Conclusions* We suggest that parents receiving a prenatal diagnosis of TS be advised of the broad phenotypic spectrum and the good quality of life observed in TS in recent years. We recommend that magnetic resonance angiography be used in addition to echocardiography to evaluate the cardiovascular system and suggest that patients with defined cardiovascular defects be cautioned in regards to pregnancy and certain types of exercise. We recommend that puberty should not be delayed to promote statural growth. We suggest a comprehensive educational evaluation in early childhood to identify potential attention-deficit or non-verbal learning disorders. We suggest that caregivers address the prospect of premature ovarian failure in an open and sensitive manner and emphasize the critical importance of estrogen treatment for feminization and for bone health during the adult years. All individuals with TS require continued monitoring of hearing and thyroid function throughout the lifespan. We suggest that adults with TS be monitored for aortic enlargement, hypertension, diabetes and dyslipidemia.

## **Introduction**

Turner syndrome (TS) affects approximately 1/2500 live-born females(1). This disorder presents the clinician with a challenging array of genetic, developmental, endocrine, cardiovascular, psychosocial and reproductive issues. There have been important advances in each of these arenas since publication of the previous recommendations for the care of girls and women with TS(2). This paper is based on the proceedings of a multidisciplinary international conference sponsored by the National Institute of Child Health and Human Development in April 2006. Discussions at this conference and the ensuing recommendations have been based upon recent, peer-reviewed scientific publications. However, there are very few TS studies that would qualify as guidance for 'evidence-based' recommendations, and hence most of the following guidelines represent the experts' consensus judgments given the best information available. The paper is divided into sections addressing:

- Diagnostic Issues
- Congenital cardiovascular disease
- Growth and development
- Psychological and educational issues
- Turner syndrome in adulthood

## **Diagnostic issues**

### *Definition*

The diagnosis of TS requires the presence of characteristic physical features in phenotypic females(3, 4) coupled with complete or partial absence of the second sex chromosome, with or without cell line mosaicism (5). Individuals with a 45,X cell population but without clinical features are not considered to have TS. Phenotypic males are also excluded from the diagnosis of TS, regardless of karyotype. Whether to diagnose individuals with sex chromosome structural abnormalities as having TS requires clinical judgment. Abnormalities such as ring X and Xq isochromosomes are common in patients with classic TS features, and many of these patients have

phenotypes indistinguishable from that of patients with apparently nonmosaic monosomy X (45,X)(5). Patients with small distal short arm deletions (Xp-) including the *SHOX* gene frequently have short stature and other TS-associated skeletal anomalies, but most are at low risk of ovarian failure and should generally not be diagnosed with TS if band Xp22.3 is not deleted (6). Individuals with deletions of the long arm distal to Xq24 frequently have primary or secondary amenorrhea without short stature or other TS features (7); the diagnosis of premature ovarian failure is more appropriate for them.

### *Prenatal diagnosis*

Sex chromosome abnormalities are increasingly detected prenatally by chorionic villous sampling or amniocentesis, and genetic counseling before any prenatal diagnostic procedure should always include discussion of the possibility of detecting them. Certain ultrasound findings indicate an increased likelihood of TS. Increased nuchal translucency on ultrasound is frequently seen in TS, but may also be observed in autosomal trisomy syndromes. The presence of cystic hygromas make the diagnosis of TS more likely (8). Other ultrasound findings suggestive of TS are coarctation of the aorta and/or left-sided cardiac defects, brachycephaly, renal anomalies, polyhydramnios, oligohydramnios, and growth retardation (9). Abnormal triple or quadruple maternal serum screening (alpha-fetoprotein, beta-hCG, inhibin A, and unconjugated estriol) may also suggest the diagnosis of TS (10). Ultrasound and maternal serum screening are not diagnostic and to make a prenatal diagnosis of TS, karyotype confirmation is obligatory.

The postnatal outcome and constitutional karyotype of individuals with prenatally diagnosed sex chromosome monosomy are uncertain, especially in mosaic cases. Therefore, chromosomes should be reevaluated postnatally in all cases. The degree of mosaicism detected prenatally is not generally predictive of the severity of the TS phenotype (11, 12). In general, any of the features of TS may be seen with virtually any of the common chromosome constitutions (5). Non-mosaic 45,X fetuses with pleural effusion or cystic hygroma often spontaneously abort (13). Nevertheless, a 45,X karyotype, even with ultrasound evidence of cystic hygroma, lymphedema, and

effusions, is compatible with delivery of a viable newborn.

Many pregnancies diagnosed prenatally with TS are currently terminated (14, 15). Decisions regarding pregnancy termination are difficult, thus it is critical that the best available information be provided to parents. While upholding personal choice about reproduction is a widely embraced ethical principle, decisions to terminate a fetus with TS should never be based upon misunderstood or unbalanced information (16). Many studies providing genotype-phenotype correlations are subject to considerable ascertainment bias. Individuals with 45,X mosaicism detected because of an abnormal antecedent ultrasound study are more likely to have clinical TS than those with 45,X mosaicism detected incidentally by screening on the basis of advanced maternal age (11, 12), which itself is not associated with an increased incidence of TS (17). Outcomes of incidentally detected 45,X/ 46,XX mosaicism are difficult to predict prenatally, but high resolution ultrasound often provides useful prognostic information. Not unexpectedly, prenatally diagnosed children tend to be less affected than those diagnosed postnatally on clinical grounds(11, 12).

Physicians and genetic counselors involved in pre- and post-diagnostic counseling need to be fully informed about the prognosis, complications, and quality of life of individuals affected with TS as well as of recent advances in management. The clinical spectrum of TS is much broader and often less severe than that described in many textbooks. Prenatal counseling should always involve discussion of the variability of features, the likelihood of short stature and ovarian failure, and their management. It should be emphasized that most individuals with TS have intelligence scores in the normal range, although they may have specific types of learning disabilities . Most adults with TS function well and independently. Girls and women in one study indicated that struggling with their infertility was the greatest challenge they faced in adapting to a life with TS(18). Speaking with children and adults with TS and their families is important for prospective parents faced with a decision about pregnancy and can be facilitated by support organizations, e.g., Turner Syndrome Societies.

### *Postnatal diagnosis*

All individuals with suspected TS (see below) should have a karyotype performed. A standard 30 cell karyotype is recommended by the American College of Medical Genetics (ACMG,2005) and identifies  $\geq 10\%$  mosaicism with 95% confidence (19), although additional metaphases may be counted or fluorescence in situ hybridization (FISH) studies performed if there is a strong suspicion of undetected mosaicism (20). The cytogeneticist should be consulted in this case. Although a peripheral blood karyotype is usually adequate, if there is a strong clinical suspicion of TS, despite a normal blood karyotype, a second tissue, such as skin, may be examined

Testing for Y chromosome material should be performed in any TS patient (or fetus) with a marker chromosome (a sex chromosomal fragment of unknown origin, *i.e.* X vs. Y). This can be achieved by DNA studies or fluorescent *in situ* hybridization (FISH) using a Y centromeric probe, supplemented as necessary by short and long arm probes. The presence of virilization in a TS patient should prompt search for a gonadal, adrenal or midline tumor as well as investigation of the karyotype for Y-material. The prevalence and clinical significance of cryptic Y material detected only by FISH or DNA analysis in patients without virilization or a marker chromosome needs further investigation. False positives may be a problem with highly sensitive PCR-based Y detection methods (21).

The patient and/or her parents should be informed of the finding of Y chromosome material with the utmost sensitivity regarding gender identity issues to minimize psychological harm. The presence of Y chromosome material is associated with an  $\sim 12\%$  risk of a gonadoblastoma, according a recent analysis of pooled data (22). Gonadoblastomas may transform into malignant germ cell neoplasms, hence, the current recommendation is for laparoscopic, prophylactic gonadectomy(22). It is often assumed that gonads in patients with TS and Y chromosome mosaicism have no reproductive potential, but spontaneous pregnancies in such women have been reported(23, 24). Thus, preservation of follicles or oocytes may be a future option for some patients undergoing gonadectomy. The gene responsible for gonadoblastoma has not been identified, but mapping data indicate that it is distinct from SRY, the male sex

determining gene (25, 26). Routine testing for SRY or the presence of Y chromosome material in 45,X individuals without masculinization is not clinically warranted at present.

#### *Indications for karyotype*

The diagnosis of TS should be considered in any female with unexplained growth failure or pubertal delay or any constellation of the following clinical findings: edema of the hands or feet, nuchal folds, left-sided cardiac anomalies, especially coarctation of the aorta or hypoplastic left heart, low hairline, low set ears, small mandible, short stature with growth velocity <10th percentile for age, markedly elevated levels of FSH, cubitus valgus, nail hypoplasia, hyperconvex uplifted nails, multiple pigmented nevi, characteristic facies, short fourth metacarpal, high arched palate, chronic otitis media.

#### *Newborn screening*

Under-diagnosis and delayed diagnosis of TS remains a problem (27). Importantly, early detection permits identification of cardiovascular system malformations such as bicuspid aortic valve that require treatment to prevent complications. Moreover, early diagnosis facilitates prevention or remediation of growth failure, hearing problems, and learning difficulties. Finally, it may be possible in future years to prevent infertility in some individuals with TS by harvesting eggs or ovarian tissue for cryopreservation from girls while they still have viable follicles (28). PCR-based screening methods to detect sex chromosome aneuploidy are feasible (29) but have not yet been validated on a newborn population sample. If and when molecular screening for TS is offered, positive findings will need karyotype confirmation, an infrastructure for follow-up and treatment of the patients with sex chromosome abnormalities, and support services to help parents and caregivers deal with the uncertainties inherent in this type of diagnosis. By extrapolation from experience with prenatal diagnosis, it is highly likely that newborn screening will also identify sex chromosome abnormalities of no clinical consequence in some phenotypically normal individuals; this risk must be weighed against the benefit of early detection of TS and other X-chromosome disorders.

## **Cardiovascular system**

### *Frequency and type of congenital defects*

The most serious, life-threatening consequences of X-chromosome haploinsufficiency involve the cardiovascular system. This is most apparent during fetal development, where major defects in cardiac and aortic development result in a very high mortality for fetuses with a 45,X karyotype (30-32). Fetuses with cardiovascular failure almost always demonstrate obstructed jugular lymphatics with nuchal cystic hygromas. These hygromas resolve as the lymphatics open later in gestation, but residual postnatal webbing of the neck predicts defects such as bicuspid aortic valve (BAV) and aortic coarctation in surviving individuals with TS (33-35). This association led to the hypothesis that the fetal cystic hygromas caused the cardiovascular defects by compressing outflow tracts (33). This view remains speculative, however, and it seems equally possible that haploinsufficiency for the same X-linked gene(s) impairs both lymphatic and vascular development.

Several recent imaging studies have investigated the prevalence of aortic coarctation and BAV in large groups of girls and women with TS (34, 36-38). These studies suggest that on average, ~11% have coarctation and ~ 16% have BAV. Aortic coarctation and BAV are each almost 4-fold more frequent in patients with webbed necks, e.g., 37% of patients with neck webbing have a BAV compared to 12% in those without webbing (34). It is important to note that coarctation may not be detected in infancy and may be first diagnosed in older children or adults, and magnetic resonance imaging studies frequently identify cases missed by echocardiography(39-43). The presence of an abnormal aortic valve is usually clinically silent in young patients, and only detected as a result of screening(44). The risks associated with BAV in TS are probably similar to those for non-syndromic cases. The abnormal valve is at risk for infective endocarditis, and, over time, it may deteriorate leading to clinically significant aortic stenosis or regurgitation. The BAV is also associated with aortic wall

abnormalities, including ascending aortic dilation, aneurysm formation and aortic dissection(45, 46).

Recent studies suggest a broader spectrum of cardiovascular system abnormalities in TS than previously recognized. Magnetic resonance angiographic (MRA) screening studies of asymptomatic individuals with TS have identified a high prevalence of vascular anomalies of uncertain clinical significance(39-42). Almost 50% have an unusual angulation and elongation of the aortic arch termed elongated transverse arch (ETA) by Ho et al. (42). By itself the ETA does not appear to be clinically significant, but there is concern that it may reflect an abnormal aortic wall prone to dilation and perhaps dissection. Additional vascular anomalies found in MRA studies include partial anomalous pulmonary connection (PAPVC) and persistent left superior vena cava, each affecting ~ 13%(42), versus <1% in the general population. PAPVC in TS frequently involves the left upper pulmonary vein which is less common than the typical right-sided presentation in the general population, and makes echocardiographic detection more challenging. Whether this defect is clinically significant depends upon the degree of the left to right shunt (47-49).

There seems to be a generalized dilation of major vessels in women with TS, including the brachial and carotid arteries as well as the aorta. The distal extent of this dilated vasculopathy is unknown. Estrogen deficiency contributes to greater intima medial thickness and altered arterial wall dynamics but not to the increased caliber of vessels (50, 51).

### *Electrocardiography*

Adults with TS have a high prevalence of electrocardiographic conduction and repolarization abnormalities. Right axis deviation, T wave abnormalities, accelerated AV conduction and QTc prolongation are significantly more common in women with TS than normal, age-matched controls (52). Right axis deviation may be associated with underlying PAPVC, but the other findings appear independent of anatomic defects (52). These data and the recent observations of an unusual resting tachycardia that begins in

utero (53) and evidence of impaired sympathovagal tone (54), suggest that there may be an intrinsic defect in autonomic regulation of the cardiovascular system in TS. The clinical significance of these recent observations is unclear, but additional monitoring of ECGs in TS seems warranted.

#### *Risk for aortic dissection*

A major concern in TS remains the rare but often fatal occurrence of aortic dilation, dissection or rupture in relatively young individuals. Dissecting aortic aneurysm in TS is usually associated with additional risk factors including BAV or other abnormalities of the aortic valve, coarctation or dilatation of the aorta and systemic hypertension (45, 55) (Gravholt in press). Systemic hypertension is common in TS, and therefore may be the most important treatable risk factor for aortic enlargement and dissection (46) (Gravholt et al., 2006). However, a few cases do not clearly document the established risk factors, raising the possibility that the vasculopathy of TS alone may predispose to dissection. The International Turner Syndrome Dissection Registry has been established in association with the Turner Syndrome Society of the United States in order to better understand this serious problem ([http://www.turner-syndrome-us.org/resource/resources\\_detail.cfm?id=193](http://www.turner-syndrome-us.org/resource/resources_detail.cfm?id=193)).

#### *Screening*

All newly diagnosed individuals need a baseline evaluation by a cardiologist familiar with the spectrum of cardiovascular issues encountered in TS (Table 1). This should include two-dimensional and color Doppler echocardiography done in the context of the clinical examination and a baseline ECG. A comprehensive postnatal echocardiogram should be evaluated by a pediatric cardiologist in all infants diagnosed with TS, even in those who had an apparently normal fetal echocardiogram. Echocardiography is usually effective in infants and children, but may be limited in some adults because of abnormal thoracic shape or obesity. It is essential that all aortic valve leaflets be clearly visualized to exclude significant abnormalities. If echocardiography is inadequate, computed tomography or cardiac magnetic resonance imaging should be performed in a center with expertise in these techniques, and should visualize the aortic

valve well and provide additional important information about smaller arteries as well as the distal aortic arch and descending aorta. It is important to note that these different modalities may not be directly comparable and use of a single imaging technique for ongoing monitoring is preferred. All individuals with TS should undergo cardiac magnetic resonance imaging at an age when the study may be performed without sedation. This should be performed at a center with appropriate technical expertise to screen for abnormalities of the aortic arch and descending aorta. If a younger child needs further imaging on clinical grounds, MR is an excellent choice even if sedation is necessary.

In addition to screening for anatomic defects, it is important to evaluate the blood pressure and ECG in all newly diagnosed patients. Hypertension affects about 25% of girls, and a larger percentage of adults with TS (46, 56, 57). Systemic hypertension is an important risk factor for aortic dilation and dissection. Therefore, blood pressure should be monitored frequently on a regular basis and treated vigorously in all patients with TS. If the baseline ECG reveals a significantly prolonged QTc, then medications which might further prolong the QT should be avoided.

#### *Growth Hormone treatment and the cardiovascular system*

To increase adult stature, most girls with TS are now treated with growth hormone (GH) (see Pediatric Care section below). Two echocardiography studies reported normal left ventricular morphology and function in GH-treated girls with TS (58, 59) and two recent MR studies found no deleterious effect of GH treatment on aortic diameter (60) or compliance (61).

TABLE 1 HERE

#### *Ongoing care*

For the patient that *has no identified cardiovascular defects* after a comprehensive evaluation, routine pediatric care is advised, with continued monitoring of blood pressure, and a re-assessment of the cardiovascular system around the time of transitioning from pediatric to adult care, including MR imaging, as mentioned above. For normotensive adults with TS who have no underlying cardiovascular disease, the

frequency or even the need for continued echocardiographic monitoring is unclear, but it seems prudent to re-evaluate aortic dimensions at 5-10 year intervals.

Patients that do *have significant cardiovascular defects* need continued monitoring by a cardiologist, with frequency of monitoring determined by the individual circumstances. Patients with (isolated) hypertension can usually be cared for by a pediatrician or internist, but aortic dimensions need to be determined on a regular basis in these patients. Patients or parents of girls that are considered at increased risk for aortic dilatation or dissection because of the presence of a BAV, coarctation or hypertension should be educated about this risk, the need for compliance with medical monitoring and treatment, and the possible presenting symptoms, e.g., chest or back pain. Patients with multiple risk factors (BAV, dilated aortic root, hypertension) that put them at high risk for aortic deterioration might want to consider carrying medical information in their wallet or on a bracelet alerting medical personnel to the aortic disease. Such patients also need to be counseled about pregnancy and appropriate exercise programs that do not stress the cardiovascular system. The adult with TS or parents to TS children must be informed that prophylactic antibiotics should be given before tooth or hip surgery.

#### *Monitoring for aortic dilatation*

Normal ascending aortic diameter is related to body size and age. Since most individuals with TS are small, one would expect their aortic diameter to be smaller than the average for age matched control females, but in general it is larger (43, 46). All measurements of the aorta should be done at end-systole. The ascending aorta should be measured at the level of the annulus at the hinge points of the valve, at the level of the sinuses of Valsalva perpendicular to the ascending aorta long axis, and at the ascending aorta 10mm above the sino-tubular junction. Normative data for aortic diameters as a function of body surface area are available (62). Additional measurements which are not as well standardized include measurement of the transverse aortic arch and the descending aorta.

Data on aortic diameters normalized to body surface area (BSA) for adults with TS are available(46) and a range of absolute diameters from both echo and MR for women with TS and age-matched controls are also available(43). Review of these data (including echocardiographic ascending aorta diameters measured at the annulus and MR diameters measured at the level of the bifurcation of the pulmonary arteries) suggests that unadjusted values greater than 28-32 mm will identify patients with diameters greater than 95% of controls, which would clearly be abnormal for women with TS who are generally *smaller*. When aortic root enlargement is found, medical therapy and serial imaging is recommended. Aggressive control of blood pressure should aim for low-normal values. Since many individuals with TS demonstrate nocturnal hypertension, 24 hour monitoring may be helpful in obtaining optimal control(54, 63). In hypertensive patients with aortic root enlargement who also have resting tachycardia, beta- adrenergic receptor blockade is an excellent therapeutic option. Beta-blockers have been shown to reduce the rate of aortic dilation and dissection in Marfan syndrome (64), although efficacy in treating aortic dilatation in TS has not yet been investigated.

### *Pregnancy*

Spontaneous or assisted pregnancy in TS should be undertaken only after thorough cardiac evaluation. Alarming reports of fatal aortic dissection during pregnancy and the post-partum period have raised concern about the safety of pregnancy in TS(65). If pregnancy is being considered, preconception assessment must include cardiology evaluation with magnetic resonance imaging of the aorta. A history of surgically repaired cardiovascular defect, the presence of BAV or current evidence of aortic dilatation or systemic hypertension should probably be viewed as relative contraindications to pregnancy. For those who become pregnant, close cardiology involvement throughout pregnancy and the post-partum period is essential.

### *Exercise*

In general "heart healthy" exercise (66), in which regular moderate aerobic activity is emphasized, should be encouraged in individuals with TS. Highly competitive sports and very strenuous or isometric exercises are associated with marked increases in heart rate and blood pressure that may have adverse effects on individuals with a dilated aortic root. Therefore, eligibility for competitive sports for all those with TS should be determined by a cardiologist after a comprehensive cardiac evaluation that includes recent magnetic resonance imaging of the aorta. Extreme exertion should be discouraged in individuals with significant aortic enlargement. The experts polled on this issue agreed that aortic enlargement in TS may be defined as an aortic sinus of Valsalva or ascending aorta, body size-adjusted Z-score  $>2$ , plus evidence of increasing Z-score on a subsequent imaging study of the aorta, OR a single Z-score  $>3$ . In those cases, participation in competitive sports is contraindicated.

### **Medical care for the Child with TS**

Once the diagnosis of TS is made, patients should be referred, if at all possible, to a center with expertise in TS and a multidisciplinary approach to treatment. Optimally, members of the pediatric care team should include specialists in pediatric endocrinology, audiology, genetics, cardiology, dermatology, development, nephrology, occupational therapy, ophthalmology, orthopedic surgery, otolaryngology, psychology, and speech therapy. Suggested guidelines for evaluation of newly diagnosed individuals with TS are summarized in Table 2 and a summary of the suggested schedule for ongoing care is given in Table 3.

Table 2 HERE

#### *Lymphatics*

Abnormalities of cardiovascular and lymphatic development are found in most TS fetuses that fail to survive the 1<sup>st</sup> trimester (31, 32). For those girls that survive, the residua of the fetal lymphedema and cystic hygromas are peripheral lymphedema and webbed neck, the principal keys to diagnosis in the newborn period. The lymphedema

seen at birth usually resolves by 2 years of age without therapy. However, lymphedema may occur or reoccur at any age, and may be associated with the initiation of salt-retaining therapies such as GH or estrogen. Some children and adolescents may require support stockings and elevation for treatment. Complete decongestive physiotherapy, a four step process involving skin and nail care, massage for manual lymph drainage, compression bandaging, and a subsequent remedial exercise regimen (67) is recommended for those with more significant lymphedema(68). Long term diuretic use should be avoided because of its marginal efficacy and problems with fluid and electrolyte imbalance. Vascular surgery should be avoided. Families can be directed towards The National Lymphedema Network (<http://www.lymphnet.org>) for more information.

### *Urinary system*

Congenital malformations of the urinary system are present in 30-40% of patients with TS (69, 70). By ultrasound, collecting system malformations are found most frequently (~20%), followed by horse-shoe kidneys (~10%) and malrotation and other positional abnormalities (~5%). If an intravenous pyelogram is also used for screening, even more abnormalities will be identified, but these tend to be clinically insignificant (71). All girls with TS should have a renal ultrasound study performed at diagnosis. Structural malformations of the kidney occur more frequently in 45,X TS while collecting system malformations occur more frequently in those with mosaic/structural X karyotypes. In a recent study (69), no patient with a normal baseline ultrasound developed renal disease during a follow-up period averaging six years. However, some of those with malformations developed hypertension and urinary tract infections.

### *Eye*

Abnormalities of the external ocular adnexa including epicanthal folds, ptosis, hypertelorism and upward slanting palpebral fissures are common in TS (72). Red-green color deficiency is present in ~ 8% of the population, a percentage similar to that found in males. Most importantly, strabismus and hyperopia (farsightedness) each

occur in 25-35% of these children putting them at high risk for amblyopia. To promote early detection and treatment and prevent visual loss, children with TS should be evaluated by a pediatric ophthalmologist at 12 – 18 months of age in addition to receiving routine ophthalmologic evaluations by their primary care physician.

### *Ear*

Hearing problems and ear malformations are common in TS and correlate with karyotype (73, 74). There is a high prevalence of otitis media (OM) that may result from an abnormal relationship between the eustachian tube and middle ear, a consequence of abnormal cranial base anatomy. As the result of otitis media, conductive hearing loss is common in young girls with TS(75). Although a more significant issue in adulthood, progressive sensorineural hearing loss with a unique dip in the 1.5-2 kHz region and/or a high frequency loss (above 8 kHz) may present as early as 6 years of age and necessitate the use of hearing aids in childhood.

Heightened surveillance for middle ear effusions should occur in girls with TS until at least 7-8 years of age, and longer for those with a history of OM. Evaluation should include otoscopic examination, preferably pneumatic otoscopy, tympanometry, or both on at least an annual basis. Therapy for OM in girls with TS should be managed aggressively because of the significant impact that hearing loss can have on speech and language development and the risk of cholesteatoma formation in those with persistent otorrhea. TS girls should be evaluated for persistence of middle ear fluid ~ 6-10 weeks after an episode of acute OM to document whether the effusion has cleared. Girls that have middle ear effusions persisting longer than 3 months or recurrent episodes of acute (suppurative) OM should be referred to an otolaryngology specialist. Common surgeries for recurrent OM and airway problems include tympanostomy tube placement, tonsillectomy and adenoidectomy. Removal of the adenoids may exacerbate palatal dysfunction and negatively influence quality of speech, factors that must be taken into consideration prior to surgery.

Girls or women diagnosed with TS at an older age should be referred to an audiologist at the time of diagnosis. For those with a history of OM or hearing loss,

audiologic evaluations are recommended annually or as per their audiologist. In older girls and women with TS with no history of hearing loss, audiologic surveillance is warranted every 2-3 years. The assiduous treatment of ENT problems in childhood and avoiding additional potential injuries to the inner ear may reduce the risk of hearing loss.

### *Orthodontics*

Distinct craniofacial features in TS include a flattened cranial base angle, a marked reduction in posterior cranial base length and a retrognathic face (76). The maxilla is generally narrow with a high, arched palate while the mandible tends to be wide and micrognathic. The prevalence of distal molar occlusion, anterior and lateral open bite, and lateral crossbite are significantly increased (77). Abnormalities in tooth development and morphology include early eruption of the secondary teeth, simple crown morphology, thinner enamel, less dentine, and short roots (78). Girls with TS are also at greater risk for root resorption, which can lead to tooth loss, especially during orthodontic treatment. It is recommended that all girls with TS see a pediatric dental specialist by age two years, and an orthodontist no later than age seven. Since growth hormone treatment can alter craniofacial proportions, all girls with TS treated with GH should receive periodic orthodontic follow-up (79). Prophylactic antibiotics should be used before dental procedures in TS with known cardiac malformations.

### *Autoimmunity*

Individuals with TS clearly have increased risk for autoimmune thyroiditis and celiac disease. Autoimmune thyroid disease is common during childhood in TS and has been reported as early as 4 years of age (80, 81). In a recent study, 24% of 84 children with TS (0-19 years old) who were followed longitudinally (mean duration = 8 years) developed hypothyroidism and 2.5% developed hyperthyroidism (80). Generally, there are no overt clinical symptoms of hypothyroidism. While thyroid antibodies identify patients at high risk, all patients with TS should be screened annually for autoimmune thyroid disease with a TSH and T4 from 4 years of age onward.

The risk of celiac disease is increased in TS, with 4-6 % of individuals affected (82). As recommended by North American Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines (83), TS girls should be screened by measurement of tissue transglutaminase IgA antibodies. Periodic screening should begin at age 4 and be repeated every 2-5 years. If HLA-typing is performed, individuals without DQ2 or DQ8 need no further antibody measurements.

### *Skin*

An increased number of acquired melanocytic nevi is seen in TS (84), but the risk for melanoma does not appear to be increased (85). A reputed propensity towards keloid formation may be a reflection more of the sites at which individuals with TS commonly undergo plastic surgery (head, neck and upper chest) rather than an intrinsic difference in healing (86).

### *Skeletal System*

Short stature is probably the most common, readily recognizable clinical feature of TS. Much of the deficit in height is caused by haploinsufficiency of the short-stature homeobox-containing gene (SHOX) located within the Xp-terminal, pseudoautosomal region of the X chromosome (87). It affects virtually all individuals with TS and results in an average adult stature 20 cm shorter than their target height (88, 89). The typical growth pattern in TS is characterized by mild intrauterine growth retardation, slow growth during infancy, delayed onset of the childhood component of growth, growth failure during childhood and the absence of a pubertal growth spurt.

Skeletal abnormalities encompass more than poor linear growth. Disproportionate growth causes many girls with TS to appear stocky, with a wide body and relatively large hands and feet (90). In addition, developmental abnormalities of individual bones account for many common findings such as short neck, cubitus valgus, genu valgum and short 4th metacarpals. Madelung deformity of the wrist, although often mentioned in connection with TS, is actually rather infrequent (91). Infants with TS have an increased risk of congenital hip dislocation. Girls with TS have higher risks for

scoliosis and kyphosis than the general population. 10-20% of girls with TS develop scoliosis, and kyphosis and/or vertebral wedging also appears to be more common (92, 93). The latter may be quite difficult to appreciate clinically, and both problems can progress with rapid growth. Phalangeal bone density has been reported to be normal during childhood (94).

Table 3 HERE

### *Growth-promoting therapy*

The goals of growth-promoting therapies are to attain a normal height for age as early as possible, progress through puberty at a normal age, and attain a normal adult height. The centerpiece of growth-promoting therapy is growth hormone (GH), which increases growth velocity and final adult stature. Girls with TS generally have a normal GH secretory pattern (95). Provocative GH testing should only be performed in those whose growth is clearly abnormal relative to that expected for TS, determined by plotting lengths and heights on TS-specific growth curves (88, 89, 96, 97).

It is well-established that GH therapy is effective in increasing final adult height. However, the magnitude of the benefit has varied greatly depending upon study design and treatment parameters. In the first randomized controlled trial to follow GH-treated TS subjects to final height (98), the Canadian GH Advisory Committee corroborated the increases in adult stature reported by studies with historical controls (99-102). In the Canadian study, girls with TS (aged 7-13 years) who were randomized to receive GH (0.3 mg/kg/wk; maximum weekly dose 15 mg) achieved a final adult stature 7.2 cm taller than the control group after an average of 5.7 years. Factors predictive of taller adult stature include a relatively tall height at initiation of therapy, tall parental heights, young age at initiation of therapy, a long duration of therapy, and a high GH dose (103-108).

The optimal age for initiation of GH treatment has not been established. Preliminary data from the Toddler Turner Study, in which 88 girls between the ages of 9 months and 4 years of age (mean age 2.0 years) were randomized to GH or no GH therapy, indicate that GH therapy is effective beginning as early as 9 months of

age(109). In addition, the safety profile appears to be similar to that observed in older TS children. Treatment with GH should be considered as soon as growth failure (decreasing height percentiles on the normal curve) is demonstrated, and its potential risks and benefits have been discussed with the family.

GH therapy in the U.S. is generally initiated at the FDA-approved dose of 0.375 mg/kg·wk. This is most effective when given daily and customarily administered in the evening. The dose can be adapted according to the patient's growth response and IGF-I levels. Growth prediction models may be helpful in determining the potential effects of changes in dosing (103). Doses substantially higher than those approved by the FDA (0.054 mg/ kg·d = 0.162 IU/ kg·d ~ 4.8 IU/m<sup>2</sup>·d) produce a relatively small gain in final height although there is no apparent increase in short-term adverse events (110). For example, in a study by the Dutch Working Group the mean gain in final height in groups treated with 4 IU/m<sup>2</sup>·d (0.045 mg/k/d), 6 IU/m<sup>2</sup>·d and 8 IU/m<sup>2</sup>·d averaged 11.9 ± 3.6 cm, 15.7 ± 3.5 cm, and 16.9 ± 5.2 cm, respectively (99). However, when GH was given at the higher doses, IGF-I levels were often above the normal range, and ideally, prolonged exposure to elevated IGF-1 levels should be avoided because of theoretical concern about potential long term adverse effects (111).

For girls below ~ 9 years of age, therapy is usually started with GH alone. In older girls, or those with extreme short stature, consideration can be given to using higher doses of GH and adding a nonaromatizable anabolic steroid, such as oxandrolone (100). The dose of oxandrolone should be 0.05 mg/kg·day or less and liver enzymes should be monitored. Higher doses are likely to result in virilization (clitoral enlargement, acne, lowering of the voice, etc.) and more rapid skeletal maturation. Therapy may be continued until a satisfactory height has been attained or until little growth potential remains (bone age ≥ 14 yr and growth velocity < 2 cm /year). GH therapy should be directed by a pediatric endocrinologist and the child monitored at intervals of 3-6 months. Evaluation for orthopedic problems as well as growth velocity should be part of the regular physical examination. Development of scoliosis or kyphosis does not necessarily preclude GH therapy, however close collaboration with an orthopedic surgeon is required.

*Puberty induction*

Absent pubertal development is one of the most common clinical features of TS although up to 30% or more of girls with TS will undergo some spontaneous pubertal development (112, 113), and 2–5% may achieve spontaneous pregnancy(114). Ultimately, over 90% of individuals with TS will have gonadal failure. Before initiation of estrogen therapy, serum gonadotropin levels should be determined to exclude the possibility of delayed spontaneous pubertal development.

When estrogen therapy is required to induce pubertal development, the form, dosing and timing should reflect the process of normal puberty. Delaying estrogen therapy until 15 years of age to optimize height potential, as previously recommended (115), seems unwarranted. This emphasis on stature tends to undervalue the psychosocial importance of age-appropriate pubertal maturation and may be deleterious to bone and other aspects of the child's health (116-118). Furthermore, recent evidence suggests that some treatment regimens using estradiol that begin replacement at the age of 12 years permit a normal pace of puberty without interfering with the positive effect that GH has on final adult height (99, 116, 119, 120).

Many forms of estrogen are available and oral estrogens have been most often used. However, both transdermal and injectable depot forms of estradiol may be more physiologic alternatives (116, 119-121). Low dose estradiol therapy can be initiated as early as 12 years of age. Replacement is usually begun at 1/10<sup>th</sup> – 1/8<sup>th</sup> of the adult replacement dose and then increased gradually over a period of 2 - 4 years. The following are equivalent doses that achieve estradiol levels in the normal range for young adult women: oral estradiol - 2 mg/day, transdermal estradiol - 0.1 mg/day, and injectable estradiol cypionate – 2.5 mg/month. To allow for normal breast and uterine development, it seems advisable to delay the addition of progestin at least 2 years after starting estrogen or until breakthrough bleeding occurs. The use of oral contraceptive pills to achieve pubertal development is best avoided, since the synthetic estrogen doses in most formulations are too high and the typical synthetic progestin may interfere with optimal breast and uterine development. It is important to educate the patient that

estrogen replacement is usually required until the time of normal menopause to maintain feminization and prevent osteoporosis (118).

During the process of pubertal development, it is important to engage the patient in a gradual discussion about how TS and its treatment may impact her sexual development and function and reproductive potential. In addition, when appropriate, counseling for the prevention of sexually transmitted diseases (and unwanted pregnancy for those with endogenous ovarian function) should also be provided.

Table 4 HERE

### *Transition Management*

The transition from pediatric to adult health care should occur at the completion of growth and puberty during late-stage adolescence (usually by age 18 years). However, transition should be initiated as a staged process. Beginning at approximately age 12, the center of care should be shifted incrementally from the parent to the adolescent with TS. The health care focus also shifts from maximizing height to inducing feminization, counseling the adolescent with TS about the evolving impact of her condition into adulthood, and promoting the development of independent self-care behaviors.

Transition is an appropriate time to assess individual risks for potential adult morbidities and promote healthy lifestyles. To help insure adequate bone mineral accrual, girls with TS are encouraged to have calcium intake of >1000 mg of elemental calcium daily in the pre-teen years, and 1200 – 1500 mg daily after 11 years of age. This will generally require oral supplementation. Counseling as to healthy eating and exercise habits, and maintaining a healthy weight are essential. During late-stage transition, the pediatric endocrinologist should engage the transition patient in developing an adult care plan in close collaboration with her new health care provider to help assure that they will continue to receive the careful monitoring that they need to optimize adult health and longevity.

## **Psychological and educational issues**

### *Cognitive and Educational performance*

The majority of individuals with TS have normal intelligence, although patients with a small ring X-chromosome clearly have an increased risk of mental retardation (122). These individuals may have a severe phenotype with features atypical for TS, apparently due to failure of small rings to inactivate (123). Individuals with TS have an increased risk for a selective impairment in nonverbal skills and, as a group, score lower on performance than on verbal subsections of standardized intelligence tests(124). In school, these impairments are manifested as math, visuospatial and executive function deficits (125). Slowed response time is observed across each of these three domains(126). The specific neuropsychological deficits include four interacting areas of functioning: visual-spatial organization deficits (e.g., difficulty with direction sense), difficulty with social cognition (e.g., failure to appreciate subtle social cues), difficulty with problem solving (e.g., mathematics), and motor deficits (124, 126-128). Some of these deficits may be improved by hormonal therapy at the time of puberty(129). A higher than expected rate of attention deficit disorder diagnoses (i.e., 24%) is reported in school age girls (130). Drawing from the broader field of educational research, it is possible that educational intervention directed at learning or attentional difficulties may offer further benefits. Despite variable degrees and areas of learning difficulties, as a group girls and women with TS excel at verbal skills and many adults with TS have university level education(131-133).

### *Psychological development*

Overall, behavioral function is normal in girls with TS. However, there may be an increased risk for social isolation, immaturity and anxiety (134, 135).

Girls with TS typically have a female pattern of gender identity, but adolescent and adult women with TS achieve sexual milestones later than their peers and are less likely to marry (136, 137). It is unclear whether this delayed sexual activity reflects some underlying genetic or hormonal influence on behavior or the timing of puberty. Recent studies do not support the influence of height (137, 138) as influential on dating and initiation of sexual activities, but the role of physical anomalies is unclear. The

developmental process is likely affected by treatments with GH and estrogen that potentially influence the child's perception of herself.

*Psychosocial function in adults with TS*

Young, GH-treated adults on average have normal self-perceived physical and mental health, but some women experience decreased self-esteem, mostly in the context of social functioning(139). Adult height does not appear to impact adult quality of life(117, 139). Formal psychiatric evaluation of 100 adult volunteers with TS participating in an NIH natural history study revealed no increase in major psychiatric diagnoses other than depression and anxiety related disorders, which were higher than those reported from a community based sample, but similar to those reported in women from a general gynecological clinic sample (140). Women with TS report significantly higher levels of shyness and social anxiety and reduced self-esteem compared with normal menstruating women, but similar to karyotypically-normal women with premature ovarian failure, suggesting that the experience of ovarian failure and infertility contribute to psychosocial dysfunction (138). Supporting this view, these same women with TS reported in open-ended interviews that dealing with premature ovarian failure and loss of fertility was the most difficult part of having TS (18).

### *Recommendations*

Significant psychosocial risks are associated with TS, including cognitive, social, and behavioral components. Plans for both medical and psychological intervention should be developed so as to reinforce and support the individual's self esteem and to insure that individuals remain in the mainstream of social, educational, and employment activities. Many of these issues are discussed in patient-oriented material available through the Turner Syndrome Society of the United States ([www.turner-syndrome-us.org](http://www.turner-syndrome-us.org)) and from other local and national TS organizations (e.g., Magic Foundation, [www.magicfoundation.org](http://www.magicfoundation.org)). Early involvement in a TS support group should be encouraged.

A comprehensive psycho-educational evaluation is recommended immediately preceding school entry, or at the time of TS diagnosis. Evaluations may need to be repeated during primary school, if indicators of academic difficulties emerge. Children with TS may also have other conditions: as for all children, if evidence of other difficulties emerge (such as dyslexia or attention deficit), evaluation and treatment should be encouraged. As with documentation of learning disability in any child, classroom accommodations and modifications may be necessary and could be considered at any age as needed. For example, in view of the slower processing speeds observed in girls with TS, untimed testing may be appropriate. In many cases it may be useful to refer children and their families to educational specialists to facilitate development of coping strategies, such as reliance on relatively superior verbal skills to mediate problem solving. In childhood, parents should be alerted to possible peer issues, and educated about strategies to deal with difficulties such as social isolation.

Age appropriate pubertal induction is recommended because of potential long-lasting psychosocial implications of delayed pubertal development. Discussions should be initiated regarding sexuality and reproductive options at age-appropriate levels. It is sometimes difficult for adult care-givers to address the ramifications of a TS diagnosis, especially infertility. However it is important to address these issues in an honest and open manner, since "secret-keeping" may have unintended negative consequences and actually amplify the problems for girls and young women (141). Age-appropriate social interactions should be encouraged. Finally, attention should be given to career

and vocational planning and preparation for transition to living independently, starting in adolescence. Learning disabilities can be a major impediment to emancipation from family and to career enhancement although many women with TS do achieve high professional status.

## **Medical care for adults with TS**

### *Medical follow-up and estrogen replacement therapy*

Adult women with TS require careful medical follow-up. Early medical intervention may decrease the substantially increased morbidity (142, 143) and mortality (144, 145) and improve the quality of life of women with TS. Ideally, the process of transition should take place over a period of 2–3 yr during the late pubertal period as described above, and should involve an adult endocrinologist and a gynecologist with expertise in premature ovarian failure. A multidisciplinary team including specialists in endocrinology, cardiology, hearing and ENT, infertility/gynecology and psychology may be developed at a tertiary care center. The agenda for such a specialist service should be developed in partnership between medical professionals and Turner support groups. Regrettably late diagnosis of TS, even in adults, is still a problem. No matter what the age of the patient, a full workup with assessment of congenital malformations should be performed, including all screening tests recommended for younger patients (Table 2)

Upon transfer to an adult care clinic, the young woman with TS should undergo a comprehensive medical evaluation, addressing not only the specific problems associated with TS but also screening for osteoporosis, hypertension, diabetes and dyslipidemia, which are increased in TS(143). All medical problems present during childhood should be followed in adults, especially congenital cardiovascular issues, thyroid and celiac disease and hearing loss (Table 3). Annual medical history and general physical evaluation should be performed, including blood pressure, heart auscultation, clinical evaluation of thyroid size and function, breast examination, and Pap smear. As in children, regular otological examination is important, as about 60% of adults with TS experience sensorineural hearing loss. The hearing loss is progressive, but tends to occur more rapidly after about 35 yr of age, leading to early presbycusis

(146). Hearing aids are frequently necessary. Otological screening should be conducted at least every 2-3 yr in patients who are asymptomatic and have previous documented normal hearing, and more frequently as indicated for those with established hearing loss or new symptoms of hearing loss.

Many of the problems of adult life in patients with TS are compounded by obesity(147, 148), partly due to low physical fitness and a sedentary lifestyle(149, 150). Lifestyle education with advice on diet and exercise must be included in a program of prevention of diabetes, osteoporosis, and hypertension. Women with TS should aim to have a body mass index below 25 kg/m<sup>2</sup> and a waist/hip ratio less than 0.80. Any exercise program should be developed with consideration of individual skeletal or cardiovascular problems, and a physical rehabilitation specialist or trainer may be of great value in designing individualized programs for patients with physical limitations.

#### *Laboratory tests*

Laboratory testing of women with TS should be carried out at 1- 2-yr intervals and include measurements of usual screening tests (hemoglobin, white blood cell count, renal function (creatinine and blood urea nitrogen), but especially include fasting blood glucose lipid profile, liver enzymes, TSH, and total or free T4. Recommendations for breast evaluation, self-examination, and mammography are the same as for the general population.

#### *Hepatic disease*

Liver enzymes, especially  $\gamma$ -glutamyl transferase, alanine amino transferase, aspartate amino transferase, and alkaline phosphatase, are commonly raised in women with TS, but their relationship to chronic liver disease is unknown (148, 151). Hepatitis serology can be checked if indicated although the prevalence of viral hepatitis is not raised in TS. Usually, elevated liver enzymes do not progress to overt hepatic disease, but regenerative nodular hyperplasia and other architectural abnormalities or biliary lesions are seen on biopsy, as is portal hypertension, which should be treated according to hepatology guidelines(152). Estrogen treatment is not associated with adverse

effects on the liver and usually lowers liver enzymes in TS and thus is not contraindicated in patients that have elevated liver enzymes(151). If elevated liver enzymes persist for more than 6-12 months, an ultrasound should be performed to rule out hepatic steatosis. If steatosis is not present and liver enzymes remain elevated or increase, a hepatology consult may be obtained with consideration of biopsy guided by the use of hepatic ultrasound with assessment of blood flow by Doppler. Potentially hepatotoxic drugs such as statins and glitazones have to be prescribed with caution in affected patients.

### Renal function

Although congenital structural anomalies of the kidney are found in about 30% of TS patients, renal function is usually normal, with the only common complication being urinary infections related to obstruction. Thus, individuals with known renal collecting system anomalies may require more frequent screening for urinary tract infections.

### *Bone metabolism*

Fractures are increased in older patients with TS, but these patients may not have received optimal estrogen treatment in the past. Most studies using dual x-ray absorptiometry (DXA) find decreased bone mineral density (BMD)(149, 153), but small size may lead to under-estimation of BMD by DXA (154). When adjusted for size, women that have received appropriate estrogen treatment usually have normal BMD in trabecular bone, e.g., the spine (149, 154). However, there seems to be an intrinsic, estrogen-independent deficit in cortical bone in TS(149, 155, 156). A baseline BMD should be obtained at the initial visit in the adult clinic, with follow-up depending on the initial result. If the BMD is normal (adjusting for size), further evaluation need not take place until age 40-50 years, or when the patient plans to discontinue estrogen treatment. If BMD is *low* in a young woman with TS, one needs to investigate and treat possible contributory factors such estrogen replacement non-compliance, tobacco use, excessive alcohol use, possible celiac disease or vitamin D deficiency. Proper estrogen treatment improves BMD, and is the mainstay of bone protection. Adequate calcium and vitamin D intake is essential, as many women have low levels of vitamin D. Weight-

bearing exercise is very important in achieving and maintaining BMD and should be encouraged.

Bisphosphonates or other anti-osteoporotic pharmaceuticals are not recommended for treating osteopenia in young women with TS, since reduced cortical BMD in TS is not proven to lead to increased fractures and bisphosphonates have not been shown to be effective in enhancing cortical BMD in TS. Furthermore these agents may blunt treatment with newer modalities in the future, and are contraindicated in women who might attempt pregnancy. For women with confirmed osteoporosis, especially those at risk for fracture, or who have already sustained a low impact fracture, the usual medical treatment for osteoporosis is indicated.

#### *Risk factors for coronary artery disease*

In addition to their burden of congenital cardiovascular disease, women with TS are at increased risk for atherosclerosis. Hypertension affects as many as 50% of young adult patients. Blood pressure should therefore be closely monitored and hypertension treated vigorously(57, 63, 150). Increased heart rate and altered autonomic innervation of the heart are common in TS (54). Type 2 diabetes is common in TS. An OGTT uncovers impaired glucose tolerance or diabetes in more than 50% of cases, usually associated with an insulin secretory defect in TS(57, 157). Insulin sensitivity may be normal in many patients, but reduced in those with obesity or a strong family history of type 2 diabetes. Often the diabetes is relatively mild and responsive to weight loss or monotherapy,

LDL-cholesterol and triglycerides are elevated, and lipid particle size is reduced in women with TS compared to age and BMI-matched women with karyotypically normal ovarian failure (158, 159), suggesting that the X chromosome deletion per se, apart from the effects of premature ovarian failure, is associated with dyslipidemia.

#### *Thyroid and celiac disease*

As indicated in the pediatrics section, continued screening for thyroid and celiac diseases may continue throughout adult life (Table 3), due to an increased risk of developing overt disease(82).

### *Ovarian hormone replacement*

It is recommended that women with TS receive cyclical estrogen and progestin. Sufficient estrogen should be prescribed to prevent the symptoms, signs, and sequelae of estrogen deficiency. An estrogen dose equivalent to 2 mg estradiol daily suffices for most adult women with TS, but individual requirements may vary from 1-4mg/day. Ideally, natural estradiol and progesterone, rather than analogues, should be delivered by transdermal or transmucosal routes so as to mimic age-appropriate physiological patterns as closely as possible. However, regimens that meet each individual woman's tolerance and preference vary widely, and the most important consideration is that women actually take ovarian hormone replacement. This is critical because the risk of clinically significant osteoporosis with spontaneous fractures is very high in young women with TS not taking estrogen (132). As with other women receiving estrogen replacement therapy, pelvic ultrasonography and endometrial biopsy should be considered when abnormal vaginal bleeding occurs. Androgen concentrations are reduced in many women with TS(160), and androgen substitution therapy may be of value in some instances. This is an area that needs further investigation. The duration of estrogen therapy should be individualized, and readjustment of dosage or discontinuation should occur at the age of normal menopause.

### *Fertility and family planning issues*

Although a few patients with TS achieve spontaneous pregnancy, most are infertile. Various assisted reproductive techniques are now available for achieving pregnancy. Recent studies show that women with TS become pregnant as easily as women with other types of infertility and carry their pregnancies to term without an increased miscarriage rate (161, 162); however, they do have an increased rate of maternal complications(65). Firstly, because of their small size, many women with TS need to deliver by cesarean section. Second, hypertension and diabetes are common in TS pregnancy(162). Most critically, the risk for dilatation and dissection of the aorta appears to increase during pregnancy(65). Karnis et al. also found that only ~50% of women in the U.S. had a cardiac workup prior to fertility treatment. Before

contemplating spontaneous or assisted pregnancy, individuals with TS need a complete medical evaluation. Particular attention should be paid to the cardiovascular system, and echocardiography, ECG and MRI need to be performed prior to any attempt at pregnancy. Women with cardiovascular issues (BAV, dilated aorta, history of coarctation), as described above, are best counselled against attempted pregnancy (163). In addition, thyroid status and glucose tolerance should be monitored. All pregnancies should be followed by a multidisciplinary team, including high-risk pregnancy specialists, endocrinologists, and cardiologists, generally at a tertiary care facility.

*Women with functional ovaries.*

Women with TS who have spontaneous menstrual cycles and ovulate normally should receive counselling on the timing of pregnancies: due to the risk of premature ovarian failure, pregnancies should not be postponed without good reason, and the possibility of oocyte or embryo cryopreservation; the risk of miscarriage and chromosomal abnormalities in the offspring; and the possibility of prenatal genetic testing.

*Women without functional ovaries.*

Oocyte or embryo donation can be used to achieve pregnancy in patients with TS who do not have functional ovaries(161). Special attention should be given to appropriate preparation of the uterus. This requires adequate hormone replacement therapy for 1-2 years before oocyte or embryo transfer, to increase the size of and improve the blood flow in the uterus. Adequate uterine preparation has to be performed (4-6-8 mg of 17 $\beta$ -estradiol and a gestagen), and optimally, the thickness of the endometrium should be 7 mm. Ideally, only one embryo should be transferred at a time, to avoid the additional risks associated with multiple pregnancies. An embryo cryopreservation program is therefore essential. Under optimal conditions, spontaneous vaginal delivery is an acceptable option. Caesarean section, however, is often employed because of a narrow pelvis. Adoption is an option for many women with TS and the use of surrogate mothers is an option in some countries.

*Cryopreservation of ovarian tissue and immature oocytes.*

New data has emerged during the last years showing that adolescents with only few signs of spontaneous puberty may still have ovaries with follicles(28). The possibility of using cryopreserved ovarian tissue and immature oocytes, obtained before regression of the ovaries occurs in childhood, is currently under intensive investigation, and results seem promising(28). Although only a research tool at present, this technique may provide the possibility of pregnancy with the patient's own oocytes.

**Summary**

This consensus statement arose from an interdisciplinary meeting of geneticists, pediatricians, cardiologists, internists, behavioural health specialists and gynecologists involved with the care of and clinical research on patients with TS. Our goal was to address new information and experience that has accrued in the past 5-6 years since the last international workshop with regard to practical implications for the diagnosis and care of individuals with TS. The first issue was the high elective abortion rate for incidentally diagnosed 45,X and 45,X/mosaic fetuses(14, 15), which seemed at odds with recent reports of a normal quality of life for individuals receiving current medical care (117, 133, 164). Another paper reviewing care for individuals with TS, in general agreement with this article, has appeared during the review process (165). It was clear that the content of prenatal counselling on the significance of such a karyotype for expectant parents needs updating and needs inclusion of TS patient and parent groups. Participants were in favour of the initiation of newborn screening for TS, with the caveat that a suitable infrastructure to provide educational and psychological support for families must be established. An expanded view of congenital cardiovascular disease in TS led to the recommendation for diagnostic cardiovascular MR study for all patients, and increased focus on regular monitoring of systemic blood pressure and aortic diameter in children and adults. Concerns have been raised about cardiovascular risks associated with pregnancy in TS and inadequate medical evaluation prior to conception (163), hence new cautions for individuals with existing cardiovascular issues. GH treatment has now been proven to increase adult height (98), although whether this

effect confers an advantage to adults with TS has not been proven(117). Because growth appears to continue apace with the gradual introduction of estradiol, pubertal development generally should not be delayed in order to further increase adult height. Pubertal delay may exacerbate the negative psychosocial impact of early ovarian failure, associated with excessive shyness and social anxiety, delayed sexual debut and decreased marriage rate. The increased frequency of non-verbal learning and attention deficit disorders in girls with TS mandates comprehensive testing at an early age so as to implement appropriate educational plans in a timely manner. The care of adults with TS has received less attention than the treatment of children, and many seem to be “falling through the cracks” with inadequate cardiovascular evaluation (166) and estrogen treatment(167).

Last, it is important to recognize that the recommendations in this document are based on the authors’ best judgments given the current level of medical knowledge. There are many questions that remain unanswered regarding care for girls and women with TS, such as identifying the optimal age of initiation and duration of GH treatment, specific interventions for attention and perceptual deficits, the best method of ovarian hormone replacement across the lifespan and the most effective monitoring for osteoporosis and cardiovascular disease.

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**Table 1 Cardiovascular Screening and Monitoring Algorithm for Girls and Women with TS**

<b><i>Screening</i></b>	
<i>All patients at time of diagnosis</i>	Evaluation by cardiologist with expertise in congenital heart disease
	Comprehensive exam including blood pressure in all extremities
	All require clear imaging of heart, aortic valve, aortic arch and pulmonary veins <ul style="list-style-type: none"> <li>• Echocardiography is usually adequate for infants and young girls</li> <li>• MR and echo for older girls and adults</li> </ul>
	Electrocardiogram
<b><i>Monitoring</i></b>	
<i>Follow-up depends on clinical situation</i>	For patients with apparently normal cardiovascular system and age-appropriate BP <ul style="list-style-type: none"> <li>• Re-evaluation with imaging at timely occasions, e.g., at transition to adult clinic, before attempting pregnancy, or with appearance of hypertension. Girls that have only had echocardiography should undergo MR when old enough to cooperate with the procedure</li> <li>• Otherwise, imaging ~ every 5-10 years</li> </ul>
	For patients with cardiovascular pathology, treatment and monitoring determined by cardiologist

**Table 2 Screening at Diagnosis of TS in Children and Adults with TS**

<b><i>All patients:</i></b>	
	Cardiovascular evaluation by specialist*
	Renal ultrasound
	Hearing evaluation by an audiologist
	Evaluation for scoliosis/kyphosis
	Evaluation for knowledge of TS; referral to support groups
	Evaluation for growth and pubertal development
<b><i>For specific age groups (in years):</i></b>	
<i>Ages 0-4</i>	Evaluation for hip dislocation
	Eye exam by pediatric ophthalmologist (if age $\geq 1$ )
<i>Ages 4-10</i>	Thyroid function tests (T4, TSH) and celiac screen (TTG Ab)
	Educational/ psychosocial evaluations
	Orthodontic evaluation (if age $\geq 7$ )
<i>Age &gt; 10</i>	Thyroid function tests (T4, TSH) and celiac screen (TTG Ab)
	Educational and psychosocial evaluations
	Orthodontic evaluation
	Evaluation of ovarian function/estrogen replacement
	LFTs, FBG, lipids, CBC, Cr, BUN
	Bone mineral density (if age $\geq 18$ )

\*See Table 1

**Table 3 Ongoing Monitoring in TS**

<i>All ages</i>	
	Cardiological evaluation as indicated*
	Blood pressure annually
	ENT and audiology every 1-5 years
<i>Girls &lt; 5 years</i>	
	Growth rate annually
	Social skills at age 4-5 yrs
<i>School age</i>	
	Liver and thyroid screening annually
	Celiac screen every 2-5 years
	Educational and social progress annually
	Dental and orthodontic as needed
<i>Older girls and adults</i>	
	Fasting lipids and blood sugar annually
	Liver and thyroid screening annually
	Celiac screen as indicated
	Age-appropriate evaluation of pubertal development and psychosexual adjustment

\*see Table 1

**Table 4 Ovarian Hormone Replacement Treatment (HRT) in TS**

Age	Age-specific suggestions	Comments
10-11 years	Monitor for spontaneous puberty by Tanner staging and FSH level	Low dose estrogen treatment may not inhibit GH-enhanced growth in stature
12-13 years	If no spontaneous development and FSH elevated, begin low dose E2	Equivalent initial E2 doses: Depot (intramuscular) E2 0.2-0.4 mg/month, transdermal E2 6.25 mcg daily*, micronized E2 0.25 mg daily by mouth
12.5-15 years	Gradually increase E2 dose over about 2 years (e.g., 14, 25, 37, 50, 75, 100, 200 mcg daily via patch) to adult dose	Usual adult daily dose is 100-200 mcg transdermal E2, 2-4 mg micronized E2, 20 mcg EE2, 1.25-2.5 mg CEE
14-16 years	Begin cyclic progesterone treatment after 2 years of estrogen or when breakthrough bleeding occurs	Oral micronized progesterone best option at present; usual adult dose is 200 mg/d days 20-30 of monthly cycle or days 100-120 of 3 month cycle
14-30 years	Continue full doses at least until age 30 since normally estrogen levels are highest between age 15 and 30 years	Some women may prefer using oral or transdermal contraceptive for HRT Monitor endometrial thickness
30-50 years	The lowest estrogen dose providing full protection vs. osteoporosis is 0.625 CEE or equivalent	Monitor osteoporosis risk factors, diet, exercise. Obtain bone mineral density and begin regular screening mammography by age 45 yr
>50 years	Decision on estrogen use based on same considerations as for other post-menopausal women	New HRT options are appearing and these recommendations may need updating in near future

\* The lowest dose, commercially available E2 transdermal patches deliver 14 and 25 mcg daily; it is not established whether various means of dose fractionation (e.g., administering a quarter patch overnight or daily or administering whole patches for 7-10 days per month) are equivalent.

CEE- conjugated equine estrogens, E2 – estradiol, EE2 – ethinyl estradiol, FSH – follicle stimulating hormone, HRT – hormone replacement treatment