Recommendations for the Diagnosis and Management of Turner Syndrome*

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ABSTRACT

Comprehensive recommendations on the diagnosis of Turner syndrome (TS) and the care of affected individuals were published in 1994. In the light of recent advances in diagnosis and treatment of TS, an international multidisciplinary workshop was convened in March 2000, in Naples, Italy, in conjunction with the Fifth International Symposium on Turner Syndrome to update these recommendations. The present paper details the outcome from this workshop. The genetics and diagnosis of the syndrome are described, and practical treatment guidelines are presented. (*J Clin Endocrinol Metab* **86:** 3061–3069, 2001)

TURNER SYNDROME (TS) is a relatively common chromosomal disorder, caused by complete or partial X monosomy in some or all cells. TS affects approximately 1 in 2000 female live births, although it has been estimated that only about 1% of 45,X fetuses survive to term and that as many as 10% of spontaneous miscarriages have a 45,X karyotype (1, 2).

Short stature and gonadal dysgenesis are two of the characteristic clinical features of the syndrome, although many organ systems and tissues may also be affected to a lesser or greater extent. The range of morbidities associated with the syndrome can have a profound effect on quality of life, and there is a clear need for an integrated multidisciplinary approach to treatment.

Since publication of the previous recommendations for the integrated management of individuals with TS in 1994 (3), important advances have been made in diagnosis and treatment. The present paper updates the 1994 recommendations and is based on detailed discussions at an international multidisciplinary workshop held in March 2000.

Diagnostic issues

Definition. Turner syndrome (or Ullrich-Turner syndrome) may be defined as the combination of characteristic physical features and complete or partial absence of the second sex chromosome, with or without cell line mosaicism. The first criterion thus excludes some individuals without clinical features of TS who may, nonetheless, meet the cytogenetic criterion. Patients with SHOX deletions are classified as having TS if the deletion is proximal to the junction between Xp22.2 and Xp22.3 (4, 5).

Prenatal diagnosis. Most prenatally detected cases of TS are discovered incidentally during chorionic villous sampling or amniocentesis performed for unrelated reasons, the most common being advanced maternal age, which itself is not

associated with an increased incidence of TS (1, 6). Genetic counseling before any prenatal genetic/chromosomal diagnostic procedure should always include discussion of the possibility of sex chromosome aneuploidy. 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 several trisomic syndromes; the presence of a cystic hygroma makes the diagnosis of TS more likely. 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. Abnormal triple or quadruple maternal serum screening (α-fetoprotein, hCG, inhibin A, and unconjugated estriol) may also suggest the diagnosis of TS (7). Neither ultrasound nor maternal serum screening should be considered diagnostic of TS, however, and karyotype confirmation should be obligatory. Even when the prenatal diagnosis has been made by karyotype, chromosomes should be reevaluated postnatally (8).

Fetuses with a 45,X karyotype have a high probability of being spontaneously aborted. Nevertheless, a 45,X karyotype, even with ultrasound evidence of cystic hygroma, lymphedema, and effusions is not incompatible with delivery of a viable newborn. Current data indicate, however, that many fetuses diagnosed prenatally are electively aborted (6, 8, 9). It is important for physicians and counselors to recognize that studies providing genotype-phenotype correlations are subject to considerable ascertainment bias, and that the phenotype of an affected fetus may be difficult to predict (10, 11). This is particularly true in the case of mosaicism, where 45,X/46,XX and 45,X/46,XY may appear phenotypically normal. In such situations, even the likelihood of short stature or infertility is impossible to predict. Physicians and genetic counselors involved in pre- and postdiagnostic 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. Prenatal counseling involves a frank discussion of the variability of somatic anomalies, the high likelihood of short stature and ovarian failure, and their correct management. It should be emphasized that individuals with TS can be healthy, happy, and productive members of society.

Although the most common forms of mosaicism (45,X/46,XX and 45,X/46,XXiq) may modify the phenotype toward normal, the degree of mosaicism detected prenatally is not, generally, predictive of the severity of the TS phenotype (10). In general, any of the features of TS may be seen with virtually any of the common karyotypes (12). Again, it is important to recognize that published TS series are all characterized by some degree of ascertainment bias. This is particularly true for 45,X/46,XY mosaicism (mixed gonadal dysgenesis), where, contrary to reports of frequent genital abnormalities in patients diagnosed postnatally, most patients diagnosed prenatally have normal male genitalia (13). These patients should not, therefore, be assigned the diagnosis of TS, although they merit repeat karyotyping on delivery and follow-up of their gonadal development and growth postnatally.

Speaking with children and adults with TS and their families can be an important source of support for parents. It is equally important that pediatric endocrinologists, reproductive endocrinologists, geneticists, and other physicians familiar with TS should be available to provide prenatal consultation.

Postnatal diagnosis. Karyotype methods: All individuals with suspected TS (see below) should have a karyotype performed. Sufficient numbers of cells should be counted to exclude low percentage mosaicism, although it is recognized that this can never be totally excluded. 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 worth assessing.

Probing for Y chromosome material should be performed in any TS patient with evidence of virilization, or when a marker chromosome (a sex chromosomal fragment of unknown origin, *i.e.* X *vs.* Y) is found (14). This can be achieved by DNA hybridization or fluorescent *in situ* hybridization using a Y centromeric or short arm probe and may require probing of multiple tissues. Probing for the *Sry* gene may fulfill this function, but it is important to recognize that although *Sry* is associated with male gonadal differentiation, it does not appear to be the gene responsible for gonadoblastoma. Routine screening of all TS patients for *Sry* does not appear warranted.

The presence of Y chromosome material may cause the development of gonadoblastoma. The risk of this has previously been estimated as more than 30% (15, 16), although more recent data suggest a lower risk of only 7–10% (17). Even so, gonadectomy remains the procedure of choice to exclude malignancy with absolute certainty. In instances where patients or parents decide against gonadectomy, detailed vaginal sonography supplemented with color Doppler sonography of the gonads at regular intervals may be sufficient to monitor some patients with Y chromosome material.

Indications for karyotype: Clinicians should always consider the diagnosis of TS in any female patient with unexplained growth failure or pubertal delay. A karyotype to rule out TS should be considered in phenotypic females with any of the following clinical findings: in the newborn/infant: 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, and small mandible; in childhood: short stature with declining growth velocity (growth velocity <10th percentile for age), markedly elevated levels of FSH, any constellation of the TS stigmata seen in the newborn period or subsequently, or any constellation of the following: cubitus valgus, nail hypoplasia, hyperconvex uplifted nails, multiple pigmented nevi, characteristic facies, short fourth metacarpal, and high arched palate; extensive and chronic problems with otitis media; and in adolescence: absence of breast development by 13 yr of age, pubertal arrest, or primary or secondary amenorrhea with elevated levels of FSH; and unexplained short stature.

Pediatric management

As described for adults (see later), a multidisciplinary approach to treatment is important to improve the quality of life of girls with TS.

Cardiac evaluation and management. A congenital heart defect (CHD) occurs in approximately 30% of patients with TS (18–21). Of those with a CHD, left-sided obstructive defects predominate, especially bicuspid aortic valve (BAV; 30–50%) and coarctation of the aorta (COA) (30%). Aortic root dilation is uncommon (~5%), but potentially devastating if rupture occurs. It is usually associated with a risk factor such as BAV, COA, or hypertension (19–21).

At the time of diagnosis, all individuals, regardless of age, should have a cardiac evaluation, including a complete physical examination and an echocardiogram. A cardiologist skilled in the assessment of congenital heart disease should interpret the echocardiogram. Patients who have had a prenatal echocardiogram that did not reveal a CHD should be examined postnatally to ensure that BAV or COA is not present. Blood pressure should be monitored at least annually in all patients with TS.

If a cardiovascular malformation is present, the patient should be followed by a cardiologist in collaboration with the primary physician. Patients with a structural CHD will require antibiotic prophylaxis for subacute bacterial endocarditis before dental work and any other contaminating procedure. Monitoring for aortic root dilation should be guided by the type and severity of the underlying cardiac problem. Thus, patients with risk factors for aortic root dilation, such as BAV, COA, aortic stenosis without BAV, aortic regurgitation, or hypertension, will require closer examination. In TS, as in the general population, patients with BAV require investigation of the aortic root (22).

If the initial cardiac evaluation from childhood does not show CHD, a repeat cardiovascular physical examination and echocardiogram, with particular attention paid to the aortic root, should be conducted at some time during adolescence (12–15 yr of age). Although the vast majority of TS patients with aortic root dilation have an underlying risk factor, a small vulnerable minority do not (20, 23, 24). In view of the limited information available in this regard, it is unclear whether more frequent echocardiography is warranted in patients without CHD (20, 21). In any case, echocardiograms should not be ordered in isolation, but should be conducted in concert with a physical examination of the patient. Recognizing that TS patients with 45,X and neck webbing are at greater risk of having COA (21, 25, 26) and that the detection of COA in the newborn can be challenging, subsequent reevaluation with ongoing monitoring of upper and lower extremity blood pressure and pulses should be performed.

If aortic root enlargement is detected, the cardiologist should obtain subsequent echocardiograms based on the severity of the dilation present. When the echocardiographic image is poor, computed tomography or magnetic resonance imaging can usually provide superior images. However, the two imaging modalities may not be directly comparable because of technical differences between the two, including edge detection, angle dependence, and operator-dependent variability. Such differences should be considered when deciding whether there has been a significant increase in the aortic root diameter. Blood pressure should be monitored carefully in patients with aortic root dilation. At present, data are inadequate to recommend routine prophylaxis with β-blocking drugs, although this therapy may be appropriate for those with significant aortic root dilation, as it is in Marfan syndrome.

Evaluation of renal anatomy. Congenital malformations of the urinary system are present in up to 30% of patients with TS. Rotational abnormalities and double collecting systems are found most frequently. Although many of these abnormalities do not have clinical significance, some may result in an increased risk of hypertension, urinary tract infections, or hydronephrosis (26). Therefore, all individuals with TS should have a renal ultrasound study performed at the time of diagnosis. If abnormalities are detected, further evaluations should be performed, and the appropriate therapy instituted. Additionally, in such individuals, ultrasound and urine cultures should be performed every 3–5 yr.

Blood pressure. Hypertension is common in TS, even in the absence of cardiac or renal malformations (26). Blood pressure should therefore be monitored at each physical examination.

Thyroid function. Between 10–30% of individuals with TS develop primary hypothyroidism, generally associated with antithyroid antibodies (27). Often, there are no overt clinical symptoms. Levels of TSH and total or free T_4 should therefore be measured at the time of diagnosis and at intervals of 1–2 yr thereafter.

Hearing. Conductive and sensorineural hearing loss are common in girls with TS (28). The outer, middle, and inner ear are all affected, and hearing problems and ear malformations correlate with the karyotype (29).

Outer ear. Mild malformation of the outer ear and low set ears occur in 30–50% of individuals with TS.

Middle ear. Otitis media is extremely common in girls with TS and may progress to mastoiditis and/or cholesteatoma formation. It occurs particularly between 1 and 6 yr of age, with a maximum incidence (>60%) at 3 yr of age. The cause is still unknown, but growth retardation of the temporal bone may be important. Aggressive treatment of otitis media is appropriate, and insertion of ventilation tubes should be considered. Careful follow-up is important. Patients with chronic middle ear problems should be operated on without delay to prevent sequelae. Short girls with extensive otitis media problems should be referred to an endocrinologist if TS has not previously been diagnosed.

Inner ear. The majority (50–90%) of women with TS have sensorineural hearing loss, manifest by a sensorineural dip in the 1.5–2 kHz region, sensorineural high frequency loss, or all of these. The sensorineural dip can occur as early as 6 yr of age and occasionally leads to hearing impairment during childhood. The condition is progressive, however, and commonly leads to hearing problems in later life, which may have serious social consequences.

Speech. Girls with TS often have speech problems (30). If speech problems occur, referral to an ear, nose, and throat clinic and a speech therapist is recommended.

Vision. Strabismus, amblyopia, and ptosis are common in TS (1). Ophthalmological evaluation should be part of the regular physical examination, with referral when appropriate.

Orthopedic evaluation. Infants with TS have an increased risk of congenital hip dislocation, which may be associated with degenerative arthritis of the hips in older women. Approximately 10% of girls with TS develop scoliosis, most commonly during adolescence (1, 31). Evaluation for orthopedic problems should be part of the regular physical examination, with referral when appropriate.

Orthodontic examination. The small and retrognathic mandible may contribute to malocclusion and other dental abnormalities. An orthodontic examination should therefore be undertaken at 8–10 yr of age.

Weight. Girls and women with TS have a predisposition to obesity, which may be exaggerated in appearance by the characteristic shield-like chest, stocky build, and short stature with relatively short legs (1, 32). Individuals should be evaluated regularly, with appropriate counseling to avoid obesity.

Lymphedema. Although most common in infants, lymphedema may occur or reoccur at any age, and may be associated with the initiation of therapy with GH or estrogen. Edema can usually be controlled with support stockings and/or diuretics. Vascular surgery may be necessary in some patients, but should be avoided unless absolutely required, as there are no clear efficacy data.

Glucose intolerance. Although there may be an increased risk of glucose intolerance, frank diabetes is rare in children with TS. Routine glucose tolerance tests are not necessary. Use of oxandrolone for growth promotion may be associated with subclinical insulin resistance (33, 34).

Plastic surgery. The risk of keloid formation in TS is high. Elective surgery (*e.g.* for webbed neck or prominent ears) should be employed judiciously. This also applies to simple procedures, such as ear piercing (35).

Management of short stature

Surveys over the last 30 yr have indicated that short stature affects at least 95% of all individuals with TS. Although this figure undoubtedly reflects some element of ascertainment bias, short stature is probably the most common, readily recognizable clinical feature of TS (36).

Short stature in TS is characterized by mild intrauterine growth retardation, slow growth during infancy, delayed onset of the childhood component of growth, and growth failure during childhood and adolescence without a pubertal growth spurt. This growth failure leads to a reduced final height (37–39), which is approximately 20 cm below the female average of the corresponding ethnic group.

Management of growth failure impacts on many other aspects of the care of individuals with TS, including estrogen replacement, socialization, and academic achievement.

Recommendations. All girls with short stature (less than the third percentile or below −2 sd on female growth curves),

even those below 2 yr of age, should have a karyotype performed if there are any features of TS present (see section on indications for karyotyping). Those who are more than 2.5 sd below the female growth curve should have a karyotype performed regardless of the presence or absence of clinical features of TS. Although peripheral blood karyotypes are usually adequate, where there is strong consideration of the diagnosis of TS on clinical grounds, fibroblast studies may be indicated in the event of a normal blood karyotype.

Heights of girls with TS should be plotted on TS-specific growth curves. Where possible, these should be specific to ethnic groups and/or nationalities (40–42).

Provocative GH testing should only be performed in girls with TS whose growth is clearly abnormal relative to that expected for TS. There is no clinical rationale for testing girls with TS whose growth is consistent with the expected pattern.

The advantages and disadvantages of GH therapy and/or anabolic steroid treatment should be discussed with the patient's family. Where appropriate, the child herself should be involved in these discussions and decisions.

From numerous studies over the previous 15 yr, it is clear that GH, with or without anabolic steroids, can accelerate growth in girls with TS. This has led to regulatory approval for the use of GH to treat the short stature of TS in many countries worldwide. Recent studies have now shown that this accelerated growth is reflected in an increase in final height. These studies have indicated that with early diagnosis and initiation of GH treatment, final height can be improved in most patients with TS and normalized in some (43–46). Thus, a final height of 150 cm is now an achievable goal for most patients. The critical factors appear to be GH dosage and the number of years of GH treatment before estrogenization.

There is also evidence from these studies that doses higher than that currently recommended for TS (0.05 mg/kg·day; 0.15 IU/kg·day) produce a greater gain in final height with no apparent increase in adverse events. It should be noted, however, that the long-term consequences of sustained supraphysiological concentrations of insulin-like growth factor I are currently unknown.

Individualized dosing should be considered, with the dose adapted according to the patient's growth response. The development of growth prediction models may help in this respect (47, 48).

Initiation of GH therapy should be considered as soon as a patient with TS has dropped below the fifth percentile of the normal female growth curve. Therapy may be started as early as 2 yr of age, although there is presently only limited experience of treating children of this age. GH therapy should be directed by a pediatric endocrinologist.

For girls below 9–12 yr of age, therapy can be started with GH alone. The recommended starting dose is 0.05 mg/kg·day (0.15 IU/kg·day). Growth should be monitored at intervals of 3–6 months, and individualization of dosing should be considered if the response to GH is not adequate.

In older girls (>9–12 yr of age) or in girls above 8 yr of age in whom therapy is started when the individual is already far below the fifth percentile of the normal growth curve, consideration should be given to the administration

of a nonaromatizable steroid, such as oxandrolone, in addition to GH. These agents should not be used alone for the promotion of growth. Excess anabolic steroids will result in virilization and overly rapid skeletal maturation and should be avoided (49).

Oxandrolone appears to be particularly suited for the promotion of growth, as, uniquely for anabolic steroids, it is not aromatized into substances with estrogenic properties (it is now recognized that estrogen is responsible for completion of epiphyseal fusion, leading to cessation of growth). Oxandrolone should not be used at doses above 0.05 mg/kg·day and should not be given to girls with TS under 8 yr of age. Girls given oxandrolone should be monitored for potential side-effects, particularly clitoral enlargement, virilization, and glucose intolerance.

Therapy may be continued until a satisfactory height has been attained or until the bone age is above 14 yr and the patient's height has increased by less than 2.0 cm over the previous year.

Estrogen, used for induction of puberty, induces fusion of the epiphyses and is the limiting factor for longitudinal bone growth. Current data indicate that there is no role for estrogen as a growth-promoting agent.

The initiation of estrogen therapy should be timed so as to minimize any negative effect on growth and adult height while inducing puberty at an approximately normal age. This highlights the need for early initiation of GH therapy.

An alternative approach for correction of short stature in girls with TS is orthopedic leg lengthening. Experience with this procedure in TS is still limited, and there are conflicting reports on the physical and emotional effects of such therapy.

Management of puberty

Sexual infantilism is one of the most common clinical findings in girls with TS. Over 90% have gonadal failure. It is important to remember, however, that up to 30% of girls with TS will undergo spontaneous pubertal development, and 2–5% will have spontaneous menses and may have the potential to achieve pregnancy without medical intervention (50–52). Pubertal development may be delayed and, in most patients, is followed by progressive ovarian failure (53).

When estrogen therapy is required to induce pubertal development, the dosing and timing should be aimed at mimicking normal pubertal development, taking account of the individual's desire to begin puberty and also of the family history of age at onset of puberty. Doses should be adjusted to the response of individual patients, which may be monitored in terms of the development of secondary sex characteristics, bone maturation, or uterine volume.

Estrogen therapy should be coordinated with the use of GH. This should be individualized for each patient so as to optimize both growth and pubertal development. When growth promotion is a priority, consideration should be given to delaying estrogen therapy to avoid compromising final height (54).

Recommendations. Before initiation of estrogen therapy, serum gonadotropin levels should be determined to exclude the possibility of delayed spontaneous pubertal development (50, 55). If gonadotropin levels are normal, a sono-

graphic examination should be undertaken to determine the status of the gonads.

Hormonal induction of feminization should be initiated and carried out in a manner that simulates the normal growth and development of secondary sex characteristics as closely as possible (56).

Estrogen therapy needs to be initiated and adjusted according to the needs and priorities of the individual with TS. Thus, if growth promotion is a priority, estrogen therapy should not be initiated before 12 yr of age unless height has already been maximized. Estrogen therapy should ideally be started by 15 yr of age (57).

Estrogen therapy should be initiated at a low dose (one sixth to one quarter of the adult dose) and increased gradually (at intervals of 3–6 months). Doses can then be adjusted to the response (Tanner stage, bone age, or uterine growth), with the aim of completing feminization gradually over a period of 2–3 yr.

A progestin, such as medroxyprogesterone, should be added either when vaginal bleeding first occurs or after 12–24 months of estrogen therapy to establish monthly menstrual cycles.

Routine counseling for the prevention of sexually transmitted diseases should be provided to all individuals with TS, as with any other adolescent.

Individuals with TS who have functioning ovaries and progress through puberty spontaneously should receive contraceptive and genetic counseling (58). However, ovulatory function should be documented (FSH and LH measurements), as a perimenopausal pattern of anovulation can lead to endometrial hyperplasia (50).

Adult management

Adult medical follow-up and estrogen replacement therapy. Adult women with TS require careful medical follow-up. Early medical intervention and prophylaxis may decrease morbidity and mortality and improve the quality of life of women with TS.

Recommendations. The transition from pediatric to adult healthcare supervision of women with TS should occur at the completion of puberty, usually by 18 yr of age. Ideally, the process of transition should take place over a period of 2–3 yr during the late pubertal period and should involve a gynecologist with expertise in fertility problems. Physicians familiar with the natural history and unique problems associated with TS should be responsible for organizing adult care. The need for a multidisciplinary approach to the care of both girls and women with TS may require referral to a tertiary center. Such tertiary centers should develop teams with the appropriate experience and expertise in treating patients with TS. These teams may include some of the following: clinical nurse specialist; endocrinologist; cardiologist; nephrologist; fertility specialist; audiological physician; ear, nose, and throat surgeon; plastic surgeon; dentist; and psychologist. In addition, the agenda for such a specialist service should be developed in partnership between medical professionals and Turner support groups.

Adult women with TS should undergo a comprehensive

medical evaluation due to the increased risk of a number of common diseases (59). All medical problems present during childhood should be followed in adults (*e.g.* CHD, hearing loss, skeletal problems, and dental and ophthalmological abnormalities). 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 15% of adults with TS experience significant hearing loss, which may be conductive and/or sensorineural (60). The sensorineural hearing loss, which is present in 50–90% of patients, consists of a sensorineural dip in the 1.5–2 kHz region and/or sensorineural high frequency loss. The hearing loss is progressive, but tends to occur rapidly after about 35 yr of age, leading to early aging with presbyacusis (61). Hearing aids are frequently necessary. If only a sensorineural dip is present, follow-up should occur every 3–5 yr. Otological follow-up assessments should be conducted every 10 yr in patients who do not have hearing problems and whose karyotype is a low risk indicator for otitis media or a sensorineural dip [*i.e.* 45,X or 46X,I(Xq)].

Many of the problems of adult life in patients with TS are compounded by obesity (62, 63), partly due to low physical fitness (64). 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^2 and a waist/hip ratio less than 0.80.

Laboratory testing of women with TS should be carried out at 2-yr intervals and include measurements of hemoglobin, renal function (creatinine and blood urea nitrogen), fasting blood glucose (59, 65), lipid profile (66), liver enzymes (64, 67), TSH, and total or free T$_4$ (27).

Liver enzymes, especially γ-glutamyl transferase, alanine amino transferase, aspartate transaminase, and alkaline phosphatase, are commonly raised in women with TS, but their relationship to chronic liver disease is unknown (64, 67). Liver enzymes should be monitored, but with current information, further investigation of liver pathology, such as by viral or autoantibody screens, imaging, or biopsy, is not warranted. Therapy with 17β-estradiol improves, rather than exacerbates, raised liver enzymes (64).

Individuals with known renal collecting system anomalies may require more frequent screening for urinary tract infections.

There is an increased incidence of all fractures in patients with TS over the age of 45 yr. Measurements of bone mineral density should therefore be performed at the initial visit in adults with TS and 3–5 yr later (59, 68). If there is no change, further measurements can be made at less frequent intervals. If there is a significant deterioration in bone mass, current standards of practice for the treatment of osteoporosis should be instituted. An oral calcium intake of at least 1.2 g/day should be recommended, as should weight-bearing exercise.

Recommendations for breast evaluation, self-examination, and mammography do not differ from those for the general population.

All patients with TS, regardless of age, CHD, or aortic root dilation, should receive cardiovascular monitoring. Patients and physicians should be aware that chest pain may be the initial symptom of aortic root dissection and may not always represent pulmonary or gastrointestinal pathology. If aortic root dilation was not present during adolescence, echocardiograms should be repeated approximately every 5 yr throughout adult life, although this schedule should be adjusted for individual circumstances. As the quality of echocardiographic images may be inadequate in individuals with certain body habituses, computed tomography or magnetic resonance imaging may be more suitable in adult patients.

Careful monitoring under the guidance of a cardiologist is advised before and during spontaneous or assisted pregnancy, as at least two instances of aortic rupture have been reported during pregnancy/delivery (69, 70). The preconceptional aortic root dimension should be obtained as a baseline measurement. Although data are not available specifically for patients with TS, age is a risk factor for aortic root enlargement in the general population and in individuals with Marfan syndrome (71). It is therefore reasonable to recommend that childbearing in women with TS should be completed early.

Hypertension is more common in patients with TS than in the general population. Blood pressure should therefore be monitored routinely and hypertension treated vigorously with reference to age-specific normal ranges (59, 63, 65).

Dyslipidemia should be treated with specific lipid-lowering drugs (66).

Individuals with TS who are contemplating any surgical procedure should be appraised of the increased risk of keloid formation, and the surgeon should take appropriate precautions.

There is a growing body of evidence that in the general population of women, estrogen with or without progesterone replacement therapy may be beneficial beyond the usual age of menopause. This concept probably also applies to women with TS, although similar data in this patient group are currently not available.

It is recommended that women with TS receive cyclical estrogen and progestin. The type and dose should be individualized, using symptoms, physical findings and bone density studies. Sufficient estrogen should be prescribed to prevent the symptoms, signs, and sequelae of estrogen deficiency. Most adult women with TS will require at least the equivalent of 2 mg 17β-estradiol daily. As with other women receiving estrogen replacement therapy, pelvic ultrasonography and endometrial biopsy should be considered when abnormal menstrual bleeding occurs. Androgen concentrations are reduced in many women with TS (72), and androgen substitution therapy may be of value in some instances.

As with adolescents, education on issues of sexuality and sexually transmitted diseases should be available as part of a healthcare program for women with TS. If issues of sexuality are identified, referral to the appropriate health professional or therapist should be considered.

Fertility and family planning issues

Although a few patients with TS are able to achieve spontaneous pregnancy, most are infertile. Various assisted reproductive techniques are now available for achieving preg-

nancy. Before contemplating pregnancy, either spontaneous or assisted, individuals with TS should undergo a complete medical evaluation. Particular attention should be paid to the renal and cardiovascular systems, and thyroid status and glucose tolerance should be determined. All pregnancies should be followed by a multidisciplinary team, including perinatologists, 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 counseling on the following issues: timing of pregnancies: due to the risk of premature ovarian failure, pregnancies should not be postponed without good reason; 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. Special attention should be given to appropriate preparation of the uterus. This requires adequate hormone replacement therapy for 3–4 months before oocyte or embryo transfer, to increase the size of and improve the blood flow in the uterus. Optimally, the thickness of the endometrium should be 7 mm. If this is not achieved using conventional hormone replacement therapy with daily estradiol and progesterone for 12 days in each cycle, the dose of estradiol should be increased. 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. Cesarian section, however, is often employed because of a narrow pelvis. Counseling should be given to both anonymous and known donors.

Cryopreservation of ovarian tissue and immature oocytes. The possibility of using cryopreserved ovarian tissue and immature oocytes, obtained before regression of the ovaries occurs in early childhood, is currently under intensive investigation. Although only a research tool at present, this technique may provide the possibility of pregnancy with the patient's own oocytes.

Psychological and educational issues

Psychosexual development. Studies of psychological development have consistently documented that girls with TS have a typically female pattern of development, with unambiguous female gender identification (73). The scant data available indicate that heterosexual romantic fantasies are common, but that dating and initiation of sexual activities may be somewhat delayed or infrequent (74–76). It is not clear whether this reflects some underlying genetic or hormonal influence on behavior or simply discomfort, given the issues of short stature, physical anomalies, and infertility with which women with TS have to cope.

Personality and social adjustment. Early research reported evidence of a similarity in personality style among women with TS, characterized by limited emotional arousal, high tolerance for adversity, unassertiveness, and overcompliance (75, 77). Subsequent research found that women with TS and those with a normal karyotype but short stature and primary amenorrhea were both less likely than control women to live independently, be married, or be sexually active. This was despite similar achievements in terms of educational attainment and employment status. Thus, short stature and delayed sexual development appear to be key factors influencing psychosocial development independently of the sex chromosome anomaly.

Adjustment problems in the areas of immaturity, difficulties in the ability to concentrate, and increased activity levels have been documented in young girls with TS (78, 79). For adolescent girls, immaturity and anxiety appear to be the central issues. Girls with TS have been found to have more problems in school and with peer relationships than short girls without TS (78).

Cognitive and academic performance. No increase in the prevalence of mental retardation is associated with TS, except for those few patients with a small ring X chromosome that fails to undergo X inactivation (80). Numerous studies have documented, however, that some individuals with TS have selective impairment in nonverbal, visual-spatial processing and as a group score lower on the performance than on the verbal subsection of standardized intelligence tests (81). The specific neuropsychological deficits that may affect adaptation include four interacting areas of functioning: visual-spatial organization deficits (*e.g.* difficulty in driving), defects in social cognition (*e.g.* failure to appreciate subtle social cues), problems with nonverbal problem solving (*e.g.* mathematics), and psychomotor deficits (*e.g.* clumsiness) (79, 82). It is possible that some of these neuropsychological deficits may be improved by estrogen therapy (83, 84).

Recommendations. Significant psychological risks are associated with TS, including social, behavioral, and educational components. The factors that affect the quality of life of individuals with TS are the same as those that affect the rest of society. Thus, psychological care should be provided within the context of helping to prevent difficulties and normalize the developmental process rather than operating from an illness model. Plans for both medical and psychological intervention should be developed so as to reinforce and support the individual's self-esteem and to ensure that individuals with TS remain in the mainstream of social, educational, and employment activities. Many of these issues are discussed in patient-oriented material available through the Turner's Syndrome Society of the United States (www.turner-syndrome-us.org); similar websites exist for other national TS organizations.

Increased attention should be given to career and vocational planning and preparation for transition to living independently. Patients with TS and their parents need to be well informed about the learning problems associated with TS, as most individuals are affected by these difficulties, if only to a mild degree. They need to understand that, even with intervention, learning difficulties do not disappear with age, but persist throughout adult life. 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.

Particular attention should be paid to sex education and orientation to adult sexuality. Because they mature more slowly than their peers, girls with TS may not be ready for or interested in sex education when it is given at school. They may also be more self-conscious in relation to beginning a sexual relationship because of being different. Adult women with TS appear to enter sexual relationships at a later age than their peers and to be less likely to develop a sexual relationship during adult life. More attention to sex education and sex therapy may be necessary to address this area. Information about assisted reproductive techniques should also be provided. Turner syndrome societies exist in the United States (www.turner-syndrome-us.org) and in many countries. They provide an invaluable service in patient and parent education.

Acknowledgment

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