



## *New Issues in the Diagnosis and Management of Turner Syndrome*

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**Key Words.** X-chromosome, congenital heart defect, prenatal diagnosis, ovarian failure, short stature

### **Introduction**

Turner syndrome (TS) occurs in phenotypic females missing all or part of one sex chromosome, with the most common karyotypes as follows: 45,X; 45,X/46XX or XY mosaics; 46,XiXq; 46,XdelXp; 46,XrX; and many of these latter groups have a 45,X cell line as well. It is one of the more common chromosomal disorders and certainly the most common genetic disorder of females, estimated to occur in approximately 1/2000–5000 live female births [1–4]. Our view of TS is evolving as prenatal screening and more sensitive postnatal diagnoses reveal a broad phenotypic spectrum with less severely affected individuals compared with early surveys based on clinically obvious cases. Nonetheless, the most constant features of TS remain short stature and early ovarian failure [5,6]. While a small number patients with ring or marker X-chromosomes interrupting the X-inactivation center may have mental retardation [7,8], the majority of girls and women with TS have normal intelligence [9]. Congenital cardiovascular defects are found in approximately 50% of girls with TS, but clinically severe defects requiring surgical correction affect only 10–15% [5,6]. The increased risk for aortic dissection is probably the most serious medical problem facing girls and women with TS [10] although many adults experience ovarian failure as their major disability [11].

### **Genotype and phenotype**

TS is the only chromosomal monosomy compatible with life. Indeed, given that one sex chromosome is inactivated in normal females, one might expect little in the way of phenotype in 45, X patients. However, a significant number of X-chromosome genes escape inactivation [12]. These include genes localized in discrete pseudoautosomal regions of the X-chromosome which have Y-alleles and are normally expressed biallelically in both sexes. The

only pseudoautosomal gene identified in the TS phenotype to date is *SHOX*, which encodes a homeobox transcription factor involved in skeletogenesis [13,14]. It is likely that haploinsufficiency for other—as yet unknown—pseudoautosomal genes may cause impaired lymphatic and cardiovascular development and sensorineural deafness found in TS as well. Many non-pseudoautosomal, X-linked genes also escape inactivation [12] and may contribute to some of the physiological differences between normal men and women, e.g., lipids and blood pressure that are both higher in men than women and higher in TS compared with age- and ovarian failure-matched 46,XX controls [15]. Another potential mechanism contributing to the TS phenotype is epigenetic in nature, i.e., genomic or parental imprinting of X-linked genes. Normal females are mosaic for maternally- and paternally-derived X-chromosomes, while men are monosomic for  $X^{\text{mat}}$ . Hence, a gene selectively expressed from  $X^{\text{pat}}$  might, as a matter of speculation, contribute to lowering lipids in normal women, and also explain the higher lipids seen in TS, the majority being monosomic for  $X^{\text{mat}}$ .

### **The diagnosis of TS**

The diagnosis of TS specifies a female phenotype and clinical features of TS, most commonly short stature and ovarian failure, associated with a cell line with only a single normal X chromosome. The other sex chromosome is either missing altogether or is structurally abnormal. Mosaicism for a normal 46,XX or XY cell line is common in predominantly 45,X individuals, reflecting the loss of a sex chromosome during an early embryonic mitotic division. Mosaicism for a 45,X cell line is often seen in predominantly 46,XiXq or 46,XrX individuals, reflecting the loss of the abnormal X chromosome in proliferating

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cell populations. There is no specific cut off level for percent of abnormal cells in the karyotype required for the diagnosis, because although apparently 'pure' 45,X individuals are typically more severely affected, there are many patients with features of TS that have a relatively small percent of abnormal cells in routine 20, or even 50-lymphocyte karyotypes. In such cases, karyotypes done on skin and/or buccal cells usually provide a more monosomic picture. Girls that have a Y-chromosome cell line, or marker chromosome shown by molecular cytogenetics to represent a Y-chromosome fragment, are at risk of developing a gonadoblastoma [16,17]. The risk in recent studies is between 5–30%. The 'tumor' in most of the recent cases has been a histological finding without clinically apparent expression, and the risk for progression of an in situ lesion to a clinically significant tumor is unknown. Nevertheless, the accepted practice is to recommend prophylactic gonadectomy in such cases [18,19]. From the clinician's point of view, the laparoscopic procedure seems safe, the gonads in these individuals appear to be functionless, and potentially a source of morbidity, hence gonadectomy seems a very rational approach. However, some girls and parents find this a very upsetting prospect. The information that a female harbors a Y-chromosome may be quite difficult to process for patients and families, raising questions of gender identity superimposed on the often devastating diagnosis of infertility. The prospect of gonadectomy, or castration, may bring additional psychic trauma. In the absence of clinical signs of a tumor, e.g., a tumor seen on pelvic ultrasound, or evidence of excessive sex steroid production, it seems prudent not to rush the surgery, and to allow enough time for patients and families to fully understand the diagnosis and its implications, and to provide genetic and/or psychological counseling to help them in this process.

#### **Ascertainment patterns in TS**

We obtained information on the source(s) of diagnosis for 194 individuals participating in the NICHD TS natural history study between 2001–2005 (Table 1). Approximately 3% were diagnosed prenatally, ~20% at birth because of lymphedema with or without congenital heart defects, ~43% during childhood because of short stature or learning or hearing difficulties, ~30% during adolescence because of pubertal delay and/or short stature, and 3% after the age of 18 yrs usually because of secondary amenorrhea/infertility. The average age of these participants was 27 years, and we would expect the prevalence or prenatal diagnoses to be higher in a younger population, as for example ~14% in a recent study of toddlers [20] reflecting the increasing use of routine prenatal screening in recent years. As incidentally diagnosed girls form an increasing proportion of the TS cohort we will expect the typical phe-

**Table 1.** Circumstances of TS diagnosis-NIH 2005

Stage at diagnosis	N (%)
Prenatal	7 (3.6)
Birth	36 (18.6)
Childhood	
Short stature	82 (42)
Hearing/learning	3 (1.5)
Adolescent	
Short stature	25 (13)
1° amenorrhea	31 (16)
Adult-2° amenorrhea	7 (3.6)

Data for 194 girls and women aged 7 to 62 yrs with TS participating in the NICHD study between 2001–2005. All study subjects had >70% 45,X or structurally abnormal X-chromosomes on a 50-cell karyotype.

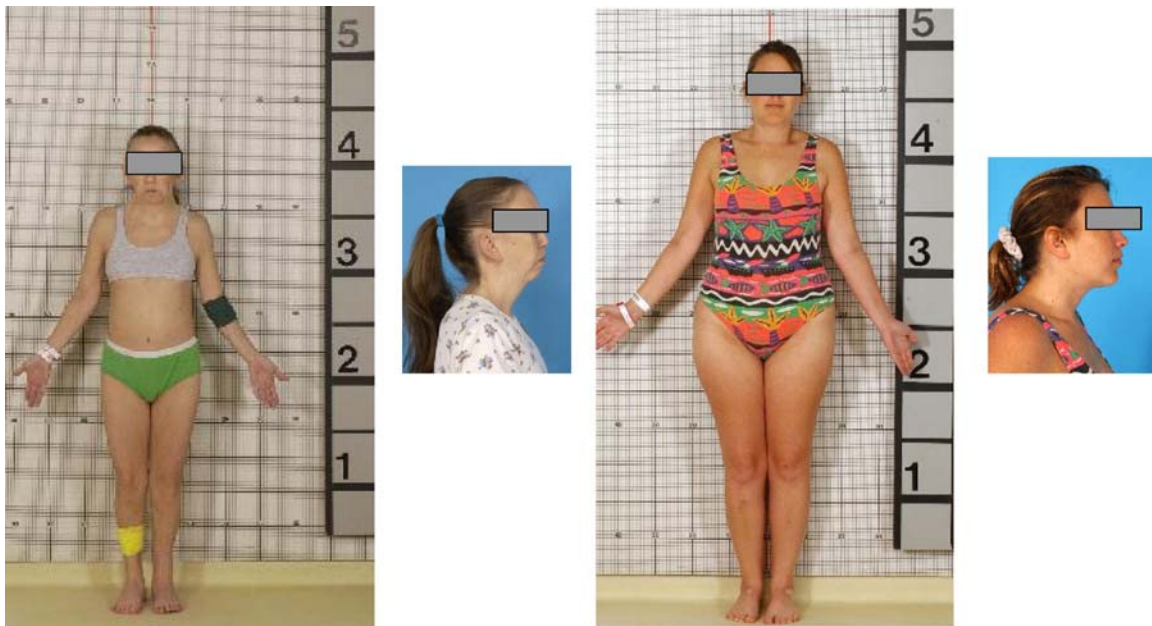
All the prenatal diagnoses were incidental to advanced maternal age screening.

notype to moderate. The average age of diagnosis appears to be decreasing. A recent study from Belgium reports the average age of diagnosis in 2003 at 6.6 yrs, compared with 11.2 in 1991 [21]. This reduction in the age of diagnosis reflects both a contribution from increased prenatal genetic screening, and the heightened awareness of short stature related to the promotion of growth hormone use.

In addition to the trend toward earlier diagnosis, increasing numbers of individuals are diagnosed as adults on the basis of reproductive failure, reflecting greater sophistication of reproductive endocrinology and more widespread availability of genetic testing. To illustrate this phenomenon, and underscore the broad spectrum in TS phenotype, Figure 1 compares two women with TS, both 'pure' 45,X based on a 50 lymphocyte karyotype. Both were 32 yrs old at the time of evaluation, and the differences in phenotype are striking. The woman at the left of the figure was diagnosed at birth because of lymphedema, and had aortic coarctation that was surgically repaired, and a bicuspid aortic valve. She did not receive growth hormone (GH) but was treated with estrogen. The normal-appearing woman on the right of the figure is short for her family, but not for population norms, so it is not surprising that she was not picked out for short stature. She had a normal pubertal development, went on oral contraceptive from age 18 until age 30, when she married and came off the pill to attempt pregnancy.

#### **The significance of prenatal diagnosis**

As prenatal screening with ultrasound and cytogenetic testing becomes more commonplace, there will be increasing numbers of parents needing to know the significance of a prenatal diagnosis of TS. It is difficult, however, to acquire reliable quantitative data on predictive value of such tests with regard to clinical outcome. The most common situation is the finding of cystic hygroma, fetal hydrops



**Fig. 1.** Variability in the 45,X phenotype. Both women are 32 years old and both are monosomic for a single normal X-chromosome based on a 50-cell, lymphocyte karyotype. The woman on the left was diagnosed at birth because of clinically obvious lymphedema and coarctation of the aorta. The woman on the right was diagnosed at age 31 due to secondary amenorrhea and infertility. Although 5'1" in height, she is actually short for her family.

or increased nuchal translucency on a routine screening ultrasound, prompting cytogenetic testing and the diagnosis of TS. While there have been no large-scale studies of the outcome of such pregnancies, available data suggest it is very poor [22–24]. Approximately 20% of these gestations turn out to have a 45,X karyotype, and survival to term is less than 10% with a very high rate of spontaneous miscarriage. Another situation is increasingly common, and presents greater difficulty in predicting outcome and counseling parents. Many women are now undergoing cytogenetic screening on the grounds of advanced maternal age, without evidence of fetal abnormality on ultrasound. Data from several European countries with cytogenetic registries suggest that the great majority of TS cases are electively terminated [25–27], and so ability to assess clinical outcome is limited. Some early data which examined both abortuses and live births found that the great majority of 45,X/46,XY mosaic gestations resulted in phenotypically normal males [28,29]. A review of Danish registry cytogenetic data reported that as many as 1/250 (chorionic villous sampling) or 1/500 (amniocentesis) pregnancies of older mothers were diagnosed as TS [3]. Of those cytogenetically diagnosed TS gestations that were allowed to come to term, 83% resulted in live-births, with 30% of these children appearing normal and having normal karyotypes on repeat tests postnatally [3]. These findings indicated a high rate of false positives and rather poor predictive value for routine prenatal cytogenetic testing [3]. A recent report from a U.S. cytogenetic laboratory reviewed

104 cases where a 45,X or 45,X/mosaic karyotype was determined [30]. Of the 6 cases diagnosed as 'pure' 45,X with normal fetal ultrasounds, one pregnancy was electively terminated and another lost to follow-up, but 4 were live born—one with signs of TS, and 3 apparently normal boys [30]. Although the number of observations is small, available data suggest that prenatal cytogenetic diagnosis of TS in the absence of abnormal fetal ultrasound has a high false positive rate and seems to be a poor predictor of clinical outcome.

Another way of assessing the significance of incidental prenatal diagnoses of TS is to compare the clinical phenotype of girls 'incidentally' diagnosed during routine prenatal screening versus those diagnosed on traditional clinical grounds after birth. Koeberl et al. found that girls diagnosed with 45,X/46,XX mosaicism during evaluation of advanced maternal age had few typical TS features compared with girls with similar karyotypes diagnosed on clinical grounds postnatally [31]. Gunther et al. found that girls with an incidental prenatal diagnosis (12/88 girls participating in growth study) had significantly fewer features of TS compared to those who were traditionally diagnosed, supporting the view that there is a distinct ascertainment bias in our traditional portrayal of TS [20]. Clearly more data are needed for both predictive value of prenatal screening tests and for clinical long-term outcome for incidental prenatal diagnoses. However, currently available data do not support the apparently very pessimistic views reflected in termination rates of 75–100%.

### **Medical screening at diagnosis**

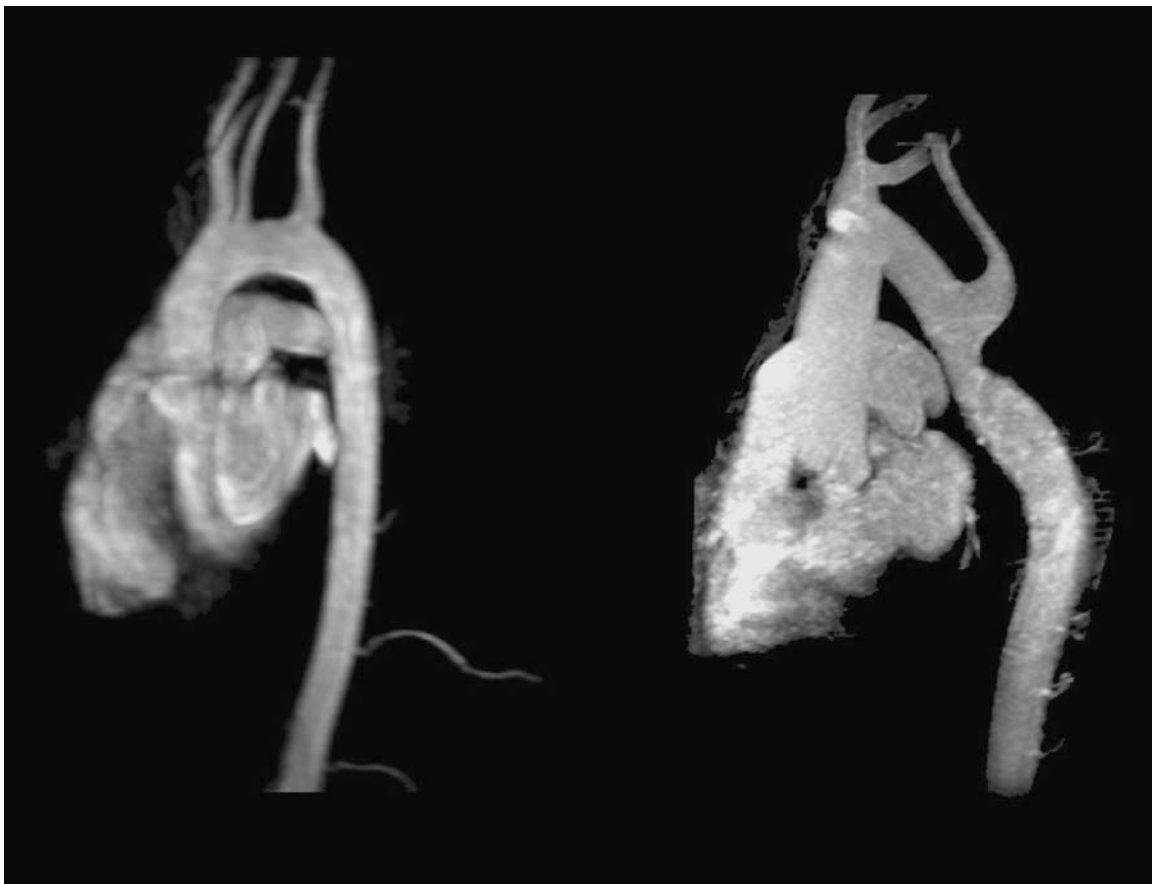
At the time of diagnosis, no matter the age, all individuals with TS need to have a comprehensive screening evaluation. Current guidelines have been summarized in previous publications [19,32]. In brief, screening potential problems in newly diagnosed TS patients starts with a comprehensive cardiac examination with echocardiogram or magnetic resonance imaging of the heart and aorta (see below). In addition, renal ultrasound; hypertension screening ideally with ambulatory monitoring; clinical and lab evaluation of thyroid and liver function; ear, nose and throat exam with audiology testing, and for children, bone age and growth evaluation.

### **Cardiac evaluation in TS**

While some defects that compromise circulatory system function are clinically evident, many of the congenital defects in TS, such as bicuspid aortic valve, may be clinically silent and difficult to detect with routine echocardiogram. In our experience of over 200 patients, we were unable to obtain adequate visualization of the aortic valve to al-

low determination of valve structure in ~30%, and our echocardiographic determination was at odds with the patient's prior test at least one third of cases. Other investigators studying TS have similar experience. Since the presence of a bicuspid valve requires antibiotic prophylaxis as well as closer monitoring as a risk factor for aortic dissection, an accurate determination of the aortic valve status is very important, and routine cardiac echo seems insufficient to this end. We have done magnetic resonance (MR) imaging in parallel to cardiac echo on all study subjects, and found that less than 1% of aortic valves cannot be adequately captured by at least one of these techniques [33]. MR has the advantage of not being limited by unusual thoracic architecture or excessive adipose tissue. Moreover, MR with gadolinium as a contrast agent (MRA) provides clear imaging of all the great vessels within the thoracic cage (Fig. 2), revealing many unsuspected anomalies, as well as considerable aortic pathology not seen by conventional cardiac echo [33–35].

Our recent MR study of 100 unselected adults with TS revealed cardiovascular anomalies in ~50% of study subjects [33]. Whereas congenital heart defects in TS



**Fig. 2.** Magnetic resonance angiography in TS. The image on the left shows a normal aortic arch and major arteries. The image on the right shows an elongated, ectatic aortic arch with a coarctation just after the origin of the left subclavian artery, which is dilated. This coarctation was not detected on echocardiogram. Adapted from Ho et al. [33].

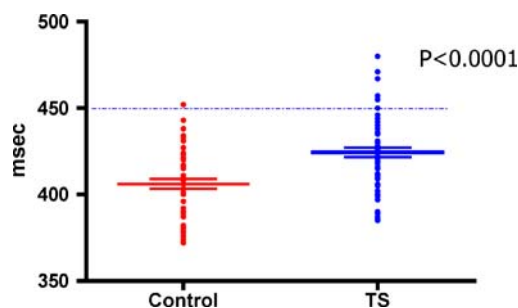
have been categorized as left-sided, outflow tract defects [36,37], MRA revealed a high prevalence of major venous malformations, including partial anomalous pulmonary venous return (~13%) and persistent left superior vena cava (~13%), with either one affecting over 20% of the study population, making the venous anomaly as prevalent as bicuspid aortic valve, usually regarded as the most common defect in TS. The most common anomaly defined in this study, and confirmed by another recent study [34], was a distinctive aortic ectasia affecting ~50% of women with TS, termed elongated transverse arch (ETA) in our study [33]. The MRA also reveals aortic diameter and detailed anatomy throughout the thorax and abdomen, and identifies occult coarctation (Fig. 2). The clinical significance of such anatomical findings remains to be determined, but it seems likely that extreme ectasia of the aorta may indicate a risk for aneurysm or dissection, and we advise that blood pressure be aggressively controlled in these patients, along with continued vigilant surveillance of aorta dimensions. The partial anomalous pulmonary venous return may be symptomatic in some cases [38,39] and require surgical correction. The fact that ~8% have anomalous origin of the right subclavian should be remembered in case of central line insertion.

Another new finding from the NIH study indicates that electrocardiogram analysis is an important aspect of cardiac screening and evaluation in TS [40]. Individuals with TS were significantly more likely to demonstrate left posterior fascicular block ( $P < 0.005$ ), accelerated AV conduction ( $P < 0.006$ ), and T wave abnormalities ( $P < 0.006$ ) (Table 2). The average heart rate in the TS group was ~20% higher than in controls ( $81 \pm 12$  vs.  $66 \pm 11$  bpm,  $P < 0.0001$ ). The PR interval was significantly shorter ( $137 \pm 17$  vs.  $158 \pm 18$  ms,  $P < 0.0001$ ) and the rate-corrected QT interval (QTc) significantly longer in women with TS ( $423 \pm 19$  ms vs.  $397 \pm 18$  ms;  $P < 0.0001$ ). Twenty-one women with TS but no controls

**Table 2.** Abnormal ECGs in TS

Finding	TS (100)	Control (100)	P
Fascicular block	16	2	0.001
T-wave abn.	29	13	0.005
AV Conduction	13	2	0.006
R. Ventricular Hypertrophy	2	0	ns
L. Ventricular Hypertrophy	1	0	ns
L. Atrial Enlargement	1	1	ns
Voltage	2	3	ns
Any abn.	55	30	0.0006

ECG tracings were compared in asymptomatic women with TS and age-matched female normal controls. Conduction and repolarization abnormalities were significantly more common in TS, and were not attributable to congenital heart defects, hypertension or medications [40].



**Fig. 3.** Prolongation of the QTc in girls with TS. Rate corrected QT intervals (using Bazett's correction) were compared in 60 girls with TS and 60 age-matched female controls. The mean duration was significantly higher in TS, and 6 girls with TS but only one control fell outside the upper limit of normal (hatched line at 450 msec).

had a QTc greater than 440 ms (Fig. 3). There was no statistically significant relation between body habitus, cardiac dimensions, evidence of CHD, or metabolic parameters and the incidence of ECG abnormalities or QTc duration in TS. Thus, cardiac conduction and repolarization abnormalities appear to be intrinsic features of TS, suggesting that deletion of the second sex chromosome has more profound effects on the cardiovascular system than previously recognized, and that ECG analysis should be included in evaluating and monitoring patients with Turner syndrome. In particular, the QTc should be monitored if considering the use of medications known to prolong the QT and increase risk of cardiac arrhythmia, which include some antibiotics and psychotropics commonly used in children [41].

**Clinical features**

The most common features of TS are short stature and premature ovarian failure [5]. The short stature is mainly due to SHOX haploinsufficiency and is characterized by a shortfall of approximately 20 cm from the predicted adult height. Various skeletal malformations possibly associated with SHOX deficiency are seen less often, A wide carrying angle and brachymetacarpia are fairly common, affecting at least a third of patients, but radial bowing or Madelung deformity is actually pretty rare. About two thirds of girls and women with TS have a high-arched or ogival palate. Other skeletal features include micrognathia, which is usually not a prominent feature and is present in approximately 30% of patients, and scoliosis, which affects 5–10% of girls with TS. The ovarian failure characteristic of TS is discussed in detail in the section on puberty. Evidence of fetal lymphedema is manifest as neck webbing (~30%), malrotation of the ears (~35%) and a low posterior hairline (~70%).

Congenital cardiovascular defects have been described above. Renal malformations are consistently reported to

affect 20–30% in TS, with the benign conditions of horseshoe kidney and duplex collecting systems being most common [5]. Imaging should reveal any evidence of obstruction or other functional problem, and in the absence of obstruction, the renal anomalies are usually clinically insignificant. Neither the renal malformations nor the congenital heart defects are implicated in the hypertension affecting ~20% of girls and ~40% of women with TS [42–45], but hypertension is associated with the risk for aortic dissection and hence must be managed in a proactive manner. Chronic, severe otitis media is common in TS and is thought to be due to obstructed drainage either from lymphatic insufficiency or skeletal dysplasia. The otitis may be associated with a conductive hearing loss in childhood, which usually resolves as otitis decreases in the young adult stage. However, sensorineural hearing loss affects many young adults with TS and worsens with age. Thus, audiological screening and care are important in both girls and women with TS.

Learning and behavioral problems may be increased in prevalence in TS [46]. Although some individuals with a ring or marker X chromosome may be mentally retarded, the great majority with other karyotypes are of normal intelligence [6]. A specific deficit in visual-spatial cognition and executive processing affects many individuals with TS [47,48]. Although performance IQs are consistently lower than verbal IQs, both average in the normal range, so this characteristic deficit does not usually present a major impediment to academic achievement. Girls with TS may be emotionally immature and are more likely to be diagnosed with attention deficit-hyperactivity syndromes than other girls [49]. Major psychiatric diagnoses are not increased in TS, however, except for depressive episodes, which occur at the same rate as seen in 46,XX women with infertility [50]. Psychosocial support for the individual with TS and family is critical to successful medical management, and helping them to connect with others with TS through the Turner Syndrome Society USA (<http://www.turner-syndrome-us.org/>) or other means is extremely important.

Autoimmune thyroid disease—usually Hashimoto's—is clearly increased in prevalence in TS, affecting about 20% of girls [5] and ~40% of adults [51]. Other forms of autoimmunity that seem to be increased are celiac disease [52], inflammatory bowel disease [53] and juvenile rheumatoid arthritis [54]. It remains unclear whether type 1 diabetes mellitus is increased in TS. A Danish registry study that defined type 1 in the basis of insulin usage found an increased prevalence of both type 1 and type 2 diabetes [55]. That finding however is consistent with the relative insulin deficiency found in TS on a non-immune basis [56]. Abnormalities of liver function tests may be found in approximately 15–20% of girls [57,58] and 40% of women with TS [59]. The etiology of liver disease in

TS is unknown but is not autoimmune in nature and may be heterogeneous, with some cases primarily vascular and others related to fatty infiltration [60].

#### ***Pediatric care in TS***

The issues that need attention in the continuing care of children with TS from infancy through adolescence have been outlined in detail by the American Academy of Pediatrics [19]. If cardiovascular defects are found upon initial evaluation, a pediatric cardiologist and possibly cardiac surgeon need to be consulted. It is important to be sure about the status of the aortic valve in TS. Cardiac echo may fail to visualize the aortic valve in a significant number of TS patients, and if the cardiologist reading the echo cannot unequivocally determine whether the valve is tricuspid or bicuspid, additional studies are necessary. An echocardiogram at a pediatric cardiology center or MRI study may clarify the issue. Girls with a coarctation repair or bicuspid aortic valve need close and continuous monitoring because they need antibiotic prophylaxis and they are at risk for aortic dissection. The frequency of cardiac evaluation and surveillance echocardiograms is based on the individual patient's picture, but is usually annually for girls with known defects, and every 3–5 years for those that appear normal [61].

In addition to cardiac monitoring, girls with TS need special attention to blood pressure, thyroid and liver function, otitis media and hearing and psychosocial development. Because of the increased frequency of impaired glucose tolerance and diabetes mellitus, fasting blood sugar should be tested, especially in children on GH. If growth seems retarded on the TS curve, or if the response to GH is poor, the possibility of celiac disease and/or hypothyroidism should be addressed. Some girls with TS have multiple medical problems and see several specialists on a regular basis. This can lead to lack of communication and working at cross purposes—for example, a psychiatrist prescribes a stimulant for hyperactivity symptoms, while a cardiologist prescribes a beta blocker for hypertension and aortic dilation. Hence, a primary caregiver who integrates or reconciles the different medical regimens and takes the time to discuss the issues with the family and patients may be of great value in the medical management of TS. The care of girls with TS is further complicated by treatment with GH and the need to induce puberty.

#### ***Growth hormone***

Although girls with TS are not normally GH-deficient, most demonstrate pronounced growth restriction and without treatment, final adult height rarely surpasses 143 cm [62,63]. The recently published randomized, controlled Canadian study of GH use in TS showed that final

adult height may be increased by ~7 cm. with pharmacological GH treatment [64]. A commentary related to this important study notes that the expected benefit in quality of life or self esteem from the GH-induced increase in height has not yet been demonstrated [65], while the short term risks, including intracranial hypertension, slipped capital epiphysis, impaired glucose tolerance and increased rates of otitis media are well established. The long term risks of pharmacological GH treatment in young children are not known, and it is important to thoroughly discuss these issues with parents considering GH treatment for their daughters. Important factors impacting height gain during GH treatment, including GH dosage and timing recommendations, and issues relating to the use of oxandrolone were recently reviewed [65–67].

### ***Puberty and uterine development***

The anachronistic term “gonadal dysgenesis” used to refer to TS and other completely unrelated disorders is not very accurate or informative and should be discarded in favor of modern terminology referring to specific, genetically defined, disorders [68]. In the absence of a Y-chromosome, undifferentiated gonads develop as ovaries, as in TS. In the absence of a 2nd X-chromosome, in most females there is early ovary degeneration (not dysgenesis) due to accelerated follicular atresia, possibly due to meiotic difficulties among aneuploid oocytes and/or haploinsufficiency for X-linked genes required for oocyte survival [69]. The ovaries may degenerate during late fetal life, in childhood or later in life. From 10–30% of girls with TS have spontaneous pubertal development [70] and spontaneous pregnancies may occur in 2–5% [71].

The current regimen for pubertal induction in those girls not experiencing spontaneous puberty mandates low dose estrogen treatment beginning between age 12–15 yrs, with gradual increases in dose until feminization is adequate, with the addition of a cyclic progestin on a regular basis after 12–24 months [18]. In Europe, most practitioners favor beginning treatment closer to age 11–12 yrs, and the great majority prescribe oral estradiol or ethinyl estradiol [72]. There has been no survey of practices in the U.S., but the great majority of girls and young adults that have participated in the NIH study were started (elsewhere) on low dose conjugated estrogens (i.e., 0.3 mg Premarin) at age 14–15 yrs, gradually increased to 1.25 or 2.5 mg and then cycled with medroxyprogesterone, or less frequently with progesterone (Prometrium). Typically, as young adults they switch to oral contraceptives or continuous-combined estrogen/progestin preparations.

Several recent studies have suggested that conventional pubertal induction does not produce optimal development of the uterus in TS [73–76]. It is not clear from these

studies whether impaired uterine development was due to delayed estrogen treatment, too low dosage, or perhaps the use of synthetic androgenic progestins. There does not seem to be any inherent defect in uterine capacity in TS, since development is normal in TS girls with spontaneous puberty [73,77]. At this time we really do not have complete information on the requirements for uterine growth and endometrial development adequate to support embryo transfer during adult life. It is not known whether there is a ‘window’ of developmental time, e.g., during adolescence, when uterine growth must occur to achieve sufficient maturity for pregnancy, or whether uterine development can be induced at a later age with sufficiently high, or properly timed estrogen treatment. This is an area that urgently requires further study given the very strong interest among many with TS and their families in reproductive options.

### ***Ovarian hormone replacement in adults***

The standard approach to ovarian hormone replacement therapy (HRT) in women with TS [18] has been questioned in recent years after the publication of many negative effects associated with menopausal estrogen treatment. Unfortunately, many women with TS have discontinued HRT, and even the use of estrogen for pubertal induction concerns some parents. Our current ad hoc approach to this subject stresses the very low risk, high benefit ratio for the use of estrogen in young patients with ovarian failure, with at least a 50% risk of clinically significant osteoporosis in those who discontinue HRT at a young age [78]. We emphasize the excellent safety record of many millions of woman-years use of oral contraceptive, the importance of estrogen for bone, and the need for estrogen effect upon the uterus if pregnancy is a future goal. We promote the physiological aspects of transdermal estradiol, and its proposed relative safety in regard to thrombosis risk, which may be increased in TS [79–81]. We aim to parallel the normal life cycle patterns of estrogen exposure, using a higher dose (e.g., 100 mcg patch) during young adulthood, and decreasing to 50 mcg patches by age 30 to 35 years, with further reduction and cessation by age 45–50 years. Also, given the current preference for all things ‘natural’, we recommend progesterone rather than any derivative, with cycling on a monthly or tri-monthly basis. These views are obviously not based on controlled clinical studies, but represent our best attempts to reconcile our patients’ concerns and available medical data. The major contraindications to estrogen use in women with TS are similar to those for women in general, i.e., history of gynecological cancer, history of thrombosis or known clotting disorder, and possibly, familial breast cancer risk.

### ***Pregnancy in TS***

Spontaneous pregnancies are reported in women with TS, most often in mosaic individuals with a high percentage of normal cells. Indeed, the widely quoted high rate of ~7% reported in Birkebaek et al. [82] included women with less than 10% abnormal cells, so the diagnosis of TS is somewhat doubtful. Nevertheless, pregnancy does occur in a small number of women with TS, including some with apparent non-mosaic 45,X karyotypes [83], or mosaic for 45,X/46,XY [84] and some that had elevated gonadotropins and been on HRT [71,85]. The number of such pregnancies is too small and scattered to allow accurate statistical assessment of risk and outcome, but case reports suggest an increased risk for miscarriage and hypertension and aortic dissection for the mother [71]. Another 'complication' in TS pregnancies is the tendency for C-section in most cases due to small maternal size. The outcome for live born infants according to compilation of case reports suggests a high incidence of chromosomal and morphological anomalies [86]. However, advances in obstetrical care may be accompanied by improved outcome for spontaneous TS pregnancies. A recent report found that of 64 live children born to TS mothers, 24 had postnatal karyotypes; 19 were normal, and most abnormal results came from a mother with a 46,XdelXp karyotype [82]. There were no cases of Down syndrome or other chromosomal anomalies in this series.

Although early reports suggested a poor response to embryo implantation in TS, recent improvement in hormonal preparation of the endometrium have apparently resulted in implantation rates equal to non-TS patients [87], although miscarriage rate was higher than normal at ~40%. Given that the conception is from donated oocytes in these assisted pregnancies, the high miscarriage rate implicates insufficiency of the uterus. A recent review of women with TS participating in oocyte donation programs in the U.S. in 1997 found that of 146 women treated, 101 (69%) became pregnant; 94 of these pregnancies resulted in the birth of a live baby, for a miscarriage rate of only 6.4% [88]. While this shows a good rate of pregnancy and live birth, the study focused on maternal complications. They noted that only ~50% of TS patients had a screening echocardiogram prior to fertility treatment, and while no deaths or major complications occurred in the reviewed cases, the authors projected a mortality rate of 2.1% based on a world literature review [88]. This report was followed by a practice alert from the American Society for Reproductive Medicine [89] warning of an 100-fold increased risk for death in women with TS attempting pregnancy, and stating that TS "is a relative contraindication to pregnancy." Importantly, the warning stresses the necessity for full cardiological evaluation prior to attempting pregnancy [89].

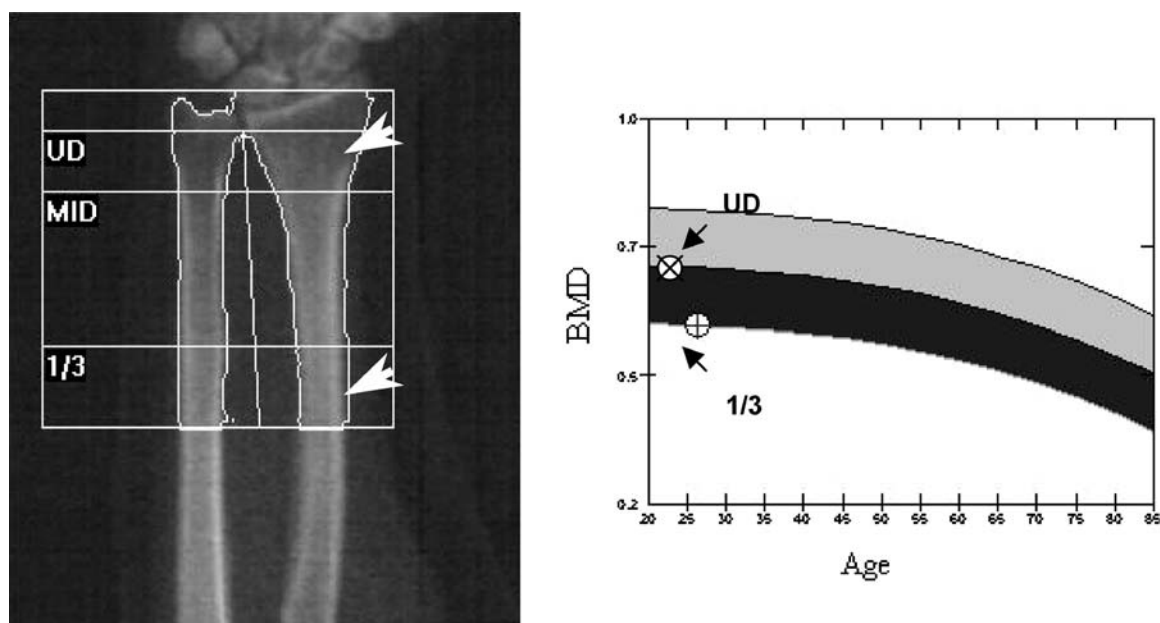
### ***Turner syndrome in the adult***

Women with TS need continued and perhaps even more aggressive cardiac care than recommended for children. Those with known cardiovascular defect such as bicuspid aortic valve need antibiotic prophylaxis and regular monitoring for valve deterioration or aortic dilatation. The frequency of imaging studies is based on individual considerations, but yearly intervals are suggested [18]. Women with TS have a number of electrocardiographic abnormalities (Table 2) including prolongation of the QTc interval [40] so the ECG should be monitored, especially if prescribing medication likely to further impair cardiac repolarization. All patients need to have blood pressure monitored and hypertension aggressively treated. If the patient has aortic dilation and/or tachycardia, a beta blocker may be valuable. If the patient has impaired glucose tolerance or overt diabetes, an angiotensin system blocker is a good choice. Impaired glucose tolerance is common in TS affecting approximately ~20% of girls and ~40% of middle-aged adults [90]. Insulin secretion capacity appears to be reduced in TS but insulin sensitivity is preserved and fasting glucose remains normal in young, non-obese individuals [56]. With aging and/or increasing adiposity, insulin sensitivity and insulin secretion both decrease, resulting in overt but usually mild diabetes in many women. Given the reduced insulin release and relatively preserved insulin sensitivity in TS, treatment with insulin or sulfonylureas may be quite successful. Patients with TS also may demonstrate increased LDL-cholesterol levels [15]. Women with TS often suffer from multiple risk factors for atherosclerotic vascular disease, including hypertension, diabetes and dyslipidemia, and registry data from Europe suggests there is indeed increased mortality from ischemic heart disease [55]. Therefore, regular screening for and vigorous treatment of these risk factors is crucial to the medical management of women with TS.

### ***Osteoporosis***

As mentioned above, the risk for osteoporosis is a major concern in TS. Problems in early studies investigating bone mineral density (BMD) in TS included the use of areal densitometry which under-estimates BMD in small-boned individuals, and the comparison of prepubertal girls with TS to age-matched but pubertal controls. Routine estrogen treatment beginning by age 16 yrs is associated with normal trabecular BMD at the lumbar spine using size-independent densitometry (quantitative CT) or using DXA with adjustment for size [91]. Discontinuation of estrogen treatment is associated with rapid loss of trabecular bone, resulting in spontaneous vertebral compression fractures and height loss [78,79]. In contrast to





**Fig. 4.** Selective reduction in cortical bone mineral density in TS. The radiograph on the left is a DXA image used to measure BMD at the wrist. The ultradistal radius (UD) is largely trabecular bone, and the proximal 1/3 radius is predominantly cortical. The score for the distal, trabecular radius is normal, but the cortical region mineral content is approximately 2 SDs below normal. Adapted from ref [94].

trabecular bone, cortical bone is selectively reduced in TS, independent of estrogen effect [92–94]. This can be seen comparing BMD in the distal radius, largely made up of trabecular bone and in the radial shaft, where cortical bone predominates (Fig. 4). Women with TS should be assessed for osteoporosis risk based on history of estrogen use, age, the presence of independent risk factors such as glucocorticoid treatment and clinical indicators such as height loss or back pain. Measurement of BMD using DXA will show reduced scores for lumbar spine in women less than 4'10" tall, with or without TS, and regardless of estrogen treatment. If estrogen treatment has been adequate, there has been no height loss and there are no other risk factors for osteoporosis, then *T*-scores of  $-1$  to  $-2$ SDs for lumbar spine should probably not be treated. If the *T*-scores are lower or there is clinical concern, then treatment with bisphosphonates is reasonable and effective. The threshold for treatment of osteoporosis at *T*-scores of  $-2.5$  SDs was based on studies of postmenopausal women. This criterion cannot be applied in the same way to adolescents or premenopausal women because the "fracture threshold" has not been set for these younger persons. Moreover, it is unknown if the selective cortical bone deficit in TS leads to increased fragility and fractures, or whether it is responsive to anti-osteoporosis agents such as bisphosphonates, SERMS or parathyroid analogs, so reductions in BMD at the wrist and femoral neck in women with TS must be evaluated on a case by case basis.

### Summary

This review has tried to update our view of TS, highlighting the less severe phenotype we are seeing today, aiming to motivate clinicians to scrutinize normal looking short girls more closely, and to provide more relevant information for those counseling prospective parents on the implications of a TS karyotype during prenatal screening. New approaches to cardiac evaluation, including imaging with MR and ECG analysis—were suggested to strengthen our ability to detect and prevent potentially life-threatening cardiac complications. The new emphasis on reproductive potential and concerns about the adequacy and safety of current HRT regimens certainly require further studies and adjustment of treatment strategies in light of new priorities and safety concerns. In the same vein, prospective studies are required to assess the outcome and safety of assisted pregnancy in TS, which, despite the warning of a potential catastrophic increase in maternal morbidity is going to become a much more common occurrence in the near future.

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