Turner Syndrome: Updating the Paradigm of Clinical Care

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Context: Turner syndrome (TS), in which there is loss of all or part of one sex chromosome, occurs in one in 2500 live-born females and is associated with characteristic findings. Detailed healthcare checklists and screening guidelines are commonly used to detect known complications affecting individuals with TS. Even with the use of these guidelines, there remains an increased morbidity and mortality seen in TS as compared to the general population, leading to significant controversy on optimal management of several aspects of TS.

Evidence Acquisition and Synthesis: A PubMed search of articles from the past 15 yr identified available studies related to the diagnosis and management of common issues related to TS as well as important historical articles. This review summarizes studies through January 2012 and highlights recent developments.

Conclusions: There remain many areas of uncertainty in the diagnosis and management of TS. Generalizations from experience in the care of other conditions in isolation (such as poor growth, follow-up of cardiac disease, or the treatment of ovarian failure) cannot be broadly applied when caring for individuals with TS. Specific differences include treatment of growth failure as early as possible; acquisition of adequate baseline cardiac studies, followed by serial magnetic resonance imaging, targeted to identify findings unique to TS that address the increased risk of aortic dissection; initiation of hormone replacement at the normal age of puberty, preferentially with transdermal estradiol; and detailed patient counseling to explain the long-term health risks commonly associated with this disorder. A revised paradigm of care using a standardized multidisciplinary evaluation, supplementing screening tests as advocated by expert opinion guidelines, can aid clinicians in interpreting the results of diagnostic testing in the context of TS. This approach optimizes medical care for women with TS and may reduce the increased morbidity and mortality currently seen in this population. **(*J Clin Endocrinol Metab* 97: E994–E1003, 2012)**

Turner syndrome (TS), in which there is loss of all or part of one sex chromosome, occurs in one in 2500 live-born females and is associated with characteristic findings, such as growth failure, pubertal delay, and cardiac anomalies (1). Expert opinion guidelines that offer detailed checklists of screening tests to perform at specific age intervals are very helpful in allowing clinicians to optimize care for individuals with TS (2, 3).

Although performing these recommended studies is relatively simple, interpretation of the results is much more complex. Recent studies show that evaluation of the clinical findings in TS cannot occur in isolation because all findings relate to the underlying pathophysiology of this genetic disorder. Consequently, clinicians cannot solely rely on knowledge gleaned from previous experience treating other isolated conditions when making diagnostic and treatment decisions for women with TS. For example, historically young girls with TS diagnosed for reasons unrelated to poor growth were treated the same as any child with short stature, with delay of initiation of GH therapy

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.
Copyright © 2012 by The Endocrine Society
doi: 10.1210/jc.2012-1245 Received January 27, 2012. Accepted March 12, 2012.
First Published Online April 3, 2012

Abbreviations: ASI, Aortic size index; BAV, bicuspid aortic valve; BMD, bone mineral density; COA, coarctation of the aorta; ETA, elongated transverse aortic arch; MRI, magnetic resonance imaging; SMR, standardized mortality ratio; TDE, transdermal estradiol; TS, Turner syndrome.

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until height velocity began to noticeably decrease. Some studies suggest, however, that girls with TS may benefit from significantly earlier treatment because their growth rates often decrease in the first few years of life (4). Similarly, it is not appropriate to use general population normative values for aortic dimensions to determine risk of aortic dissection in TS, which can occur at much lower body surface area adjusted aortic diameters. These findings have provoked a number of clinical controversies due to the identification of increased morbidity and mortality in women with TS compared with the general population, particularly as this relates to cardiovascular disease (1).

This clinical review therefore focuses on the latest updates in diagnostic and management modalities for the most common clinical concerns related to TS. Beginning with current controversies in the diagnosis of TS, we then review the latest evidence aiding in the evaluation and management of growth failure, cardiovascular disease, and ovarian failure. We conclude with a review of how best to implement current clinical guidelines to optimize care for young women and adults with TS.

Diagnosis

Prenatal diagnosis

TS is increasingly diagnosed prenatally, but significant ascertainment bias exists in that the underlying reason for prenatal chromosome analysis often impacts the validity of the findings (5). When a prenatal karyotype identifying TS is sent in response to specific ultrasound findings, such as increased nuchal translucency, the result is fairly specific (6). If a cystic hygroma is present, this ultrasound finding alone can predict TS in 30–70% of cases (7). It is important to recognize that both of these ultrasound findings can be seen in autosomal trisomy syndromes, and the specificity for TS depends on the gestational age at which the findings appear (7, 8). In general, when 45,X fetuses are discovered due to specific ultrasound findings, "classic" phenotypic findings are likely (9).

Prenatal counseling is important because the rate of spontaneous fetal loss for 45,X fetuses with an ultrasound finding is high. TS may occur in as many as 3% of all fetuses and may cause up to 10% of all spontaneous fetal loss, with 99% of 45,X embryos terminating spontaneously during the first and second trimesters (7, 10). In addition, in some countries over 60% of TS fetuses are electively terminated (11). Despite this, prenatal counseling must include an explanation that even with an ultrasound finding, delivery of a viable newborn is possible, and many of these children go on to have an excellent quality of life.

When a prenatal karyotype is performed for other reasons, such as advanced maternal age or abnormal maternal screening tests, false-positive results can occur. If diagnosed incidentally, the fetus with a 45,X karyotype or partial loss of the X chromosome can have fewer or sometimes no phenotypic findings (5). When a mosaic karyotype is discovered, not only can the fetus have fewer phenotypic findings, but the result of the karyotype can be nonspecific. A review of the Danish cytogenetic registry showed that up to 30% of cases of TS diagnosed prenatally showed a normal karyotype at delivery (11). The results of this study are complicated by the fact that mosaicism is not an uncommon finding in chorionic villus sampling or amniocentesis in general (12). When properly accounted for, the high rate of spontaneous and elective terminations makes the true false-positive rate likely much lower than 30%.

High-resolution ultrasound and fetal echocardiography may offer additional diagnostic information. The use of maternal biomarkers or maternal plasma DNA sequencing to detect fetuses with TS is promising but is still in preliminary stages (13, 14). Therefore, we recommend that families should be counseled that the incidental finding of a TS karyotype without clinical ultrasound findings is often, but not always, associated with a mild phenotype and can be a poor predictor of outcome. Given this uncertainty, a postnatal karyotype is required for confirmation of the diagnosis.

Postnatal diagnosis

Lymphedema is the most common reason to screen for TS during infancy (97% of cases), whereas short stature most commonly leads to evaluation during childhood and adolescence (82% of cases) (15). A standard 30-cell karyotype is recommended by the American College of Medical Genetics and identifies at least 10% mosaicism with 95% confidence (16). Genotyping of additional tissues may be warranted if the peripheral karyotype is normal in individuals for whom there is a high suspicion of TS.

Karyotype analysis reveals that Y-chromosomal material may be present in 5% of individuals with TS, and an additional 3% of individuals may have a marker chromosome (a chromosome fragment of X or Y origin) (17, 18). Current guidelines advocate screening for Y material if signs of virilization develop or a marker chromosome has already been identified (2), because the risk of developing gonadoblastoma with Y material present ranges from 5–30% in recent studies (19–22). Gonadectomy is recommended if Y material is identified. Although some authors have advocated screening all nonmosaic individuals with TS with fluorescence *in situ* hybridization to search for Y material (23), the clinical significance of cryptic Y

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material in a 45,X individual without virilization is not clear. Therefore current clinical practice guidelines do not yet recommend routine use of fluorescence *in situ* hybridization or PCR in 45,X patients with TS (2).

Despite a general trend toward earlier age of diagnosis, retrospective analyses have shown that there is often a delay in the diagnosis of TS, averaging 5 yr after patients had fallen below the 5th percentile in height to time of diagnosis (24). In some studies, over 20% of patients are diagnosed after age 12 yr (25). This leads to the important question of how to diagnosis TS earlier. Earlier diagnosis, particularly if this could be done noninvasively or as part of newborn screening, would allow for detection of cardiovascular and renal anomalies that often remain unidentified until the time TS is diagnosed (26), and could facilitate earlier treatment of growth failure.

Recent advances have illustrated the value of high-throughput pyrosequencing of buccal swabs for TS (27). This testing, which uses pyrosequencing to quantitate relative allele strength, can readily detect loss of an entire X-chromosome or mosaicism with up to 97% sensitivity. The applicability of this technology has yet to be established, but already it can be very useful for noninvasive screening for TS. The potential for mass screening is appealing, perhaps as part of future newborn screening or other mass screening programs.

Growth-Promoting Therapies

Growth failure is the most common abnormality in TS (28). It begins prenatally, with poor growth often evident within the first 3 yr of life (4). Adult height is on average 20 cm below expected norms (29). Adults with TS have increased IGF binding protein-3 proteolytic activity and low IGF-I, but are generally not GH deficient (30, 31). In a controlled, randomized study to adult height, patients with TS gained 7.3 cm over a mean of 5.7 yr of treatment with GH, even using doses slightly lower than those approved today in both Europe and the United States (32).

There has been extensive research suggesting that GH treatment in TS may be of benefit in areas other than linear growth. GH has been shown to improve body proportions and may contribute to lower diastolic blood pressure in TS, even after treatment is discontinued (33). Similar beneficial effects have been seen in relation to total cholesterol, low-density lipoprotein, and high-density lipoprotein (34). Insulin resistance was shown to improve in some studies of young girls with TS because abdominal adiposity was reduced during treatment (35), although other studies have not shown the same improvement, and it appears that insulin resistance generally correlates to the gain in body mass index and loss of lean body mass that occurs in individuals with TS over time (34, 36, 37). GH therapy does not appear to have any negative effects on cardiac and aortic dimensions (38, 39). Bone mineral density (BMD) is also unaffected (40).

Further escalation of dosing beyond the Food and Drug Administration approved 0.375 mg/kg · wk has produced additional small gains in adult height, but higher doses correlate with elevated IGF-I levels (41). Because both slipped capital femoral epiphysis and idiopathic intracranial hypertension (with some cases of persistent visual deficits) have been reported with GH treatment in TS and appear to occur at a higher rate compared with the treatment of GH deficiency or idiopathic short stature (42–44), further attempts to increase GH dosage appear unwarranted. Instead, monitoring of IGF-I and height velocity response to treatment, in the context of growth prediction models, can be used to further adjust dosing (45).

Adult height is highest in TS patients with taller stature at initiation of GH therapy, taller parental heights, younger age at initiation of treatment, longer duration of therapy, and higher GH doses (46–52). Recognizing that 90% of young girls with a 45,X karyotype will fall below the 5th percentile in height by 5 yr of age, treatment with GH is warranted as soon as growth failure becomes evident (28). This raises the following questions: Since we know individuals with TS will almost universally have short stature, why wait to treat until abnormal height velocity is apparent if young women are diagnosed for other reasons? And is it safe to treat with GH in the first few years of life? This clinical dilemma is highlighted in Fig. 1.

The safety and efficacy of GH treatment in the early years of life for young girls with TS was assessed in two recent studies. The randomized, controlled Toddler Turner Study showed that GH rapidly normalized height SDS after just 2 yr of treatment beginning between 9 months and 4 yr of age (53). In this study, none of the 88 girls with TS suffered GH-related complications. More recently, the 2011 publication of the French Collaborative Young Turner Study Group showed that for girls with TS who were younger than 4 yr of age (mean age, 2.6 yr), early treatment with GH over 4 yr allowed 80% of the treatment group to achieve a height in the normal range (54). Although treatment was well tolerated, one child experienced transient glucose intolerance, and 75% of the treatment group had elevated IGF-I levels despite using a dose of GH less than that typically used to treat TS in the United States. Given these findings, careful follow-up of long-term height data and tolerance to GH-related side effects are warranted before it can be inferred that treatment with GH should be considered even before growth failure is

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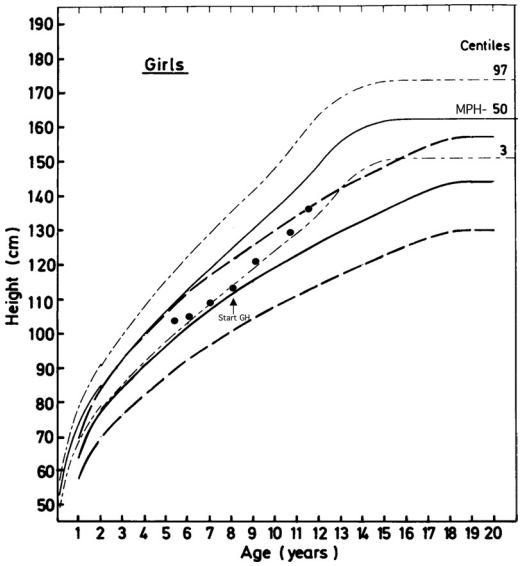

FIG. 1. This growth chart for a girl with TS started on GH after her growth rate declined demonstrates that she will not achieve her midparental height (MPH). Because adult height is highest in girls with TS with earlier initiation and greater duration of therapy, this chart prompts discussion on whether starting GH before a decline in growth velocity would prevent poor growth and whether GH therapy should be started for all girls with TS at a young age. Recent studies treating young girls with TS before 4 yr of age show good short-term improvements in height gain, but long-term safety and efficacy data are not yet available. [Reproduced from A. J. Lyon *et al.*: Growth curve for girls with Turner syndrome. *Arch Dis Child* 60:932–935, 1985 (121), with permission. © BMJ Publishing Group Ltd.]

demonstrated, especially for mosaic patients with a normal cell line who can have normal growth.

The completion of the 1987 National Institutes of Health trial comparing GH and early low-dose estrogen treatment (also published in 2011) adds to the discussion on optimal ways to supplement GH treatment (55). In this trial, patients were started on low-dose oral ethinyl estradiol as early as 5 yr of age (mean age, 9.3 yr), as opposed to beginning by age 12, as is generally done today. They showed a synergistic effect of GH and estrogen treatment, with an increase of 2.1 cm in adult height beyond the 5-cm height gain when GH was used alone and ethinyl estradiol was introduced at age 12. The frequent finding of gynecological disorders (usually inappropriate feminization) and the unknown long-term consequences (such as possible risk of breast cancer) suggest that additional research is needed before this practice could be recommended for routine use (56). Repeated studies with transdermal estrogens and alterations to the timing of pubertal induction may further clarify the risks and benefits of such a regimen.

Less commonly used alternatives to increase adult height are delaying pubertal induction until 15 yr of age or adding the nonaromatizable anabolic steroid oxandrolone. Delaying pubertal induction can increase adult height by up to 4 cm, but this fails to recognize the importance of age-appropriate pubertal maturation, may have a deleterious effect on bone health, and may not be necessary given newer routes of estrogen administration (see *Ovarian Failure, Pubertal Induction, and Effects on BMD*) (57–59). In girls above 9 yr of age or those with severe short stature, consideration can be given to adding oxandrolone. At doses of 0.05 mg/kg · d or less (maximum dose, 2.5 mg), signs of virilization (clitoral enlargement, acne, voice lowering) are generally minimized, and follow-up to adult height has shown gains averaging 4 cm beyond those achieved with GH alone (57, 60). However, patients must be cautioned that the use of oxandrolone can be associated with liver dysfunction, virilization, hypertension, and deceleration of breast development (60, 61). If doses need to be lowered to account for such side effects (to 0.03 mg/kg · d), height gains are much more modest, discouraging conventional use (61).

Longer duration of treatment with GH (at least 3 to 4 yr in some studies) is needed to see a meaningful impact on adult height (52, 62). Treatment should be discontinued when little growth potential remains (bone age $\geq$ 14 or growth velocity $<$ 2 cm/yr) (2). Follow-up for patients with TS who are on GH should include regular follow-up with a pediatric endocrinologist to assess the efficacy of GH treatment and monitoring of thyroid function and carbohydrate metabolism. Scoliosis and kyphosis occur in 10–20% of girls with TS, most commonly during adolescence, although in some studies the baseline prevalence is much higher (63). Scoliosis is reported more commonly with GH treatment in TS than in other conditions (64), so careful monitoring for scoliosis in addition to the above noted side effects is warranted.

Cardiovascular Disease

Congenital cardiovascular structural abnormalities affect approximately 50% of individuals with TS (65). Cardiovascular disease is a major cause of premature mortality in TS, associated with standardized mortality ratio (SMR) of 3.5 for coronary disease, and an SMR of 24 related to congenital anomalies, likely attributable to malformations of the heart and great arterial vessels (1).

Structural abnormalities

At the time of diagnosis, an evaluation for congenital structural abnormalities to include coarctation of the aorta (COA), bicuspid aortic valve (BAV), and partial anomalous pulmonary venous return must be performed. Infants with TS require comprehensive evaluation by a pediatric cardiologist and additional imaging studies, even if the fetal echocardiogram was normal, because BAV and

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COA are often not appreciated on fetal echocardiogram. Up to 30% of patients with TS have been found to have BAV when adequate imaging studies are performed (66). The presence of neck webbing, indicative of fetal lymphedema, is significantly associated with BAV and COA, suggesting that fetal lymphedema contributes to congenital cardiovascular defects (67).

If a baseline echocardiogram does not adequately rule out congenital structural abnormalities such as COA or partial anomalous pulmonary venous return, then magnetic resonance imaging (MRI) can be used to identify them (68–71). Although there are data suggesting that MRI can identify aortic valve disease in some cases that were missed by transthoracic echocardiography (66), this was reported from a center with experience performing cardiac MRI for TS. Cases of "late-onset" COA or BAV that have been diagnosed after an initial cardiac evaluation may have been diagnosed earlier if referring providers specifically request imaging of the known structural abnormalities associated with TS at the time of diagnosis (adequate imaging of the aortic valve and root) (72, 73). In some studies, echocardiography was equally as efficacious as MRI in imaging the aortic root and the ascending thoracic aorta, and it may suffice for the initial imaging study in children and young adults as long as adequate views are obtained (74). When congenital structural heart disease is found, close follow-up with a cardiologist is required.

Aortic dilation/dissection

The incidence of aortic dissection in TS has been estimated to be 0.6–1.4% (*vs.* 0.006% for women in the general population) and occurs at a median age of 30–35 yr (75, 76). Spontaneous cases have ranged from 16 to 60 yr of age, with approximately 10% having no previous risk factors such as BAV, COA, or high blood pressure (75, 77–79). Aortic dilation, reported in 15–30% of girls with TS, is also a significant risk factor for dissection but is dependent on how dilation is defined (80, 81). In the first prospective study of aortic dissection in TS, three of 158 women with TS experienced aortic dissection. All three had an elongated transverse aortic arch (ETA), a prominent kinking of the aortic arch past the site of the insertion of the ductus, among other cardiac abnormalities, but their ascending aortic diameters ranged from 3.7 to 4.8 cm, below the 5-cm cutoff traditionally used for intervention in adults (82). Given the smaller size of most women with TS, it was therefore recommended that finding a body surface area-adjusted aortic size index (ASI) greater than 2 cm/m^2 should warrant close follow-up and referral to a center with extensive experience in treating young patients with aortic disease if the ASI is greater than 2.5 cm/m^2 (Fig. 2) (77). Aggressive control of blood pressure with β-adrenergic blockade is warranted if dilation is present, targeting the low-normal range (82).

Ongoing monitoring

Recent guidelines suggest that cardiac MRI should be routinely performed in all patients with TS, even in those without structural heart disease, once they are in their teenage years and can cooperate with the exam, and then every 5–10 yr as adults (2). The advantage of MRI with gadolinium is that it can clearly visualize the entire aortic arch and identifies anomalies such as ETA, which may be associated with future risk of aortic dissection in TS (82). Nevertheless, it appears that echocardiography can be adequate in many cases under expert cardiology guidance, with MRI complementing the cardiac evaluation every 5 to 10 yr to better visualize the thoracic aorta for possible ETA (Fig. 2). More frequent use of MRI is strongly rec-

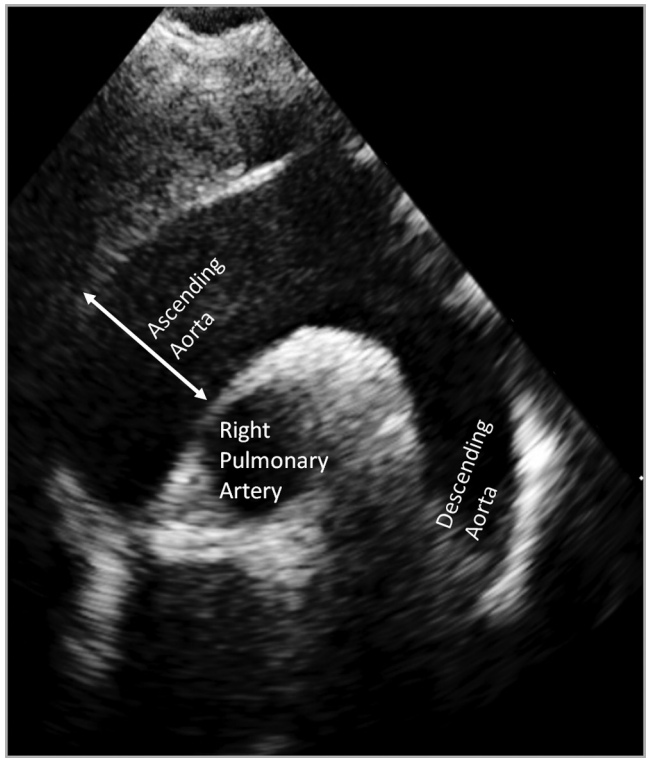

FIG. 2. Echocardiographic view of the aortic arch from the suprasternal notch view. For most patients, experienced echocardiographers can obtain this image for aortic dilation surveillance. The ascending aortic diameter should be measured at the level of the right pulmonary artery. Interpretation of these measurements should be adjusted for body surface area (BSA). (Figure 2 was provided by C. Becket Mahnke, M.D., Pediatric Cardiology, Tripler Army Medical Center, Honolulu, Hawaii).

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ommended for women with TS with hypertension, previous finding of ETA, history of aortic dilation, or in those contemplating pregnancy (83).

The risk of death from aortic dissection in the perinatal period is approximately 2% for women with TS (84, 85). The recent update to the American Society for Reproductive Medicine acknowledges this risk and recommends an ASI above 2 cm/m^2 and/or any significant cardiac abnormality as an absolute contraindication to pregnancy. Careful follow-up for those women who decide to attempt pregnancy after thorough counseling, in addition to the treatment of hypertension, is also recommended (85).

Nonstructural abnormalities

Adults with TS frequently show electrocardiographic abnormalities, including right axis deviation, T wave abnormalities, accelerated AV conduction, and QTc prolongation, often independent of structural defects (86). They also may have a proathererogenic lipid profile and a higher risk of impaired glucose tolerance (with progression to type 2 diabetes), which together with a likely intrinsic vasculopathy potentially explains higher rates of mortality from coronary and cerebrovascular disease (1, 87–89). Hypertension affects up to 25% of adolescents and 50% of adults. It is mostly systolic and is often nocturnal (90). Intensive treatment of hypertension is justified given the concerns noted above.

Ovarian Failure, Pubertal Induction, and Effects on BMD

Ovarian failure in TS begins by 18 wk gestation, after which accelerated fibrous degeneration of ovarian follicles takes place. FSH and LH levels show a rise in infancy and early childhood, gradually decline until 6 yr of age, and then rise again at the normal age of puberty (91). Up to one third of girls with TS can have spontaneous pubertal development, especially those with mosaic karyotypes (92, 93). Only a small percentage will have spontaneous menarche, with almost all eventually showing signs of ovarian failure. Spontaneous pregnancies are rare (2–5%) (93, 94).

Previous recommendations to delay estrogen replacement therapy until 15 yr of age, with the goal of preventing early epiphyseal fusion, appear unwarranted (95, 96). Current recommendations to start low-dose estrogen therapy at 12 yr of age allows for normalized development of secondary sexual characteristics, as well as uterine and bone mineral development. Earlier treatment may also improve cognitive and hepatic function and quality of life, all of which are affected in individuals with TS (58, 97–99). Low-dose estrogen treatment given at this age does not appear to impair the effects of GH treatment or significantly impair adult height when given in transdermal or depot forms (100, 101).

Recognizing that conventional BMD measurements can give falsely low readings if not adjusted for body size (102, 103), it is nonetheless clear that prolonged estrogen deficiency is linked to low BMD in adults with TS (104, 105). Despite this, a trend of declining estrogen use for young women with TS has been reported (106). Concerns for possible increased risk of breast cancer or myocardial infarction were the cited justification, although treatment with estrogens has not been shown to increase cancer risk in women with TS (107).

Recent investigations suggest that thrombosis may be more common than previously appreciated in TS, raising concerns for possible increased risk of thrombosis with hormone replacement therapy (108, 109). This is especially concerning given the SMR of 3.5 for coronary disease and 2.2 for cerebrovascular disease in individuals with TS (1). The use of transdermal estradiol (TDE) may help to alleviate these fears because TDE treatment appears to be linked to a lower risk of thrombosis when compared with oral estrogens (110, 111). In addition, TDE has been shown to improve overall body composition more favorably in TS (112). TDE patches can be cut to administer very low doses, with suggested dosing guidelines to induce and advance puberty already published (2, 113). Despite these benefits, it has been reported that only 8–10% of physicians prescribe TDE for women with TS (114).

There appears to be a reduction in cortical bone mass in women with TS independent of ovarian function (115). In addition, adolescents with TS who have spontaneous puberty and subsequent normal pubertal development have been reported to maintain normal BMD into early adulthood, whereas those with induced puberty more often do not (116). This suggests that low-dose estrogen treatment may have a role in protecting BMD if given early enough, although this has not been formally assessed in any study to date.

Long-Term Follow-Up

Additional aspects of TS that require regular follow-up are well described in published clinical guidelines (2). From these guidelines it is clear that the long-term care of individuals with TS requires input from a variety of subspecialists. The best way to ensure that all recommended testing is appropriately interpreted in the context of treating an individual with TS is to use a standardized multidisci-

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plinary approach. Freriks *et al.* (117) recently reported in *JCEM* on their experience in which all patients underwent evaluation by an endocrinologist, gynecologist, cardiologist, otorhinolaryngologist, and if needed a psychologist. They discovered many patients with previously undiagnosed BAV, COA, ETA, aortic dilation, osteoporosis, renal anomalies, hypothyroidism, celiac disease, glucose intolerance, dyslipidemia, hypertension, liver dysfunction, and hearing loss, all of which occur at higher rates in TS. Although the majority of women with TS have normal intelligence, psychological consultation was needed for many women to address complications related to the neurocognitive profile that is often seen (118). Other groups have documented similar benefits to using this approach, suggesting the value of a coordinated multidisciplinary evaluation every 1 to 2 yr, especially after transition to adult care (119, 120).

Conclusion

New insights into the care of women with TS allow for improvements in the treatment of growth failure, cardiac disease, and ovarian failure. Although screening for endocrinopathies such as thyroid disease may be straightforward, this review emphasizes that the interpretation of recommended diagnostic tests and the management of associated disorders cannot be generalized from our experience in treating each of these conditions in isolation. A revised paradigm of care using a standardized multidisciplinary evaluation, supplementing screening tests as advocated by expert opinion guidelines, can aid clinicians in interpreting the results of diagnostic tests and making treatment decisions in the context of TS. This may help to reduce the increased morbidity and mortality currently seen in this population.

Acknowledgments

The author thanks Dr. C. Becket Mahnke, Dr. Daniel Roy, Dr. Matthew Studer, and Ms. Jill Inafuku for their assistance in preparing this manuscript.

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Disclosure Summary: The author has no relevant disclosures.

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