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Turner Syndrome: An Update

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• Turner syndrome • Short stature • Long-acting growth hormone • Infertility

Key points

- Turner syndrome is the most common sex chromosome abnormality in women.
- Girls with Turner Syndrome almost all have short stature.
- Growth hormone is an effective treatment of girls with Turner syndrome.

The diagnosis of Turner syndrome is sometimes made at birth in the patient with classic physical features such as webbed neck and congenital lymphedema. Other patients are diagnosed later, when they present with either growth failure in childhood, failure to enter or complete puberty, or early ovarian failure.

INTRODUCTION

It has been more than 80 years since Henry Turner, an internist, reported in 1938 the clinical characteristics of the 7 patients whose phenotype now bears his name [1]. These women had short stature in association with sexual infantilism, webbing of the neck, low posterior hairline, and increased carrying angle of the elbows (cubitus valgus). In 1930, Ullrich described an 8-year-old girl with short stature; lymphedema of the neck, hands, and feet; subsequent neck webbing, cubitus valgus, and other phenotypic abnormalities (including a high arched palate, ptosis, low-set auricles, and small upwardly curved nails); and several other features that are now associated with Turner syndrome. This gave rise to the less common, but more appropriate eponym Ullrich–Turner syndrome.

Ullrich later recognized that his patients and those of Turner seemed to have the same condition [2]. He also called attention to the work of Bonnevie, who

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described a group of congenital anomalies in mice consisting of the distention of the neck and malformations of the ears, face, and limb buds-all secondary to the dissection of the subcutaneous tissues by fluid. This "bleb" mechanism for producing multiple anomalies was suggested by Ullrich as being responsible for the cervical lymphangiectasia noted in some human female abortuses that seemed to produce a scarred webbed neck (pterygium colli). Ullrich proposed the eponym status Bonnevie-Ullrich to describe the set of specific anomalies arising from a single mechanism (lymphangiectasia) and resulting in the phenotype of Turner syndrome.

The links among these phenotypic descriptions, the pathologic evidence of streak ovaries, and the abnormal X chromosomes came with the introduction of the technique for sex chromatin identification by Barr and the demonstration that most patients with Turner syndrome lacked sex chromatin material [3]. Initially, this absence of sex chromatin (or lack of a Barr body) was associated with "maleness" because a similar pattern was found in normal phenotypic men. Only after it was demonstrated that it was the second X chromosome that in the inactivated state constituted the Barr body was it clear that the 45,X karyotype would result in a chromatin pattern similar to the normal 46,XY karyotype.

It was not until 1961 that techniques became available for the analysis of the chromosomal constitution and the sex chromosome constitution was shown in a 14-year-old phenotypic female with Turner syndrome to be, indeed, 45,X[4]. Thus, patients with Turner syndrome were not XY males, but in most cases 45,X females. The original patient of Ullrich was studied in the 1960s and found to have a 45,X karyotype (D. Knorr, personal communication to the author). One of the original 7 patients Turner described was also reinvestigated and found to have a 45, X chromosomal karyotype [4].

INCIDENCE

Turner syndrome is the most common sex chromosome abnormality in women and occurs in approximately 1 in 2500 live births [5]. Turner syndrome is now more commonly diagnosed prenatally via amniocentesis and chorionic villous sampling. Gravholt and colleagues found that the prenatal prevalence of TS is 176 in 100,000 via amniocentesis and 392 in 100,000 via chorionic villous sampling [6]. The true prevalence, however, is uncertain as those with mild phenotypes may remain undiagnosed [7].

PATHOGENESIS

Molecular studies have shown that maternal X is retained in two-thirds of patients with Turner syndrome and paternal X in the remaining one-third [8]. More than one-half of all patients with Turner syndrome have a mosaic chromosomal complement (eg, 45,X/46,XX) detectable in peripheral blood leukocytes [9,10]. Mosaicism with a normal cell line in the fetal membranes may be necessary in all affected cases for adequate placental function and fetal survival [11].

The identification of mosaicism depends directly on the method of ascertainment. It varies from 34% with conventional cytogenetic techniques to 60% with fluorescence in situ hybridization (FISH) techniques to 74% in a study in which reverse transcriptase polymerase chain reaction (PCR) assays were used [12].

Some patients with Turner syndrome lack only part of one sex chromosome, and the Turner syndrome phenotype can be seen with a variety of structural abnormalities, such as isochromosomes, rings, or terminal deletions [13]. A rare but very informative class of Turner syndrome includes patients who have deletions of the Y chromosome that remove the testes-determining gene, SRY; these individuals develop as women. Based on this finding and the fact that men require only one X chromosome for normal development, Ferguson-Smith hypothesized that copies of Turner syndrome genes are also present on the Y chromosome.

Specific localization of Turner syndrome candidate genes proved elusive until one group successfully identified a pseudoautosomal deletion encompassing a novel homeobox gene, SHOX (short stature homeobox-containing gene on the X chromosome), which is associated with short stature not only in Turner syndrome but also in Leri–Weill dyschondrosteosis and in an estimated 2 to 15% of cases of idiopathic short stature [14–17].

The telomeres of the short arms of chromosome X and Y are logical sites for Turner syndrome genes, as sex chromosomes undergo meiotic recombination within the pseudoautosomal region and all genes in this region that have been examined escape X-inactivation. Characterization of XYp females provides additional support for the hypothesis of a distinct Turner syndrome stature locus: most of these patients have unbalanced X,Y translocations and, in the most fully documented patients with this karyotype, 2 intact copies of the pseudoautosomal region are present. It is not surprising that these patients attain normal stature, despite the presence of features consistent with Turner syndrome. As noted above, an absence of SHOX was identified as the genetic cause of the short stature phenotype in patients with Turner syndrome [14,16].

Studies that have examined the relationship between the chromosomal and karyotypic abnormalities and clinical findings in patients with Turner syndrome have been disappointing [18]. Short stature is the only clinical finding invariably associated with the 45,X karyotype; it also is the only phenotypic abnormality present in virtually 100% of patients. Specific karyotypic abnormalities may also correlate with the presence of hypothyroidism. The webbing of the neck, shield chest, and probably the ear malformations, renal anomalies, and cardiac defects may be a consequence of fetal lymphedema, which interferes with organ development [19–22].

Deletions of the long arm of the X chromosome have been reported in otherwise normal women (ie, normal stature) with secondary amenorrhea [23]. A 45,X/46,XY karyotype has been associated with a variety of phenotypes ranging from the typical phenotype of Turner syndrome to ovotesticular disorder of sexual development with genital ambiguity, to a normal male phenotype with infertility [24].

CLINICAL MANIFESTATIONS

Typical features- The most characteristic feature of girls and women with Turner syndrome is their short stature (Table 1). Other common features are a "shield" chest with widely spaced nipples, webbed neck, cubitus valgus, and Madelung deformity of the forearm. Neonates may have congenital lymphedema of the hands and feet and 2 or more of the following dysmorphic features: webbed neck, nail dysplasia, high-arched palate, and short fourth metacarpal [25]. The height of patients with Turner syndrome should be plotted on growth curves specific to this disorder [26,27].

Hearing loss, hypothyroidism, and liver function abnormalities can occur as these women get older [28,29]. Liver enzymes are mildly elevated in approximately 35 to 45% of adult patients [30,31], and improve with postmenopausal hormone therapy [30]. Intelligence is usually within the normal range, but patients may have specific neurocognitive deficits, for example, problems with visuo-spatial organization.

Other manifestations include autoimmune disease (including chronic autoimmune thyroiditis) [32] and specific morphologic defects of facial development and cardiovascular, urologic, and bone structure [28,33,34].

Ovarian failure- Although most affected women have no pubertal development and primary amenorrhea, some develop normally and then have secondary amenorrhea, while occasionally others have no morphologic defects and achieve normal stature. It should be noted that adrenarche is normal in Turner syndrome.

As an example, a retrospective study of 522 patients with Turner syndrome who were over the age of 12 years found that 84 (16%) had spontaneous menarche at an average age of 13.2 years; 30 of these women still had regular menses 9 years after menarche, and 3 became pregnant without medical assistance [35].

In a second retrospective study of 276 adults with cytogenetically proven Turner syndrome, 5 women had spontaneous puberty and spontaneous pregnancies, despite high-grade monosomy (45,X in $\geq$ 90% of a 50-cell karyotype) [36].

Manifestations in older patients include primary hypogonadism occurring either before or after puberty (gonadal dysgenesis). It is one of the most common causes of premature ovarian failure [37].

The ovaries in Turner syndrome characteristically consist of small amounts of connective tissue and no follicles or only a few atretic follicles ("streak gonads"). However, the degree of ovarian dysfunction and the extent of the defects are variable.

Careful histologic studies of the ovaries of 8 aborted 45,X fetuses many years ago are the basis of our understanding of the gonadal failure in Turner syndrome [38]. These ovaries contained apparently normal numbers of primordial germ cells for up to at least 6 weeks of gestation, but at later gestational ages, the numbers of germ cells were decreased and connective tissue was increased, as compared with age-matched normal fetuses. These results

Table 1
Clinical features in girls with Turner syndrome

Physical diagnosis		Percentage affected
Skeletal	Short stature	100
	Short neck	40
	↑ Upper: lower body ratio	97
	Cubitus valgus	47
	Short metacarpal	37
	Scoliosis	12.5
	Madelung deformity	7.5
	Micrognathia/high palate	60
Lymphatic obstruction	Neck Webbing	25
	Low posterior hairline	42
	Edema of hands/feet	22
	Nail dysplasia	13
Others	Strabismus	18
	Ptosis	11
	Multiple nevi	26
Screening Evaluation		
Cardiovascular anomaly	All	44
	Bicuspid aortic valve	30
	Aortic coarctation	12
	Dilated aorta	11
	Other*	12
Renal anomaly	All	18
	Horseshoe Kidney	11
	Duplicated collecting ducts	4
	Unilateral agenesis	3
Liver disorder	All	36
	Abnormal liver function tests(LFTs)	27
	Fatty infiltration	19
Hypertension	All	34
	Prehypertension	14
	Overt hypertension	20
Autoimmunity	All	51
	Hashimoto thyroiditis	51
	Graves' disease	1
	Type 1 diabetes	0
	Celiac	5
	Inflammatory bowel	3

''Physical Diagnosis'' describes findings from physical examinations of more than 200 girls seen by Drs Barbara Lippe and paul Saenger between 1985 and 2000. Information on puberty development is not included because many girls were not old enough to assess. The ''screening evaluation'' data are from 100 girls aged 7 to 17 who underwent standardized imaging laboratory testing as a part of the NIH natural history study performed between 2001 and 2008. The cardiovascular evaluation included MRI and cardiac echo. Under the cardiovascular listing, the ''other'' category included partial anomalous pulmonary veins, aberrant right subclavian monitors. All patients also had renal and hepatic ultrasound studies. Abnormal liver function was defined as greater than 10% elevation of aminotransferase(s). Hashimoto's was defined by the history of clinical hypothyroidism or elevation of circulating thyroid antibodies.

indicate that the gonadal dysgenesis may be caused by accelerated apoptosis rather than abnormal germ cell formation.

Another study evaluated 104 girls aged 0.2 to 17.4 years with complete or partial X chromosome deletions using pelvic ultrasonography [39]. Approximately one-third have visible, nonstreak ovaries. The girls with visible ovaries had apparently normal ovarian growth and follicular development up to the time of puberty, and were more likely to have spontaneous breast development and uterine growth, indicating some ovarian function; many, but not all, of these girls had incomplete X chromosome deletions. These findings are consistent with several case reports of adult women with both 45,X and partial X deletions who have conceived and borne children before developing secondary amenorrhea [40,41].

Thus, the consequences of X chromosome deletions are highly variable, ranging (at the extremes) from intrauterine death to normal health with normal menarche and normal reproductive function for a few years thereafter. The incidence of 45,X and 45,X/46,XX mosaic karyotypes in women with normal fertility is unknown.

Only one X chromosome is active in somatic cells after the third week of gestation. As a result, deletion of any part of one X chromosome will affect fertility only if the normal copies of the missing gene or genes do one of the following:

- Imprint somatic cells before 3 weeks of gestation
- Escape inactivation so that 2 copies are normally required
- Are critical for oocyte development (as oocytes have 2 active X chromosomes).

Short stature– Short stature combined with a square appearance is the most common clinical feature of Turner syndrome. The adult height of untreated patients correlates significantly with midparental height (ie, the height corresponds to the average of the height percentiles of the mother and the father).Is this correct? I would have thought for the untreated patients, the height would be lower than that correlated with midparental height. Recombinant human growth hormone therapy is recommended to maximize final height (see later in discussion).

Renal anomalies–Renal anomalies are common in patients with Turner syndrome. Congenital malformations of the urinary system are present in approximately 30 to 40%. The most common abnormalities are collecting system malformations (20%) and horseshoe kidneys (10%), followed by malrotation and other positional abnormalities (5%) [5]. Patients should undergo renal ultrasonography at the time of diagnosis, and, if structural abnormalities are identified, the patient should be monitored yearly for urinary tract infection.

Anomalies associated with the obstruction of the ureteropelvic junction can produce clinically significant hydronephrosis or pyelonephritis. Idiopathic hypertension is common in Turner syndrome, even in the absence of recognizable renal or cardiac malformations. Blood pressure should, therefore, be monitored carefully, and hypertension treated vigorously.

Cardiovascular disease–There is an increased risk of cardiovascular morbidity in women with Turner syndrome, presumably due to their risk of cardiovascular malformations, renal abnormalities, and hypertension [42,43]. The malformations are associated with increased risks for aortic dissection and increased mortality rates. Neck webbing and increased thoracic anterior-to-posterior diameters are predictors for cardiovascular abnormalities [44].

In a series of 173 patients with Turner syndrome at a single center, the following rates of cardiac malformations were reported [43]: any malformation 44.5%; aortic valve abnormalities (primary bicuspid aortic valve) 34.1%; aortic arch abnormalities (primarily coarctation) 19.1%; systemic venous abnormalities 8.1%; ventricular septal defects 5.2%; pulmonary venous abnormalities 4%; hypoplastic left heart/single ventricle 3.5%, atrial septal defects 1.7%; coronary artery abnormalities 1.6%.

Coarctation/aortic valve disease–The prevalence of cardiovascular malformations in patients with Turner syndrome is variable across studies. Approximately 30% have aortic valve disease, while up to 30% have coarctation [42,43,45–47]. Patients with the relatively common anomaly of a bicuspid aortic valve are more likely to have other cardiovascular abnormalities, such as aortic arch defects [43,47]. The variability among estimates could be due to differences in the age group examined, the degree of mosaicism in the population, or a technical difficulty in visualizing the valvular defect using echocardiography. Usually, MRI will give better results than echocardiogram because shield chest phenotype in patients with Turner syndrome can cause challenges for reliable echocardiograms. The prevalence of cardiovascular malformations seems to be higher in those with 45,X compared with those with a mosaic chromosomal complement (45,X/46,XX) (38 vs 11%) [45]. Even when initial magnetic resonance imaging does not show aortic root dilation or coarctation, subsequent imaging may show the development of these abnormalities during the next 2 to 6 years [48].

Aortic dissection–Aortic dissection or rupture is an increasingly recognized cause of death in women with Turner syndrome [49,50]. In a study of 166 women with Turner syndrome and 26 healthy controls, one-third of the patients had aortic size index values (ascending aortic diameters normalized to body surface area) greater than the 95th percentile (2.0 cm/m^2) [50]. After 3 years of follow-up, aortic dissections occurred in 3 patients (all 3 had an aortic size index >2.5 cm/m^2), for an annualized rate of 618 cases/100,000 woman-years, approximately 100-fold higher than that seen in women of similar age without Turner syndrome. In a report of 20 women with Turner syndrome who had already experienced an aortic dissection, mean aortic size index as 2.7 ± 0.6 cm/m [2,51].

Pregnancy–Of greater concern is a possible increase in mortality due to aortic dissection or rupture that has been reported in women with Turner syndrome achieving pregnancy through in vitro fertilization (IVF) with oocyte donation [52]. Therefore, before attempting to become pregnant, women with Turner syndrome should undergo a complete medical evaluation, with particular

attention paid to blood pressure, cardiovascular and renal function, as recommended by the American Society of Reproductive Medicine [53].

To minimize the risk of dissection, the authors suggest close cardiovascular monitoring in patients with Turner syndrome with a dilated ascending aorta [37].

Hypertension–Hypertension is more common in women with Turner syndrome compared with controls [54–56]. In a series of 62 patients (age range 5–22 years) with Turner syndrome, 30% were mildly hypertensive and 50% had an abnormal diurnal blood pressure profile as measured by 24-h ambulatory blood pressure monitoring [54], the physiologic nighttime dip in blood pressure did not occur. Neither the presence of renal or cardiac abnormalities nor treatment with growth hormone or estrogen had an effect on blood pressure.

Other–Other cardiovascular anomalies have been reported in patients with Turner syndrome. A prolonged QT interval has been reported in some series, including in young children with Turner syndrome [57–60]. In a study of 93 women with Turner syndrome, 11 with 46,XX primary amenorrhea, and 25 normal controls, mean carotid intima-media thickness was increased to a similar degree in the 2 hypogonadal groups, suggesting a primary role for estrogen deficiency [61]. However, the patients with Turner syndrome had additional abnormalities when compared with both the 46,XX primary amenorrhea and control groups, including increased common carotid, aortic root, and brachial artery diameters, suggesting additional genetic factor that contribute to their vasculopathy.

Osteoporosis–Osteoporosis and fractures have been reported to be common in women with Turner syndrome, thought to be due to both ovarian failure and possibly haploinsufficiency for bone-related X chromosome genes [62,63]. However, in some studies, patients who receive standard estrogen therapy seem to have normal bone density when compared with age-matched healthy women. As an example, in a study of 70 adult women with Turner syndrome who underwent bone mineral density testing (by dual-energy x-ray absorptiometry [DXA]), osteoporosis was diagnosed in 7 (10%), six of whom were more than 45 years [64]. None of the women with osteoporosis had ever received prolonged estrogen replacement. Fracture rates in the patients who had received estrogen therapy were no different from age-matched controls while in untreated patients, fracture rate was markedly elevated, radial fracture being the most common.

Some of the osteopenia reported in patients with Turner syndrome may be due to an underestimation of bone mineral density in short subjects. This was suggested in a study of 40 adult women with Turner syndrome, in which osteoporosis was overdiagnosed in patients less than 150 cm tall unless bone mineral density measurements were adjusted for body size (and therefore bone size). After adjustment for body size, the prevalence of osteoporosis and fractures in patients with Turner syndrome who had been treated with estrogen was the same as age-matched controls without Turner syndrome [65].

However, the ideal controls to which patients with Turner syndrome should be compared are women with ovarian failure and a normal karyotype, thereby controlling for the ovarian hormone deficiency. In a study comparing 41 women with Turner syndrome to a control group of 35 karyotypically normal women with premature ovarian failure, a selective reduction in cortical (forearm) bone mineral density was seen in patients with Turner syndrome [66]. This difference persisted after adjustment for height, age of puberty, lifetime estrogen exposure, and serum 25-hydroxyvitamin D concentrations.

Thus, there seems to be a selective reduction in bone mineral density in women with Turner syndrome that is independent of ovarian hormone exposure.

Risk of malignancy–Women with Turner syndrome whose karyotype includes a Y chromosome (such as 45,X/46,XY mosaicism), are at increased risk for gonadoblastoma, a neoplasm that occurs in dysgenetic gonads [67]. In a population-based study that included 3425 women with Turner syndrome followed for a mean of 17 years, 5 women, all with Y chromosome material, developed gonadoblastoma (cumulative risk of 7.9% by age 25 years) [68].

These patients may also be at increased risk for other tumors. In the population-based study noted above, the overall risk of cancer was not increased, but site-specific risks were increased for meningioma, childhood brain tumors, bladder, and uterine cancer (but not breast cancer), when compared with the general population. However, the clinical importance of this finding is unclear, as the number of cases was small.

The risk of breast cancer has been a concern in women with Turner syndrome who receive long-term postmenopausal hormone therapy, but no excess risk has been reported thus far.

Ocular abnormalities–Ocular abnormalities are common among patients with Turner syndrome [69]. Amblyopia, strabismus, ptosis, hypertelorism epicanthus, farsightedness, and red-green color blindness have been noted in small case series [70,71]. Keratoconus, glaucoma, anterior lenticonus, cataracts, retinal vascular changes, and retinal detachment have been noted in case reports [69,72].

Autoimmune disorders–Turner syndrome is associated with an increased risk of autoimmune disorders, most importantly hypothyroidism (Hashimoto's thyroiditis), celiac disease, and inflammatory bowel disease [32,73,74]. The best evidence comes from a prospective study of autoimmune diagnoses in women with Turner syndrome (n = 244) or karyotypically normal (46,XX) primary ovarian insufficiency (POI; ovarian failure) (n = 457), compared with normative data for the United States population of women [32]. Autoimmune hypothyroidism (Hashimoto's thyroiditis) occurred in 37% of women with Turner syndrome compared with 15% in women with POI; the prevalence in both groups was higher than that in normally cycling women (5.8%).

The prevalence of both inflammatory bowel disease and celiac disease was significantly increased in Turner syndrome (4 and 2.7%, respectively), but not in POI. No other autoimmune diagnosis, including type 1 diabetes or hyperthyroidism due to Grave's disease, was increased.

In the second study of 389 girls with Turner syndrome screened with IgA antigliadin antibodies and/or antiendomysial antibodies, 25 (6.4%) had celiac disease [75]. Of these, 10 had typical symptoms, 8 had atypical symptoms, and 7 had no symptoms. The prevalence of celiac disease in the general population is estimated to be 1 in 184 (0.54%) [37].

Metabolic issues–Patients with Turner syndrome are at risk for metabolic disorders. Insulin resistance, as measured by euglycemic clamp studies, is an early metabolic defect in girls with Turner syndrome [76]. Abdominal adiposity is lower and glucose tolerance better in growth hormone-treated girls with Turner syndrome compared with untreated girls [13]. In addition, an increased frequency of central obesity, insulin resistance, type 2 diabetes, and dyslipidemia has been reported in adult women with Turner syndrome when compared with women without Turner syndrome [29].

Skin–Girls with Turner syndrome may be more likely than others to develop pilomatricoma, an uncommon benign skin neoplasm thought to arise from cells of the hair follicle [77–81]. In one study, these asymptomatic papules or nodules that most typically develop as single lesions on the head or neck were identified in 8 of 331 patients (2.6%) with Turner syndrome; there was no association between prior growth hormone therapy and the presence of skin lesions [77]. Although the prevalence of pilomatricoma in the general population is not known, it is thought to be considerably lower than 2.6%.

An increased rate of pigmented nevi has been reported in Turner syndrome [80] especially after growth hormone treatment, but a higher rate of melanoma has not; in fact, a lower rate has been observed [81]. It was previously thought that the risk for keloid formation was increased in these patients, but that is no longer the case.

Otologic Disorders–Perhaps the most common medical problem experienced by girls with Turner syndrome is bilateral otitis media. Anderson and coworkers [82] first described medically significant middle ear pathology in girls with Turner syndrome, with many recurrent episodes, spontaneous perforations, frequent need for surgical treatment, and significant hearing loss in about 25%. Additional studies confirmed the problem of recurrent, often refractory, otitis in Turner syndrome, usually associated with conductive hearing loss and correlated with karyotypes demonstrating loss of the C chromosome short arm, XP [83–86].

The chronic and severe otitis does not seem to be related to a specific or generalized immunologic dysfunction. Other types of infections and disorders of the mucous membranes do not occur with increased frequency in Turner syndrome. It seems rather that the frequent otitis may be the consequence of abnormalities in the growth of the cranial base disturbing the relationship of the middle ear to the Eustachian tube, which coupled with abnormalities in the shape of the palate, create a predisposition to fluid collection and secondary infection.

Conductive hearing loss is most common and severe in children and is correlated with middle ear pathology [83], whereas sensorineural hearing loss is

more common in adults. This sensory defect is generally bilateral and characterized by symmetric sensorineural dips in the audiogram in the midfrequency range. Thus, the sensorineural hearing deficit seems to progress over time and is not strictly a congenital abnormality. There remains a significant conductive component of hearing loss in adults with Turner syndrome that may signify ongoing middle ear pathology [83]. The assiduous treatment of ear, nose, and throat problems in childhood and avoiding potential injuries to the inner ear may reduce the risk of hearing loss.

Liver disease–Minor elevations of hepatic aminotransferases are common in girls and women with Turner syndrome, usually in the absence of signs or symptoms of liver disease. Approximately 20% to 25% of girls [87] and 40% of women [88] demonstrate abnormal liver function tests including aspartate-, alanine-, and gamma-glutamyl transferaseand, less commonly, alkaline phosphatase. In some cases, liver enzyme elevations may be associated with pharmacologic estrogen, progestin, or oxandrolone treatments [87,89], but over the long-term estrogen treatment is associated with the normalization of hepatic enzymes [88]. Among 100 girls from age 7 to 17 evaluated in the NIH natural history study between 2002% and 2007%, 27% had modest transaminase elevation that was not correlated with growth hormone (GH) or estrogen use, nor with fatty infiltration observed on liver ultrasound [90]. Aside from a rare case report, there does not seem to be any association between autoimmunity and hepatic abnormalities. Liver biopsies in adults with typical enzyme abnormalities have not consistently defined any unique or diagnostic pathology in women with Turner syndrome [91]. Roulot and coworkers have suggested hepatic disorder may be linked to intrinsic vascular disease. Gravholt and colleagues reported an increased frequency of cirrhosis in a Danish National Health registry study, but this has not been observed in clinical series on health in patients with Turner syndrome.

MANAGEMENT

Once the diagnosis of Turner syndrome has been established and a chromosomal confirmation established, additional diagnostic procedures are indicated. These diagnosis and management strategies have been published as recommendations from consensus workshops [92].

Initial and Follow-up Evaluation–Screening studies at the time of diagnosis and ongoing monitoring for age groups are summarized in Table 2. All newly diagnosed patients require a thorough cardiovascular evaluation. Blood pressure should be measured in all 4 extremities, and 24-h ambulatory monitoring may be helpful in detecting nocturnal hypertension in girls as disappearance of the night time dip in blood pressure is one of the earliest signs of beginning hypertension. Routine renal ultrasound may detect structural abnormalities in renal architecture or collecting system anatomy. If no abnormalities are present, follow-up studies are not routinely indicated. If significant abnormalities are detected, follow-up evaluation and therapy may be indicated and long-term screening for urinary tract infection may be necessary. Scoliosis and

Table 2
Recommendations for screening in Turner syndrome (excluding cardiac and neuropsychological screening recommendations)

	At diagnosis	After Diagnosis (Childhood)	After Diagnosis (adults)
Weight/BMI	Yes	Every visit	Every visit
Blood pressure	Yes	Every visit	Every visit
Thyroid function tests (TSH and T4 or free T4)	Yes	Annually beginning around 4 y of age	Annually
Lipids			Annually if at least 1 cardiovascular risk factor[a] or regional recommendation
Liver enzymes (ALT, AST, GGTP, and alkaline phosphate)		Annually after 10 years of age	Annually
HbA1c with or without fasting plasma glucose		Annually after 10 years of age	Annually
25-hydroxyvitamin D		Every 2–3 y after 9–11 y of age	Every 3–5 y
Celiac screen		Starting at 2 y; thereafter, every 2 y	With suggesting symptoms
Renal ultrasound	Yes		
Audiometric evaluation	Yes[b]	Every 3 y	Every 5 y
Ophthalmologic examination	Yes[c]	Every 3 y	
Dental evaluation	Yes, if no previous care has been established		
Clinical investigation for congenital hip dysplasia	Yes, in newborns		
Skin examination	Yes	Annually	Annually
Bone mineral density			Every 5 y and when discontinuing estrogen
Skeletal assessment		Spine radiographs at 5–6 y and at 12–14 y of age	

The recommendations are for screening only. A clinical suspicion of active disease should always lead to relevant investigations. For details, please refer to UpToDAte topic text, or to the guideline cited later in discussion.

Abbreviations: ALT, alanine aminotransferase; AST, Aspartate aminotransferase; BMI, body mass index; GGTP, Gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; T4, thyroxine; TSH, Thyroid-stimulating hormone.

[a]Cardiovascular risk factor: hypertension, overweight, tobacco use, diabetes, and physical inactivity.

[b]When 9 to 12 month old.

[c]When 12 to 18 month old.

From Gravholt CH et, al; International Turner Syndrome Consensus Group. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017 Sep;177(3):G1-G70. https://doi.org/10.1530/EJE-17-0430. PMID: 28705803.

kyphosis are evaluated at diagnosis and during growth. If noted, the degree and cause of scoliosis should be determined radiographically.

Otologic and ophthalmologic consultations should begin by age 2 to 3 years and continue as clinically indicated. Otitis media is extremely common and should be treated vigorously. Myringotomy and polyethylene tube placement are considered the primary modes of therapy for serous otitis media in Turner syndrome. The high prevalence of hearing loss, either primary or secondary to residual serous otitis media, mandates that regular ENT evaluation with audiometry is needed for most patients. In infancy, feeding measures such as specific bottles and nipples often used for patients with cleft palate may also be indicated. Because abnormalities in speech may be a consequence of palatal deformity, speech evaluation is needed for most girls by age 7, as the narrow palate and small jaw cause malocclusion and crowded dentition frequently requiring orthodontic treatment.

Screening for autoimmune thyroid and celiac diseases begins at age 4 and includes thyroxine, thyroid-stimulating hormone, antithyroid antibodies, and tissue transglutaminase antibodies. Subsequently, thyroxine and thyroid-stimulating hormone or thyroid-stimulating hormone alone should be determined at 1- to 2-year intervals. Celiac screen is usually repeated every few years or as indicated by signs or symptoms. Metabolic screening including liver function tests, renal function tests, fasting glucose, or hemoglobin A1c and lipids should commence at about age 10 or earlier in the context of excess adiposity.

Hypertension is common in Turner syndrome, and blood pressure should be measured at each visit. In addition, 24-h ambulatory monitoring is ideal for detecting nocturnal or stress-related hypertensive episodes that may support the introduction of antihypertensive treatment.

The decision to seek consultation for plastic surgery to correct the webbed neck deformity or the forwardly displaced ears is individual. It must be pointed out to the patient and family that in addition to the webbing, the neck may also be short. Therefore, cosmetic surgery may be somewhat disappointing. In some cases, however, satisfactory results are achieved. Potentially increased keloid formation after plastic surgery should be discussed with the patients.

If, or when, psychometric testing should be performed is an individual family decision. Nevertheless, a preschool evaluation to rule out major areas of cognitive dysfunction might be advisable. School performance should be monitored, and specific problems should be attended to with skilled cognitive specialists. Girls with hearing loss will benefit from preferential seating in the classroom, and those with attention deficit disorder (ADD) may benefit from untimed testing in school when appropriate. The Turner Syndrome Society of the United States (www.turnerysyndrome.org) is an excellent resource.

Growth hormone–In the 1990s, recombinant human growth hormone (GH) was shown to increase growth velocity and final adult height for girls with Turner syndrome. Rosenfeld and coworkers demonstrated a gain in height compared with historical controls [92] and Sas and colleagues showed a clear

dose-response effect with increasing GH doses associated with increasing height [93]. The first randomized study with an untreated contemporaneous control group showed that adult height was increased by about 7.3 cm after an average duration of 5.7 years of treatment, at a dose of 0.3 mg/kg/wk [94], which is lower than the current recommended dose of 0.375 mg/kg/wk. Very young girls 9 months to 4 years of age treated with GH maintained a normal growth rate compared with untreated Turner controls [95]. The results of a randomized, double-blind, placebo-controlled study begun at the NI in the Netherlands in 1987 showed an average gain in adult height of 3 cm with GH alone, and 5 cm with GH combined with prepubertal treatment with ultra-low-dose ethinyl estradiol [96]. The ethinyl estradiol dose for girls younger than 12 in the NIH study was less than 1 μg/d, compared with 20 μg in the low-dose birth control pill. These findings are consistent with a growth promoting effect of low, nonfeminizing estradiol levels in the prepubertal years. The growth-enhancing effects of low-dose estradiol are in contrast to the growth-inhibiting effect of feminizing doses of estrogen used to induce pubertal development [97], which is associated with epiphyseal fusion. Ranke and colleagues analyzed height prediction for GH treatment in Turner syndrome [98]. Height at the start of treatment, GH dose, and duration of treatment are identified as important predictive factors.

GH treatment has been evaluated for safety in a group of approximately 5000 girls with Turner syndrome followed for 10 to 20 years in the Genetech National Cooperative Growth Study [99]. An increased frequency of intracranial hypertension (pseudotumor cerebri), scoliosis, and slipped epiphyses was noted, as well as an unexpected higher incidence in the diagnosis of type 1 diabetes. On the beneficial side, GH treatment tends to normalize body proportions, although foot size is disproportionally enlarged [100]. GH treatment has beneficial effects on body composition, as shown in a comparison of age-matched girls who have never received GH ($n = 26$) to girls treated with GH ($n = 76$) participating in the NIH natural history study. BMI and visceral adiposity were significantly greater and glucose tolerance significantly worse in the untreated group (off GH treatment of 2 weeks before and during the study), with effects apparent years after the discontinuation of therapy [101].

GH treatment seems to have no adverse effects on the cardiovascular system over short-term follow-up, with body size-adjusted ventricular and aortic dimensions similar in treated and untreated patients [102,103]. Moreover, systemic lipids and aortic compliance were relatively better in girls treated with high-dose GH. A comparison of cortical and trabecular bone in GH-treated and age-matched untreated controls with Turner syndrome reveals no apparent effect of GH treatment on bone mineral density [104].

Late diagnosis of Turner syndrome in girls age 10 and older is a common problem that compromises the attainment of optimal adult stature. In the past, such girls were treated with GH for several years and induction of puberty was delayed to age 15 or older. Such a delay in puberty is now viewed as detrimental to social and sexual development and may impair optimal bone

mineralization. Statural growth in these girls may be increased by treatment with the nonaromatizable androgen oxandrolone at a dose of 0.05 mg/kg/d or less, in addition to GH, which may augment growth by up to 4 cm, usually without virilizing effects [105,106]. Oxandrolone is also used to enhance stature when GH is not available, but patients and families must be warned about potential adverse metabolic effects and diminution of breast development associated with androgen treatment.

GH treatment usually begins at the standard recommended dose of 0.05 mg/kg/d, with close monitoring for height velocity, IGF1 level, and potential adverse effects of intracranial hypertension, scoliosis, and slipped capital epiphyses. Treatment of 3 to 4 years is usually required to experience significant height gain and is discontinued when the target height is attained, when bone age is greater than 14 years, or when growth velocity is less than 1.5 cm per year. It is important to keep in mind that the safety data for GH in Turner syndrome represent intermediate-range follow-up of girls in whom treatment was typically initiated in mid-childhood and continued for several years at the preceding dosage. Although reaching an adult height of 5 feet or greater seems desirable from many points of view, there are as yet no proven medical or psychosocial benefits to this pharmacologic achievement, and hence safety should never be compromised to this end.

Extensive reviews of the emerging field of long-acting growth hormone (LAGH) have recently seen published, including by the author of this article [107–109]. The approaches taken for the development of LAGH preparations vary and can influence the pharmacokinetics and/or the pharmacodynamics of rhGH. To date, LAGH preparations have been developed using various approaches to prolong GH action, including forming emulsions (using gelatin and triglycerides), GH encapsulation (using degradable microspheres), GH pegylation, GH conjunction (to albumin or amino acid ''tails''), and GH fusion proteins (by means of linking an inert peptide with rhGH at a region that does not interact with the growth hormone receptor) [107,109].

As the era of LAGH approaches, we need to consider whether there will be additional safety risks of LAGH compared with daily rhGH. In this regard, we need to consider issues related to the persistent elevation of GH and GH-related biomarkers, such as IGF1, as well as issues related to the mechanism of making GH long acting. Depending on the structure of LAGH, there may be off-target effects due to components of LAGH not present in rhGH. Treatment with daily rhGH given at bedtime attempts to mimic the normal daily profile of increased GH production overnight. However, daily rhGH is a single peak of GH action, which differs from the physiologic GH production of multiple GH pulses of different durations and intensities. Thus, our current daily rhGH treatment regimen does not provide a physiologic GH profile. LAGH products will likely have different pharmacokinetic profiles of GH release from the injection site into the bloodstream, to the target tissue, and to the GH receptor. The peak and trough levels of IGF1 during daily rhGH and LAGH therapy have been an area of intense debate. The goal of GH therapy

has been to increase the IGF1 to promote growth. It remains to be determined whether LAGH will achieve similar or better growth than daily rhGH and whether individualizing LAGH therapy to target IGF1 to the upper part of the normal range would improve efficacy without decreasing safety. Due to the differing pharmacodynamics profile or different forms of LAGH, it will be important to determine the best time to measure IGF1 for safety and efficacy [110].

Puberty–As noted earlier, spontaneous puberty develops in 10% to 30% of girls with Turner syndrome. The higher rate applies mainly to girls with mosaicism for cells with more than one X chromosome, but a significant number of girls with less favorable chromosomal constitutions will also start puberty on their own. Aside from karyotype, the major indicators of potential natural pubertal onset are normal-range values for FSH and anti-Mullerian hormone (AMH). AMH may be particularly informative, because hormone levels directly reflect the presence of developing ovarian follicles and hence potential fertility [111]. Pelvic ultrasound may be helpful, although failure to visualize ovarian tissue does not preclude the presence of follicles. Patients and families are often very interested in potential fertility, and the clinician needs to have this information to provide counseling about reproductive options (discussed later). In most girls more than the age of 10, FSH will have elevated into the menopausal range, and AMH will be undetectable with pelvic ultrasound showing no evidence of ovaries and an immature uterus; these patients will need pubertal induction and maintenance estrogen/progestin treatment.

The aim of estrogen treatment in Turner syndrome is to mimic the beneficial effects of endogenous estrogen in breast and genital development, healthy fat distribution, and bone mineralization, while minimizing the risk for estrogen-associated gynecologic cancers and thrombogenic complications. In the past, the choice for estrogen treatment was limited to metabolized estrogens purified from pregnant mare urine (conjugated equine estrogens [CEE], "Premarin."), and the highly potent, synthetic ethinyl estradiol (EE2). In recent years, transdermal patches containing the natural ovarian product, 17-beta estradiol have become available and are now the preferred delivery method. In addition to replicating the molecular action of the ovary's natural hormone, this formulation is directly absorbed into the venous circulation, bypassing first-pass hepatic effects associated with excessive production of prothrombotic proteins. Moreover, the administration of transdermal estradiol allows the measurement of estradiol levels in the circulation, which may be helpful for monitoring adherence. Because estradiol levels vary widely throughout the monthly cycles in eugonadal females, target estradiol levels in pharmacologic treatment are not known. In sexually mature girls, the average daily ovarian estradiol production over the monthly cycle is 100 μg/d, which is approximated by transdermal patches delivering 100 μg/d. Physiologic estradiol repletion is not expected to normalize the FSH level, because FSH secretion is jointly regulated by estrogen and other ovarian products such as the inhibins. Thus, suppression of FSH is not a measure of adequate estrogen therapy.

Current recommendations for estrogen treatment of the induction of puberty suggest beginning the therapy at age 12 for most girls [112]. The aim of treatment is to initiate development with the lowest possible dose so that sexual maturation will begin on par with peers, while avoiding premature fusion of the epiphyses that would limit growth in stature. Thus, breast development and bone age are evaluated at 6-month intervals during estrogen treatment of pubertal induction. A sufficient phase of "unopposed" estrogen exposure is required for optimal breast development, and androgen or progesterone treatments may inhibit optimal development. Thus, oxandrolone should be discontinued before the initiation of estrogen treatment, and progestins should not be initiated until breast development is satisfactory. Some girls with prominent stigmata of fetal lymphedema may have damaged breast anlage and demonstrate minimal development in response to estrogen. These girls may benefit from breast implantation surgery, if so inclined.

Progestin treatment is necessary to suppress estrogen's proliferative effect on the uterine endometrium and should be introduced after 1 to 2 years of unopposed estrogen treatment, or sooner if breakthrough bleeding occurs. This recommendation is given because chronic exposure to estrogen treatment, in the absence of progestin effect, leads to endometrial hyperplasia and risk for hemorrhage and neoplasia. The most physiologic form of progestin is progesterone, which is available in a micronized form for oral administration and in cream and gel form. Regrettably, there have been no controlled studies to establish the most effective form of estrogen/progestin treatment of girls with Turner syndrome. The accepted dose of oral micronized progesterone proven to protect the uterus is 200 mg taken at bedtime for the last 10 to 12 days of a monthly cycle, or the last 20 to 30 days of a trimonthly cycle. Progesterone is soporific and hence the bedtime administration. The efficacy of topical progesterone in preventing uterine hyperplasia is unknown. More androgenic, synthetic progestins such as medroxyprogesterone or norethindrone may inhibit optimal breast and uterine development and have unfavorable metabolic effects in some individuals, although these agents are effective in endometrial protection.

Patients and families must be educated as to the importance of this physiologic hormone treatment regimen for healthy growth and development, especially with regard to building and maintaining strong bones. Discontinuation of hormone therapy during young adulthood is all too common and may result in irreversible loss of bone minerals especially in the spine, leading to height loss, kyphosis, and chronic pain and disability. Families may have legitimate concerns about the risks of heart disease and cancer associated with hormone replacement therapy, and it must be explained that these adverse effects were observed in postmenopausal women receiving less physiologic forms of treatment. It is also important to discuss "natural" hormones that are widely touted on women's health sites as an alternative to standard treatments underlining the fact that these products are not known to be effective or safe. Many older girls and young women may prefer taking oral or transdermal contraceptive

formulations for reasons of convenience, tolerability, or financial concerns. Although these are not the most physiologic choices and have greater thrombogenic risk, estrogen/progestin contraceptive formulations are effective in maintaining bone mineralization and protecting the uterus.

It is important to point out that spontaneous puberty, even with menses that seem cyclic, does not always mean that normal ovulatory cycles are occurring or will continue to occur. Some girls have anovulatory cycles that do not achieve normal endometrial maturation and predispose them to endometrial hyperplasia, dysfunctional bleeding, or cancer. Irregular cycles may lead to the discontinuation of treatment in many cases. Every effort should be made to educate patients and parents as to the importance of continuing hormone replacement, with openness to consultation with experts in adolescent gynecology and adoption of alternative regimes such as oral contraceptive treatment that may ensure continued adherence. Girls with irregular cycles may still have an occasional ovulatory cycle and, if sexually active, are at risk for unplanned pregnancy. For these girls, contraceptive formulations may be the best choice for hormone therapy.

Hormone treatment requires regular breast examinations, and patients should be instructed about monthly self-examination. Girls who become sexually active need regular gynecologic follow-up with annual pelvic examinations and Pap tests. Regular discussion of issues of concern related to sexual maturation and counseling on the need for ongoing hormone treatment to maintain strong bones will be of paramount importance. There is no need to measure bone mineral density during childhood or adolescence unless there is an unusual clinical concern-for example, a low-impact or atraumatic fracture. Short stature is associated with the underestimation of bone mineral density obtained by DXA and results need to be normalized for bone size [113]. Size-adjusted vertebral bone mineral density is usually normal in adults with Turner syndrome that have received routine hormone replacement treatment, but it may decline dramatically with the discontinuation of treatment [114]. Bone mineral density of the hip and wrist is often lower than normal, reflecting a selective reduction in cortical bone that is not sensitive to estrogen [115] but may reflect the SHOX defect in bone.

Reproductive options–About 2% of women with Turner syndrome may have spontaneous pregnancies. Assisted reproduction using donor oocytes with in vitro fertilization has been successful when the uterus has been given adequate hormonal preparation before embryo transfer [116]. However, both spontaneous and assisted pregnancies are associated with a high risk for maternal complications, including catastrophic aortic dilatation, dissection, and rupture [117]. In most well-documented cases, the women had preexisting risk factors for dissection such as bicuspid aortic valve or aortic coarctation, although these problems were often not detected before pregnancy due to inadequate screening [118]. Patients known to have such defects should be counseled about alternatives to pregnancy such as adoption or surrogacy. If not already done, girls and young women with Turner syndrome should have a

cardiovascular MRI before getting involved in counseling about reproductive options, because significant aortic malformations are often not detected on routine echocardiography and their presence would discourage planning for pregnancy. Girls with ovarian function may be candidates for the cryopreservation of recovered oocytes or ovarian tissue obtained by laparoscopy [116] given the very high probability of premature ovarian failure. This technology has been successful in preserving fertility for girls and women undergoing cancer treatment, although pregnancy resulting from this approach has not yet been reported in Turner syndrome. Girls and families interested in this possibility should be referred to reproductive endocrinology specialists associated with an academic medical center for consultation.

Psychological and educational issues–Psychologic assessment should be part of the initial evaluation and ongoing management plan for each child with Turner syndrome. Assessment of intellectual skills, learning skills, motor skills, and social maturity is recommended before enrollment in preschool programs [119]. Intelligence is usually normal, except in the rare patient with a tiny X-ring chromosome, who may have severe mental retardation because tiny X-ring chromosomes fail to undergo X inactivation [120,121].

Although most individuals with Turner syndrome have normal intelligence, there are increased risks for selective impairment in nonverbal skills [5,122]. This may include deficits in social cognition; difficulty with nonverbal problem-solving tasks such as mathematics; psychomotor deficits, such as clumsiness; and problems with visual-spatial organization, which may cause difficulty driving [18]. There is also an increased risk of attention deficit disorder. By contrast, verbal skills are often strong. These neurodevelopmental abnormalities may result from the X chromosome monosomy or from sex steroid deficiencies due to gonadal dysgenesis.

Imprinting by material from the paternal X chromosome was suggested in one report, implying that social functioning is influenced by an imprinted gene on the X chromosome that is switched off when this gene is inherited from the mother [123]. The existence of such a gene may partly explain the male–female differences in social cognition; it does not, however, provide an explanation for all psychological findings in Turner syndrome. Such an explanation would most likely involve an interplay between many genes and interacting environmental factors.

As these young women make the transition to independent living, counselors should stress that their learning difficulties do not disappear with age.

Family support–Information for caregivers and patients can be obtained from:

Turner Syndrome Society of the United States Tel: 1 to 800 to 365 to 9944
www.turnersyndrome.org
Turner Syndrome Society of Canada Tel: 1 to 800 to 465 to 6744
www.TurnerSyndrome.ca
Turner Syndrome Society of UK Tel: +44(0)1389 to 380385
www.tss.org.uk/

SUMMARY

- Turner syndrome, the most common sex chromosome abnormality (loss of part or all of an X chromosome), affects approximately 1 in every 2500 liveborn female newborns. It is a disorder of growth and development that is almost always associated with short stature and primary amenorrhea due to early ovarian failure.
- Girls/women with Turner syndrome whose karyotype includes a Y chromosome (such as 45,X/46,XY mosaicism) are at increased risk for gonadoblastoma, a neoplasm that occurs in dysgenetic gonads. These patients require gonadectomies.
- Patients with Turner syndrome are at increased risk for cardiovascular morbidity, presumably due to their risk of cardiovascular malformations, renal abnormalities, and hypertension. Abnormalities include aortic valvular disease, aortic arch anomalies (primarily coarctation), systemic venous abnormalities, ventricular septal defects, and hypoplastic left heart syndrome. Patients are at risk for aortic dissection, particularly during pregnancy.
- Osteoporosis and fractures are common in women with Turner syndrome, thought to be due to both ovarian failure and possibly haploinsufficiency for bone-related X chromosome genes.
- Girls with Turner syndrome are more likely than girls without Turner syndrome to develop abdominal obesity, insulin resistance, and type 2 diabetes; all may improve with growth hormone therapy. Patients with Turner syndrome are at increased risk for autoimmune endocrinopathies, most importantly, hypothyroidism.
- The diagnosis of Turner syndrome is sometimes made at birth in the patient with classic physical features such as webbed neck and congenital lymphedema. Other patients are diagnosed later, when they present with either growth failure in childhood, failure to enter or complete puberty, or early ovarian failure.

CLINICS CARE POINTS

- Turner syndrome, the most common sex chromosome abnormality (loss of part or all of an X chromosome), affects approximately 1 in every 2500 liveborn female newborns. It is a disorder of growth and development that is almost always associated with short stature and primary amenorrhea due to early ovarian failure.
- Girls/women with Turner syndrome whole karyotype includes a Y chromosome (such as 45,X/46,XY mosaicism) are at increased risk for gonadoblastoma, a neoplasm that occurs in dysgenetic gonads. These patients require gonadectomies.
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- Osteoporosis and fractures are common in women with Turner syndrome, thought to be due to both ovarian failure and possibly haploinsufficiency for bone-related X chromosome genes.
- Girls with Turner syndrome are more likely than girls without Turner syndrome to develop abdominal obesity, insulin resistance, and type 2 diabetes; all may improve with growth hormone therapy. Patients with Turner syndrome are at increased risk for autoimmune endocrinopathies, most importantly, hypothyroidism.

Disclosure

The authors have nothing to disclose.

References

[1] Turner HH. A syndrome of infantilism, congenital webbed neck and cubitus valgus. Endocrinology 1938;23:566.
[2] Ullrich O. Turner's syndrome and status Bonnevie-Ullrich. Am J Hum Genet 1949;1:179.
[3] Barr ML, Bertram EG. A morphological distinction between neurons of the male and female and the behavior of the nucleolar satellite during accelerated nucleo-protein synthesis. Nature 1949;163:676.
[4] Males JL, Seely JR. Turner's syndrome: Index case after 44 years (a tribute to Dr. Henry H. Turner). K Clin Endocrinol Metab 1978;46:163.
[5] Bondy CA, Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab 2007;92:10.
[6] Gravhold CH, Juul S, Naeraa RW, et al. Prenatal and postnatal prevalence of Turner's syndrome: a registry study. BMJ 1996;312(7022):16–21.
[7] Gunther DF, Eugster E, Zagar AJ, et al. Ascertainment bias in Turner syndrome: new insights from girls who were diagnosed incidentally in prenatal life. Pediatrics 2004;114:640.
[8] Mathur A, Stekol L, Schatz D, et al. The parental origin of the single X chromosome in Turner syndrome: lack of correlation with parental age or clinical phenotype. Am J Hum Genet 1991;48:682.
[9] Ferguson-Smith MA. Karyotype-Phenotype correlations in gonadal dysgenesis and their bearing on the pathogenesis of malformations. J Med Genet 1965;2:142.
[10] Simpson JL. Gonadal dysgenesis and abnormalities of the human sex chromosomes: current status of phenotypic-karyotypic correlations. Birth Defects Orig Artic Ser 1975;11:23.
[11] Held KR, Kerber S, Kaminsky E, et al. Mosaicism in 45,X Turner syndrome: does survival in early pregnancy depend on the presence of two sex chromosomes? Hum Genet 1992;88:288.
[12] Binder G, Koch A, Wajs E, et al. Nested polymerase chain reaction study of 53 cases with Turner's syndrome: is cytogenetically undetected Y mosaicism common? J Clin Endocrinol Metab 2008;93:2109.
[13] Wooten N, Bakalov VK, Hill S, et al. Reduced abdominal adiposity and improved glucose tolerance in growth hormone-treated girls with Turner syndrome. J Clin Endocrinol Metab 2008;93:2109.
[14] Rao E, Weiss B, Fukami M, et al. Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. Nat Genet 1997;16:54.
[15] Ross JL, Scott C Jr, Marttila P, et al. Phenotypes Associated with SHOX Deficiency. J Clin Endocrinol Metab 2001;86:5674.

[16] Ross JL, Kowal K, Quigley CA, et al. The phenotype of short stature homeobox gene (SHOX) deficiency in childhood: contrasting children with Leri-Weill dyschondrosteosis and Turner syndrome. J Pediatr 2005;147:499.
[17] Huber C, Rosilio M, Munnich A, et al. High incidence of SHOX anomalies in individuals with short stature. J Med Genet 2006;43:735.
[18] Sybert VP, McCauley E. Turner's syndrome. N Engl J Med 2004;351:1227.
[19] Loscalzo ML, Van PL, Ho VB, et al. Association between fetal lymphedema and congenital cardiovascular defects in Turner syndrome. Pediatrics 2005;115:732.
[20] Clark EB. Neck web and congenital heart defects: a pathogenic association in 45 X-O Turner syndrome? Teratology 1984;29:355.
[21] Mazzanti L, Cacciari E. Congenital heart disease in patients with Turner's syndrome. Italian Study Group for Turner Syndrome (ISGTS). J Pediatr 1998;133:688.
[22] McCarthy K, Bondy CA. Turner syndrome in childhood and adolescence. Expert Rev Endocrinol Metab 2008;3:771.
[23] Wyss D, DeLozier CD, Daniell J, et al. Structural anomalies of the X chromosome: personal observation and review of non-mosaic cases. Clin Genet 1982;21:145.
[24] dos Santos AP, Andrade JG, Piveta CS, et al. Screening of Y chromosome microdeletions in 46, XY partial gonadal dysgenesis and in patients with a 45,X/46,XY karyotype or its variants. BMC Med Genet 2013;14:115.
[25] Sävendahl L, Davenport ML. Delayed diagnoses of Turner's syndrome: proposed guidelines for change. J Pediatr 2000;137:455.
[26] Ranke MB, Pflüger H, Rosendahl W, et al. Turner syndrome: spontaneous growth in 150 cases and review of the literature. Eur J Pediatr 1983;141:81.
[27] Brook CG, Mürset G, Zachmann M, et al. Growth in children with 45,XO Turner's syndrome. Arch Dis Child 1974;49:789.
[28] Sylvén L, Hagenfeldt K, Bröndum-Nielsen K, et al. Middle-aged women with Turner's syndrome. Medical status, hormonal treatment and social life. Acta Endocrinol (Copenh) 1991;125:359.
[29] Freriks K, Timmermans J, Beerendonk CC, et al. Standardized multidisciplinary evaluation yields significant previously undiagnosed morbidity in adult women with Turner syndrome. J Clin Endocrinol Metab 2011;96:E1517.
[30] Elsheikh M, Hodgson HJ, Wass JA, et al. Hormone replacement therapy may improve hepatic function in women with Turner's syndrome. Clin Endocrinol (Oxf) 2001;55:227.
[31] El-Mansoury M, Berntorp L, Byman I, et al. Elevated liver enzymes in Turner syndrome during a 5-year follow-up study. Clin Endocrinol (Oxf) 2008;68:568.
[32] Bakalov VK, Gutin L, Cheng CM, et al. Autoimmune disorders in women with turner syndrome and women with karyotypically normal primary ovarian insufficiency. J Autoimmun 2012;38:315.
[33] Chiovato L, Larizza D, Bendinelli G, et al. Autoimmune hypothyroidism and hyperthyroidism in patients with Turner's syndrome. Eur J Endocrinol 1996;134:568.
[34] Ostberg JE, Conway GS. Adulthood in women with Turner syndrome. Horm Res 2003;59:211.
[35] Pasquino AM, Passeri F, Pucarelli I, et al. Spontaneous pubertal development in Turner's syndrome. Italian Study Group for Turner's Syndrome. J Clin Endocrinol Metab 1997;82:1810.
[36] Hadnott TN, Gould HN, Gharib AM, et al. Outcomes of spontaneous and assisted pregnancies in Turner syndrome: the U.S. National Institutes of Health experience. Fertil Steril 2011;95:2251.
[37] Saenger P. Clinical manifestations and diagnosis of Turner syndrome (gonadal dysgenesis). UpToDate 2015.
[38] Singh RP, Carr DH. The anatomy and histology of XO human embryos and fetuses. Anat Rec 1966;155:369.

[39] Massarano AA, Adams JA, Preece MA, et al. Ovarian ultrasound appearances in Turner syndrome. J Pediatr 1989;114:568.
[40] King CR, Magenis E, Bennett S. Pregnancy and the Turner syndrome. Obstet Gynecol 1978;52:617.
[41] Reyes FL, Koh KS, Faiman C. Fertility in women with gonadal dysgenesis. Am J Obstet Gynecol 1976;126:668.
[42] Gravholt CH, Juul S, Naeraa RW, et al. Morbidity in Turner syndrome. J Clin Epidemiol 1998;51:147.
[43] Cramer JW, Bartz PJ, Simpson PM, et al. The spectrum of congenital heart disease and outcomes after surgical repair among children with Turner syndrome: a single-center review. Pediatr Cardiol 2014;35:253.
[44] Ho VB, Bakalov VK, Cooley M, et al. Major vascular anomalies in Turner syndrome: prevalence and magnetic resonance angiographic features. Circulation 2004;110:1694.
[45] Gøtzsche CO, Krag-Olsen B, Nielsen J, et al. Prevalence of cardiovascular malformations and association with karyotypes in Turner's syndrome. Arch Dis Child 1994;71:433.
[46] Elsheikh M, Casadei B, Conway GS, et al. Hypertension is a major risk factor for aortic root dilatation in women with Turner's syndrome. Clin Endocrinol (Oxf) 2001;54:69.
[47] Sachdev V, Matura LA, Sidenko S, et al. Aortic valve disease in Turner syndrome. J Am Coll Cardiol 2008;51:1904.
[48] Ilyas M, Chu C, Ettles D, et al. Evaluation by magnetic resonance imaging of aortic dilatation and coarctation in adult Turner syndrome patients. Clin Endocrinol (Oxf) 2006;65:154.
[49] Lin AE, Lippe B, Rosenfeld RG. Further delineation of aortic dilation, dissection, and rupture in patients with Turner syndrome. Pediatrics 1998;102:e12.
[50] Matura LA, Ho VB, Rosing DR, et al. Aortic dilatation and dissection in Turner syndrome. Circulation 2007;116:1663.
[51] Carlson M, Airhart N, Lopez L, et al. Moderate aortic enlargement and bicuspid aortic valve are associated with aortic dissection in Turner syndrome: report of the international turner syndrome aortic dissection registry. Circulation 2012;126:2220.
[52] Karnis MF, Zimon AE, Lalwani SI, et al. Risk of death in pregnancy achieved through oocyte donation in patients with Turner syndrome: a national survey. Fertil Steril 2003;80:498.
[53] Practice Committee of the American Society for Reproductive Medicine. Increased maternal cardiovascular mortality associated with pregnancy in women with Turner syndrome. Fertil Steril 2006;86:S127.
[54] Nathwani NC, Unwin R, Brook CG, et al. The influence of renal and cardiovascular abnormalities on blood pressure in Turner syndrome. Clin Endocrinol (Oxf) 2000;52:371.
[55] Landin-Wilhelmsen K, Bryman I, Wilhelmsen L. Cardiac malformations and hypertension, but not metabolic risk factors, are common in Turner syndrome. J Clin Endocrinol Metab 2001;86:4166.
[56] Fudge EB, Constantacos C, Fudge JC, et al. Improving detection of hypertension in girls with turner syndrome using ambulatory blood pressure monitoring. Horm Res Paediatr 2014;81:25.
[57] Bondy CA, Van PL, Bakalov VK, et al. Prolongation of the cardiac QTc interval in Turner syndrome. Medicine (Baltimore) 2006;85:75.
[58] Bondy CA, Bakalov VK. Investigation of cardiac status and bone mineral density in Turner syndrome. Growth Horm IGF Res 2006;16(Suppl A):S103.
[59] Bondy CA, Ceniceros I, Van PL, et al. Prolonged rate-corrected QT interval and other electrocardiogram abnormalities in girls with Turner syndrome. Pediatrics 2006;118:e1220.
[60] Dalla Pozza R, Bechtold S, Urschel S, et al. QTc interval prolongation in children with Turner syndrome: the results of exercise testing and 24-h ECG. Eur J Pediatr 2009;168:59.
[61] Ostberg JE, Donald AE, Halcox JP, et al. Vasculopathy in Turner syndrome: arterial dilatation and intimal thickening without endothelial dysfunction. J Clin Endocrinol Metab 2005;90:5161.

[62] Rubin K. Turner syndrome and osteoporosis: mechanisms and prognosis. Pediatrics 1998;102:481.
[63] Gravholt CH, Vestergaard P, Hermann AP, et al. Increased fracture rates in Turner's syndrome: a nationwide questionnaire survey. Clin Endocrinol (Oxf) 2003;59:89.
[64] Landin-Wilhelmsen K, Bryman I, Windh M, et al. Osteoporosis and fractures in Turner syndrome- importance of growth promoting and oestrogen therapy. Clin Endocrinol (Oxf) 1999;51:497.
[65] Bakalov VK, Chen ML, Baron J, et al. Bone mineral density and fractures in Turner syndrome. Am J Med 2003;115:259.
[66] Bakalov VK, Axelrod L, Baron J, et al. Selective reduction in cortical bone mineral density in turner syndrome independent of ovarian hormone deficiency. J Clin Endocrinol Metab 2003;88:5717.
[67] Gravholt CH, Fedder J, Naeraa RW, et al. Occurrence of gonadoblastoma in females with Turner syndrome and Y chromosome material: a population study. J Clin Endocrinol Metab 2000;85:3199.
[68] Schoemaker MJ, Swerdlow AJ, Higgins CD, et al. Cancer incidence in women with Turner syndrome in Great Britain: a national cohort study. Lancet Oncol 2008;9:239.
[69] Denniston A. Turner's syndrome. Lancet 2001;358:2169.
[70] Chrousos GA, Ross JL, Chrousos G, et al. Ocular findings in Turner syndrome. A prospective study. Ophthalmology 1984;91:926.
[71] Adhikary HP. Ocular manifestations of Turner's syndrome. Trans Ophthalmol Soc U K 1981;101(Pt 4):395.
[72] Mason JO 3rd, Tasman W. Turner's syndrome associated with bilateral retinal detachments. Am J Ophthalmol 1996;122:742.
[73] Elsheikh M, Wass JA, Conway GS. Autoimmune thyroid syndrome in women with Turner's syndrome—the association with karyotype. Clin Endocrinol (Oxf) 2001;55:223.
[74] El-Mansoury M, Bryman I, Berntorp K, et al. Hypothyroidism is common in turner syndrome: results of a five-year follow-up. J Clin Endocrinol Metab 2005;90:2131.
[75] Bonamico M, Pasquino AM, Mariani P, et al. Prevalence and clinical picture of celiac disease in Turner syndrome. J Clin Endocrinol Metab 1991;87:85495.
[76] Caprio S, Boulware S, Diamond M, et al. Insulin resistance: an early metabolic defect of Turner's syndrome. J Clin Endocrinol Metab 1991;72:832.
[77] Handler MZ, Derrick KM, Lutz RE, et al. Prevalence of pilomatricoma in Turner syndrome: findings from a multicenter study. JAMA Dermatol 2013;149:559.
[78] Wood S, Nguyen D, Hutton K, et al. Pilomatricomas in Turner syndrome. Pediatr Dermatol 2008;25:449.
[79] Bengtzen AR, Grossniklaus HE, Bernardino CR. Multiple pilomatrixoma in Turner syndrome. Ophthal Plast Reconstr Surg 2009;25:229.
[80] Brazzelli V, Larizza D, Martinetti M, et al. Halo nevus, rather than vitiligo, is a typical dermatologic finding of Turner 's syndrome: clinical, genetic, and immunogenetic study in 72 patients. J Am Acad Dermatol 2004;51:354.
[81] Lowenstein EJ, Kim KH, Glick SA. Turner's syndrome in dermatology. J Am Acad Dermatol 2004;50:767.
[82] Anderson H, Filipsson R, Fluur E, et al. Hearing impairment in Turner's syndrome. Acta Otolaryngol Suppl 1969;247:1.
[83] King KA, Makishima T, Zalewski CK, et al. Analysis of auditory phenotype and karyotype in 200 females with Turner syndrome. Ear Hear 2007;28:831–41.
[84] Barrenäs ML, Nylén O, Hanson C. The influence of karyotype on the auricle, otitis media and hearing in Turner syndrome. Hear Res 1999;138:163–70.
[85] Stenberg AE, Nylén O, Windh M, et al. Otological problems in children with Turner's syndrome. Hear Res 1998;124:85–90.
[86] Dhooge IJ, De Vel E, Verhoye C, et al. Otologic disease in Turner syndrome. Otol Neurotol 2005;26:145–50.

[87] Salerno M, Di Maio S, Gasparini N, et al. Liver abnormalities in Turner syndrome. Eur J Pediatr 1999;158:618–23.
[88] Koulouri O, Ostberg J, Conway G. Liver dysfunction in Turner's syndrome: prevalence, natural history, and effect of exogenous oestrogen. Clin Endocrinol 2008;69:306–10.
[89] Wemme H, Pohlenz J, Schönberger W. Effect of oestrogen/gestagen replacement therapy on liver enzymes in patients with Ullrich-Turner syndrome. Eur J Pediatr 1995;154: 807–10.
[90] McCarthy K, Bondy C. Turner syndrome in childhood and adolescence. Expert Rev Endocrinol Metab 2008;3:771–5.
[91] Roulot D. Liver involvement in Turner syndrome. Liver Int 2013;33:24–30.
[92] Rosenfeld RG, Attie KM, Frane J, et al. Growth hormone therapy of Turner's syndrome: beneficial effect on adult height. J Pediatr 1998;132:319–24.
[93] Sas TC, de Muinck Keizer-Schrama SM, Otten BJ, et al. Normalization of height in girls with Turner syndrome after long-term growth hormone treatment: results of a randomized dose-response trial. J Clin Endocrinol Metab 1999;84:4607–12.
[94] Stephure DK. Impact of growth hormone supplementation on adult height in turner syndrome: results of the Canadian randomized controlled trial. J Clin Endocrinol Metab 2005;90:3360–6.
[95] Davenport ML, Crowe BJ, Travers SH, et al. Growth hormone treatment of early growth failure in toddlers with Turner syndrome a randomized, controlled, multicenter trial. J Clin Endocrinol Metab 2007;92:3406–16.
[96] Ross JL, Quigley CA, Cao D, et al. Growth hormone plus childhood low-dose estrogen in Turner's syndrome. N Engl J Med 2011;364:1230–42.
[97] Chernausek SD, Attie KM, Cara JF, et al. Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. Genentech, Inc., Collaborative Study Group. J Clin Endocrinol Metab 2000;85:2439–45.
[98] Ranke MB, Lindberg A, Chatelain P, et al. Prediction of long-term response to recombinant human growth hormone in Turner syndrome: development and validation of mathematical models. KIGS International Board. Kabi international Growth Study. J Clin Endocrinol Metab 2000;85:4212–8.
[99] Bolar K, Hoffman AR, Maneatis T, et al. Long-term safety of recombinant human growth hormone in Turner syndrome. J Clin Endocrinol Metab 2008;93:344–51.
[100] Sas TC, Gerver WJ, de Bruin R, et al. Body proportions during long-term growth hormone treatment in girls with Turner syndrome participating in a randomized dose-response trial. J Clin Endocrinol Metab 1999;84:4622–8.
[101] Wooten N, Bakalov NK, Hill S, et al. Reduced abdominal adiposity and improved glucose tolerance in growth hormone-treated girls with Turner syndrome. J Clin Endocrinol Metab 2008;93:2109–14.
[102] Matura LA, Sachdev V, Bakalov VK, et al. Growth hormone treatment and left ventricular dimensions in Turner syndrome. J Pediatr 2007;150:587–91.
[103] Bondy CA, Van PL, Bakalov VK, et al. Growth hormone treatment and aortic dimensions in Turner syndrome. J Clin Endocrinol Metab 2006;91:1785–8.
[104] Ari M, Bakalov VK, Hill S, et al. The effects of growth hormone treatment on bone mineral density and body composition in girls with Turner syndrome. J Clin Endocrinol Metab 2006;91:4302–5.
[105] Zeger MP, Shah K, Kowal K, et al. Prospective study confirms oxandrolone-associated improvement in height in growth hormone-treated adolescent girls with Turner syndrome. Horm Res Paediatr 2011;75:38–46.
[106] Gault EJ, Perry RJ, Cole TJ, et al. Effect of oxandrolone and timing of pubertal induction on final height in Turner's syndrome: randomized, double blind, placebo controlled trial. BMJ 2011;342:d1980.
[107] Saenger PH, Mejia-Corletto J. Long-acting growth hormone: an update. Endocr Dev 2016;30:79–97.

[108] Yuen KCJ, Miller BS, Biller BMK. The current state of long-acting growth hormone preparations for growth hormone therapy. Curr Opin Endocrinol Diabetes Obes 2018;25(4):267–73.
[109] Christiansen JS, Backeljauw PF, Bidlingmaier M, et al. Growth Hormone Research Society perspective on the development of long-acting growth hormone preparations. Eur J Endocrinol 2016;174(6):C1–8.
[110] Collett-Solberg PF, Jorge AA, Boguszewski MC, et al. Growth hormone therapy in children; research and practice—A review. Growth Horm IGF Res 2019;44:20–32.
[111] Hagen CP, Aksglaede L, Sørensen K, et al. Serum levels of anti-Mullerian hormone as a marker of ovarian function in 926 healthy females from birth to adulthood and in 172 Turner syndrome patients. J Clin Endocrinol Metab 2010;95:5003–10.
[112] Bondy CA. Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab 2007;92:10–25.
[113] Bakalov VK, Chen ML, Baron J, et al. Bone mineral density and fractures in Turner syndrome. Am J Med 2003;115:257–62.
[114] Hanton L, Axelrod L, Bakalov VK, et al. The importance of estrogen replacement in young women with turner syndrome. J Women's Health (Larchmt) 2003;12:971–7.
[115] Bakalov VK, Axelrod L, Baron K, et al. Selective reduction in cortical bone mineral density in Turner syndrome independent of ovarian hormone deficiency. J Clin Endocrinol Metab 2003;88:5717–22.
[116] Hovatta O. Ovarian function and in vitro fertilization (IVF) in Turner syndrome. Pediatr Endocrinol Rev 2012;9(Suppl. 2):713–7.
[117] Hadnott TN, Bondy CA. Risks of pregnancy for women with Turner syndrome. Expert Rev Obstet Gynecol 2011;6:217–27.
[118] Boissonnas CC, Davy C, Bornes M, et al. Careful cardiovascular screening and follow-up of women with Turner syndrome before and during pregnancy is necessary to prevent maternal mortality. Fertil Steril 2009;91:929 e5–e7.
[119] Bender B, Puck M, Salbenblatt J, et al. Cognitive development of unselected girls with complete and partial X monosomy. Pediatrics 1984;73:175.
[120] Migeon BR, Luo S, Stasiowski BA, et al. Deficient transcription of XIST from tiny ring X chromosomes in females with severe phenotypes. Proc Natl Acad Sci U S A 1993;90:12025.
[121] Collins AL, Cockwell AE, Jacobs PA, et al. A comparison of the clinical and cytogenetic findings in nine patients with a ring (X) cell line and 16 45,X patients. J Med Genet 1994;31:528.
[122] McCauley E, Feuillan P, Kushner H, et al. Psychosocial development in adolescents with Turner syndrome. J Dev Behav Pediatr 2001;22:360.
[123] Skuse DH, James RS, Bishop DV, et al. Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. Nature 1997;387:705.