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REVIEW

Transition from pediatrics to adult health care in girls with turner syndrome

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ABSTRACT

Introduction: Turner Syndrome is a rare condition secondary to a complete or partial loss of one X chromosome, leading to a wide spectrum of clinical manifestations. Short stature, gonadal dysgenesis, cardiovascular malformations, and dysmorphic features characterize its common clinical picture.

Areas covered: The main endocrine challenges in adolescent girls with Turner Syndrome are puberty induction (closely intertwined with growth) and fertility preservation. We discuss the most important clinical aspects that should be faced when planning an appropriate and seamless transition for girls with Turner Syndrome.

Expert opinion: Adolescence is a complex time for girls and boys: the passage to young adulthood is characterized by changes in the social, emotional, and educational environment. Adolescence is the ideal time to encourage the development of independent self-care behaviors and to make the growing girl aware of her health, thus promoting healthy lifestyle behaviors. During adulthood, diet and exercise are of utmost importance to manage some of the common complications that can emerge with aging. All clinicians involved in the multidisciplinary team must consider that transition is more than hormone replacement therapy: transition in a modern Healthcare Provider is a proactive process, shared between pediatric and adult endocrinologists.

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Turner syndrome; transition; puberty; growth hormone; fertility preservation

1. Introduction

Turner Syndrome (TS) is a rare condition, affecting 1 in 2500 live-born girls [1]. It is due to a complete or partial loss of one X chromosome, leading to a wide spectrum of clinical manifestations. Beyond the specific clinical picture, characterized by short stature, gonadal dysgenesis, cardiovascular malformations, and dysmorphic features, TS is associated with a wide range of abnormalities affecting multiple organs during all stages of life, requiring a multidisciplinary care approach.

Treatment of patients with TS is different according to age, phenotype, and comorbidities (reassumed in Figure 1) [2]. During childhood and adolescence, most girls with TS required treatments with growth hormone to increase their final height and with estrogens to induce puberty. Both growth and puberty are crucial aspects that should be completed when planning a transition of the patients from childhood to adulthood. Age of transition often corresponds to 2–4 years after puberty, which is associated with several changes in the psycho-physical state and in the social, emotional, and educational environment of adolescents. The transition from pediatric to adult care represents an important challenge for young women with TS. All these aspects should be considered by pediatric and adult endocrinologists and shared with patients and their parents/caregivers to avoid the risk of dropping-out the transition and future follow-up, leading to increased morbidity and mortality.

In this expert opinion, we will discuss the most important clinical and educational aspects that should be faced when planning an accurate and seamless transition of girls with TS.

2. Genetics of turner syndrome

TS is one of the most common sex chromosomal abnormalities and is caused by the complete or partial loss of one X chromosome. It is recommended to consider TS in phenotypic females with even one typical clinical findings [2]. The phenotype is extremely variable and can range from the classic form with a complete typical picture to a mild presentation. Diagnosis is confirmed by chromosomal analysis, performed on a peripheral blood sample, which shows complete X monosomy or different forms of mosaicism [3]. Mosaicism, defined as the presence of different karyotypes in the same person, develops after a meiotic nondisjunction and contributes to phenotypic variability [4,5]. Prenatal diagnosis of TS can be performed with invasive testing (chorionic villi or amniocytes) in case of advanced maternal age or presence of ultrasonographic anomalies (as increased nuchal translucency, cystic hygroma, left-sided cardiac defects) [6].

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Article highlights

- All Referral Healthcare Providers for rare conditions must adopt a multidisciplinary group to offer the best-practice care to patients with Turner Syndrome. The group should include endocrinologists (both pediatric and adult physicians), relevant specialists (medical geneticists, cardiologists, psychologists, gynecologists, ENTs, and so on), and stakeholders (including patient's association).
- Several concerns might emerge in all teenagers because adolescence is a complex time. The transition from pediatric to adult care should be seamless, with appropriate involvement of girls and caregivers, in order to avoid the risk of dropping-out.
- Growth should start in early infancy (6–8 years old) and must be completed before the transition; puberty should be induced at 11–12 years of age in those patients with amenorrhea, and hormonal replacement therapy should be continued until menopause.
- An appropriate fertility counseling should be offered: controlled ovarian stimulation and oocyte cryopreservation can increase the chance of pregnancy. An adequate cardiovascular assessment must be performed before pregnancy, since a high risk of complications.
- Several factors in patients with Turner Syndrome enhance cardiometabolic risk, increasing cardiovascular-related morbidity and mortality. Therefore, we suggest increasing the awareness to adopt a healthy lifestyle and to promote adherence to treatment and periodic follow-up during transition.

Around 99% of fetuses with the complete loss of one X chromosome will miscarry prematurely: it has been hypothesized that patients with 45, X karyotype who survive may have some degree of cryptic mosaicism [7]; therefore, karyotype should be repeated after birth [2].

The most frequent karyotype in TS is complete monosomy X (45, X), which is found in about 40–50% of cases, followed by mosaicism karyotype with a normal cell line 45,X/46,XX (15–25%) [2,8]. Other karyotypes are the mosaicism with an abnormal second or third cell line, such as 45,X/47,XXX or 45,X/46,XX/47,XXX, or the presence of structural variants of the X chromosome, even in mosaicism, such as isochromosome Xq or isodicentric Xp, partial deletions of Xp or Xq and ring X. Y chromosome material may be detected in 10–12% of patients with TS, including mosaic karyotype 45,X/46,XY [2,3].

Clinical severity is associated with the amount of X chromosome deficiency: patients with complete monosomy X show the highest morbidity and mortality, while those with mosaic karyotype generally present a milder phenotype [9]. Mosaic karyotypes 45,X/46,XX and 45,X/47,XXX, are associated with a better gynecological and reproductive outcome, or with a lower probability of developing obesity and hypertension [8]. Monosomic patients have the highest prevalence of bicuspid aortic valve, while the severity of left-sided congenital heart defects is lower in patients with mosaicism and intermediate in patients with Y material and isochromosome [8,10]. Also hearing loss may be related to karyotype: the number of patients with 45,X/46,XX or 45,X/46,XY, and ring X using hearing aids is lower than those with a different karyotype [8]. Regarding the cognitive aspect, the highest risk for neurocognitive or intellectual impairment is associated with ring X chromosome [11].

The genetic background of the patient with TS should be discussed during transition, with peculiar attention to those aspects that can be a challenge in adolescents-young adults (fertility, cognitive impairment, and cardiovascular risk).

3. Growth in girls with turner syndrome

Short stature characterizes patients with TS. Mean birth length and weight in newborns with TS are close to the 10^{th}-25^{th} percentile, suggesting a fetal growth retardation [12]. Height is often within the normal range during infancy, and usually falls below the 5^{th} percentile of the general population before 5 years of age [13,14], and finally adult height is reduced [15]. The goal of growth-promoting therapy is to facilitate the attainment of normal height during adolescence: recombinant human growth hormone (rhGH) is the mainstay treatment. GH secretion is normal in patients with TS: GH stimulation testing is considered

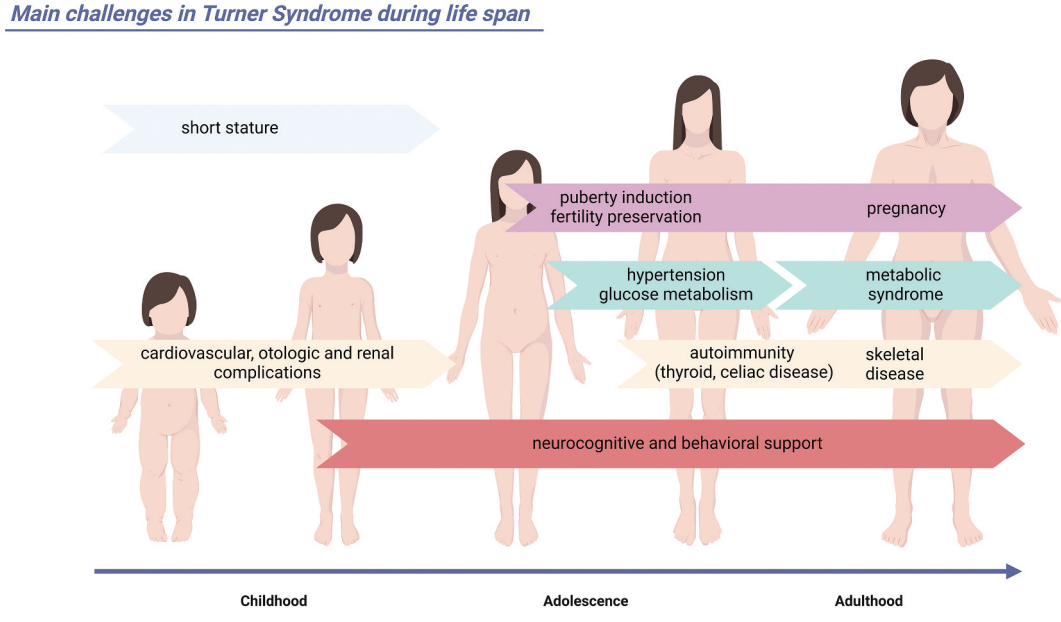

Figure 1. Health surveillance with some of the main aspects that must be considered in the multidisciplinary evaluation throughout the lifespan in patients with turner syndrome (created with BioRender.com).

unnecessary [14]. Only recently the mechanisms that explain a reduced adult height in TS have been described [1]. The absence of a copy of the short-stature homeobox-containing gene (SHOX) located in the distal pseudoautosomal region of the X chromosome has been reported. The degree of SHOX protein deficiency is different, according to karyotype [1,16]. The haploinsufficiency of SHOX is involved in the etiopathogenesis of short stature and of the disproportionate general appearance, because mesomelic shortening of the extremities compared with the trunk is a clinical hallmark of SHOX insufficiency, and rhGH therapy does not improve the height disproportion [17]. The SHOX protein plays a role in several pathways of the growth plate: decreased SHOX expression explains part of the reduced linear growth in patients with TS [3,5]. In addition, SHOX haploinsufficiency is generally associated with the presence of other phenotypic features of TS as scoliosis, micrognathia, high-arched palate, cubitus valgus (50%), short fourth metacarpal (35%), and reduced leg length [18]. SHOX deletions are reported in 2–15% of individuals with idiopathic short stature, in 50–90% of individuals with Leri-Weill dyschondrosteosis, and in almost 100% of girls with TS [19]. SHOX protein regulates the proliferation and maturation of chondrocytes [18]. Some of the main characteristics of SHOX deficiency that overlap with TS presentation develop over time and can appear during adolescence or transition phase [19].

GH treatment has been demonstrated to be effective in increasing height and growth in patients with SHOX deficiency by stimulating chondrocytes proliferation and maturation [20]. In clinical practice, the height target in girls with TS is within the lower range for the female population. A meta-analysis in 2018 in 11 publications reported mean increase of 7 cm after rhGH therapy [21]. A placebo-controlled trial (without rhGH and estrogen, with only rhGH or estrogen, or with combined rhGH and estrogen) in young children (mean 7–9 years) demonstrated that the overall effect of GH alone on final height was 5 cm; a modest synergy was documented in the GH plus estrogen group (2.1 cm) [22]. Overall, 1 cm of final height gain per year of rhGH therapy is a reasonable expectation [2]. Recently, it has been reported that early age at rhGH start with higher rhGH dose resulted in greater prepubertal height gain, permitting early estrogen start and attaining normal adult height at the age of transition [23].

A study of an international cohort of 686 prepubertal girls with TS demonstrated that in the first year of GH treatment the most influential variable for linear growth response was the weekly rhGH dose; from the second to fourth year the positive predictors were height velocity and weekly rhGH dose (age was the only negative factors discovered) [24]. Treatment with rhGH is safe: no blood pressure elevation, onset of cardiovascular disease or glucose metabolism alterations, or increase in mortality were observed [25,26]. The rapid increase in linear growth stimulated by rhGH can partially explain the observation that some rare complications (intracranial hypertension, slipped capital femoral epiphysis, scoliosis progression) were more common in girls with TS [2].

The optimal time for GH treatment initiation has not been established yet [2]; however, younger girls (starting from 6 years of age) achieved a greater effect on final height [27]. Therapy with rhGH should be offered to girls with growth failure (below the 50th percentile of height velocity over 6 months) or with a likelihood of short stature (short parents with reduced predicted adult height) [2]. The consensus recommended starting rhGH around 4–6 years of age (preferably before 12–13 years) with an initial rhGH dose of 1.3–1.5 mg/m^2/day (45–50 µg/kg/day), with clinical monitoring of growth every 4–6 months [2]. The mean dose of 46 µg/kg/day [21] has been confirmed also in a recent Brazilian paper (50 µg/kg/day) [28] and in an observational post-marketing surveillance study with a biosimilar rhGH (36–50 µg/kg/day) [29]. In clinical practice, almost half of girls with TS received GH doses below practice guidelines and label recommendations [30], achieving an adequate final growth on the standard dose of 30 µg/kg/day [31]. IGF-1 should be measured at least annually and should be no greater than two SDS above the mean for age. Low or very-low estrogen supplementation to promote further growth is not suggested. Growth should be completed before the transition from pediatric to adult care, and rhGH treatment should be discontinued after the transition [2]. A body composition study reports that the beneficial effects on regional fat deposition of GH treatment may outweigh GH-induced insulin antagonism: total and abdominal fat were increased in GH-untreated TS; reduced fasting insulin, low insulin secretion during oral glucose tolerance test, and improved glucose tolerance were reported in GH-treated girls (mean age 14 years [32]. In authors' opinion, a balanced diet combined with physical exercise must be encouraged in all young adults with TS.

4. Puberty induction and sex hormone replacement therapy

The puberty onset represents the beginning of adolescence: physical and psychological changes characterize the transition from childhood to adulthood. Spontaneous puberty and menarche are occasionally seen in patients with TS and are highly dependent on karyotype: only 6–9% of women with 45,X karyotype and up to a third of women with mosaic TS have a spontaneous menarche; however, most of them develop premature ovarian insufficiency (POI) due to gonadal dysgenesis [33]. Therefore, most girls with TS will need estroprogestinic replacement therapy to induce puberty and then to achieve adequate peak bone mass and uterine growth (before pregnancy planning), to improve sexual function and quality of life, and to prevent bone demineralization, metabolic disorders, and cardiovascular disease. This is a crucial step in the life of girls with TS and adequate information on features and aims of the treatment and related psycho-physical changes should be shared with patients and parents before starting the process.

Gonadotropins should be measured annually starting at 11 years or earlier to confirm hypergonadotropic hypogonadism before pubertal induction. If gonadotropin levels are normal for age, observation for spontaneous puberty is suggested; hormone replacement therapy (HRT) should be initiated if gonadal failure occurs and continued until the age of usual menopause. Anti-Mullerian hormone (AMH) can be measured to evaluate the ovarian reserve and the chance of fertility preservation [34].

Puberty should be induced at a 'normal age' in girls with TS, between 11 and 12 years of age, ideally with a dosage regimen that mimics the physiological increase of serum estradiol levels during puberty [2]. According to TS guidelines [2], low doses of

estrogens are the cornerstone treatment to induce puberty without interfering with the growth potential related to rhGH therapy, if ongoing [35]. Incremental doses of estrogen approximately every 6 months can mimic the normal progression of puberty in girls, reaching adult doses after 2–3 years [36].

The optimal estrogen regimen to induce puberty is still debated, but low-dose transdermal 17-β estradiol (TDE) is now considered the preferred treatment. The benefits of TDE use are the more physiologic route of delivery, bypassing hepatic metabolism, and avoiding the supraphysiologic concentrations of estrogens in the liver observed after the oral administration. By avoiding first-pass metabolism, TDE presents a better bioavailability and a reduced induction of liver protein synthesis, such as markers of inflammation, coagulation, and fibrinolysis, compared with orally administered estrogens [37].

Previous studies did not show significant differences in metabolic profile, bone mineral density, and uterine development according to the route of administration and formulation of estrogen, but solid evidence-based evidence is missing [38,39]. Even the risk of breast cancer after long-term transdermal or oral estrogen remains low in women with TS [40].

Availability of different preparations of TDE, as patch or gel, differs among countries, and formulations dedicated to younger patients are lacking. For example, in Italy, the lowest dose commercially available is 25 µg TDE patch. When used to induce puberty, the patch is initially cut into four or six parts and one of these parts is applied on a healthy site of the skin (belly or lower part of back) and changed every 3–4 days, releasing the recommended starting dose of about 3–7 µg/day [2,36]. Dosage is usually doubled every 6 months in accordance with the clinical evaluation, including weight, height, blood pressure, Tanner stage, and patient satisfaction. The usual adult dose of estradiol is approximately 50–100 µg TDE patch or 2–4 mg by oral route.

During estrogen treatment routine monitoring of gonadotropins is not recommended, while estradiol measurement could be useful to titrate the dosage, especially if it results in the low range using an ultrasensitive assay. Pelvic ultrasonography before and during puberty induction allows to evaluate uterine development, recommended for future fertility.

After 2 years of estrogen therapy or after the first breakthrough bleeding, progestin supplementation should be started to reduce the risks of irregular bleeding and endometrial hyperplasia or cancer due to prolonged unopposed estrogen [2,36]. Oral/vaginal natural micronized progesterone (100–200 mg daily), and oral dydrogesterone (10 mg daily) can be used at least 10–14 days per month [41].

After induction, HRT with estrogen and progesterone should be continued using different regimens according to patients' requests, clinical features, and contraindications. TDE remains the first choice, cyclically associated with progesterone or a progestin for 10–14 days. However, other options can be considered, such as oral combined estroprogestinic formulations. Among oral contraceptives with ethinyl-estradiol (EE), the combinations with the third- or fourth-generation progestogens show a slightly higher risk of venous thromboembolism in comparison to formulations with the first- and second-generation components [42]. The recent development of new combined oral contraceptives containing natural estrogens (17-estradiol, 17-estradiol valerate, and estetrol) seems to be a valid therapeutic alternative in patients with TS as HRT, showing more favorable effects on metabolic profile and coagulation cascade compared with EE [43]. Further studies are needed to evaluate the impact on bone turnover and the long-term safety of these new compounds in TS patients.

Routine screening for thromboembolic risk is not recommended [2]. However, considering the increased incidence of the most common mutations associated with thromboembolism in TS, it is advisable to perform a complete thrombophilia screening before starting HRT in girls with TS, especially in case of thromboembolism history [44]. HRT should be continued at least up to the physiological menopause age, at 50 years.

5. Thyroid disease in turner syndrome

Autoimmune thyroid diseases (ATDs) are detected in 60% of patients with TS (median age of onset 22 years) [45]. The rate of overt hypothyroidism (defined with increased TSH levels) detection was higher in girls with TS than matched controls with positive ultrasound or autoantibodies, after 5 years of observation [46]. In particular, Hashimoto's thyroiditis (HT) is more frequent than Grave's disease [45]. In a recent monocentric prospective study on 134 patients with TS (mean age 9 years), Wegiel *et al*. reported a high incidence of thyroid autoantibodies (30%), combined with an earlier diagnosis of HT (13 years), estradiol exposure does not affect new-onset autoimmune diseases [47]. In clinical practice, we suggest that the transition phase is crucial to detect ATDs, especially those asymptomatic forms with only positive autoantibodies: thyroid function and ultrasound evaluation should be performed during the first visit of an adult endocrinologist, then thyroid function should be assessed yearly. Further studies are needed to establish the impact of iodine prophylaxis campaigns in the development of ATDs [48]. Patients with isochromosome X karyotype had a higher risk of developing ATDs than patients with monosomy or other karyotypes (66% vs 37% vs 33%, respectively), lower incidence ATD is reported in patients with mosaic karyotype 45,X/46,XY [8]. FOXP3 maps the short arm of X chromosome (Xp11.23) and is crucial for T cells regulation. A missing Xp in 46,X,del(Xp) or 46,X,i(Xq) could predispose to thyroid autoantibodies positivity [49].

Concerning the risk of thyroid cancer development in TS, the studies are inconclusive: the high number of thyroid ultrasounds can detect also small cancers. Only one study reported an increased diagnosis of papillary thyroid cancer with a cumulative incidence of 5% and an incidence rate of 0.18 per 100 person-year [45].

6. Skeletal growth and disease in TS

The puberty transition is the age of skeletal maturation in adolescents, which depends on a complex interplay of inherited and acquired factors (genetics, diet, physical activity, environment, local paracrine, and endocrine milieu) [50]. Low or absent estrogen levels partially explain low bone mass, irrespective of karyotype [51]: GH-treated adolescents with TS show adequate bone mineral density [52]. In clinical practice, we do not consider normal bone mineralization in the decision regarding the optimal time to initiate estrogen replacement [52]. A skillful HRT, combined with rhGH, is necessary for most adolescents with TS to achieve proper adult peak bone mass [5].

Despite optimal estrogen treatment and final growth achievement with GH therapy, the fracture risk is still increased in women with TS: a nationwide questionnaire survey in Denmark (collecting data from 322 patients and 1169 controls) reported an increased hazard ratio for fracture risk in TS [53]. Observed fractures in patients with TS are more than twice than expected (up to 22 times for metacarpal bone and 10 times for femoral fractures) [54] and have been reported either in the cortical or in the trabecular bones. Women with TS are short in height and it must be considered when areal bone density is measured: females <150 cm are likely to be misdiagnosed with osteoporosis, unless adjustments for body size [55]. Moreover, the different bone sizes and geometry due to SHOX deficiency may contribute to a falsely reduced bone mineral density [55]. The HRT is effective in reducing fracture risk: low bone mineral density and fractures were common in patients with TS after 45 years of age, especially if they do not receive HRT continuously [56].

Prepubertal-aged patients with TS (<13 years old) have normal bone density for height age, but significantly decreased bone density of the wrist for chronological age, leading to an increased prevalence of wrist fractures compared with healthy girls [57]. Cortical density in patients with TS is reduced with sparing of trabecular bone: a study with peripheral quantitative computed tomography in 22 patients (mean age 13 years) treated with rhGH revealed a reduction in cortical bone mineral density and thickness, leading to a biomechanical disadvantage that predisposes to bone fragility and fractures [58]. Also trabecular microarchitecture is compromised in adult women with TS: bone volume per tissue volume is reduced, trabecular number was lower resulting in higher trabecular spacing [59].

Reduced bone mineral density has been observed in TS with induced puberty. The delay to start estrogen treatment is associated with lower bone mineral density: in patients with primary amenorrhea (83% of the cohort, 52% of those treated with rhGH) spine and hip mineral content were inversely associated with age commencing estrogen or years of estrogen deficiency, and a measured reduction in Z-score of 0.12 and 0.09 at the spine and hip, respectively, was calculated for every year of estrogen therapy delay [60]. A 6-year longitudinal study revealed that during HRT and calcium/vitamin D supplementation bone mineral density remained unchanged at the forearm-ultradistal radius-hip level, while it increased at the spine level [61]. During adulthood, lumbar spine bone mineral density was 20% reduced in women not taking HRT, with respective prevalence of osteoporosis and vertebral fractures of 38% and 19% [62].

In case of increased fracture risk, as osteoporosis diagnosis during dual-energy X-ray absorptiometry or discovery of a fracture, the treatment of a patient with TS is similar to the general population. After puberty induction, the first screening for reduced mineralization should be performed by bone densitometry scan, and then repeated every 5 years. On the hand of prevention, effective strategies and screening programs for osteoporosis should be started during childhood: several factors in patients with TS increase the risk of fractures (hypogonadism, bone morphology due to SHOX deficiency, calcium, or vitamin D deficiency) [61,63]. Regarding bone markers, bone ALP and osteocalcin levels were lower in subjects with TS, and sclerostin or DKK-1 levels were higher than in the controls, correlated with HRT [64]. Women with TS have decreased 25-OH vitamin D and increased parathyroid hormone [63]. The role of vitamin D in preventing bone disease is well known: vitamin D status should be assessed at first between the ages of 9 and 11, and then every 2 years [65]. In case of vitamin D deficiency, malabsorption and celiac disease should be excluded, as well as vitamin B12 and iron status should be assessed. Treatment with eldecalcitol (a new analog of active vitamin D) is associated with a gain in bone mineral density during HRT [66].

7. Cardiovascular and metabolic complications in patients with TS

Cardiovascular-related mortality and morbidity are increased in patients with TS: several factors enhance an unfavorable cardiometabolic risk, predisposing to adverse cardiac and cerebrovascular outcomes in young adulthood. Metabolic syndrome enhances *per se* cardiovascular risk, nonetheless in patients with TS some key factors of metabolic syndrome (hypertension, glucose metabolism impairment, dyslipidemia [67–69] are more prevalent than in the general population. A proactive management dedicated to increase the awareness of patients with TS and their caregivers should consider efforts to enhance all the preventive measures recommended in the general population (physical activity, healthy diet, adequate sleep, and avoiding smoking). The benefits of physical exercise are widely recognized; thus, it is considered the best non-pharmacological prevention tool for cardiovascular diseases. In patients with TS, lower physical activity has been reported, secondary to greater anaerobic stress during exercise than control subjects, leading to increased muscle fatigue with short bursts of activity [70].

Hypertension onset and development characterize patients with TS during adolescence: increased blood pressure levels are diagnosed in 21–40% of young women [71], worsening with age [72]. The pathogenesis is multifactorial and largely unknown: recent hypotheses include altered sympathetic tone, vasculopathy (increased tendency for premature derangement of arterial function), endocrine factors, overweight, and renal disease [69]. Blood pressure should be measured in every outpatient visit, at least once a year, and ambulatory 24-h blood pressure measurement is beneficial in the detection of nocturnal hypertension, non-dipping profile and to unveil white-coat hypertension. An echocardiogram, with particular attention paid to the aortic root, should be repeated during adolescence in hypertensive patients, even without congenital heart defects.

The relative risk of both Type 1 and Type 2 diabetes mellitus is increased (respectively, 12 and 4 times [68]. Isochromosome Xq and ring X are more likely to develop diabetes [8]. Prevalence of diabetes is increased up to 12% in women with TS, with a mean age of onset of 38 years: glucose tolerance test is more sensitive than basal glucose or HbA1c for the diagnosis [73]. In cross sectional-analysis, the diagnosis of diabetes in children is rare, and the first discovery of impaired fasting glucose levels occurs in adolescents and young adults [71]: plasma glucose should always be checked during transition phase, and then annually [2].

Women with TS have a higher body mass index with peculiar body composition: impaired waist-to-hip ratio, increased total and visceral fat mass, and decreased skeletal muscle mass [74]. Hepatosteatosis is associated with metabolic syndrome and insulin-resistance [75]. Hyperlipidemia is highly prevalent in patients with TS (up to 50%) and is mainly unaffected by age, except total cholesterol [2,67]. Lipid profile is associated with body mass index, and similar in different kariotypes, characterizing the atherogenic profile in adult women with TS. Interestingly, HRT did not seem to affect the lipid profile, especially after its discontinuation in the age of natural menopause (51–53 years) [67].

8. Reproductive outcomes and fertility preservation in TS

TS is often accompanied by difficulties in achieving successful pregnancies due to a severe reduction of ovarian reserve with POI [76,77], and cardiac or cardiovascular issues related to TS can further complicate the pregnancy (hypertension, diabetes, cardiac malformations [2,36,78,79]. Patients with TS undergo an accelerated ovarian germ cell depletion before the birth and the follicle loss continues postnatally, leading to POI [76]. The main involved mechanism seems to be an accelerated apoptosis of ovarian germ cells during the fetal life and some women with TS have streaky ovaries at birth without follicles [2,80]. The rate of follicle depletion is different and 5–10% of women with TS have spontaneous puberty and also pregnancy [33,81]. The different depletion rates of ovarian reserve have been related to the level of aneuploidy [81]: monosomic 45,X is linked to a greater reduction of ovarian reserve than patients with mosaicism [81]. In clinical practice, the rate of mosaicism in the ovarian cells can be different from that of lymphocytes [82]. Patients with monosomic 45,X in lymphocytes with a severe reduction of the ovarian reserve, mosaic in granulosa cells and normal karyotype in oocytes have been described [82]. Genetic alterations of granulosa cells are not free from negative implications as they can cause an impaired folliculogenesis [83] with higher risk of the development of empty follicles or incompetent oocytes [84].

No guidelines are available for fertility preservation options in patients with TS, but practical algorithmic approaches to decision-making have been proposed [85]. The combination of controlled ovarian stimulation and oocyte cryopreservation is the first choice for fertility preservation, when feasible [85]. In patients with TS, there is usually a negative outcome: the possibility of no oocyte collection is higher than that of women with normal karyotype and more ovarian stimulations are required [86]. Patients who had spontaneous puberty, regular menses, mosaic karyotype, and better ovarian reserve indexes, have better fertility preservation results [81]. The only feasible fertility preservation technique in prepubertal patients is the ovarian tissue cryopreservation (OTC) [2,85]. Despite the great development of this technique that led to more than 150 live births, there is still an Achilles heel to be addressed: the follicles loss that occurs during the first days after transplantation due to transitory ischemia [87]. Even if several methods have been used to improve the vascularization of the graft in order to minimize the ovarian reserve loss, up to 2/3 of the harvested primordial follicles are lost after transplantation [88] and this could lead to the nonfunctioning of the graft in women with an initial reduced ovarian reserve. While in women without TS the ovarian endocrine function is restored in most patients, Rodriguez-Wallberg *et al* [76]. recently reported no regained ovarian functionality in none of the transplanted patients with TS, neither after repeated transplantations: it should be discussed during the counseling [87]. As no studies evaluated if the unilateral oophorectomy in patients with TS may impair the spontaneous puberty or may cause an earlier menopause, should OTC be routinely recommended in patients with TS since the possibility that no follicles are present in the tissue is high [84]? As OTC is performed in childhood in patients with TS, it will be many years before these patients will come back to reuse the tissue. In the meantime, one would hope that researches on the in vitro activation and in vitro growth of the follicles will achieve positive results [82].

In prepubertal, patients with TS ovarian reserve should be monitored and OTC should be suggested when the ovarian reserve is reduced. When the ovarian reserve is not exhausted in post-pubertal patients with TS, oocyte cryopreservation should be the first option, otherwise oocyte donation or adoption should be discussed [85]. During the counseling, pre-implantation genetic testing for aneuploidy should be discussed in patients with TS using their oocytes [89].

In patients with TS, the risk of pregnancy complications (pre-eclampsia and fetal growth restriction) is high [79]. Pregnancy itself might be a life-threatening condition due to medical issues related to TS, such as cardiovascular and metabolic complications [79]. A recent retrospective study performed in the UK evaluated the outcomes of 127 pregnancies in 81 women with TS [90]: there were 17 miscarriages, 3 terminations of pregnancy, 2 stillbirths (one at 25 weeks associated with early onset pre-eclampsia, and the other one at 28 weeks complicated by early onset fetal growth restriction) and 105 live births, 9% were preterm. The main results were the high rate of cesarean section (67%) and the relatively low rates of gestational diabetes mellitus, gestational hypertension, and pre-eclampsia compared with other studies (7%, 10%, and 9%, respectively). However, there were three major adverse cardiac events: two aortic dissection (one fatal) in 45,X karyotype with bicuspid aortic valves, and ovum donation pregnancies; a third patient required aortic root replacement within 6 months of delivery. Pregnancy in TS should always be considered at high risk, especially for aortic dissection. Pregnancy itself causes structural changes in the intima and media in the absence of aortic disease, which could lead to aortic dilation and an increased risk of aortic dissection during delivery. Cauldeweel *et al*. reported that 57% of pregnancies performed cardiovascular imaging within the 24 months before conception [90]. The adequate cardiac surveillance and treatment of cardiovascular risk factor is fundamental in all women with TS before and during pregnancy, and the prevention of cardiovascular disease, as well as diagnosis of cardiac malformation, should start early during adolescence (and re-assessed during transition, especially in the view of a pregnancy). The management of these women should always be performed in a multidisciplinary team including a maternal-fetal medicine specialists, a cardiologist, and an endocrinologist [91]. Transthoracic echocardiogram, cardiac magnetic resonance imaging, oral glucose tolerance test, evaluation of thyroid function, weight

optimization, liver enzymes, and renal functions are needed to verify the feasibility of the pregnancy and to correct preexisting health issues before the pregnancy [91]. When there is a contraindication for the pregnancy, adoption or gestational carrier can be considered [85].

9. Unmet needs in patients with TS: an interview with the President of the patient advocacy group

9.1. What is your role in patients with TS?

In the 30 years of activity of the Italian Association of Families of Individuals with Growth Hormone Deficiency and other Rare Diseases (AFaDOC) we have been able to observe many girls, adolescents, and young adults with TS.

In all these patients, we have seen how the complexity and multifactorial nature of TS can subtly but substantially affect the quality of life of young patients and their families. For this reason, according to our experience, these patients require psychological, neuro-cognitive, and neuropsychiatric interventions, starting from the first years of life.

9.2. What are the most important challenges in adolescents with TS?

TS can affect 'subtle' aspects of cognitive, emotional, and relational functioning, aspects that can have an impact on the ability to grasp and process even social signals. We could observe that the greatest difficulties are the processing of non-verbal information and the execution of complex processes, where the ability to be flexible and integrate different information is fundamental. Poor cognitive flexibility induces rigid responses to complex stimuli, increases the difficulty of evaluating a point of view different from one's own, and makes it difficult to adapt to constantly changing situations, all aspects at the basis of the ability to manage the reciprocity and complexity inherent in social relations.

For these reasons, we believe that greater attention must be given to adequate psychological support of these subjects from early childhood to adulthood, with particular attention during adolescence, a period in which relational difficulties are emphasized, especially if already encountered in childhood. In Figure 2 we reported the most important psycho-social features that increase with aging (from adolescence).

9.3. What activities are endorsed by the association for adolescents?

Several activities are created for teenagers, such as summer camps and meetings with the presence of health specialists with skills in different fields answering questions from patients and families. The activities are aimed to:

- Develop self-awareness for emotions, attitudes, and thoughts that can facilitate or hinder interpersonal relationships.
- Develop reflection on one's interactive methods.
- Improve communication skills in the group.
- Promote the ability to compare and build rewarding relationships.
- Encourage the learning of more assertive ways of relating.

9.4. What do you expect during transition?

It would be desirable that in the periodic checkup of girls with TS, the clinician in collaboration with the psychologist would also pay attention to the related psychological problems, with

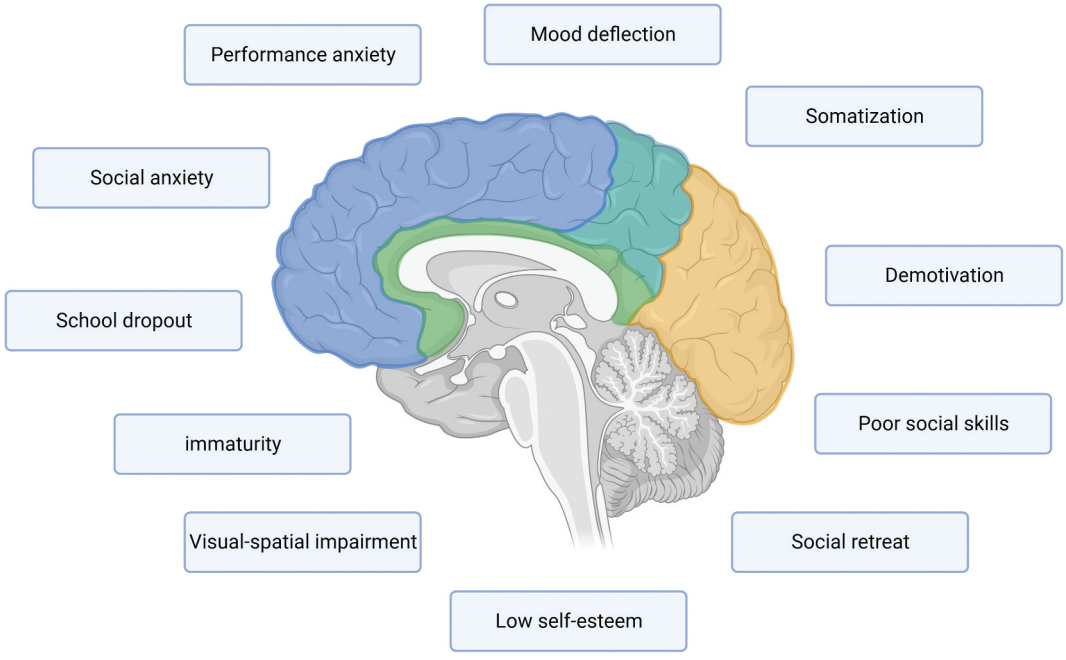

Figure 2. Psycho-social features of patients with TS, most of the aspects indicated are suggested in the interview with the President of the Patient Advocacy Group and discussed in the paragraph 10 'expert opinion' (created with Biorender.com).

effective screening tools, such as the regular administration of specific and standardized test for the early diagnosis of the neurocognitive and psychological difficulties to which these patients are predisposed. Interviews with the family and instrumental investigations have to start from the diagnosis communication, in order to identify families and patients at higher risk and direct them toward therapies specific support.

10. Expert opinion and future perspectives: the seamless transition from pediatric to adult care in girls with TS

Adolescence is a complex time for girls and boys: several concerns might emerge in all teenagers, not only in those with chronic conditions. As indicated in the previous paragraph, reporting the interview with the President of the Patient Advocacy Group, patients and caregivers need guidance from a psychologist. Therefore, not only endocrinologists (at least pediatric and adult physicians) but all relevant specialists and stakeholders (including patient's association) must be involved, to ensure that all patients with TS are appropriately transferred from pediatric to adult care. It is largely accepted that a holistic approach with an optimal model of transition is of utmost importance; nevertheless, the widespread adoption of this best practice remains elusive. The ideal age for transition has yet to be defined, but it generally occurs at about 17–18 years of age in our clinical practice and is shared with the patient and her caregivers, after a gradual preparation toward the end of adolescence. Pediatric endocrinologists are responsible for ensuring the continuation of care in adult clinics, and propose the outpatient visit, accompanied by a summary sheet of the pediatric medical file. Adult service for women with TS should offer all specialists required for multidisciplinary care, able to ensure the continuity of cure for any diseases diagnosed during childhood and detecting any potential associated disorders during adulthood.

However, growing evidence suggests that young people with chronic conditions are doubly disadvantaged during this period of transition, affecting their global developmental processes, comorbidities, psychosocial adjustment, and quality of life [92]. Among risky behaviors, poor adherence to treatment is commonly viewed by physicians and parents. Moreover, in the absence of appropriate primary care or specialized adult services, the risk of young people with chronic conditions is dropping out of health care, with several health consequences. In addition, the focus on a healthy diet, regular physical activity, and refraining from the use of tobacco and alcohol are just some of the aspects that should be reinforced in adolescence.

Even the transition of girls with TS from the pediatric endocrinologist to the adult team can be a challenge. The transition should coincide with the end of puberty: it is the start of an autonomous self-confidence of the patient, who has been accompanied by her parents since childhood [92]. TS is a chronic condition and requires lifelong clinical visits, with routine intervals that expand from childhood (screening of comorbidities, rhGH therapy, induction of puberty, study of psycho-behavioral conditions) to the adolescents that grow older (in adulthood visits are often less frequent despite lifelong health needs) [2]. Patients with TS have a peculiar neurocognitive profile, characterized by poor adaptive skills, impairments in visuospatial and memory areas, dyscalculia, and deficits in attentional control [93]. If the transition phase coincides with the high school, physicians must consider some peculiar aspects of girls with TS [94]. Mathematical skills can be impaired, and the difficulties with number recognition result in reduced understanding of time and money concepts. In early grade school, response time is longer and visual perceptual is different: young women with TS tend to require additional time and repetition to acquire specific math skills, resulting in a mathematical learning disability [95]. Current recommendations for young adults with TS include routine neuropsychological assessments, especially at transition time points from elementary to middle school, middle to high school, and high school to postsecondary education [2].

Table 1. Clinical practice monitoring in women with TS in Padova.

Comorbidities	Parameters	First screening	Frequency of controls
Obesity	Weight, waist circumference	At diagnosis	Every visit, annually
Hypertension	Blood pressure	At diagnosis	Every visit, annually
Thyroid function	TSH, fT4 ± anti-TPO antibodies and US	At diagnosis	Every visit, annually
Dyslipidemia	Total cholesterol, HDL cholesterol, triglycerides	After 10 years of age	Annually
Diabetes mellitus	Fasting glucose, HbA1c ± oral glucose tolerance test	After 10 years of age	Annually
Liver alterations	AST, ALT, gamma-GT, alkaline phosphatase Liver ultrasound	After 10 years of age	Annually As needed
Celiac disease	IgA anti-transglutaminases, IgA total	At 2 years	Every 5 years
Skeletal disorders	25-hydroxyvitamin D Spinal X rays	At diagnosis	Every 3–5 years As needed
Osteopenia	Bone densitometry scan	After puberty	Every 5 years
Cardiovascular abnormalities	Electrocardiogram, transthoracic echocardiography	At diagnosis	As needed, every 3–5 years if low risk
Renal abnormalities	Blood creatinine, renal ultrasound	At diagnosis	As needed
Infertility	FSH, LH, serum estradiol, AMH, pelvic ultrasound	After 12 years of age or after spontaneous puberty	As needed
Otological abnormalities	Audiometric evaluation	At diagnosis	
Ophthalmologic abnormalities	Ophthalmological evaluation	At diagnosis	As needed
Dental abnormalities	Dental evaluation	At diagnosis	As needed
Melanoma	Skin examination	At diagnosis	Annually
Neuropsychological disorders	Psychological consultation ± psychometric tests	At diagnosis	As needed

Optimal care of patients with TS requires the participation of several medical specialties, depending on the phenotypic presentation: a regular follow-up and proactive screening of comorbidities is depicted in Table 1. Since multimorbidity occurs during adult life, the endocrinologist should act as the 'anchor' physician during adult care and promote patient education, ensuring that women with TS realize the need for continued follow-up during adulthood [5].

Puberty induction starts in early adolescence (10–12 years) in girls with POI: proactive counseling regarding reproductive options should be offered. During adolescence or early adulthood, patients with TS with residual ovarian reserve, as in the case of mosaicism, should be evaluated not only for fertility preservation options but also for contraception. TS is also associated with psychosocial risks, including cognitive, social, and behavioral components. Age-appropriate social interactions should be investigated and encouraged during adolescence. Medical and psychological intervention should be considered in case of psychosocial alterations to improve emancipation from family and future career enhancement [96]. Some aspects of socialization are different in women with TS, including difficulties forming and maintaining social relationships and having fewer close friends [94]. Therefore, an effort should be made to provide appropriate support and guidance during adolescence: a better understanding of strengths and weaknesses could guide to offer a holistic approach to fully understand the social challenges experienced by affected women [97]. If a social difficulty appears to be a critical issue in girls with TS, an appropriate counseling to patients and caregivers may prove useful in advancing their social adaptation [98]. The use of a validated questionnaire such as the Transition Readiness Assessment Questionnaire (TRAQ) can be useful to start the process of transition: it has been developed to assess teenagers' and young adults' transition readiness: it has good psychometric properties and the best contributors of transition readiness were older age and female gender [99].

It is essential to define the member of the pediatric care team that will implement each core element and design an office workflow to support transition. Helping the patients with TS and their family to identify the adult endocrinologist and the other required clinicians (such as gynecologist, cardiologist, nephrologist, audiological physician, and psychologist) is recommended to ensure a continuity of follow-up for any diseases diagnosed during childhood and detecting any potential associated disorders during adulthood [96]. An initial co-management between the pediatric and adult endocrinologist may be helpful to share the key medical elements and essential information that need to be addressed: the two endocrinologists should share the same access to the electronic health records. In case of different Healthcare Providers, the distance should not preclude the quality of the transition process. The use of telemedicine platforms and dedicated websites with recommendations/information may open the door to a novel transition strategy. The development of national registries should be encouraged to improve our knowledge regarding the natural history of this rare condition. Reference centers in Italy offer free treatments to patients with TS. They are usually included in the European Reference Network for Rare Endocrine Conditions (Endo ERN), which is an important tool to connect patients and healthcare providers across Europe, providing knowledge and resources for diagnosis and treatment of rare conditions.

In conclusion, optimal care of women with TS requires the collaboration of several medical specialties. The transition of girls with TS from the pediatric endocrinologist to the adult team is a vulnerable time. It is necessary that a planned transition process shared between referring physicians, to encourage patients to develop independent self-care behaviors and to avoid the risk of dropping out of future follow-up.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Sybert VP, McCauley E. Turner's syndrome. N Engl J Med. 2004;351(12):1227–1238. doi: 10.1056/NEJMra030360
2. Gravholt CH, Andersen NH, Conway GS, et al. 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;177(3):G1–G70. doi: 10.1530/EJE-17-0430
   - **of interest: international consensus guidelines on how best to diagnose and manage TS.**
3. Gravholt CH, Viuff M, Just J, et al. The changing face of turner syndrome. Endocr Rev. 2023;44(1):33–69. doi: 10.1210/endrev/bnac016
4. Gravholt CH, Friedrich U, Nielsen J. Chromosomal mosaicism: a follow-up study of 39 unselected children found at birth. Hum Genet. 1991;88(1):49–52. doi: 10.1007/BF00204928
5. Gravholt CH, Viuff MH, Brun S, et al. Turner syndrome: mechanisms and management. Nat Rev Endocrinol. 2019;15(10):601–614. doi: 10.1038/s41574-019-0224-4
6. Bronshtein M, Zimmer EZ, Blazer S. A characteristic cluster of fetal sonographic markers that are predictive of fetal turner syndrome in early pregnancy. Am J Obstet Gynecol. 2003;188(4):1016–1020. doi: 10.1067/mob.2003.230
7. Hook EB, Warburton D. Turner syndrome revisited: review of new data supports the hypothesis that all viable 45,X cases are cryptic mosaics with a rescue cell line, implying an origin by mitotic loss. Hum Genet. 2014;133(4):417–424. doi: 10.1007/s00439-014-1420-x
8. Cameron-Pimblett A, La Rosa C, King TFJ, et al. The turner syndrome life course project: karyotype-phenotype analyses across the lifespan. Clin Endocrinol (Oxf). 2017;87(5):532–538. doi: 10.1111/cen.13394

9. Schoemaker MJ, Swerdlow AJ, Higgins CD, et al. Mortality in women with turner syndrome in Great Britain: a national cohort study. J Clin Endocrinol Metab. 2008;93(12):4735–4742.
10. Prakash SK, Lugo-Ruiz S, Rivera-Dávila M. The impact of somatic mosaicism on bicuspid aortic valve and aortic dissection in turner syndrome. Am J Med Genet C Semin Med Genet. 2019;181(1):7–12. doi: 10.1002/ajmg.c.31689
11. Knickmeyer RC, Davenport M. Turner syndrome and sexual differentiation of the brain: implications for understanding male-biased neurodevelopmental disorders. J Neurodev Disord. 2011;3(4):293–306. doi: 10.1007/s11689-011-9089-0
12. Wisniewski A, Milde K, Stupnicki R, et al. Weight deficit at birth and Turner's syndrome. J Pediatr Endocrinol Metab. 2007;20(5). doi: 10.1515/JPEM.2007.20.5.607
13. Isojima T, Yokoya S. Growth in girls with turner syndrome. Front Endocrinol. 2023;13(January):1–7. doi: 10.3389/fendo.2022.1068128
14. Los E, Rosenfeld RG. Growth and growth hormone in turner syndrome: looking back, looking ahead. Am J Med Genet Part C, Semin Med Genet. 2019;181(1):74–78. doi: 10.1002/ajmg.c.31680
15. Davenport ML, Punyasavatsut N, Stewart PW, et al. Growth failure in early life: an important manifestation of turner syndrome. Horm Res Paediatr. 2002;57(5–6):157–164. doi: 10.1159/000058376
16. Malaquias AC, Scalco RC, Fontenele EGP, et al. The sitting Height/Height ratio for age in healthy and short individuals and its potential role in selecting short children for SHOX analysis. Horm Res Paediatr. 2013;80(6):449–456. doi: 10.1159/000355411
17. AL ADK, Şükür NM, Özturan EK, et al. Body proportions in patients with turner syndrome on growth hormone treatment. Turkish J Med Sci. 2023;53(2):518–525. doi: 10.55730/1300-0144.5612
18. Fukami M, Seki A, Ogata T. SHOX Haploinsufficiency as a cause of syndromic and nonsyndromic short stature. Mol Syndromol. 2016;7(1):3–11. doi: 10.1159/000444596
19. Binder G. Short stature due to SHOX deficiency: genotype, phenotype, and therapy. Horm Res Paediatr. 2011;75(2):81–89. doi: 10.1159/000324105
20. Blum WF, Ross JL, Zimmermann AG, et al. GH treatment to final height produces similar height gains in patients with SHOX deficiency and turner syndrome: results of a multicenter trial. J Clin Endocrinol Metab. 2013;98(8):E1383–E1392. doi: 10.1210/jc.2013-1222
21. Li P, Cheng F, Xiu L. Height outcome of the recombinant human growth hormone treatment in turner syndrome: a meta-analysis. Endocr Connect. 2018;7(4):573–583. doi: 10.1530/EC-18-0115
• **of interest: meta-analysis of growth hormone therapy results.**
22. 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(13):1230–1242. doi: 10.1056/NEJMoa1005669
23. Kriström B, Ankarberg-Lindgren C, Barrenäs ML, et al. Normalization of puberty and adult height in girls with turner syndrome: results of the Swedish growth hormone trials initiating transition into adulthood. Front Endocrinol. 2023;14. doi: 10.3389/fendo.2023.1197897
24. 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. J Clin Endocrinol Metab. 2000;85(11):4212–4218. doi: 10.1210/jcem.85.11.6976
25. Bannink EMN, van der Palen RLF, Mulder PGH, et al. Long-term follow-up of GH-Treated girls with turner syndrome: BMI, blood pressure, body proportions. Horm Res Paediatr. 2009;71(6):336–342. doi: 10.1159/000223418
26. Quigley CA, Child CJ, Zimmermann AG, et al. Mortality in children receiving growth hormone treatment of growth disorders: data from the genetics and neuroendocrinology of short stature international study. J Clin Endocrinol Metab. 2017;102(9):3195–3205. doi: 10.1210/jc.2017-00214
27. Wasniewska M, Aversa T, Mazzanti L, et al. Adult height in girls with turner syndrome treated from before 6 years of age with a fixed per kilogram GH dose. Eur J Endocrinol. 2013;169(4):439–443. doi: 10.1530/EJE-12-1032
28. Dantas NCB, Braz AF, Malaquias A, et al. Adult height in 299 patients with turner syndrome with or without growth hormone therapy: results and literature review. Horm Res Paediatr. 2021;94(1–2):63–70. doi: 10.1159/000516869
29. Backeljauw P, Kanumakala S, Loche S, et al. Safety and effectiveness of recombinant human growth hormone in children with turner syndrome: data from the PATRO children Study. Horm Res Paediatr. 2021;94(3–4):133–143. doi: 10.1159/000515875
30. Blankenstein O, Snajderova M, Blair J, et al. Real-life GH dosing patterns in children with GHD, TS or born SGA: a report from the NordiNet® international outcome study. Eur J Endocrinol. 2017;177(2):145–155. doi: 10.1530/EJE-16-1055
31. Cappa M, Iughetti L, Loche S, et al. Efficacy and safety of growth hormone treatment in children with short stature: the Italian cohort of the GeNeSIS clinical study. J Endocrinol Invest. 2016;39(6):667–677. doi: 10.1007/s40618-015-0418-0
32. 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(6):2109–2114. doi: 10.1210/jc.2007-2266
33. Bernard V, Donadille B, Zenaty D, et al. Spontaneous fertility and pregnancy outcomes amongst 480 women with turner syndrome. Hum Reprod. 2016;31(4):782–788. doi: 10.1093/humrep/dew012
34. Lunding SA, Aksglaede L, Anderson RA, et al. AMH as predictor of premature ovarian insufficiency: a longitudinal study of 120 turner syndrome patients. J Clin Endocrinol Metab. 2015;100(7):E1030–8. doi: 10.1210/jc.2015-1621
35. van Pareren YK, de Muinck Keizer-Schrama SMPF, Stijnen T, et al. Final height in girls with turner syndrome after long-term growth hormone treatment in three dosages and low dose estrogens. J Clin Endocrinol Metab. 2003;88(3):1119–1125. doi: 10.1210/jc.2002-021171
36. Klein KO, Rosenfield RL, Santen RJ, et al. Estrogen replacement in turner syndrome: literature review and practical considerations. J Clin Endocrinol Metab. 2018;103(5):1790–1803. doi: 10.1210/jc.2017-02183
37. Goodman MP. Are all estrogens created equal? A review of oral vs. Transdermal therapy. J Women's Heal. 2012;21(2):161–169. doi: 10.1089/jwh.2011.2839
38. Cintron D, Rodriguez-Gutierrez R, Serrano V, et al. Effect of estrogen replacement therapy on bone and cardiovascular outcomes in women with turner syndrome: a systematic review and meta-analysis. Endocrine. 2017;55(2):366–375. doi: 10.1007/s12020-016-1046-y
39. Zaiem F, Alahdab F, Al Nofal A, et al. Oral Versus Transdermal Estrogen In Turner Syndrome: A Systematic Review And Meta-Analysis. Endocr Pract. 2017;23(4):408–421. doi: 10.4158/EP161622.OR
40. Bösze P, Tóth A, Török M. Hormone replacement and the risk of breast cancer in Turner's syndrome. N Engl J Med. 2006;355(24):2599–2600. doi: 10.1056/NEJMc062795
41. Nordenström A, Ahmed SF, van den Akker E, et al. Pubertal induction and transition to adult sex hormone replacement in patients with congenital pituitary or gonadal reproductive hormone deficiency: an endo-ERN clinical practice guideline. Eur J Endocrinol. 2022;186(6):G9–G49. doi: 10.1530/EJE-22-0073
•• **of considerable interest: European Rare Disease Network (ENDO-ERN) guideline of sexual hormones replacement.**
42. Fruzzetti F, Cagnacci A. Venous thrombosis and hormonal contraception: what's new with estradiol-based hormonal contraceptives? Open Access J Contracept. 2018;9:75–79. doi: 10.2147/OAJC.S179673
43. Gemzell-Danielsson K, Cagnacci A, Chabbert-Buffet N, et al. A novel estetrol-containing combined oral contraceptive: European expert panel review. Eur J Contracept Reprod Heal Care. 2022;27(5):373–383. doi: 10.1080/13625187.2022.2093850
44. Calcaterra V, Gamba G, Montani N, et al. Thrombophilic screening in turner syndrome. J Endocrinol Invest. 2011;34(9):676–679.

45. Gambineri A, Scarano E, Rucci P, et al. New insights into the comorbid conditions of turner syndrome: results from a long-term monocentric cohort study. J Endocrinol Invest. 2022;45(12):2247–2256. doi: 10.1007/s40618-022-01853-z
46. Wasniewska M, Salerno M, Corrias A, et al. The evolution of thyroid function after presenting with hashimoto thyroiditis is different between initially euthyroid girls with and those without turner syndrome. Horm Res Paediatr. 2016;86(6):403–409. doi: 10.1159/000452722
47. Wegiel M, Antosz A, Gieburowska J, et al. Autoimmunity predisposition in girls with turner syndrome. Front Endocrinol. 2019;10:511. doi: 10.3389/fendo.2019.00511
48. Censi S, Salmaso L, Ceccato F, et al. Hyperthyroidism incidence in a large population-based study in northeastern Italy. Endocr Connect. 2023;12(12): doi: 10.1530/EC-23-0292
49. Pessach IM, Notarangelo LD. X-linked primary immunodeficiencies as a bridge to better understanding X-chromosome related autoimmunity. J Autoimmun. 2009;33(1):17–24. doi: 10.1016/j.jaut.2009.03.003
50. Wood CL, Lane LC, Cheetham T. Puberty: normal physiology (brief overview). Best Pract Res Clin Endocrinol Metab. 2019;33(3):101265. doi: 10.1016/j.beem.2019.03.001
51. Shi K, Liu L, He YJ, et al. Body composition and bone mineral status in patients with turner syndrome. Sci Rep. 2016;6(1):4–11. doi: 10.1038/srep38026
52. Neely EK, Marcus R, Rosenfeld RG, et al. Turner syndrome adolescents receiving growth hormone are not osteopenic. J Clin Endocrinol Metab. 1993;76(4):861–866. doi: 10.1210/jcem.76.4.8473397
53. Gravholt CH, Vestergaard P, Hermann AP, et al. Increased fracture rates in Turner's syndrome: a nationwide questionnaire survey. Clin Endocrinol (Oxf). 2003;59(1):89–96. doi: 10.1046/j.1365-2265.2003.01807.x
54. Gravholt CH, Juul S, Naeraa RW, et al. Morbidity in Turner syndrome. J Clin Epidemiol. 1998;51(2):147–158. doi: 10.1016/S0895-4356(97)00237-0
55. Bakalov VK, Chen ML, Baron J, et al. Bone mineral density and fractures in turner syndrome. Am J Med. 2003;115(4):259–264. doi: 10.1016/S0002-9343(03)00364-4
56. 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(4):497–502. doi: 10.1046/j.1365-2265.1999.00841.x
57. ROSS JL, LONG LM, FEUILLAN P, et al. Normal bone density of the wrist and spine and increased wrist fractures in girls with Turner's syndrome. J Clin Endocrinol Metab. 1991;73(2):355–359. doi: 10.1210/jcem-73-2-355
58. Holroyd CR, Davies JH, Taylor P, et al. Reduced cortical bone density with normal trabecular bone density in girls with turner syndrome. Osteoporos Int. 2010;21(12):2093–2099. doi: 10.1007/s00198-010-1170-0
59. Hansen S, Brixen K, Gravholt CH. Compromised trabecular microarchitecture and lower finite element estimates of radius and tibia bone strength in adults with turner syndrome: a cross-sectional study using high-resolution-pQCT. J Bone Miner Res. 2012;27(8):1794–1803. doi: 10.1002/jbmr.1624
60. Nguyen HH, Wong P, Strauss BJ, et al. Delay in estrogen commencement is associated with lower bone mineral density in turner syndrome. Climacteric. 2017;20(5):436–441. doi: 10.1080/13697137.2017.1325461
61. Cleemann L, Hjerrild BE, Lauridsen AL, et al. Long-term hormone replacement therapy preserves bone mineral density in turner syndrome. Eur J Endocrinol. 2009;161(2):251–257. doi: 10.1530/EJE-09-0020
62. Hanton L, Axelrod L, Bakalov V, et al. The importance of estrogen replacement in young women with turner syndrome. J Women's Heal. 2003;12(10):971–977. doi: 10.1089/154099903322643893
63. Gravholt CH, Lauridsen AL, Brixen K, et al. Marked disproportionality in bone size and mineral, and distinct abnormalities in bone markers and calcitropic hormones in adult turner syndrome: a cross-sectional study. J Clin Endocrinol Metab. 2002;87(6):2798–2808. doi: 10.1210/jcem.87.6.8598
64. Chiarito M, Piacente L, Chaoul N, et al. Role of wnt-signaling inhibitors DKK-1 and sclerostin in bone fragility associated with turner syndrome. J Endocrinol Invest. 2022;45(6):1255–1263. doi: 10.1007/s40618-022-01760-3
65. Chiarito M, Brunetti G, D'Amato G, et al. Monitoring and maintaining bone health in patients with turner syndrome. Expert Rev Endocrinol Metab. 2020;15(6):431–438. doi: 10.1080/17446651.2020.1834846
66. Tsuburai T, Nakamura T, Yoshikata H, et al. Eldecalcitol increases bone mass in patients with turner syndrome who have insufficient bone mass acquisition after estrogen replacement therapy. Endocr J. 2018;65(6):629–638. doi: 10.1507/endocrj.EJ17-0498
67. Sandahl KJ, Just J, Erlandsen M, et al. A prospective study of lipids in adult women with turner syndrome. J Endocr Soc. 2023;7(11):bvad124. doi: 10.1210/jendso/bvad124
68. Davis SM, Geffner ME. Cardiometabolic health in turner syndrome. Am J Med Genet Part C, Semin Med Genet. 2019;181(1):60–66. doi: 10.1002/ajmg.c.31678
69. Jones L, Blair J, Hawcutt DB, et al. Hypertension in turner syndrome: a review of proposed mechanisms, management and new directions. J Hypertens. 2023;41(2):203–211. doi: 10.1097/HJH.0000000000003321
70. Wells GD, O'Gorman CS, Rayner T, et al. Skeletal muscle abnormalities in girls and adolescents with turner syndrome. J Clin Endocrinol Metab. 2013;98(6):2521–2527. doi: 10.1210/jc.2012-4016
71. Lebenthal Y, Levy S, Sofrin-Drucker E, et al. The natural history of metabolic comorbidities in Turner Syndrome from childhood to early adulthood: comparison between 45,X monosomy and other karyotypes. Front Endocrinol. 2018:9. doi: 10.3389/fendo.2018.00027
72. Sandahl K, Wen J, Erlandsen M, et al. Natural history of hypertension in turner syndrome during a 12-year pragmatic interventional study. Hypertens (Dallas, Tex 1979). 2020;76(5):1608–1615. doi: 10.1161/HYPERTENSIONAHA.120.15292
73. Ibarra-Gasparini D, Altieri P, Scarano E, et al. New insights on diabetes in turner syndrome: results from an observational study in adulthood. Endocrine. 2018;59(3):651–660. doi: 10.1007/s12020-017-1336-z
74. Gravholt CH, Hjerrild BE, Mosekilde L, et al. Body composition is distinctly altered in turner syndrome: relations to glucose metabolism, circulating adipokines, and endothelial adhesion molecules. Eur J Endocrinol. 2006;155(4):583–592. doi: 10.1530/eje.1.02267
75. Calcaterra V, Brambilla P, Maffè GC, et al. Metabolic syndrome in turner syndrome and relation between body composition and clinical, genetic, and ultrasonographic characteristics. Metab Syndr Relat Disord. 2014;12(3):159–164. doi: 10.1089/met.2013.0075
76. Rodriguez-Wallberg KA, Sergouniotis F, Nilsson HP, et al. Trends and outcomes of fertility preservation for girls, adolescents and young adults with turner syndrome: a prospective cohort study. Front Endocrinol. 2023;14. doi: 10.3389/fendo.2023.1135249
77. Oktay K, Bedoschi G. Fertility preservation in girls with turner syndrome: limitations, current success and future prospects. Fertil Steril. 2019;111(6):1124–1126. doi: 10.1016/j.fertnstert.2019.03.018
78. Kooijman SS, Duijnhouwer AL, van Kimmenade RRJ, et al. Influence of pregnancy on aortic diameter in women with the Turner syndrome. Am J Cardiol. 2021;140:122–127. doi: 10.1016/j.amjcard.2020.10.047
79. Donadille B, Bernard V, Christin-Maitre S. How can we make pregnancy safe for women with turner syndrome? Am J Med Genet Part C, Semin Med Genet. 2019;181(1):34–41. doi: 10.1002/ajmg.c.31682
80. Schleedoorn MJ, van der Velden AAEM, Braat DDM, et al. To freeze or not to freeze? An update on fertility preservation in females with turner syndrome. Pediatr Endocrinol Rev. 2019;16(3):369–382. doi: 10.17458/per.vol16.2019.svb.tofreezeornot
81. Bouchlariotou S, Tsikouras P, Dimitraki M, et al. Turner's syndrome and pregnancy: has the 45,X/47,XXX mosaicism a different prognosis? Own clinical experience and literature review. J Matern Neonatal Med. 2011;24(5):668–672. doi: 10.3109/14767058.2010.520769
82. Schleedoorn M, Fleischer K, Braat D, et al. Why turner patients with 45, X monosomy should not be excluded from fertility preservation

services. Reprod Biol Endocrinol. 2022;20(1):143. doi: 10.1186/s12958-022-01015-z
83. Peek R, Nadesapillai S, Thi Nguyen TY, et al. Assessment of folliculogenesis in ovarian tissue from young patients with turner syndrome using a murine xenograft model. Fertil Steril. 2023;120(2):371–381. doi: 10.1016/j.fertnstert.2023.04.008
84. Mamsen LS, Charkiewicz K, Anderson RA, et al. Characterization of follicles in girls and young women with turner syndrome who underwent ovarian tissue cryopreservation. Fertil Steril. 2019;111(6):1217–1225.e3. doi: 10.1016/j.fertnstert.2019.02.003
85. Oktay K, Bedoschi G, Berkowitz K, et al. Fertility preservation in women with turner syndrome: a comprehensive review and practical guidelines. J Pediatr Adolesc Gynecol. 2016;29(5):409–416. doi: 10.1016/j.jpag.2015.10.011
86. Borini A, Coticchio G. Oocyte quantity and quality are crucial for a perspective of fertility preservation in women with turner syndrome. Fertil Steril. 2019;111(3):461–462. doi: 10.1016/j.fertnstert.2018.12.009
87. Marin L, Bedoschi G, Kawahara T, et al. History, evolution and Current state of ovarian tissue auto-transplantation with cryopreserved tissue: a successful translational research journey from 1999 to 2020. Reprod Sci. 2020;27(4):955–962. doi: 10.1007/s43032-019-00066-9
88. Oktay KH, Marin L, Petrikovsky B, et al. Delaying reproductive aging by ovarian tissue cryopreservation and transplantation: is it prime time? Trends Mol Med. 2021;27(8):753–761. doi: 10.1016/j.molmed.2021.01.005
89. Li C, Dang Y, Li J, et al. Preimplantation genetic testing is not a preferred recommendation for patients with X chromosome abnormalities. Hum Reprod. 2021;36(9):2612–2621. doi: 10.1093/humrep/deab177
90. Cauldwell M, Steer P, Adamson D, et al. Pregnancies in women with turner syndrome: a retrospective multicentre UK study. BJOG An Int J Obstet Gynaecol. 2022;129(5):796–803. doi: 10.1111/1471-0528.17025
91. Practice Committee of American Society For Reproductive Medicine. Increased maternal cardiovascular mortality associated with pregnancy in women with turner syndrome. Fertil Steril. 2012;97(2):282–284. doi: 10.1016/j.fertnstert.2011.11.049
92. Sawyer SM, Drew S, Yeo MS, et al. Adolescents with a chronic condition: challenges living, challenges treating. Lancet. 2007;369(9571):1481–1489. doi: 10.1016/S0140-6736(07)60370-5
93. Rovet JF. The psychoeducational characteristics of children with turner syndrome. J Learn Disabil. 1993;26(5):333–341. doi: 10.1177/002221949302600506
94. Hutaff-Lee C, Bennett E, Howell S, et al. Clinical developmental, neuropsychological, and social–emotional features of turner syndrome. Am J Med Genet Part C, Semin Med Genet. 2019;181(1):42–50. doi: 10.1002/ajmg.c.31687
95. Dennis M, Berch DB, Mazzocco MMM. Mathematical learning disabilities in special populations: phenotypic variation and cross-disorder comparisons. Dev Disabil Res Rev. 2009;15(1):80–89. doi: 10.1002/ddrr.54
96. Bondy CA. Care of girls and women with turner syndrome: a guideline of the turner syndrome study group. J Clin Endocrinol Metab. 2007;92(1):10–25. doi: 10.1210/jc.2006-1374
97. Wolstencroft J, Skuse D. Social skills and relationships in turner syndrome. Curr Opin Psychiatry. 2019;32(2):85–91. doi: 10.1097/YCO.0000000000000472
98. Mccauley E, Feuillan P, Kushner H, et al. Psychosocial development in adolescents with turner syndrome. J Dev Behav Pediatr. 2001;22(6):360–365. doi: 10.1097/00004703-200112000-00003
99. Chapados P, Aramideh J, Lamore K, et al. Getting ready for transition to adult care: tool validation and multi-informant strategy using the transition readiness assessment questionnaire in pediatrics. Child Care Health Dev. 2021;47(5):645–653. doi: 10.1111/cch.12872