REVIEW ARTICLE

Turner disease: a contemporary clinical approach

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Submitted: 09 March 2025
Revised: 02 November 2025
Accepted: 12 November 2025
Online First: 20 November 2025
Published: 24 December 2025

Check for updates

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Summary

Turner syndrome (TS) is a rare genetic disorder in females caused by partial or complete loss of one X chromosome. It presents with multisystem clinical manifestations that require lifelong multidisciplinary care and monitoring. Phenotypically, TS is characterized by short stature, short neck with lateral skin folds (pterygium colli), low-set ears, and a low posterior hairline. Clinically, it is associated with cardiovascular diseases (CVD) and primary hypogonadism. The diagnosis of TS is based on clinical presentation and genetic analysis, with early prenatal detection possible. In newborns, TS should be suspected in the presence of oedema of the hands and feet. Short stature becomes evident in early childhood, while delayed puberty and primary amenorrhea are common later findings. CVDs may be congenital or acquired; coarctation of the aorta is a key diagnostic sign, whereas aortic dissection and rupture of an aortic aneurysm are life-threatening complications. Most women with TS have primary hypogonadism and high infertility rates. Spontaneous pregnancies are rare, and fertility preservation options, such as oocyte or embryo cryopreservation, should be considered early. Associated autoimmune diseases, kidney anomalies, liver disorders, and hearing loss are also common. Hormone replacement therapy is essential for pubertal induction, maintenance of general health, and prevention of long-term complications of untreated hypogonadism. Due to numerous comorbidities and variable phenotypes, an individualized multidisciplinary approach is required. With early diagnosis, appropriate management, and psychosocial support, individuals with TS can lead a good quality of life despite ongoing health risks.

Keywords: Turner syndrome, Turner syndrome genetics, primary ovarian insufficiency, hormone replacement treatment

INTRODUCTION

Turner syndrome (TS) is a genetic condition that affects females and results from the complete or partial absence of a second sex chromosome (1). TS was described by Henry H. Turner in 1938 and identified as a sex chromosome abnormality by Charles Ford in 1959 (1,2). Nowadays, Turner syndrome is diagnosed primarily based on clinical features, with genetic testing confirming the diagnosis. Key signs include reduced height for age, neck webbing, congenital heart defects, inferiorly placed ears, broad chest, and cubitus valgus (1). Endocrine disorders are common, accompanied by a higher likelihood of celiac disease, osteoporosis, and cardiovascular diseases (2).

EPIDEMIOLOGY

The prevalence of Turner syndrome is 25-50 per 100,000 women, with no significant difference between countries and ethnicities (1,3). Cardiovascular diseases represent the leading cause of fatal outcomes, responsible for half of the three times higher mortality in these patients (4). Turner syndrome affects 1 in 2,500 to 3,000 liveborn girls, making it one of the most frequently observed sex chromosome anomalies (3). The average age for diagnosing Turner syndrome is 15 years, though many cases are identified late, with some patients never receiving a diagnosis. The condition is often diagnosed at one of three stages: prenatally through ultrasound or screening tests, in female neonates, where dorsal oedema of the hands and feet may represent the earliest clinical sign and an important diagnostic clue-highlighting the crucial role of the neonatologist in recognizing Turner syndrome during childhood to early adulthood (ages 5 to 20) when symptoms such as growth delays, delayed puberty, or irregular menstruation arise, or in adulthood (ages 30 to 40) due to infertility. Recent studies suggest a decline in 45, X karyotype cases and an increase in mosaicism, likely due to improved screening and legal abortions (1). Close to half of the individuals diagnosed with TS exhibit a monosomy 45, X chromosome pattern (5).

Additionally, 15–25% have 45, X/46, XX mosaicism. Y chromosome fragments are found in 10 to 12 percent of cases. Other rare karyotypes include 45, X/47, XXX, 45, X/46, XX/47, XXX, and unbalanced X-autosomal translocations. The remaining 15% of patients have structural abnormalities of the X chromosome, including isochromosome Xq, isodicentric Xp, or proximal deletion of Xp. Ring X chromosomes are rare **(Figure 1)** (3,6,7).

GENETICS AND CLINICAL IMPLICATIONS

Karyotyping of peripheral blood lymphocytes is the benchmark diagnostic tool for TS (5). It is recommended to analyze at least 30 metaphases during a chromosome examination as the primary test (7). If karyotype testing reveals a 46, XX pattern, yet the physical characteristics strongly suggest Turner syndrome, it is recommended to perform karyotyping or fluorescence in situ hybridization (FISH) analysis on a second tissue sample (e.g., skin, buccal cells, or urine) (3, 5, 7). In cases where a quicker result is required, such as prenatal or newborn screening, alternative techniques, such as microarray, FISH, or polymerase chain reaction (PCR), may be utilized as the first-choice test, with chromosome analysis conducted as a follow-up confirmatory test (7).

Embryo genetic assessment before implantation is increasingly used in the external fertilization techniques, particularly for women experiencing repeated pregnancy loss or unsuccessful embryo implantation. Prenatal genetic screening can detect fetuses with a greater probability of TS. Additional diagnostic procedures are necessary to establish the diagnosis with certainty. Ultrasound signs that may refer to Turner syndrome include thickened nuchal tissue, fluid-filled cervical masses consistent with cystic hygroma, narrowing of the aortic arch (suggestive of coarctation), structural anomalies affecting the left side of the heart, altered cranial shape, kidney issues, polyhydramnios, oligohydramnios, and growth restriction. Cystic hygroma is a key prenatal indicator suggestive of TS. However, ultrasound and serum screening cannot confirm the diagnosis; karyotyping is required

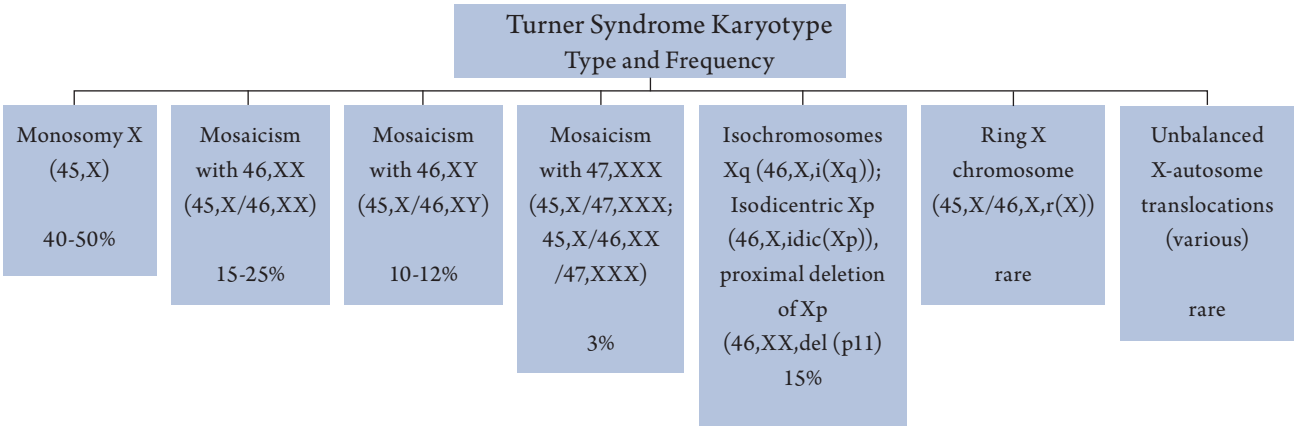

Figure 1. Turner syndrome karyotypes, variants, and distribution (3,6,7)

for verification. Turner syndrome karyotype can be determined prenatally through amniocentesis or chorionic villus sampling, with genetic counselling recommended before and after testing. Karyotype analysis is advised when certain risk indicators are present, including advanced maternal age, atypical maternal serum screening results (e.g., altered levels of AFP, hCG, inhibin A, or uE3), or multiple fetal abnormalities. The diagnosis must be confirmed after birth through karyotype testing (3,8).

Mosaic forms of Turner syndrome typically present with milder phenotypes than monosomy, particularly in cases of congenital heart disease. Individuals with a ring X chromosome exhibit a higher prevalence of metabolic disturbances, including glucose intolerance and elevations in hepatic enzymes (5). However, the presence of a ring X chromosome may correlate with cognitive impairment (3). Congenital cardiovascular and lymphatic malformations are lower in those with 45, X/46, XX mosaicism. The extent of mosaicism may differ between tissues and across ages. Individuals with 45, X/46, XX mosaicism typically retain greater reproductive potential compared to those with a non-mosaic 45, X karyotype, though they still face a higher risk of early pregnancy loss. Those with 45, X/47, XXX mosaicism often exhibit a less severe clinical presentation (3). Detecting a Y chromosome is crucial for preventing gonadoblastoma, which may warrant gonadectomy (5).

One hypothesis suggests that embryos identified as 45, X may carry mosaicism via a viable "rescue line." The ability to detect mosaicism depends on the markers used, the tissues sampled, the severity of the phenotype, and the number of cells analyzed. It is estimated that 1-1.5% of pregnancies that appear as 45, X are actually mosaic, though 99% of these pregnancies do not survive. Most 45, X embryos likely acquire this karyotype after fertilization due to mitotic factors. If no rescue line is found in blood or tissues, the placenta may harbor it. The PSF2RA gene deletion in the PAR1 locus of the X chromosome, which is essential for placental function, may account for the high embryonic mortality rate in TS (9).

The clinical features of Turner syndrome can be affected by whether the retained X chromosome is inherited from the mother or the father, suggesting imprinted genetic loci that cause gene expression from only one parent. Between 60% and 80% of women with Turner syndrome inherit their X chromosome from their mother. Parental origin is determined by analyzing X-linked microsatellite markers, Y-chromosome markers, and genes encoding the androgen receptor. One study found kidney malformations, lower LDL, and higher BMI linked to the maternal X. In contrast, the paternal X was associated with higher spontaneous miscarriage rates, more ocular abnormalities, and higher scholastic achievement. (10)

The maternal X chromosome increases the risk of skeletal anomalies, while the paternal X chromosome shows a correlation between parental and offspring height. This may be explained by epigenetic modification of a key growth regulator encoded by the SHOX gene, which is altered on the maternal X but not the paternal X (11).

Cytogenetic data suggest that features typical of Turner syndrome are associated with genes located on the Xp and Yp chromosomal regions. Research indicates that Xp deletions lead to the typical Turner syndrome phenotype. In contrast, Xq deletions result in a milder or normal phenotype, emphasizing the role of genes on the short arm in the disorder (12,13).

The X chromosome harbors a disproportionately high number of genes active in female reproductive tissues, underscoring its importance in fertility. Ongoing research seeks to clarify the roles of specific X-linked genes in shaping the TS phenotype. Deletions of "escape" genes and dysregulation of non-coding RNAs are frequently observed in primary ovarian insufficiency (POI) (14). Research shows that SHOX deficiency contributes to skeletal features of Turner syndrome, affecting bone development, growth plate function, apoptosis, and potentially brain development (15). The COLIA1 gene also serves as a biomarker of bone mass, structural integrity, fracture susceptibility, and age-related bone loss in postmenopausal women. However, it cannot predict osteoporosis risk in younger patients with POI. (16) Monoallelic expression of genes typically expressed biallelically is related to morbidity in TS, with particular relevance to escape genes, pseudoautosomal region genes, and X-Y homologous gene pairs. In the ring X phenotype, functional disomy of monoallelic genes contributes to the condition. Among the candidate genes associated with comorbidities are PRKX (linked to urinary malformation), KDM6A (associated with primary ovarian insufficiency, or POI), and ZFYVE9 and TIMP1 (related to aortic aneurysm) (17).

CLINICAL FEATURES

Turner syndrome and growth

Patients with Turner syndrome typically experience disproportionate short stature of the mesomelic type, characterized by an increased upper-to-lower segment ratio. However, the earliest sign may be lymphedema of the hands and feet in a newborn female infant. The average adult height varies by country, typically ranging between 138 and 147 cm. While short stature is a universal characteristic, skeletal abnormalities are less frequent. These include shortened fourth and/or fifth metacarpals and metatarsals, cubitus valgus, genu valgum, a small lower jaw (micrognathia), Madelung deformity, an elevated palate arch, a neck webbing, a broad chest, and ears positioned lower than usual **(Figure 2)** (3, 15, 7). Bone development in girls with Turner syndrome typically shows minor differences compared to peers with normal

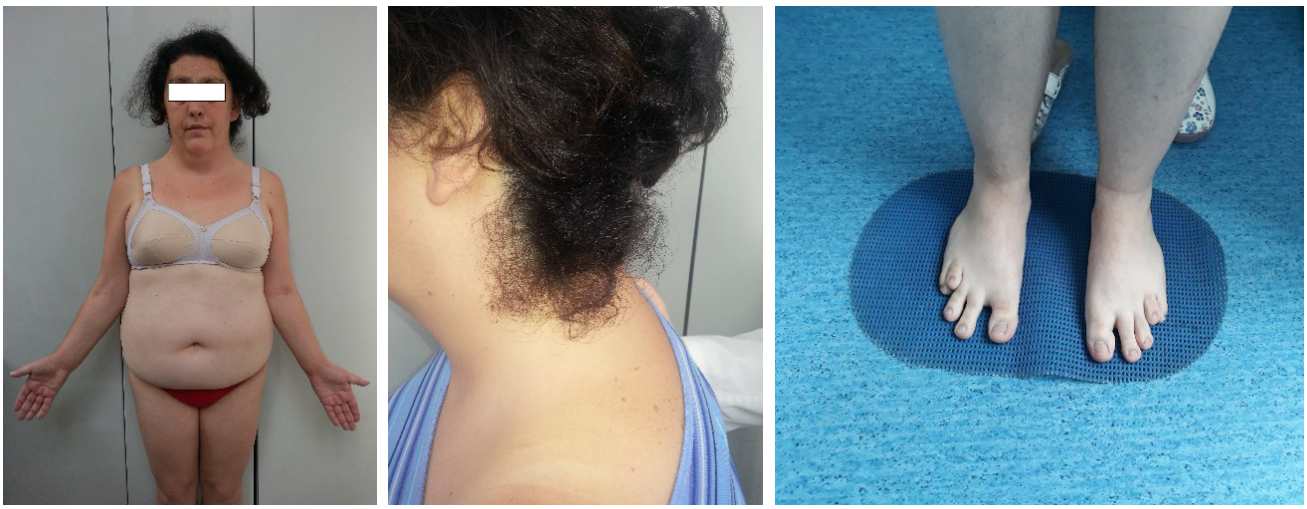

Figure 2. A patient with Turner syndrome has a short, webbed neck, small chin, low-set ears, broad chest, cubitus valgus, multiple melanocytic naevi, a posterior cervical hairline lower than typical, and bilateral short fourth metatarsals. The authors obtained written informed permission to publish these images in a scientific/medical journal.

chromosomes before age 10, with more noticeable divergence emerging during puberty (2). Other standard features include kyphosis, scoliosis, and disproportionate growth, where the trunk is longer than the legs. (3, 7). When diagnosed early and adequately treated, girls with Turner syndrome can reach an adequate adult height and experience normal sexual development. Treatment typically includes growth hormone (GH) at higher doses than those used for standard hormone replacement (18). Early administration of growth hormone (GH) is advised in Turner syndrome to counteract prenatal growth impairment that intensifies during early childhood and to support height potential. GH therapy may start as early as age two in cases of growth failure or short stature and can continue later if the growth plates remain open. The initial growth hormone dose is typically 45–50 μg/kg/day (1.3–1.5 mg/m^2/day) and may be raised to 68 μg/kg/day (2.0 mg/m^2/day) if the treatment response is insufficient or if the adult height prognosis is notably reduced. (7).

Monitoring the effectiveness of GH treatment is recommended through height measurements every 6 months, plotted on a standard reference and/or Turner Syndrome-specific height chart. Serum insulin-like growth factor 1 (IGF-1) levels should be checked annually to keep them within the normal range for age, pubertal stage, and sex, with potential reduction in GH dosage if levels remain high (3, 7). However, the impact of growth hormone on the cardiovascular system warrants careful consideration. Studies indicate a potential link between GH therapy and increased aortic widening or accelerated aortic growth, underscoring the need for cardiovascular imaging both before and during treatment. Conversely, certain research suggests that growth hormone may exert cardioprotective effects, particularly by improving lipid profiles. Although GH is known to increase insulin resistance, metabolic disturbances are relatively rare, probably attributable to reduced adiposity and increased lean muscle mass (18). Growth hormone increases IGF-1 levels, which promote cell growth and prevent cell death, though a direct link between GH therapy and malignancy has not been conclusively proven (19). Furthermore, various microRNAs on the X chromosome are implicated in cancer, indicating that changes in X chromosome dosage or structure may impact cancer risk, especially for solid tumors and melanoma in women with TS (20).

Primary ovarian insufficiency

Primary ovarian insufficiency presents as hypergonadotropic hypoestrogenic amenorrhea in women below 40 years of age. (12, 21). This condition arises from accelerated oocyte loss and a decline in germ cell count, accompanied by accelerated ovarian aging. Certain genes regulate the number of oocytes undergoing ovulation and determine the timing of reproductive function cessation (22). Women with Turner syndrome are affected by POI, although the exact biological mechanisms that lead to germ cell atresia and infertility in these patients are not fully understood. Since telomeres are essential for accurate chromosomal pairing and early meiotic and oogenic processes, alterations in their length or function may underlie the primary ovarian insufficiency seen in Turner syndrome. Other potential factors for germ cell depletion in TS include epigenetic changes resulting from asynapsis and the resetting of the epigenome during early development. Moreover, impairments in recombination-dependent DNA repair may hinder oogenesis in cells lacking a complete second sex chromosome (23). Gonadal dysgenesis is a hallmark of Turner syndrome, and POI typically manifests early in life. Approximately 80% of individuals with TS often do not experience spontaneous puberty, and by adulthood, 90% experience ovarian reserve depletion, resulting in hypergonadotropic hypogonadism and infertility. Research indicates that ovarian development

in Turner syndrome fetuses proceeds normally until 12 weeks of gestation, after which oocyte loss accelerates. Conversely, in typical 46, XX fetuses, oocyte meiosis initiates around 18 weeks, with primordial follicles appearing by 20 weeks and antral follicles by 26 weeks. In 45 X fetuses, oocytes are at similar stages, but follicles are absent. The significant reduction of germline cells in fetuses with TS during the second trimester suggests accelerated apoptosis contributes to follicle depletion (24).

Pregnancy and fertility

Infertility presents a significant challenge to the well-being of individuals with Turner syndrome. In cases where some ovarian function remains, fertility preservation options like egg or tissue freezing may be used. If ovarian function is absent, options include donor eggs, surrogacy, or adoption. (24). Fertility preservation is feasible in Turner syndrome, as many individuals still have detectable follicles into their late teens, and some with mosaicism maintain ovarian reserve into adulthood despite early menopause. Oocyte donation is advised only after comprehensive screening and genetic counselling (3). LH, FSH, and anti-Müllerian hormone (AMH) should be measured annually from ages 8–9 to 11–12 to identify candidates who may benefit from proactive preservation of reproductive potential. For post-menarche females with fertility potential and psychological maturity, guided follicular stimulation and frozen oocyte storage should be considered in specialized centers with expert care and psychosocial support. These options are not suitable for premenarcheal individuals or those lacking the cognitive capacity or maturity to comprehend or participate in the process (7, 25). Research suggests that even in young girls with Turner syndrome, primordial follicles may persist in the ovaries (25). Favorable indicators for the presence of ovarian follicles in individuals with Turner syndrome include mosaic karyotypes, spontaneous onset of puberty, occurrence of menarche, and hormone profiles within normal ranges for FSH and AMH.

Despite being rare, spontaneous conception is reported in approximately 4–7% of individuals with Turner syndrome, primarily in those with mosaic karyotypes. In those affected by primary ovarian insufficiency, the multifaceted influences of hormonal, immune, hematologic, and psychological factors are frequently underrecognized in clinical care. Identifying the right time for oocyte donation is essential after addressing these issues, improving endometrial receptivity, and ensuring psychological readiness. Untreated disturbances can lead to cardiovascular diseases, diabetes, thyroid disorders, coagulopathies, and other complications (26, 27). The primary concern in Turner syndrome is the increased maternal mortality rate, particularly due to aortic dissection and other cardiovascular diseases. Turner syndrome is not an absolute barrier to pregnancy; however, comprehensive preconception screening by a multidisciplinary team is necessary, accompanied by thorough counseling regarding potential risks. This screening should include an assessment of aortic diameter, thyroid and liver function, blood pressure, and blood glucose levels (28). The likelihood of spontaneous miscarriage is substantially greater in women with Turner syndrome than in the general population. This elevated risk may result from multiple contributing factors, such as fetal chromosomal defects, suboptimal oocyte integrity, reduced uterine dimensions, limited endometrial development and receptivity, as well as a higher frequency of autoimmune disorders in this population (29).

Cardiovascular diseases

Congenital and acquired cardiovascular diseases affect nearly half of all women diagnosed with TS and represent the primary cause of death in this population. Several studies suggest a potential connection between neck webbing and congenital cardiovascular malformations, implying that fetal lymphedema may be related to the development of heart and blood vessel diseases (30). Turner syndrome is recognized as an independent risk factor for a range of cardiovascular conditions, including congenital cardiac anomalies, aortic enlargement and dissection, valvular abnormalities, systemic hypertension, thromboembolic events, myocardial infarction, and cerebrovascular accidents (4). Aortic dissection has been reported in approximately 1–2% of individuals with TS, reflecting a significantly elevated risk compared to the general population (2). The risk of aortic dissection in women with Turner syndrome is markedly elevated, with reported rates up to 100 times greater than those observed in the general population. It accounts for 2–8% of premature deaths in these individuals (30). Several anatomical and physiological factors contribute to increased susceptibility to aortic dissection, including aortic dilation, bicuspid aortic valve, aortic regurgitation, coarctation of the aorta, structural anomalies of the aortic arch, aberrant right subclavian artery, and elevated blood pressure (1). A bicuspid aortic valve is present in up to 30% of women with Turner syndrome, a prevalence significantly higher than the 1–2% observed among people in general (2). Aortic coarctation is identified in approximately 7–18% of individuals with TS (3). Factors such as body mass index (BMI), age, bicuspid aortic valve, and an elongated aortic arch contribute to the risk of aortic dilation. Diagnostic assessment often includes evaluating the aortic size index (ASI) and the ratio between the ascending and descending aortic diameters (30). Hypoplastic aortic arch is another congenital cardiovascular abnormality commonly seen in Turner syndrome. Clinical manifestations vary from mild aortic stenosis to more complex anomalies like transverse arch hypoplasia, interrupted aortic arch, or hypoplastic left heart syndrome. Women with Turner

syndrome often exhibit increased carotid artery thickness and arterial diameter, potentially linked to estrogen deficiency, which might be alleviated through estrogen replacement therapy. Additionally, abnormalities in the venous system, such as portal vein hypoplasia, have been documented, with vascular atrophy believed to play a role in the liver dysfunction observed in these patients. Between 21% and 40% of women with Turner syndrome experience hypertension. Hypertension in these patients may arise from factors such as aortic coarctation and impaired renal function, leading to salt and water retention and increased blood volume. Additional contributors include obesity, metabolic syndrome, and vascular abnormalities, all of which heighten the risk for myocardial infarction, aortic dissection, ischemic events, and stroke (2,30,7). People with TS often exhibit elevated heart rates, which may be attributed to heightened sympathetic nervous system activity (1). Evidence indicates that individuals with Turner syndrome may exhibit prolonged QT intervals, potentially associated with a heightened risk of tachycardia (2). Recent findings suggest that QTc prolongation, defined by Hodges criteria (>450 ms in girls under 15 and >460 ms in adult women), occurs at comparable rates in TS and the general population (7).

Metabolic disorders

Individuals with TS often present with altered body composition, including an average adult height approximately 20 cm below the expected target. Typical findings include elevated BMI, increased visceral adiposity, and decreased lean body mass. The development of metabolic syndrome in this population is multifactorial, driven by elements such as dyslipidemia, primary ovarian insufficiency with consequent estrogen deficiency, central fat accumulation, insulin resistance, and underlying genetic susceptibility (1). Metabolic syndrome, defined by the co-occurrence of several cardiometabolic risk factors, prominently includes abdominal obesity and confers elevated risk for both cardiovascular disease and type 2 diabetes mellitus (31). Diabetes mellitus occurs significantly more often in individuals with TS, with prevalence rates up to four times higher than those in the general population. Both type 1 and type 2 diabetes are more frequent across all age groups. Impaired glucose tolerance is observed in approximately 70% of affected women, and up to 25% develop overt diabetes. This increased susceptibility has been associated with insulin resistance, hyperinsulinemia, and diminished pancreatic β-cell function (32). Screening for diabetes mellitus in individuals with Turner syndrome is advised beginning between the ages of 10 and 12, or earlier if clinical signs emerge, using either hemoglobin A1c or fasting glucose levels. Evaluating diabetes-related autoantibodies at diagnosis is also recommended to aid in distinguishing between Type 1 and Type 2 diabetes, as this differentiation can be particularly challenging in this population (7). Girls with Turner syndrome often experience reduced bone mineral density (BMD) and delayed skeletal maturation in adolescence, which is frequently linked to insufficient estrogen exposure. Their BMD is typically lower than that of the general population, especially in cortical bone. As a result, osteopenia and osteoporosis are more commonly diagnosed in these individuals. Besides estrogen deficiency, a SHOX gene deficiency, which affects bone geometry and microarchitecture, may also contribute to lower bone mineral density.

The SHOX gene is integral to skeletal development, influencing multiple pathways essential for proper bone formation and growth (12). Routine assessment for vitamin D insufficiency is recommended between the ages of 9 and 11, with follow-up every 2-3 years thereafter. If necessary, standard vitamin D supplementation should be provided. BMD assessment via dual-energy X-ray absorptiometry (DXA) is advised after growth completion but before age 21. Subsequent evaluations are generally recommended at intervals of 5 to 10 years during adulthood. More frequent DXA monitoring may be necessary for individuals at elevated risk of bone loss, including those with a history of fractures, suboptimal estrogen replacement, autoimmune conditions such as gluten-sensitive enteropathy, or other relevant health concerns. Monitoring should also continue after the onset of menopause or the cessation of estrogen therapy (7).

Autoimmune diseases

People with Turner syndrome have a heightened risk of developing autoimmune disorders, including those that typically affect women—such as Hashimoto's thyroiditis, celiac disease, rheumatoid arthritis, Crohn's disease, and ulcerative colitis—as well as conditions more frequently seen in men, like type 1 diabetes, ankylosing spondylitis, reactive arthritis, and, less commonly, amyotrophic lateral sclerosis. The prevalence of male-predominant diseases in these patients is higher not only compared to women with typical chromosomal patterns but also relative to men. This phenomenon is likely attributable to insufficient gene expression in the pseudoautosomal regions of the X chromosome, which are typically balanced by corresponding alleles on the Y chromosome in males (33). Regular assessment of thyroid function is advised beginning at age 2, with thyroid-stimulating hormone (TSH) levels evaluated every 1 to 2 years, or sooner if new clinical symptoms arise. In cases of elevated TSH, testing for anti-thyroid antibodies may help clarify the underlying cause. In addition to thyroid monitoring, healthcare providers should educate patients and families about the potential signs of autoimmune disorders. Screening protocols should include evaluations for B12 hypovitaminosis, coeliac sprue, autoimmune skin conditions, and Immune-mediated bowel disorders (7).

Liver and kidney diseases

Studies have shown elevated liver enzyme levels in many women with Turner syndrome, although the histological findings can vary. Hormone replacement therapy (HRT) has been found to reduce these elevated liver enzyme levels (34). Monitoring of liver health should begin in early childhood, with periodic evaluation of liver enzymes. Alanine aminotransferase (ALT) should be checked from a young age and repeated every one to two years starting at age 10, continuing throughout life. In adulthood, a more comprehensive liver panel is recommended, including aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) (7).

Liver complications in Turner syndrome frequently progress without noticeable symptoms. Nonetheless, individuals with elevated liver enzyme levels may develop hepatic conditions such as fatty liver, liver inflammation, biliary abnormalities, cirrhosis, or nodular regenerative changes. In parallel, renal and urinary tract malformations are observed in approximately one-third to two-thirds of those with Turner syndrome. These anomalies include structural irregularities of the ureters that can cause urine backflow, congenital absence of one kidney, fusion of the kidneys (commonly referred to as a horseshoe kidney), duplication of the renal collecting system, presence of only one kidney on one side, and formation of renal cysts or abnormal cilia (2). At the time of diagnosis, individuals with Turner syndrome should undergo a renal ultrasound to identify any structural abnormalities in the kidneys or urinary tract. If symptoms such as urinary tract infections or elevated blood pressure develop, further diagnostic testing or follow-up imaging is warranted. For those with known renal anomalies, such as unilateral kidney absence, underdeveloped kidneys on both sides, or fused kidneys, routine annual urine testing to screen for protein is recommended (7). Among those with TS, the most common kidney abnormality is the horseshoe kidney, present in 20% to 45% of cases. In contrast, this condition is found in fewer than 3% of people without the syndrome. Although horseshoe kidneys generally maintain normal function, the presence of underdeveloped kidneys (renal hypoplasia) can compromise kidney function (2).

Otologic and ophthalmologic health

Hearing loss is prevalent in Turner syndrome, impacting 63–70% of individuals. Hearing issues in individuals with Turner syndrome can result from multiple structural and developmental abnormalities. These may include persistent or repeated middle ear infections, loss of inner ear function, and malformations in the semicircular canals. Additionally, irregularities in facial and ear cartilage and bone development are commonly observed (2). Both conductive hearing loss due to middle ear problems and progressive sensorineural hearing impairment are frequently observed in individuals with Turner syndrome. These issues may often remain undetected without proper monitoring. As a result, routine hearing evaluations are commonly advised to ensure early identification and management of auditory deficits in this population (35).

Refractive errors affect approximately 40% of individuals with TS. Approximately one in three females with Turner syndrome may present with eye alignment issues, such as strabismus or reduced visual acuity in one eye (amblyopia). Additional eye-related characteristics frequently observed include drooping of the upper eyelid (ptosis), inner eyelid folds (epicanthic folds), increased distance between the eyes (hypertelorism), and a downward tilt of the eye openings. Red-green color vision deficiency (daltonism) is observed in about 8% of individuals with Turner syndrome, a rate comparable to that seen in males (3).

Turner syndrome and malignancies

Individuals with TS may face an increased likelihood of developing certain types of tumors, including non-cancerous growths in the central nervous system, colorectal malignancies, and both benign and malignant skin lesions. In contrast, their risk for breast cancer is generally lower than that of the broader population. Notably, prolonged use of HRT in this group has not been shown to elevate cancer risk (36). Multiple microRNAs on the human X chromosome regulate cancer-related processes, and changes in their expression may affect cancer susceptibility in individuals with X chromosome abnormalities, such as aneuploidy or structural alterations. Furthermore, disruptions or deletions of immune-associated genes on the X chromosome could increase predisposition to certain solid tumors (20).

Neurocognitive disorders

Cognitive ability in individuals with Turner syndrome typically falls within the normal range, though average scores may be slightly below the population mean. These individuals face an increased risk of neurodevelopmental and psychiatric conditions, including autism spectrum disorder, schizophrenia, emotional and behavioral difficulties, and disordered eating patterns. In contrast, issues related to the misuse of psychoactive substances appear to be less prevalent in this population compared to the general public (37). People with Turner syndrome frequently exhibit a consistent profile of cognitive challenges, particularly in visuospatial reasoning, mathematical ability, and certain aspects of memory. These difficulties tend to be specific rather than global, with verbal intelligence often preserved or above average (15).

SEX HORMONE TREATMENT

The majority of girls with Turner syndrome present with hypergonadotropic hypogonadism and require estrogen-progestin therapy to initiate puberty and support the formation and preservation of secondary sexual features. This treatment also helps optimize bone mineral density and promote uterine maturation. The primary aim of hormone replacement is to replicate the natural course of puberty, aligning with expected physical and psychosocial development, while also minimizing potential complications and supporting height outcomes (38). There is a debate about the most appropriate age to start therapy. Initiating treatment is generally recommended between the ages of 11 and 12 when elevated gonadotropin levels or decreased AMH levels are observed. If hormone levels remain within the expected age range, regular monitoring is conducted to assess for signs of natural pubertal development. Gonadal failure, which occurs in more than 90% of individuals with Turner syndrome, is managed with sex hormone replacement therapy. The dosage should be gradually increased every 6 months until the adult dose is reached, which typically takes 2 to 4 years. This dose is then maintained until menopause. Whenever possible, transdermal 17β-estradiol (E2) is preferred for hormone replacement, with oral E2 as a secondary option. Although ethinyl estradiol is associated with a higher risk profile, it remains preferable to withholding treatment entirely. To ensure effective pubertal progression and to preserve long-term bone and reproductive health, periodic evaluations are essential. These should include monitoring of breast development, stature, pelvic ultrasound to assess uterine size, bone mineral density, and serum E2 measurements. The goal is to reach serum estradiol concentrations between 100 and 150 pg/mL (350–500 pmol/L) once complete adult dosing is achieved (37, 7). Cyclic progestogen therapy should be initiated either upon the onset of breakthrough bleeding or following two years of estrogen treatment. This approach aims to lower the risk of endometrial complications, such as hyperplasia, irregular uterine bleeding, and the potential for malignancy linked to prolonged unopposed estrogen exposure. A commonly recommended regimen involves administering 200 mg of micronized progesterone daily for 10 to 12 days each month (38, 7). Estrogen-progestin regimens can be either combined sequentially or continuously with both hormones. Estrogen stimulates the growth of the endometrial lining.

In contrast, the addition of progestin mimics the luteal phase of the menstrual cycle and helps prevent excessive endometrial growth from prolonged estrogen exposure. In younger patients, a sequential hormone therapy schedule is often favored as it induces regular menstrual-like bleeding. In contrast, continuous regimens that suppress endometrial bleeding are generally more suitable for older female adults (38). HRT is generally continued until the average age at which menopause occurs naturally. After reaching this stage, a clinical reassessment is advised to determine whether ongoing treatment with reduced doses of estradiol and progesterone remains beneficial (7).

IMPACT ON QUALITY OF LIFE

Although individuals with Turner syndrome typically report a quality of life comparable to the general population, the presence of associated health conditions may influence certain dimensions of their daily functioning and overall well-being. A thorough diagnosis, ongoing health monitoring, and appropriate treatment are crucial. Cardiovascular, endocrinological, and metabolic conditions, along with delayed puberty, infertility, and dissatisfaction with height, can affect quality of life. Neurocognitive and otological issues can make social interactions challenging and contribute to feelings of disability and isolation. Timely identification of TS, coupled with the appropriate use of growth hormone and estrogen therapy, can contribute positively to physical, mental, and emotional health. To further enhance outcomes beyond clinical care, healthcare providers should collaborate on creating a comprehensive support plan. This plan should equip patients and their families with the tools needed to advocate for accommodations in educational settings and in the broader community. Such support can foster stronger academic progress and emotional resilience. (3,7)

CONCLUSION

Clinical manifestations of Turner syndrome can present across various female chromosomal compositions, regardless of whether the X chromosome is partially or entirely missing. The condition can affect numerous organ systems, resulting in a broad spectrum of medical concerns that may vary in severity and onset and that influence not only quality of life but also life span. The significant variability in the phenotype of TS requires a multidisciplinary, individualized approach to treatment. Neonatologists and pediatric endocrinologists serve as the primary specialists in identifying and managing Turner syndrome, followed by cardiologists, adult endocrinologists, gynecologists, otorhinolaryngologists, ophthalmologists, psychiatrists, and geneticists, with additional psychological and social support as needed. While modern medical management of Turner syndrome has made significant progress, additional studies are needed to deepen our understanding and improve treatment for these patients. Education for both medical professionals and the general public is crucial for timely diagnosis and optimal therapy, ultimately improving the overall well-being of people living with Turner syndrome.

Acknowledgment: N/A
Funding Information: N/A
Conflicts of interest: N/A

Author contributions: Conceptualization: MTG and SV; Data acquisition: MM, M, BT; Data interpretation and analysis: all authors; Preparing the manuscript draft: MTG, MM, and BT; Revising and editing of the manuscript: MTG, SV, MS, MM. Approval of the submitted manuscript version: all authors.

Ethical approval: N/A

Informed Consent: The authors hereby confirm that they have obtained the patient's signed informed consent to publish her photograph in a scientific journal.

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TARNEROVA BOLEST: SAVREMENI KLINIČKI PRISTUP

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Sažetak

Tarnerov sindrom (TS) je retko genetsko oboljenje žena, koje se rađaju sa delimičnim ili potpunim nedostatkom jednog X hromozoma, a tokom života imaju multisistemske kliničke manifestacije, koje zahtevaju doživotno multidispciplinarno lečenje i praćenje. TS se fenotipski prezentuje niskim rastom, kratkim vratom uz kožne nabore na bočnim stranama vrata (pterigij vrata) nisko postavljenim ušima i zadnjom linijom vlasišta kose, a klinički kardiovaskularnim bolestima (KVB) i primarnim hipogonadizmom. Dijagnoza TS se postavja na osnovu kliničke slike i genetskih analiza. Rana dijagnoza je prenatalna. Kod novorođenčeta, neonatolog treba da posumnja na TS na osnovu edema dorzuma šaka i stopala. Nizak rast postaje evidentan u periodu malog i pretškolskog deteta. Ako se ne javi zbog niskog rasta, devojčica će doći zbog zakasnelog puberteta i primarne amenoreje. KVB mogu biti urođene i stečene. Koarktacija aorte je ključni dijagnostički znak TS dok su disekcija aorte i ruptura aortne aneurizme po život opasne kardiovaskularne komplikacije. Većina žena sa TS ima primarni hipogonadizam i visoku stopu infertiliteta. Spontane trudnoće žena sa TS su retke, te blagovremeno treba razmotriti sve opcije za povećanje fertiliteta, uključujući krioprezervaciju oocita ili embriona. Česte su i udružene autoimune bolesti, anomalije bubrega, bolesti jetre i gubitak sluha. Terapija polnim hormonima je neophodna kako za indukciju puberteta, tako i za očuvanje opšteg zdravlja i prevenciju dugoročnih komplikacija nelečenog hipogonadizma. Brojni komorbiditeti i impresivna varijabilnost fenotipa zahtevaju multidisciplinarni i individualni pristup lečenju žena sa TS. Uz ranu dijagnozu, odgovarajući tretman i psihološko-socijalnu podršku, osobe sa TS mogu voditi kvalitetan život uprkos zdravstvenim rizicima.

Ključne reči: Tarnerov sindrom, genetika Tarnerovog sindroma, primarna insuficijencija jajnika, hormonska supstituciona terapija

Primljen: 09.03.2025. | **Revidiran:** 02.11.2025. | **Prihvaćen:** 12.11.2025. | **Online First:** 20.11.2025. | **Objavljen:** 24.12.2025.

Medicinska istraživanja 2025