Review Article

Gonadal dysgenesis: a clinical overview of Turner syndrome

Ethel Gonzales Clemente, Patricia Vining Maravolo, Claire L. Tanager

Department of Pediatric and Adolescent Medicine, Homer Stryker M.D. School of Medicine, Western Michigan University, Kalamazoo, MI, USA

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Correspondence to: Ethel Gonzales Clemente, MD. Department of Pediatric and Adolescent Medicine, Homer Stryker MD School of Medicine, Western Michigan University, 1000 Oakland Drive, Kalamazoo, MI 49008-1284, USA. Email: ethel.clemente@med.wmich.edu.

Abstract: Gonadal dysgenesis is a term used to describe conditions that impair gonadal development leading to varying degrees of gonadal dysfunction and disorders of sexual development. Turner syndrome (TS) affects approximately 1 in every 1,500–2,500 live female births and is characterized by a constellation of symptoms resulting from complete or partial loss of function in the second X chromosome. The diagnosis carries life-long health burdens involving multiple organ systems, hence requires a multidisciplinary care approach. Timely diagnosis is essential to ensure proper management and treatment to lessen the impact of disease burden on affected individuals. Growth, pubertal and sexual development, particularly fertility issues, are considered major concerns that affect one's lifespan with overall impact on quality of life. Although treatment guidelines and recommendations are in place for TS patients to address comorbid conditions, further data to elucidate on the optimal management are needed, especially in hormone replacement therapy and options for fertility preservation.

Keywords: Fertility; gonadal dysgenesis; growth; puberty; Turner syndrome (TS)

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Introduction

Gonadal dysgenesis refers to conditions that cause impaired or defective formation of the gonads, with clinical manifestations and varying degrees of genital ambiguity determined by the level of dysfunction or malformation. The complex process of sex determination and differentiation is dependent on specific responses to hormones produced by the gonads (1). Thus, any sex chromosome aberration or mutations in genes involved in this process can lead to complete or partial loss of gonadal development, hence dictating the variable phenotypic expression and disorders of sexual development. Depending on the resulting gonad morphology, the different forms of gonadal dysgenesis can be classified as either complete or partial.

Conditions causing gonadal dysgenesis are rare, some of which are associated with well-defined syndromes. Among these conditions, Turner syndrome (TS) and its variants are most notable and will be the focus in this review. TS is relatively more common than other forms of gonadal dysgenesis with a female phenotype. TS represents issues that are common to most of these conditions, namely issues with puberty and sexual maturation, ovarian failure, and limitations of future fertility. Additionally, TS may present with comorbid conditions, which are unique among the gonadal dysgenesis disorders, such as aortic malformation and renal dysgenesis, among other, this must be considered in the clinical management of TS.

TS

Genetic errors in cell division contribute to the variation of genotypic and phenotypic expression observed in gonadal dysgenesis. Mosaic genotypes (*Figure 1*) typically have less severe phenotypic symptoms as compared to

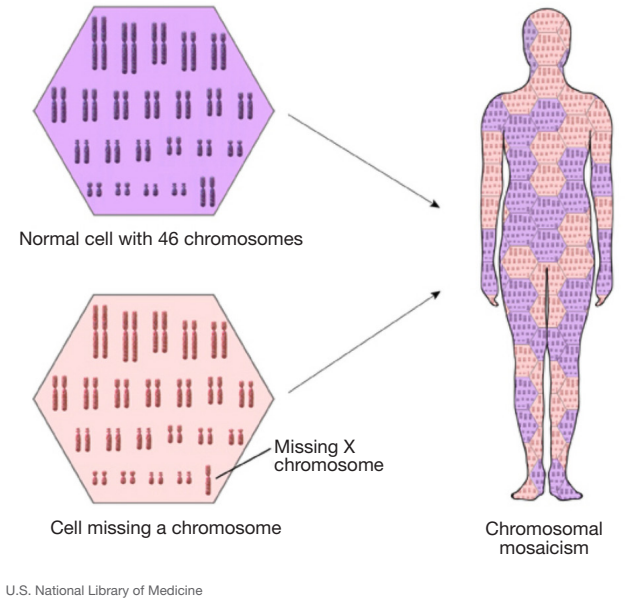

Figure 1 Chromosomal mosaicism. Credit: U.S. National Library of Medicine https://ghr.nlm.nih.gov/condition/turner-syndrome#. Image in public domain: accessed May 25, 2019 U.S. National Library of Medicine.

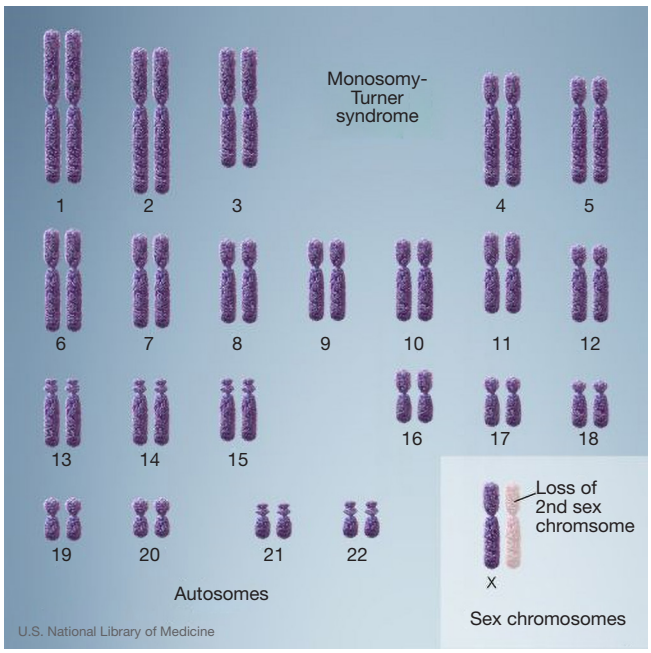

Figure 2 Monosomy Turner syndrome. Credit: U.S. National Library of Medicine https://ghr.nlm.nih.gov/condition/turner-syndrome#. Image in public domain: accessed May 25, 2019 U.S. National Library of Medicine.

purer genotypes (2). TS occurs in approximately 1 of every 1,500–2,500 live female births (3,4), and is the most common sex chromosome abnormality in women. The characteristic features of TS result from either complete (*Figure 2*) or partial functional loss (*Figure 3*), particularly loss at the tip of the short arm or complete absence of the second sex chromosome with the presence of one intact X chromosome. Functional loss or absence of the second X chromosome can occur during either the meiotic or mitotic phases of cell division. Absence of the second sex chromosome can be the result of either the ovum or spermatozoon lacking the sex chromosome. Recent studies report 70–80% of TS cases are caused by the loss of the parental sex chromosome (2).

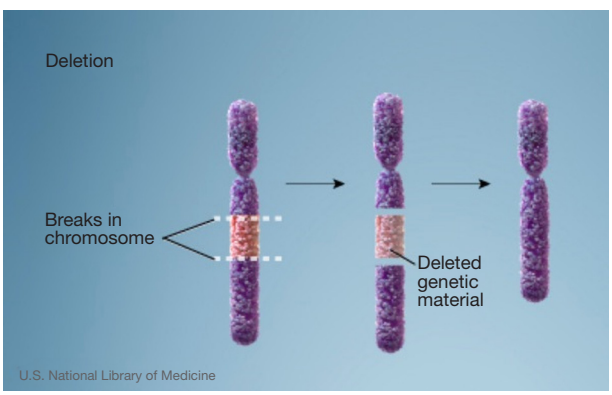

Figure 3 Partial deletion. Credit: U.S. National Library of Medicine https://ghr.nlm.nih.gov/condition/turner-syndrome#. Image in public domain: accessed May 25, 2019 U.S. National Library of Medicine.

Clinical presentation

Traditional characteristic features associated with TS include classical facial appearance (flat nasal bridge, low set, misshapen ears, high arched palate, ptosis, hypertelorism, upward slanting palpebral fissures, and epicanthal folds), low posterior hair line (*Figure 4*), neck webbing (*Figure 5*), lymphedema, broad chest with wide spaced nipples, and short stature. Additional clinical features and associated comorbid conditions are summarized in *Table 1* (4-6).

Prenatally, chromosome abnormalities detected in chorionic villous sampling or in the amniotic fluid by amniocentesis may suggest TS. Findings on pre-natal

Figure 4 Low hairline on the back of the neck. Credit: United States Library of Medicine National Human Genome Institute https://elementsofmorphology.nih.gov/index.cgi?tid=efe02d35c10721b6. Image in public domain: accessed May 25, 2019 U.S. National Library of Medicine.

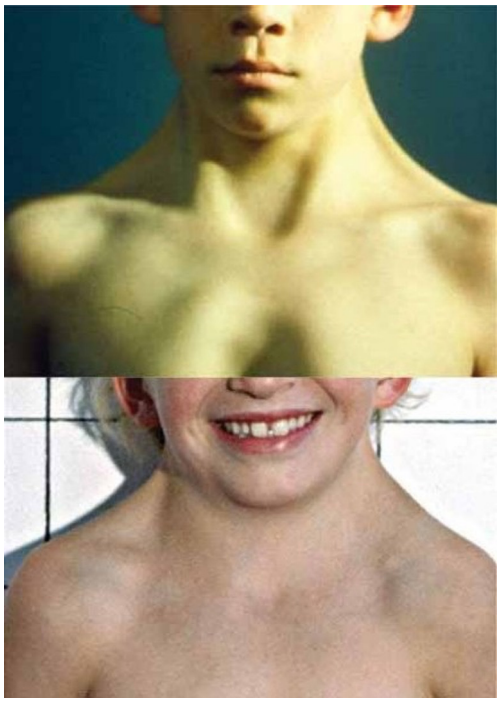

Figure 5 Webbed neck. Credit: United States Library of Medicine Elements of Morphology, National Human Genome Research Institute https://elementsofmorphology.nih.gov/index.cgi?tid=1236af621234b150; https://ghr.nlm.nih.gov/condition/turner-syndrome. Image in public domain: accessed May 25, 2019 U.S. National Library of Medicine.

ultrasound suggestive of TS include increased nuchal translucency, coarctation of aorta (*Figure 6*) or evidence of left sided cardiac defects, brachycephaly, renal anomalies, polyhydramnios, oligohydramnios and growth retardation. Abnormal findings on maternal triple or quadruple testing are suggestive of TS (4). The presence of cystic hygroma is more suggestive of TS (4).

Suspicion for TS should warrant further evaluation and testing for the newborn or young girl who presents with lymphedema of the extremities, history of developmental delay, failure to thrive, and poor growth or weight gain. In many cases, the clinical features are insufficient to allow early diagnosis and diagnosis is delayed until late childhood or adolescence when the female presents with concerns for short stature or delayed onset of puberty.

Short stature is the most common finding in TS, mostly as a result of haploinsufficiency of the short-stature homeobox-containing gene on the X chromosome (*SHOX*). Haploinsufficiency of *SHOX* expression is associated with several other features of TS, such as high arched palate, prominent ears, chronic otitis media, obstructive sleep apnea, increased sensitivity to noise, and problems with speech articulation (7). It is established that untreated females with TS will have an adult height approximately 20 cm shorter than peers. Although short stature in TS is not from growth hormone (GH) deficiency, it is observed that GH secretion in these females is low, and they respond to GH therapy similar to those with isolated *SHOX* gene deficiency (8).

Gonadal failure occurs in almost all females with TS. In individuals with TS, the germ cells develop normally early; however, there is a rapid progression to ovarian insufficiency because of progressive loss of oocytes in an accelerated manner. Thus, a delayed or absent puberty development and infertility is a major concern in women with TS. About one third of girls will have spontaneous puberty development, but only a smaller percentage will continue on with puberty progression to occurrence of menarche (9). With the ensuing hypergonadotropic hypogonadism from gonadal dysgenesis, most females would then need hormone replacement therapy, initially for induction of puberty, and later on in life, for maintaining secondary sexual characteristics and possibly, pregnancy.

Individuals with Noonan syndrome present with clinical

Table 1 Associated clinical features and comorbid conditions in Turner syndrome

System	Associated clinical features
Cardiovascular	Bicuspid aortic valve, coarctation of the aorta, aortic dilatation/aneurysm
ENT	Hearing defects, frequent middle ear infections, external ear defects
Ophthalmologic	Errors of refraction, amblyopia, strabismus, ptosis
Dental/orthodontic	Abnormal dental development, micrognathia, high arched palate
Endocrine/metabolic	Autoimmune thyroiditis, glucose intolerance, diabetes, hypertension
Gynecologic	Delayed or absent puberty development, premature ovarian failure
Gastrointestinal	Transaminitis, celiac disease, inflammatory bowel disease
Renal	Horseshoe kidney, renal ectopia, abnormal position or duplication of ureters or vessels
Skeletal	Scoliosis, decreased bone mineral density, osteoporosis, vitamin D deficiency, cubitus valgus, genu valgum, Madelung deformity, flat feet
Neurocognitive/psychosocial	Emotional immaturity, nonverbal learning disorders, attention-deficit hyperactivity disorder, psychological and behavioral issues

ENT, ear, nose, and throat.

features similar to that of TS, which include similar facial characteristics: low posterior hair line, webbed neck, skeletal anomalies, broad chest with wide spaced nipples, and congenital cardiovascular anomalies, primarily pulmonic stenosis (10). Additional differentials to consider include Leri-Weill dyschondrosteosis and mosaic forms of gonadal dysgenesis (11). Once the diagnosis for TS is established, immediate management and therapy is necessary to improve outcomes, specifically growth and pubertal development.

Diagnostic testing

Karyotyping with a minimum of 30 cells analyzed remains the recommended diagnostic tool in TS (4,12). If standard karyotype is reported normal and there is a strong suspicion for TS based on phenotype, cytogenetic study of a second tissue should be done (12). Fluorescent in situ hybridization (FISH) studies using X and Y probes should be considered, particularly in females with virilizing or masculinized features (12). About half would have a 45,X karyotype, approximately 30% would demonstrate mosaicism, and the rest would have structural abnormalities. Presence of Y chromosome material poses an increased risk for gonadal neoplasms, thus the importance of its detection in at-risk females (13).

Prenatal diagnosis can be done by karyotyping using chorionic villous sampling or amniocentesis. Other non-invasive prenatal screening tests are also available, using cell-free fetal DNA in maternal blood stream by 10 weeks' gestation, to detect aneuploidy (14,15). It is imperative, however, to repeat karyotyping postnatally on all females who had positive prenatal findings suggestive of TS.

Additional diagnostic studies are indicated based on other associated clinical manifestations. As such, the importance of a multi-disciplinary team working together with patients and families soon after diagnosis is essential in subsequent care planning and management.

Treatment

GH therapy

Beginning GH therapy as early as 4–6 years of age optimizes normal growth pattern mimicking a similar growth pattern for peers of the same age (4). Initiating GH late will affect growth outcomes and may delay pubertal development. Final adult height is influenced by GH exposure, which has been demonstrated to be dependent on dose and duration (16). Additionally, a delayed diagnosis of associated or concomitant conditions, such as hypothyroidism, celiac disease, and congenital heart disease, may affect growth and potential final adult height until these conditions are also controlled or treated (16). Adherence to GH therapy can also affect final adult height. Non-modifiable factors affecting final adult height include parental heights and height of female at start of GH treatment.

In the absence of GH therapy and a normal pubertal

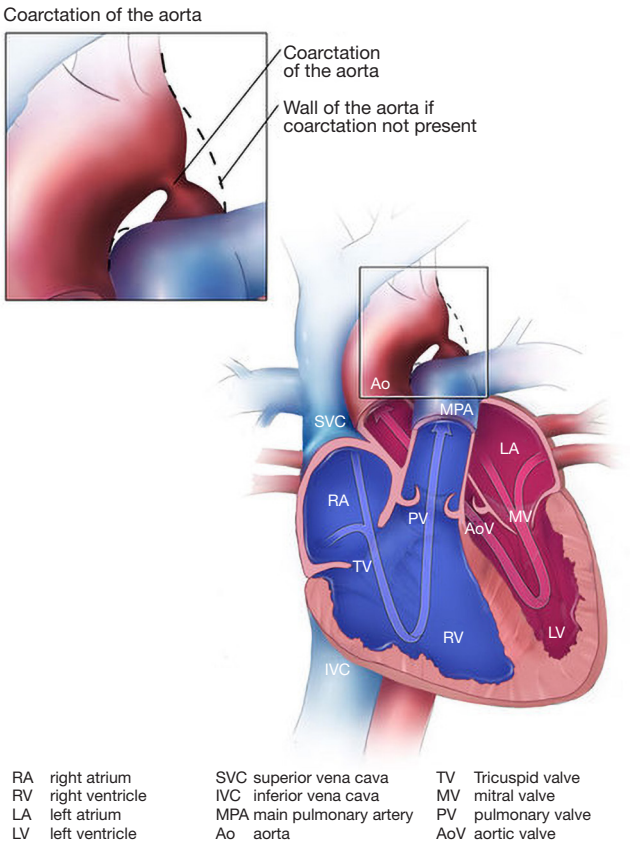

Figure 6 Coarctation of aorta. Credit: Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities https://www.cdc.gov/ncbddd/heartdefects/coarctationofaorta.html. Image in public domain: accessed May 25, 2019 U.S. National Library of Medicine.

growth spurt, the mean average height for girls with TS is cited to be approximately 142–144 cm, which is 20 cm below the population mean height (16). In contrast, girls with TS treated with GH exhibit a 1–2 cm/year gain in height per year of GH therapy (4,16). In addition, GH increases bone mass, promotes lipid and glucose metabolism, and acts on muscle to increase amino acid transport (16). Current guidelines recommend initiation of GH treatment at 0.35–0.375 mg/kg/week (4), Higher doses of GH may be considered in girls with poor height prognosis (4).

Concomitant use of oxandrolone may be considered if the diagnosis of TS is delayed, and/or if final adult height attainment is expected to be poor. However, despite some studies indicating a synergistic effect of oxandrolone, when used with GH, on height acceleration, there is potential for undesirable effects such as delayed pubertal development and virilization (4,16,17). The use of oxandrolone with GH has been shown in studies to increase final adult height approximately 2–5 cm compared to girls with TS treated with GH alone (4).

Hormone replacement therapy

The goal of estrogen replacement therapy in TS is to attain the physiologic effects of endogenous estrogen in puberty induction, progression, and maintenance of secondary sexual characteristics. Estrogen is also essential for its metabolic effects on bone, and vasomotor and cardiovascular health. Potential estrogen-related risks such as gynecologic cancers and thrombogenic complications should be carefully considered when starting estrogen replacement therapy. Estrogen deficiency in TS is associated with elevated intrahepatocellular lipids, glucose resistance, decreased bone density, poor uterine growth, poor cardiovascular outcomes, decreased cognitive and motor reaction times, behavioral problems, low self-esteem, and low scores on measures of the quality of life (18,19).

The recommendation is to initiate estrogen replacement around the age of 11–12 years, to mimic the normal progression of pubertal development of girls who do not have TS (4,19). Annual measurements of gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), can aid in the detection of early ovarian failure. Initiation of estrogen replacement may need to be delayed to permit optimal linear growth potential in girls diagnosed late with TS; however, it should not be delayed for a prolonged period of time to prevent the effects of estrogen deficiency on uterine and bone health.

Starting a low dose estrogen has not been shown to affect growth response to GH therapy (4). Although there are still ongoing studies to determine the optimal type of hormone replacement therapy, current practice is to use systemic, transdermal estradiol preparations. A typical regimen is to start with a pubertal initiation dose of approximately 3–7 μg/day of transdermal 17β-estradiol using matrix patches cut into smaller sizes, with the dose incrementally increased every 6 months to attain adult dosing of 25–100 μg/day in about 2–3 years (4).

Progestin therapy is then added after 2 years of puberty induction, or once menstrual bleeding or spotting has commenced. The rationale of starting progestins is based on the finding that girls with TS usually have a normal uterus, with unopposed estrogen treatment leading to endometrial

hyperplasia and the potential risk of endometrial cancer (20).

Once adult dosing for hormone replacement therapy has been attained, therapy should be continued, with further assessment and monitoring for risks associated with estrogen therapy. The decision to stop therapy around the age of menopause will be based on individualized consideration.

Fertility and pregnancy

During the reproductive age, women with TS report infertility as the most common concern (21). The occurrence of spontaneous pregnancy in women with TS is approximately 4–7% (4). The majority of women with TS eventually would be infertile because of premature ovarian insufficiency.

It is worth noting that girls, who are diagnosed with TS early on, depending on their genotype, may have ovarian follicles that may be preserved for later reproductive consideration. Clinical guidelines clearly specify recommendations for fertility preservation in women with TS, thus adding to the importance of timely diagnosis, treatment, and management of girls with TS to optimize the quality of life (4,22). More often, TS is diagnosed antenatally, and in terms of an affected women's potential for preserving fertility in the future, providing options early on remains the challenge. It is clear that women with TS with mosaicism have a higher potential for preservation of fertility.

Measurement of serum anti-Mullerian hormone has proven to be helpful in assessing ovarian reserve and is used to determine who may benefit from fertility preservation (22-25). Various fertility preservation methods have been reported, that include cryopreservation of mature oocytes after ovarian stimulation and immature oocytes that were matured in vitro (26,27). However, only the former has been reported as successful in women with TS, and the success rate of cryopreservation in TS is still not fully elucidated. Ovarian tissue cryopreservation and embryo cryopreservation are other techniques that hold promise but are still considered experimental and pose significant medical and ethical concerns (22).

Another option for women with TS desiring pregnancy would be assisted reproductive technology with oocyte donation (OD), with a clinical pregnancy rate of about 16–40% (4). Although this poses a higher success of pregnancy, there is still a slightly higher associated rate of miscarriages in women with TS compared with women without TS (28).

Because of its impact on quality of life for an adult woman with TS, counseling and discussion about future fertility and risks of pregnancy should be considered early on, initially with parents or families of girls with TS, continued on to include the girls themselves. Regardless of how they would want to proceed with fertility preservation, it is important to discuss the associated risks of pregnancy in women with TS, with or without associated cardiovascular anomalies. Because of the significantly higher risk of maternal mortality of about 1–2%, careful cardiac evaluation as part of a comprehensive pre-pregnancy planning is essential (4,22,29).

Conclusions

It is important to acknowledge the impact on the quality of life that associated health burdens have on the females with TS. Therefore, any treatment that can optimize the quality of life of girls with TS can have significant impact on immediate and future outcomes. The importance of multidisciplinary care with different subspecialty providers is essential in managing the female with TS to ensure optimal outcomes. Specifically, for the girls with TS, optimizing the use of GH and estrogen replacement to induce puberty and normal height have been shown to positively impact the quality of life and social adjustment (18). Optimizing care throughout the lifespan of the females with TS is imperative to ensure proper management of comorbidities, as well as addressing psychosocial concerns as they arise. In the absence of a timely diagnosis and management, quality of life for women with TS can be greatly compromised. Current expert consensus significantly aids in this process, as well as the increased awareness of both the medical and lay community about TS and its related issues. However, further evidence on optimal management are needed, particularly regarding hormone replacement therapy and options for fertility preservation.

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Footnote

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