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GENETIC SYNDROMES IN ADULTS

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Recognition and management of adults with Turner syndrome: From the transition of adolescence through the senior years

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Abstract

Turner syndrome is recognized now as a syndrome familiar not only to pediatricians and pediatric specialists, medical geneticists, adult endocrinologists, and cardiologists, but also increasingly to primary care providers, internal medicine specialists, obstetricians, and reproductive medicine specialists. In addition, the care of women with Turner syndrome may involve social services, and various educational and neuropsychologic therapies. This article focuses on the recognition and management of Turner syndrome

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from adolescents in transition, through adulthood, and into another transition as older women. It can be viewed as an interpretation of recent international guidelines, complementary to those recommendations, and in some instances, an update. An attempt was made to provide an international perspective. Finally, the women and families who live with Turner syndrome and who inspired several sections, are themselves part of the broad readership that may benefit from this review.

KEYWORDS

clinical history, hormone replacement therapy, infertility, sex chromosome abnormality syndrome, transitioning, Turner syndrome

1 | INTRODUCTION

Turner syndrome is a rare, but familiar, sex chromosome abnormality syndrome in which there is complete or partial absence, or a structural abnormality, of the second sex chromosome (Gravholt et al., 2017b, table 1). One of the first lessons and memorable images learned by students of pediatrics, genetics, endocrinology, and cardiology is that of an infant or young girl with Turner syndrome, sometimes described using "45,XO" instead of the current 45,X. The external features of short stature, short neck with webbing, characteristic facial appearance (down-slanting palpebral fissures, ptosis, prominent pinnae), and lymphedema comprised the sole composite phenotype for many years, sometimes portrayed in unflattering photos. However, the external appearance, internal anomalies, and neuropsychologic performance of individuals with Turner syndrome vary greatly. No longer a disorder familiar only to pediatricians, endocrinologists, and cardiologists, Turner syndrome is now more widely encountered by primary care providers and other internal medical specialists who therefore need to be well-informed of their medical needs. There is great value in collecting and sharing longitudinal information as demonstrated by recent reviews about other syndromes including holoprosencephaly (Weiss et al., 2018); neurofibromatosis (Stewart, Korf, Nathanson, Stevenson, & Yohay, 2018); Marfan syndrome (Pyeritz, 2018); and Klinefelter syndrome (Gravholt et al., 2018).

This review article was written to inform a broad readership extending beyond medical geneticists to include the needs of primary care and specialty providers, as well as patients and family members. The focus will be the recognition and management of Turner syndrome in adults, whom we view as a diverse group having medical, neuropsychologic, and social needs different than younger individuals with Turner syndrome. Discussion about clinical management will be supplemented by insights into phenotype, development, genetic basis, and epidemiology. Several authors (C.H.G, A.E.L., S.P., M.L.C., and N.H.A.) of this current article participated in the 2016 International Turner Syndrome Consensus Meeting. Rather than re-stating the clinical practice guidelines from the international symposium (referred to as "the Guidelines" for this article) (Gravholt, Andersen, et al., 2017b), this article aims to serve as a companion supplement. It should be noted that the cardiovascular guidelines were updated shortly after the meeting (Silberbach et al., 2018). Because the Guidelines is a long, heavily referenced and detailed article, Dr. Philippe Backeljauw and Dr. Claus Gravholt assisted the Turner Syndrome Society of the United States (TSSUS) to publish a patient-oriented version of the Guidelines, "Brief Synopsis for Turner Syndrome Girls and Women and for their Parents/Caregivers/Families" (known as the "Synopsis").This is available on the TSSUS website (URL included on the list of Websites). Streamlined surveillance guidelines are listed in full-color tables, for example, Table 4. Guidelines for Adult Health Surveillance: Items for Review and Suggested Frequency. A complementary series of articles focusing on clinical and basic science research were published as a recent Special Issue addressing "Turner Syndrome Science" from the Proceedings of the 2018 Turner Syndrome Resource Network (Kruszka & Silberbach, 2019).

Following an overview of genetics and epidemiology as they relate to the adolescent and adult with Turner syndrome, individual sections discuss clinical features, lifestyle, neuropsychologic, and mental health issues. Transition is discussed from the familiar viewpoint of the adolescent advancing to adulthood pursuing health maintenance, independence, education, career and social development. In addition, we acknowledge an additional major transition for the oldest women with Turner syndrome who have similar goals as their independence and social support commonly decreases. Comparisons will be noted between the variation in counseling and management provided to women with Turner syndrome in the United States and other countries as relates to differences in social, cultural, and healthcare systems.

2 | METHODS

2.1 | Literature

The Guidelines (Gravholt, Andersen, et al., 2017b; Silberbach et al., 2018) publications were based on exhaustive literature searches and serve as the starting point for the additional literature update in this review. The Guidelines will be cited often instead of historical references (which can be found in its bibliography). Rather than reprinting specific tables from the Guidelines, reference will be made when applicable. There are several reviews based on original data (of at least 100 patients) which focus on the overall management of adults with

Turner syndrome (Cameron-Pimblett, La Rosa, King, Davies, & Conway, 2017; Elsheikh, Dunger, Conway, & Wass, 2002; Freriks et al., 2011; Gawlik & Malecka-Tendera, 2014; Trolle, Mortensen, Hjerrild, Cleemann, & Gravholt, 2012a). In general, percentages will be rounded off, unless specific data are cited.

2.2 | New patients

To supplement published information, the lead authors reflect on their clinical experiences and past publications with data derived from their affiliated clinics: the Massachusetts General Hospital (MGH) Turner Syndrome Program (founded 2011, ~170 patients 16–76 years, PHRC IRB Protocol #2015P001173), the UTHealth Turner Syndrome Adult Comprehensive Care Center (founded 2013, ~100 patients, 16–63 years), and the Turner Syndrome Clinic at the Department of Endocrinology, Aarhus University Hospital, Denmark (founded 2006, ~300 patients, 16–80 years).

3 | GENETICS

3.1 | Definition and diagnosis

Turner syndrome is a chromosomal disorder that affects phenotypic females who have one intact X chromosome and complete or partial absence of the second sex chromosome, in association with one or more clinical manifestations (Sybert & McCauley, 2004). The karyotype in Turner syndrome ranges from 45,X in all cells to mosaicism with a normal (46,XX or 46,XY) cell line and an abnormal second or third cell line. Structural abnormalities include deletions of Xp and Xq, ring X and isochromosome Xq (also known as isodicentric Xp) which often occur in mosaic form (Table 1, adapted from table 1 in Gravholt, Andersen, et al., 2017b).

The diagnosis of Turner syndrome should be strongly considered for any woman with unexplained growth failure or delayed puberty; lymphedema (edema of the hands or feet, nuchal fold, neck webbing, low hairline and hyperconvex or hypoplastic nails); characteristic facial features such as epicanthal folds, down-slanting palpebral fissures, low-set ears, and micrognathia; left-sided cardiac anomalies, such as coarctation of the aorta, bicuspid aortic valve (BAV), and aortic stenosis; markedly elevated follicle-stimulating hormone (FSH); infertility; cubitus valgus; multiple pigmented nevi; bone anomalies including short fourth metacarpal or metatarsal, Madelung deformity, and scoliosis; chronic otitis media and conductive or sensorineural hearing loss; or learning disabilities affecting visuospatial or nonverbal skills (Eckhauser, South, Meyers, Bleyl, & Botto, 2015; Gravholt, Andersen, et al., 2017b, section 1.3). Because Turner syndrome is still frequently diagnosed in adolescence or adulthood, clinicians should be aware that the most prominent signs and symptoms of Turner syndrome might change with age and maintain vigilance for prompt evaluation of women who meet these criteria (Apperley et al., 2018; Lee & Conway, 2014; Sävendahl & Davenport, 2000). Since many women may be detected as part of a fertility evaluation and discovered to have mosaicism, often at a low level, there are some adults with minimal external features.

TABLE 1 Type and frequency of chromosome abnormalities in Turner syndrome (TS) (adapted from table 1 in Gravholt, Andersen, et al., 2017b)

Karyotype	%	Description
45,X	40–50%	Monosomy X
45,X/46,XX	15–25%	Mosaicism with "XX"
45,X/47,XXX; 45,X/46,XX/47,XXX	3%	Mosaicism with "Triple X", or trisomy X
45,X/46,XY	10–12%	Mixed gonadal dysgenesis
46,XX, del(p22.3)	5%	Xp deletion
46,X,r(X)/46,XX	1%	Ring X chromosome
46,X i(Xq); 46,X,idic(Xp)	10–15%	Isochromosome Xq; Isodicentric Xp
X-autosome translocation, unbalanced	Rare	Various
46,XX,del(q24)	Not TS	Premature ovarian failure
46,X,idic(X) (q24)	Not TS	Isodicentric Xq24

Standard chromosome analysis remains the method of choice to diagnose Turner syndrome. All individuals with suspected Turner syndrome should have a standard 20-cell karyotype as recommended by the American College of Medical Genetics and Genomics (ACMGG), which will identify at least 10% mosaicism with 95% confidence limits in the blood (Hook, 1977; Wolff, Van Dyke, & Powell, 2010 and Corrigendum 2012). Although the original ACMGG guideline recommended counting 30 cells, the 2012 Corrigendum explained the rationale for 20 cells. Indications for chromosome analysis are shown in Table 2. Any adult woman with suspected Turner syndrome without a documented karyotype should be retested. Although a standard (rather than high resolution) peripheral blood karyotype is usually adequate, a second tissue, such as skin fibroblasts, buccal mucosa cells or possibly urine for bladder epithelial cells, may be examined if there is a strong clinical suspicion of Turner syndrome despite a normal blood karyotype or low-level mosaicism (Hook & Warburton, 2014). If mosaicism is strongly suspected but not demonstrated with a standard karyotype, additional metaphases may be counted or fluorescence in situ hybridization (FISH) studies performed. Although a karyotype is preferred, comparative genomic hybridization (CGH), or single nucleotide polymorphism (SNP) microarrays are equally effective to detect Turner syndrome (Prakash et al., 2014). Suspected Turner syndrome that is diagnosed by microarray analysis should subsequently be confirmed by a karyotype. Because of the complex implications of the diagnosis and the potential need for follow-up testing, patients should be referred for counseling by a geneticist or genetic counselor before and after any genetic test for Turner syndrome (Davenport, 2010). However, if Turner syndrome is suspected, most individuals are not referred before the test and thus, the first genetics encounter may come after test results are completed. In women less than 50 years of age, the lower limit of 45,X mosaicism that defines Turner syndrome has been considered to be 5% (Homer et al., 2010; Klásková et al.,

TABLE 2 Indications for chromosome analysis to diagnose Turner syndrome in adolescents and adults (adapted from table 2 in Gravholt, Andersen, et al., 2017b)

As the only clinical feature:
• Idiopathic short stature
• Obstructive left-sided congenital heart defect[a]
• Unexplained delayed puberty or menarche
• Couple with infertility
• Characteristic facial features in a female[b]
At least two of the following:
• Renal anomaly (horseshoe, absence, or hypoplasia)
• Madelung deformity of wrist
• Neuropsychologic and/or psychiatric issues
• Multiple typical or melanocytic nevi
• Dysplastic or hyperconvex nails
• Other congenital heart defects[c]
• Hearing impairment younger than 40 years together with short stature.

[a]Bicuspid aortic valve, coarctation of the aorta, aortic stenosis (with/without bicuspid aortic valve), mitral valve anomalies, hypoplastic left heart syndrome.
[b]Down-slanting palpebral fissures, epicanthal folds, low-set anomalous pinnae, micrognathia, narrow palate, short broad neck and webbing.
[c]Partial anomalous pulmonary venous return; atrial septal defect, secundum type, ventricular septal defects, muscular or membranous.

2015). Women over the age of 50 years with less than 5% 45,X cells are excluded from the diagnosis of Turner syndrome, because 45,X mosaicism may develop in older women as part of the aging process (Machiela et al., 2016). There is currently insufficient evidence to withhold routine surveillance from Turner syndrome individuals with even low levels of mosaicism, because the long-term clinical outcomes of these women are not well defined (Prakash et al., 2018; Tuke et al., 2019a; Tuke et al., 2019b). With increased research, this approach may be modified.

3.2 | Karyotype-phenotype correlation

The number and severity of Turner syndrome features are generally correlated with the percentage of cells that have a single X chromosome (El-Mansoury et al., 2007). Mosaicism with a 45,X/46,XX or 45,X/47,XXX karyotype is associated with milder cardiovascular phenotypes, including less prevalent and less severe congenital heart defects (CHD) and lymphatic abnormalities compared with non-mosaic Turner syndrome (Cameron-Pimblett et al., 2017; Klásková et al., 2015; Tokita & Sybert, 2016). Many features, including lymphedema, diabetes (both type 1 and type 2, T1D and T2D, respectively), neuropsychiatric traits, and left-sided heart lesions, are more specifically associated with having a single copy of Xp (Bakalov, Cheng, Zhou, & Bondy, 2009; Bondy et al., 2013; Zinn et al., 1998). However, only one Xp gene has been directly implicated in a Turner syndrome phenotype: decreased expression of the pseudo-autosomal *SHOX* gene is associated with short stature and skeletal deformities (Rao et al., 1997). Because congenital heart defects (CHDs) including BAV are more common in 45,X females (30–50%) than in 46,XY males (2%) or 46,XX females (0.5%), reduced dosage of X chromosome genes that escape X inactivation may contribute to Turner syndrome phenotypes. Males may be partially protected from Turner syndrome-related malformations by Y chromosome homologs of Xp genes with compensatory developmental functions. Moreover, monosomy X is not always sufficient to cause heart and vascular malformations by itself, because up to half of Turner syndrome patients with non-mosaic 45,X do not have congenital heart or vascular abnormalities. Therefore, the frequency of heart and lymphatic problems in Turner syndrome may be best explained by a combination of copy number variation of X chromosome genes and altered expression of autosomal genes that also contribute to congenital defects in the general population. Recent studies identified autosomal gene mutations or epigenetic changes in women with Turner syndrome who have cardiac abnormalities, providing the first evidence to support this hypothesis (Corbitt et al., 2018; Prakash et al., 2016; Rajpathak, Vellarikkal, Patowary, Sivasubbu, & Deobagkar, 2014; Trolle et al., 2016).

Smaller X chromosome deletions and other X chromosome structural variants may cause distinct clinical features and are not included in the definition of Turner syndrome. Females with small distal deletions of Xp frequently have short stature and other Turner syndrome-associated skeletal anomalies. They do not appear to be at higher risk for cardiac anomalies, neuropsychiatric issues or ovarian failure, which are often present in women with 45,X karyotypes. In contrast, neurocognitive deficits typical of 45,X women are common in individuals with cytogenetically visible deletions of Xp22.3 (Zinn et al., 2007). Females who have deletions distal to Xq24 frequently have primary or secondary amenorrhea due to premature ovarian failure without short stature or other Turner syndrome features (Beke et al., 2013).

3.3 | Implications of Y chromosome

Mosaicism involving 45,X/46,XY can be associated with a spectrum of phenotypes ranging from typical female (with a low proportion of 46,XY) or typical male (with a low proportion of 45,X), to males with hypogonadism or ambiguous genitalia. For this reason, the term "male Turner syndrome" should be avoided, and individuals can be referred to as having mixed gonadal dysgenesis, or simply mosaicism for 45,X/46,XY (Lindhardt Johansen et al., 2012; Nomura et al., 2015; Wu et al., 2017).

Individuals with Turner syndrome who retain Y chromosome sequences are at increased risk to develop gonadoblastoma (Gravholt, Fedder, Naeraa, & Muller, 2000). At least 10% of females with Turner syndrome harbor Y sequences, and up to 10% of these individuals may develop a gonadoblastoma. However, there is considerable variation in risk estimates, possibly related to methodology, sample size, and potential selection bias (Mancilla et al., 2003; Mazzanti et al., 2005; Sallai et al., 2010; Zelaya, Lopez Marti, Marino, Garcia de Davila, & Gallego, 2015). Notably, large epidemiologic studies have failed to document an increased risk of mortality due to gonadoblastoma among individuals

with Turner syndrome (Schoemaker, Swerdlow, Higgins, Wright, & Jacobs, 2008a; Stochholm, Juul, Juel, Naeraa, & Gravholt, 2006). The rate of gonadoblastoma among individuals with Turner syndrome without detectable Y chromosome sequences in their karyotypes is low (1%) (Rojek, Obara-Moszynska, Kolesinska, Rabska-Pietrzak, & Niedziela, 2017). For these reasons, gonadectomy is recommended for all Turner syndrome individuals with Y chromosome material identified in standard karyotypes. However, for women who are more than 40 years old when Y chromosome material is detected, it may be reasonable to offer a more flexible approach, because gonadoblastoma typically develops earlier in life. Fluorescent in situ hybridization (FISH) with X and Y centromere probes should therefore be used to determine the origin of ring or marker chromosomes that are too small to identify on standard karyotypes (Bianco, Lipay, Melaragno, Guedes, & Verreschi, 2006). When virilization is present, it may be necessary to test two to three tissues to exclude cryptic Y material; FISH of buccal cells may detect Y mosaicism that is not detectable in peripheral blood (Freriks et al., 2013). Molecular screening to detect Y chromosome sequences is currently recommended only in individuals with masculine features who are negative for Y material by conventional cytogenetic and FISH analyses. In these individuals, multiple sequences adjacent to the Y centromere should be amplified using PCR (Wolff et al., 2010).

4 | EPIDEMIOLOGY

4.1 | Prevalence and diagnosis

Although Turner syndrome is considered a rare syndrome, this may not be true in utero. Up to 99% of Turner syndrome fetuses are spontaneously miscarried during the first trimester (with intrauterine mortality peaking between weeks 11–13), and thus, the prenatal prevalence of Turner Syndrome exceeds the postnatal (birth) prevalence several-fold (Gravholt, Juul, Naeraa, & Hansen, 1996; Hook & Warburton, 1983). In countries with national prenatal screening for chromosome abnormalities, a higher detection rate of Turner syndrome is evident (Boyd et al., 2011). Nevertheless, ascertainment is incomplete, and in Denmark, prenatal screening for Down syndrome also captures up to 40% of fetuses with Turner syndrome (Viuff, Stochholm, Uldbjerg, Nielsen, & Gravholt, 2015). Remarkably, there was no difference between the capture rates for 45,X cases compared with all other Turner syndrome karyotypes. Early epidemiological studies estimated the prevalence from prospective chromosome surveys of newborns (Nielsen & Wohlert, 1990). A prevalence of 50 per 100,000 newborn girls was later confirmed by two large Danish registry studies (Gravholt et al., 1996; Stochholm et al., 2006).

Table 3 compares crude estimates for four European countries, noting that the figures do not account for deaths, duration of study period or immigration, and are based on the total number of diagnoses in comparison to the population size. Acknowledging the differences in study design and the span of 11 years, the highest average prevalence of 40 per 100,000 was found by the Danish registry study (the highest prevalence being 59 per 100,000 of Turner syndrome during 1961–1985) (Berglund et al., 2019). Based on the assumption that the real prevalence of Turner syndrome is 50 per 100,000 females, Table 3 demonstrates a considerable rate of non-diagnosis with only 26–80% of the expected number of females with Turner syndrome diagnosed. Furthermore, it appears that the Turner syndrome population is changing with decreases in the proportion of 45,X cases, likely due to prenatal testing followed by elective termination (Berglund et al., 2019).

Although additional data from other countries are needed to confirm these studies, very few countries have the ability to report population-based epidemiologic data on Turner syndrome. Such information is invaluable for planning health care, educational and social resources. Only countries with national registries such as Denmark, Sweden, and England have been able to obtain population-based estimates; regrettably, there are no national prevalence data from the United States. The median age at diagnosis is of 15 years with three distinct diagnostic peaks in infancy, adolescence, and adulthood. About half of women with Turner syndrome are not diagnosed until adulthood, or go through life undiagnosed (Schoemaker et al., 2008b; Stochholm et al., 2006). Vigilance should be high among physicians taking care of adolescents and adults with short stature, reduced fertility, BAV, and endocrine disorders.

TABLE 3 Beyond birth prevalence: Crude estimates of the prevalence of women with Turner syndrome in different European countries (figures do not account for deaths, duration of study period or immigration, and are based only on the total number of diagnoses in comparison to the population size in 2018)

Country	Great Britain	Sweden	Ukraine	Denmark
Author, year	Schoemaker et al., 2008b	Ji, Zoller, Sundquist, & Sundquist, 2016	Zelinska et al., 2018	Berglund et al., 2019
Number of women with Turner syndrome	4,909	1,409	538	1,156
Female population size	32,500,000	5,060,000	4,100,000 (0–18 years)	2,900,000
Study period	1959–2002	1969–2010	2005–2015	1961–2014
Women with Turner syndrome per 100,000	15.1	27.8	13.1	39.9
Percent diagnosed	30%	56%	26%	80%

A recent study characterized the prevalence of X chromosome aneuploidy in a population of 244,848 women from the UK Biobank using SNP array data (Tuke et al., 2019a). The prevalence was almost 4 times higher than expected, although the majority had a 45,X/46,XX mosaic karyotype. Most of these individuals were not aware of their condition. The prevalence of 45,X karyotype was only half of the expected (12 per 100,000), perhaps explained by the tendency for healthy individuals to participate more often in a biobank and the omission of childhood morbidity (comments in Prakash et al., 2018; reply by Tuke et al., 2019b).

4.2 | Morbidity

The early Danish population based cohort studies (n = 594) showed an increased risk of endocrine disorders, autoimmunity, cardiovascular disorders and specific cancer risk. Another national Danish cohort-based study (n = 798) focused on autoimmune disease confirmed a doubling of the overall risk, and an increased prevalence of Hashimoto thyroiditis and T1D (Jorgensen et al., 2010). This increased risk of autoimmunity in Turner syndrome remains an enigma and is also present in another sex chromosome abnormality, Klinefelter syndrome (47,XXY) (Bojesen, Juul, Birkebaek, & Gravholt, 2006; Harris et al., 2016; Seminog, Seminog, Yeates, & Goldacre, 2015). The overall cancer risk in Turner Syndrome does not seem to be increased in comparison to the general female population (Gravholt et al., 1998a; Schoemaker, Swerdlow, Higgins, Wright, & Jacobs, 2008a). The largest epidemiological analysis of 3,425 women with Turner syndrome in the United Kingdom were identified through cytogenetic centers and linked to national death data registries (Schoemaker, Swerdlow, Higgins, Wright, & Jacobs, 2008a). Specific cancers and benign tumors were seen more frequently, including an increased risk of central nervous system (CNS) tumors, especially meningiomas, and childhood brain tumors. Furthermore, the risk of cutaneous melanoma and urinary tract cancers was significantly increased (Schoemaker, Swerdlow, Higgins, Wright, & Jacobs, 2008a). The risk of breast cancer does not seem increased in women who used hormone replacement therapy (HRT) with estrogen and progesterone as reported in a small study from Hungary (Bosze, Toth, & Torok, 2006). The findings of decreased risk of breast cancer and the increased risk of meningioma and melanoma were reproduced in a Swedish registry study (n = 1,409) (Ji et al., 2016). A large European study found no increased incidence of cancer in Turner syndrome women (n = 3,189) treated with growth hormone (GH) (Swerdlow et al., 2017).

As discussed previously, Turner syndrome mosaicism with Y chromosome material is associated with a higher risk of gonadoblastoma (or related germ cell tumor), but these tumors can occur in women with Turner syndrome without apparent Y chromosome material (Cools, Looijenga, Wolffenbuttel, & T'Sjoen, 2014; Gravholt et al., 2017a; Gravholt, Andersen, et al., 2017b, section 1.3).

4.3 | Mortality

The overall mortality in Turner syndrome is increased threefold (Fuchs, Attenhofer Jost, Babovic-Vuksanovic, Connolly, & Egbe, 2019; Schoemaker et al., 2008b ; Stochholm et al., 2012) and there is a 13–15 years reduction in lifespan (Fuchs et al., 2019; Price, Clayton, Collyer, De Mey, & Wilson, 1986; Stochholm et al., 2006). Important differences exist between karyotype groups. Mortality from all causes is raised four to fivefold in women with 45,X karyotype, but only twofold in 45,X/46,XX mosaicsm (Schoemaker et al., 2008b). The increased mortality is primarily due to cardiovascular and endocrine disorders (Schoemaker et al., 2008b; Stochholm et al., 2006). Almost 50% of the excess mortality is caused by cardiovascular disease including aortic events, aortic valve disease, hypertension, and ischemic heart disease (Schoemaker et al., 2008b; Swerdlow et al., 2001). Early onset of calcified coronary plaques in Turner syndrome has been demonstrated using coronary computed tomography angiography (Schoepp et al., 2018) and also coronary artery anomalies (Viuff et al., 2016). Endocrine disorders such as diabetes also contribute to the increased mortality (Schoemaker et al., 2008b; Stochholm et al., 2012). The cohort study from Great Britain found an increased risk of death from neurological conditions such as epilepsy (SMR 9.0 (3.3–19.7)), particularly under age 15 years (Schoemaker et al., 2008b). The digestive system (SMR 4.5) also contributes to mortality because of liver disease and colitis, most prominent between ages 15–44 (Schoemaker et al., 2008b; Swerdlow et al., 2001).

Although mortality has been well-studied using registry-based cohorts, larger epidemiological studies are needed to investigate the effect of hormone therapy on survival. Estrogen deficiency causes an increased risk of cardiovascular diseases in women with primary ovarian insufficiency (Colditz et al., 1987). Appropriate treatment with physiologic hormone replacement might reduce morbidity and mortality in women with Turner syndrome and hypogonadism.

4.4 | Socioeconomic factors

A national Danish cohort study (n = 979) demonstrated a disparate socioeconomic profile of women with Turner syndrome, with fewer partnerships, reduced motherhood and earlier retirement, while the educational level and rate of unemployment were similar to the background population (Stochholm et al., 2012). A clinical study from the National Institute of Health (NIH), with acknowledged referral bias (n = 240, age 25–67 years), found that 70% of women with Turner syndrome had a college bachelor degree or higher, compared to 30% of the American female background population with no confounding of height or age at diagnosis (Gould, Bakalov, Tankersley, & Bondy, 2013). Interestingly, women with Turner syndrome in that cohort were more likely to choose employment in healthcare and social services compared to women in the general United States population, and less likely to enter office and administrative support jobs.

5 | TRANSITIONING FROM PEDIATRIC TO ADULT CARE

5.1 | Rationale for deliberate transitioning

Pediatric caregivers will provide the first experience with Turner syndrome medical care issues for girls diagnosed and treated before

TABLE 4 Clinical presentations of adolescents and adults with Turner syndrome (in ascending order of age) to convey the wide range of management issues

Clinical presentation	Management issues
Healthy 15-year-old girl beginning transition under the direction of her longtime pediatrician and pediatric specialists.	Having been diagnosed in childhood, and familiar with Turner syndrome, she feels she is part of this process. Transition should proceed with relative ease.
Healthy 18-year-old girl who was diagnosed recently because of short stature and inconsistent menses. She is unsure why she is being evaluated by various specialists because parents have not disclosed the diagnosis of Turner syndrome.	Of the various medical issues related to transition, the primary concern will be informing her as an autonomous young adult. Parents may request that "the doctor do it", but family-centered techniques should be explored before discussing the karyotype.
Healthy 19-year-old woman who thrived in high school experience, is thrilled to be in college, but very disappointed that her first semester grades included three nearly failed courses. She thought she had coped with academic challenges in high school using extra time, and abundant parental support, but now feels her academic abilities are inadequate.	At her initial evaluation by a Turner syndrome specialist, she should be screened about her mood and coping (to exclude depressive disorder). The next steps would include an offer to participate in formal neuropsychologic testing to determine skills and challenges. Longer term educational planning would follow regarding coursework, school, tutoring, etc. As needed, a referral to psychiatry for heretofore undiagnosed anxiety or weakness in executive function could be made.
20-year-old woman with severe overweight, hypertension and poor personal hygiene who completed high school, but has not been able to find employment. She lives at home with supportive parents who are frustrated at the lack of social supports. She has no friends, and rarely leaves house. Media provides most of her entertainment.	Identifying a suitable Turner syndrome care team and creating a pathway to providers would initiate an intervention of medical and psychosocial needs. Importantly, the woman herself would need to express an interest in seeking help. Care will likely require many small steps. The visits to mental health providers may be declined, and/or not as frequently as needed.
32-year-old woman with non-mosaic 45,X and amenorrhea feels despondent, having been informed as a teen that she was "infertile". However, she has heard from current providers and peers that pregnancy is indeed a consideration for many women with Turner syndrome.	Acknowledgement of her feelings of disappointment and clarification of medical aspects could establish a relationship. Having received differing viewpoints on pregnancy in Turner syndrome, she may benefit from more nuanced, in-depth counseling sessions on parenthood options at this time with an experienced multispecialty team.
35-year-old successful, single woman, has many friends in the Turner syndrome community. With a bubbly personality, she loves theater and willingly express the joys and challenges at Turner syndrome support meetings.	Encourage this woman to continue to advocate for others with Turner syndrome. There are a growing number of support group activities including local and annual national meetings, summer symposium, committees to engage peers, and public health initiatives.
50-year-old woman was happily employed at same location for many years, but recently faces stress because of increased demands. She is also having medical problems with metabolic syndrome (elevated glucose, lipids, weight).	Her primary care provider and Turner syndrome specialist can acknowledge that some of these issues are not uncommon for people in her age group. There is a potential to modify tasks which are relevant to Turner syndrome, such as requiring her to reach higher shelves (limited by short stature), lifting heavy objects (limited by aortic dilatation), or a stressful style used by a supervisor. Working with her professional human resource office, as well as consideration of mental health counseling may be appropriate.
60-year-old woman who had successful repair of coarctation of the aorta and non-stenotic bicuspid aortic valve was found on recent MRA scan to have an increase in ascending aortic dimension (aneurysmal).	If she is in longitudinal adult CHD care, the rationale for performing interval imaging had been discussed. Shared decision making will be relevant in considering timing of intervention and anxiety management. This will be a "redo" surgery which may carry memories for the patient. Coronary evaluation will raise the specter of atherosclerotic disease with aging in addition to CHD. "Heart to heart ambassadors" (other patients with similar history trained to help others) may be beneficial.
72-year-old woman who is thriving as a "golden butterfly" and attends the annual TSSUS family conference almost every year. A confident, articulate woman, she raises the question with her PCP, "how can I donate my body to science?"	Working with a Turner syndrome specialist or any provider with whom she feels comfortable, this woman can review guidelines in a recent article which addresses this topic (see Prakash et al., 2019a). This contains a combination of philosophical and practical points.

Abbreviations: CHD, congenital heart disease; PCP, primary care provider (pediatrician, family physician); TSGA, Turner Syndrome Global Alliance; TSSUS, Turner Syndrome Society of the United States.
Note: These presentations do not portray specific individuals, but represent composite "phenotypes" of numerous individuals.

adolescence. However, every adolescent will need to make the transition from pediatrics to a new team of adult caregivers at an age dependent upon local medical custom. Transition may be completed as early as 16–17 years or younger in some care systems, or not until the early twenties in others. The transition process may be initiated much earlier, as early as 12 years old, when the pediatric care team begins to assess the individual's level of understanding of the medical issues and readiness to take a more active role in personal care (American Academy of Pediatrics, 2011).

This transition can be particularly difficult in girls with Turner syndrome and must be carefully planned because of great variation in their needs for social and medical support. Many require a later and

more extended transition than typical adolescents. Table 4 presents examples of various clinical scenarios including adolescents with markedly different medical and psychosocial phenotypes, which must be respected in the course of such planning. The challenges of transitioning care are not unique to Turner syndrome. The majority of children with complex genetic and non-genetic medical conditions are now surviving into adulthood (Mahan, Betz, Okumura, & Ferris, 2017; Taylor, Edwards, & Ku, 2006). The goal of this process is to gradually foster responsibility for independent self-care and ongoing participation in preventive care (Rubin, 2008). Transition is best thought of as a partnership between the young woman with Turner syndrome; her parents/guardians, who have been her primary caregivers; and her medical care team. Adult physicians are often less knowledgeable about rare genetic conditions, highlighting the need for improved education (Taylor et al., 2006). Thus, the challenge and responsibility of transition falls increasingly to pediatricians and pediatric subspecialists. Traditionally, the transition process has been championed by the pediatric endocrinologist. However, in transition to adult care, this role may be assumed more often by a primary care physician, or in some cases by a reproductive endocrinologist (Rubin, 2008).

As children with complex conditions grow older, it has become increasingly clear that if transition is not accomplished well, these individuals have decreased access to quality care, less optimal health outcomes, and decreased educational achievement as well as fewer opportunities for employment, all leading to a decreased quality of life (QoL) (Mahan et al., 2017). In addition to the physician's role, psychological and educational supports as well as exposure to support groups for other individuals with the same condition are valuable (Lucaccioni et al., 2015). These include the TSSUS, Turner Syndrome Support Society in the United Kingdom, and similar organizations in most European countries, Australia, and Japan.

5.2 | Models for care transition

Models for care transition have been suggested by the American Academy of Pediatrics (AAP) and the American College of Physicians (ACP). The AAP plan focuses on preventive care as well as acute and chronic illness management. They emphasize co-management between the pediatric and adult physician during the transition of care (American Academy of Pediatrics, 2011). The ACP, collaborating with the Endocrine Society, Hormone Health Foundation, and Turner Syndrome Foundation, compiled a High Value Care document with recommendations for transition specific to Turner syndrome. This includes the elements of transition readiness assessment; clinical summary and transfer record; dosing standards for estrogen; recommended approach to transitioning into adult practice; and recommended approach for planning pediatric practices (ACP, 2016). Guidelines specific to the transition of adolescents with Turner syndrome and other endocrine disorders stress the ongoing monitoring by both the pediatric and adult endocrinologist (Hokken-Koelega et al., 2016). These models provide an important starting point for practitioners to begin the conversation about care transition in this population.

In Germany, pediatricians caring for individuals with Turner syndrome have initiated a process in which the pediatrician identifies an adult endocrinologist, gynecologist, cardiologist, or other provider at their institution or in proximity, and mentors this physician to become an "anchor physician" for the ongoing care in adulthood. Although not formally studied, this personalized and practical approach may be useful in order to establish a quality network for comprehensive adult care when clinics affiliated with academic institutions are not available.

5.3 | Tools and support

The Guidelines (Gravholt, Andersen, et al., 2017b, section 5.3) include detailed recommendations suggesting that transition begin in early adolescence and be coordinated by the pediatric endocrinologist or other Turner syndrome-specific provider. The core steps of transition should be documented using available tools or those specifically adapted for the practice setting. They emphasize that while there are different health care models, the pediatric and adult care teams must have a coordinated workflow to ensure a smooth transfer of care (Gravholt, Andersen, et al., 2017b, figure 3).

Transition is best performed as a staged process (Rubin, 2008). Recurrent assessments of the young adolescent's knowledge and readiness to participate in her care are undertaken over the course of the intervening years. Specific tasks, appropriate to the teen's maturity and psychosocial development, are assigned to the teen to foster independence from parents/caregivers. A gradual shift in responsibilities from the parents/caregivers to adolescents with Turner syndrome encourages and empowers them to gain more control over their care. Some individuals have cognitive and/or emotional challenges that do not allow for full independence from caregivers. However, they should still be encouraged to gradually assume that the responsibilities are within their capabilities. For example, teens should be encouraged to schedule and cancel their own appointment, answer questions at the physician's office regarding their interval history and medication usage/schedule, and call the pharmacy for medication refills. In our experience, caring for these adolescents, even those with ostensibly normal or high social and academic functioning requires patience. Emancipation from parental oversight for these active tasks may not occur until the third decade. Support group meetings are invaluable in providing teen-friendly "breakout sessions" to coach and support.

During transition, the pediatric care team must also continue to educate and foster the adolescent's knowledge of her medical history as well as the need for continuous lifelong screening for other possible comorbidities. To facilitate communication between pediatric and adult care teams, young adults graduating from pediatric care should be provided with a written summary (AAP, 2011; ACP, 2016; Gravholt, Andersen, et al., 2017b, section 5.1) of their past medical history, current health status, related comorbidities, and current medication list. The medical summary should include the results of relevant laboratory and imaging studies, especially karyotype; echocardiography (occasionally, catheterization or aorta imaging), electrocardiogram (ECG); studies of bone mineral density (BMD); pelvic and renal ultrasound; thyroid function studies, liver function studies, FSH,

anti-Mullerian hormone (AMH); celiac screening; and neuropsychiatric evaluation. The transition summary is of great value to the patient, the family, and the adult care team. Some young adult women with Turner syndrome may benefit from a visit to the adult provider before discharge from the pediatric practice. Rubin (2008) suggested a "patient passport" to guide through the transition process. While this can be useful, some young women with Turner syndrome who have learning disabilities may find the additional form and checklist overwhelming. The advent of the electronic medical record can be invaluable for care coordination across providers and institutions and has allowed for a built-in record for much of this process.

Incorporating support and advocacy group contacts into the transition process is encouraged (Gravholt, Andersen, et al., 2017b, section 5.1) because they can help provide a framework for planning transition. Several resources for transition care plans as well as assessment tools and portable medical summaries are listed under the Website references.

6 | ENDOCRINE ISSUES

6.1 | Growth hormone

6.1.1 | Perspective from childhood to transition

Although the management of adult women with Turner syndrome does not include GH treatment, it is reviewed in the context of the transition to adulthood, and to understand the impact on overall health of adult women who received or did not receive this treatment during growth.

A number of treatment trials starting in the 1980's demonstrated that girls with Turner syndrome treated with biorecombinant GH until they were close to full adult height were taller than both the initially predicted adult height and height expected from previously collected Turner syndrome population height standards (Gault et al., 2011; Li, Cheng, & Xiu, 2018; Rosenfeld et al., 1992; Ross et al., 2011; Stahnke, Keller, & Landy, 2002; Van Pareren et al., 2003). Height increase was greater the earlier the girl was treated, and a dose response could be elucidated as well (Van Pareren et al., 2003). Studies in very young children demonstrated that their height could be normalized with early GH treatment (Davenport et al., 2007; Linglart et al., 2011). A definitive Canadian study, which included a prospective control group of untreated girls with Turner syndrome, clearly demonstrated that GH therapy enhanced adult height (increased by about 7 cm) and was greatest in girls who started treatment at 7 or 8 years (Stephure et al., 2005). Several studies demonstrated that the addition of the non-aromatizable androgen, oxandrolone, to the treatment regimen, allowed girls to reach adult height more rapidly, and seemed particularly useful in older girls who started receiving GH after a late diagnosis (Gault et al., 2011; Menke et al., 2010; Rosenfeld et al., 1992). Use of low dose oxandrolone can enhance adult height effectively with minimal virilization despite a small delay in breast tissue development -(Menke et al., 2010; Sas et al., 2014; Sheanon & Backeljauw, 2015). For these reasons, most girls who are diagnosed early and are making the transition to adult caregivers have completed a course of GH therapy and have reached a height close to 5 ft tall (153 cm) or even taller. Rare complications of growth associated with GH treatment may include slipped capital femoral epiphysis, increased intracranial pressure, and worsened scoliosis (Bolar, Hoffman, Maneatis, & Lippe, 2008; Darendeliler, Karagiannis, & Wilton, 2007). Acne, hirsutism, voice deepening, or clitoromegaly have been reported in adults post-oxandrolone treatment (Freriks et al., 2012). GH dosing, calculated as a weekly dose in the United States and as a daily dose in Europe and Japan, is based upon weight, or less commonly, body surface area (Schrier et al., 2014).

GH treatment of girls with Turner syndrome has effects on carbohydrate, lipid, and protein metabolism. Body composition changes include decreased fat mass and increased muscle mass (Ari, Bakalov, Hill, & Bondy, 2006; Gravholt et al., 2002c; Jeż et al., 1994; Wooten, Bakalov, Hill, & Bondy, 2008). Treatment with GH can cause an increase in circulating insulin levels, and occasionally glucose intolerance, which may necessitate discontinuation of therapy (Baronio et al., 2017; Sas, de Muinck Keizer-Schrama, Aanstoot, Stijnen, & Drop, 2000). Coarsening of facial features and increase in the size of hands and feet as would be expected with elevated levels of IGF-1 (observed in acromegaly) are uncommon (Vilar, Vilar, Lyra, Lyra, & Naves, 2017). The increase in IGF-1 during GH therapy is not intended to be much above normal levels and is monitored during therapy.

As GH treatment paradigms have matured and clinical decision-making has begun to rely more on levels of surrogate markers of GH excess, the subjective opinion of the authors is that many girls are treated with much lower levels of GH and may not be growing as well as anticipated from the clinical studies which lead to approval by regulatory agencies. This is relevant to providers treating women who have suboptimal height despite GH therapy. Peripheral levels of IGF-1 may not adequately serve as surrogate markers for growth plate IGF-1 or even for free and available IGF-1 derived largely from hepatic production in response to exogenous GH (Bannink, van der Palen, Mulder, & de Muinck Keizer-Schrama, 2009). Future longitudinal studies on the side effects and height outcome of GH treatment in large populations of young women with Turner syndrome should inform best clinical practice in this area.

6.1.2 | Impact of GH on adolescents in transition

Discontinuation of GH therapy may occur during transition to adult care, and may be accompanied by changes in body habitus, decreased muscle mass and increased fat mass (Van Pareren, de Muinck Keizer-Schrama, Stijnen, Sas, & Drop, 2002). Alerting young adolescents to the fact that these changes are to be expected can alleviate concern. Throughout their lifespan, but especially as they enter adulthood, young women with Turner syndrome should be counseled about exercise and proper nutrition because of the long-term challenges with weight gain, inactivity, and abnormal metabolism.

The long-term side effects of GH therapy seem to be minimal. Facial feature accentuation when IGF-1 levels are high is similar to that experienced by most children during puberty (Juloski et al., 2016), and

becomes less prominent after discontinuation of treatment. Increased shoe size is considered a real advantage in girls with Turner syndrome, who usually have such small feet that buying shoes is very difficult. Lipid abnormalities and hyperinsulinism with insulin resistance generally revert to normal after discontinuation of GH (Van Pareren et al., 2002). Girls with Turner syndrome have an increased risk of T2D as well as T1D, but insulin resistance in these girls seems more related to inactivity and weight gain with no correlation with previous GH therapy. Although there has been concern about malignancy risk with GH treatment, no such risk has been identified in most girls with Turner syndrome (Swerdlow et al., 2017). Girls with Turner syndrome need to be reassured that they are not truly deficient in GH. In adolescence, they can be reminded that they took GH solely to increase their adult height, and that their ability to release normal amounts of GH returns quickly after stopping GH. The major negative QoL issues for girls with Turner syndrome relate to short stature and concerns about feelings of loneliness and handicap (Jeż et al., 2018). Health-related QoL seemed improved after GH treatment in one study (Bannink, van Doorn, Stijnen, Drop, & de Muinck Keizer-Schrama, 2006a) but others could find no effect of GH therapy on QoL, despite taller stature (Amundson, Boman, Barrenas, Bryman, & Landin-Wilhelmsen, 2010; Taback & Van, 2011). Most girls with Turner syndrome, and their parents, request treatment in order to enhance adult height, to avoid stigmatization, and for cosmetic and convenience indications. As important as the research is which followed girls who used GH in clinical trials, there is also a need for studies to compare the health and comorbidities in older women who used GH with those who either declined, were partially compliant, or lacked access to GH treatment.

6.2 | Hormone replacement therapy

6.2.1 | Overview of ovarian insufficiency

Women with Turner syndrome, like women with a 46,XX karyotype, are endowed with a finite number of germ cells, most of which undergo atresia. They attain the same peak germ cell mass at 20 weeks of intrauterine life (approximately 6–7 million), accompanied by an accelerated loss of germ cells (1 million at birth and 400,000 by puberty). The decline is clinically imperceptible in childhood, as the hypothalamic–pituitary-ovarian axis is quiescent, but is activated at puberty when the hormonal events of the menstrual cycle ensue. By menopause, germ cells are essentially depleted. In a minority of women with Turner syndrome, puberty and menarche occur spontaneously (Negreiros, Bolina, & Guimaraes, 2014; Tanaka et al., 2015). In a cohort from Italy, 32% had spontaneous puberty and menarche occurred in 16%, mainly in those with mosaic karyotype containing a 46,XX cell line (Pasquino, Passeri, Pucarelli, Segni, & Municchi, 1997). Even when spontaneous menarche is achieved, most of these young women develop irregular menses and early menopause (Negreiros et al., 2014). Thus, the majority of girls and women with Turner syndrome experience ovarian failure represented by hypergonadotropic hypogonadism, low AMH (Lunding et al., 2015) as well as undetectable inhibin B (Gravholt, Naeraa, Andersson, Christiansen, & Skakkebaek, 2002a; Hagen, Main, Kjaergaard, & Juul, 2010) and require induction of puberty and hormone replacement therapy (HRT).

6.2.2 | Pubertal induction

The induction of puberty in Turner syndrome is reviewed in order to appreciate the use of hormone replacement therapy in adolescents in transition, and ultimately as adult women. The Guidelines (Gravholt, Andersen, et al., 2017b, section 2.5) recommend confirming ovarian dysfunction, and starting estrogen replacement between 11 and 12 years of age in order to promote normal growth and psychosocial development. Low doses of estradiol are initiated and titrated to promote secondary sexual characteristics and uterine growth without early closure of the growth plates, ensure a normal tempo of bone mineralization (Cleemann et al., 2011), normalize cognitive maturation (Ross, Roeltgen, Feuillan, Kushner, & Cutler Jr., 1998; Ross, Roeltgen, Feuillan, Kushner, & Cutler Jr., 2000), body composition (Cleemann et al., 2017), reduce lipids (Gravholt, Naeraa, et al., 1998a) and liver enzymes (Koulouri, Ostberg, & Conway, 2008) and reduce cardiovascular risk in the long term (Gravholt, Naeraa, et al., 1998a; Ostberg et al., 2007). Transdermal estradiol is the preferred method for estrogen administration (Gravholt, Andersen, et al., 2017b, section 6.1; Klein et al., 2018), but oral estradiol can also be used. Estrogen replacement strategies for pubertal induction in girls with Turner syndrome (Gravholt, Andersen, et al., 2017b, table 5) recommend increasing the dose by 25 to 100% every 6 months to attain adult dosing over the span of 2–3 years. Routine measurement of gonadotropins is not recommended (Gravholt, Andersen, et al., 2017b, section 2.5); instead, careful monitoring of Tanner staging; bone age and growth rates; and uterine volume via pelvic ultrasound; are more useful in guiding estrogen titration. Progesterone therapy, which is discussed in detail in the following section, is initiated once breakthrough bleeding occurs or after 2 years of estrogen therapy.

6.2.3 | Hormone replacement therapy in adults

In most young women with Turner syndrome, HRT is the cornerstone of long-term medical treatment. After puberty induction, HRT must be continued at least until the age of natural menopause (approximately 50 years or later), depending on an individual assessment of risks and benefits. In adolescents with Turner syndrome who undergo natural puberty and menstruate on their own, the patient and her physician must be vigilant of her menstrual history, as early menopause or ovarian failure is likely. In such cases, HRT can be initiated when menses occur less frequently or cease for a few months. At this time, hormonal evaluation will show high FSH and low AMH concentrations. Hormone replacement has multiple benefits including a sense of well-being and feminization, bone health (Högler et al., 2004), improvement in vascular function (Ostberg et al., 2007), and improvement in lipids and blood pressure (Gravholt, Naeraa, et al., 1998a). In addition, HRT is important for appropriate development of uterine volume if future in vitro fertilization is required. The impact of karyotype (45,X vs. mosaicism) on uterine volumes varies (Bakalov, Shawker, Ceniceros, &

Bondy, 2007; Doerr et al., 2005), although the duration of treatment and dose of estrogen are likely to influence uterine size.

The estrogen compounds used for replacement in Turner syndrome include 17β-estradiol (E2), conjugated equine estrogens (CEE), and ethinyl estradiol (EE). 17β-estradiol is the natural estrogen secreted by the ovaries. Conjugated equine estrogens consist of over 100 forms of estrogens of different receptor affinity and potency. Ethinyl estradiol, used in most oral contraceptive pills, is a potent synthetic E2 analog that is not metabolized to E2 (Klein et al., 2018). Use of oral contraceptives for HRT is generally not recommended in young women with Turner syndrome; EE is the least physiologic and potential adverse effects include higher blood pressure, insulin resistance, and it may also be suboptimal for bone health (Herrmann & Seibel, 2010). Exceptionally, young women with Turner syndrome mosaicism who have spontaneous cycles and desire contraception, may wish to use oral contraceptives containing EE. Similarly, while previously more popular, CEE is currently less favored as HRT.

Table 5 of the Guidelines shows the recommended estrogen replacement options for adult women with Turner syndrome (Gravholt, Andersen, et al., 2017b). The preferred estrogen for HRT in Turner syndrome is E2, which is available in oral, transdermal, and gel forms. All are used in Turner syndrome and are effective in achieving the desired goal of increasing estradiol levels to the range seen in normally cycling women; however, transdermal E2 is favored over oral therapy. Doses of transdermal E2 range from 25 to 200 μg daily, usually 50 μg or higher. However, some patients may be allergic to the adhesive in patches and E2 gels may be more expensive in some countries (or less desirable to patients); under such circumstances, oral E2 may be appropriate. Doses of oral E2 range from 1–4 mg daily (Cleemann et al., 2017). A recent randomized study using oral conventional (2 mg/day) or higher doses (4 mg/day) of estradiol for 5 years, showed that the high dose group had a greater increase in muscle mass during treatment, while BMD was similar in the two groups. This may be important, knowing that females with Turner syndrome have a skewed body composition with higher fat mass and lower muscle mass than control women. It may also be relevant to metabolic syndrome or T2D seen in Turner syndrome (Cleemann et al., 2017). These E2 formulations are available in many countries. Depot E2 may be available to some practitioners, but it is generally not used.

Progestins must be given, along with estrogen, to prevent endometrial hyperplasia and protect the uterus in Turner syndrome after puberty induction. The three most commonly used progestins for endometrial protection are micronized progesterone, norethisterone acetate, and medroxyprogesterone. These can be given cyclically, to mimic the normal menstrual cycle with menses occurring after progestin withdrawal, or daily to avoid menses. Micronized progesterone is prescribed as 100 mg daily or 200 mg for 12 days each month and medroxyprogesterone acetate as 2.5 mg daily or 10 mg given for 10 days each month. Norethisterone acetate (1 mg) is typically added in sequential combination pills with E2 and used for 10 days each month.

Cyclic therapy is generally preferred in Turner syndrome, to mimic normal ovarian cyclicity. Some women with Turner syndrome may wish to avoid menses in which case continuous therapy, as above, is appropriate. Combination patches containing E2 and a progestin are available in many countries and depending on the preparation, the patient applies one patch weekly or twice weekly. Combination oral formulations containing E2 and a progestin (norethindrone or drospirenone) are available in the United States, but the 1 mg E2 dose may be low for younger women with Turner syndrome. In Europe, several 2 mg containing E2 formulations are also available (Klein et al., 2018), combined with a progestin. The woman should be advised that with continuous treatment, episodes of erratic bleeding might occur in the first 6 months; if they persist, evaluation may be required. Alternatively, protection of the endometrium may be afforded with the use of an intrauterine contraceptive device releasing the progestin, levonorgestrel. Androgen concentrations are also decreased in women with Turner syndrome. A randomized controlled trial in 14 women with Turner syndrome showed improvements in lipid profile, BMD, body composition, neurocognition, QoL, and sexual desire when methyltestosterone was added to HRT versus placebo (Zuckerman-Levin et al., 2009). Additional research is needed in this area before androgen supplementation can be considered as a necessary adjunct to therapy.

Despite recommendations promoting the many benefits of HRT, in the authors experience approximately 15% of adolescents and adults are not using HRT, although formal trend analysis across the lifespan is not yet available. Failure or reluctance to use HRT is multifactorial, variably related to lack of education, financial resources, or access to caregivers. Early on there can be a deliberate rejection of medication that causes menses. Clearly, education of the individual patient, outreach toward the Turner syndrome community, and research should be prioritized because lack of HRT may be associated with increased morbidity from bone loss and other signs of increased aging.

6.3 | Type 2 diabetes incidence and management

6.3.1 | Incidence and risk factors

The evaluation and management of cardiometabolic health are key components in the care of girls and women with Turner syndrome, given the extent to which components of metabolic syndrome (central obesity, hypertension, diabetes, and dyslipidemia) contribute to the increased morbidity and mortality observed in this population (Davis & Geffner, 2019; Gravholt, Andersen, et al., 2017b, section 6.1). More than 50% of women with Turner syndrome have an abnormality in glucose homeostasis including insulin resistance, impaired glucose tolerance, and T2D (Sun et al., 2019). Indeed, diabetes has been reported to contribute to 22% of all deaths in the Danish cohort of women with Turner syndrome (Stochholm et al., 2006). It is therefore crucial that Turner syndrome providers recognize this increased risk throughout the lifespan and incorporate lifelong vigilance for T2D into their approach to care.

Most cases of overt diabetes in Turner syndrome occur in adult women (Lebenthal et al., 2018; Sybert & McCauley, 2004). However, since current data do not always present age-specific frequency and

risk factors, it is necessary to include girls and younger women in this discussion. Impaired glucose tolerance is seen in 10–40% of girls and women with Turner syndrome, a prevalence that is significantly higher than that seen in both healthy controls and age-and weight-matched women with ovarian failure due to other causes (Bakalov et al., 2004; Lebenthal et al., 2018). Epidemiologic studies indicate that the relative risk of T2D in adult women with Turner syndrome is three to fivefold higher than controls (Bakalov et al., 2009; Gravholt, Juul, Naeraa, & Hansen, 1998b) with prevalence estimates ranging from 12.4 to 25% (Bakalov et al., 2009; Ibarra-Gasparini et al., 2018). Most of the increased risk of diabetes in Turner syndrome relates to T2D, although evidence also points to T1D as a potential autoimmune manifestation of the syndrome. A Danish registry study demonstrated an 11-fold increased incidence of T1D, while the National Cooperative Growth study showed a more modest increased risk in a U.S. cohort that did not quite reach statistical significance, with a standardized incidence ratio of 0.92–4.18 (Bolar et al., 2008; Gravholt, Juul, et al., 1998b).

Estimates of diabetes risk are influenced by several factors including age, body weight, use of hormone therapy (GH, HRT), whether the diagnosis of diabetes is based on known cases reported in national registries, or whether screening tests are employed. Age appears to be the strongest independent predictor of diabetes in Turner syndrome (Ibarra-Gasparini et al., 2018; Lebenthal et al., 2018). Incidence of impaired glucose tolerance shows a stepwise increase from 10% of children to 16% in adolescents and 41% in adults with Turner syndrome (Lebenthal et al., 2018). Genetic mechanisms have been invoked to explain this phenomenon, with the hypothesis that it arises from haploinsufficiency of genes involved in insulin signal transduction and β-cell function that are located on the X chromosome (Sun et al., 2019). Some have hypothesized that those with an isochromosome Xq have greater risk for developing T2D due to overexpression of Xq genes (Bakalov et al., 2009), but this increased risk has not been well-documented in the clinical data available, particularly in adult populations (Cameron-Pimblett et al., 2017). While the primary defect is thought to be a decrease in the first phase insulin response, the increases in BMI and visceral fat that occur during late childhood and adolescence and are characteristic of adult women with Turner syndrome may further contribute to diabetes risk by adding insulin resistance to the β-cell dysfunction already present (Gravholt et al., 2006; Sun et al., 2019).

Hormone therapy with GH to treat short stature and gonadal hormones to treat primary gonadal failure are standard of care for girls with Turner syndrome, and both have the potential to influence insulin sensitivity. As noted by the Guidelines (Gravholt, Andersen, et al., 2017b, section 6.1), the risk of T2D posed by GH treatment (Cutfield et al., 2000; Wooten et al., 2008) as well as HRT (Sun et al., 2019; Trolle, Hjerrild, Cleemann, Mortensen, & Gravholt, 2012b) remains poorly understood. Most studies show a neutral effect on glucose metabolism (Gravholt et al., 2005; Ibarra-Gasparini et al., 2018). However, it is difficult to drawn definitive conclusions given the small sample sizes and differences in the type of hormone replacement used (natural estradiol and progesterone at physiologic doses versus use of an oral contraceptive pill with ethinyl estradiol and a synthetic progestin).

6.3.2 | Management

Screening for diabetes in Turner syndrome can be performed by measuring fasting plasma glucose or glycated hemoglobin (HbA1C) or by doing an oral glucose tolerance test (OGTT). Recommendations in the Guidelines are for lifelong annual measurement of HbA1C with or without fasting plasma glucose starting at age 10 (Gravholt, Andersen, et al., 2017b, section 6.1). It is recommended that an OGTT be considered if HbA1C is in the pre-diabetic range given the pitfalls of fasting plasma glucose in properly detecting defects of insulin secretion (Gravholt, Andersen, et al., 2017b, table 8). While less convenient for patients, an OGTT is the most sensitive screening test with one study showing that out of 13 patients diagnosed with diabetes by OGTT, only one had a fasting glucose above 126 mg/dL and only two had HbA1C values above 6.5% (Adler, Herschkowitz, & Minder, 2005; Ibarra-Gasparini et al., 2018). Once a diagnosis of diabetes has been established, it is recommended that glutamic acid decarboxylase (GAD-65) antibodies be measured to aid in distinguishing T1D from T2D and that the patient be referred to a diabetes specialist.

Optimal management of diabetes in adolescents and women with Turner syndrome includes correction of any modifiable risk factors such as a sedentary lifestyle, poor nutrition, and substitution of medications that promote weight gain with weight-neutral alternatives. One survey of women with Turner syndrome found that they liked physical activity during childhood and adolescence less than the control group (Næss, Bahr, & Gravholt, 2010), signaling perhaps that early lifestyle habits may play a role. It is important for physicians to encourage women with Turner syndrome to adopt the preventive measures recommended for the general population, such as at least 1 hr of moderate-to-vigorous intensity physical activity daily as well as a healthy diet with a low intake of calorie-dense foods and refined carbohydrates. Consultation with a nutritionist is helpful in this regard. In patients with a significantly elevated HbA1C level at diagnosis or with persistent hyperglycemia despite lifestyle changes, medical therapy should be initiated. However, there are currently no studies to guide choice of oral hypoglycemic agent for optimal management of diabetes in Turner syndrome. Pending the results of clinical trials in this area, Turner syndrome providers can follow the guidelines for management of hyperglycemia published jointly by the American Diabetes Association and the European Association for the Study of Diabetes (Davies et al., 2018).

6.4 | Bone health

6.4.1 | Overview

The key elements in caring for the skeleton of women with Turner syndrome include the diagnostic assessment of bone density to monitor for osteoporosis, avoidance of fractures, and promotion of bone health in diet and lifestyle. Adolescents are introduced to these issues

during wellness visits, which include a review of nutritional calcium, sun exposure, and exercise. They may not realize that their use of GH and estrogen, when applicable, contributes positively to their final adult bone "phenotype". Low BMD (osteoporosis) may be clinically evident 2–3 decades earlier in women with Turner syndrome than typically noted for postmenopausal females. The risk of fracture may be doubled, especially affecting the femoral neck, lower spine, and forearm (Davies, Gulekli, & Jacobs, 1995; Gravholt et al., 2002b) with peaks in childhood and in adulthood (Gravholt, Juul, et al., 1998b). Fracture estimates are likely overestimated as they are based on older patients who may not have been treated with GH or estrogen, or whose treatment was delayed. Factors that may contribute to fractures include bone geometry and reduced muscle power, which itself is a mechanical stimulus for bone development.

6.4.2 | Genetic basis of bone metabolism

Haploinsufficiency of X-linked genes that escape X-inactivation is one of the key factors responsible for the clinical phenotypes of Turner syndrome. Haploinsufficiency of the *SHOX* gene plays a key role in growth failure (see Section 6.1) and is likely the cause of other skeletal alterations in Turner syndrome. While the exact effect of *SHOX* on bone is not known, it has been suggested that its deficiency may alter bone geometry and microarchitecture (Soucek et al., 2013), as similar changes in bone geometry at the proximal radius have been found in patients with isolated *SHOX* deficiency.

6.4.3 | Diagnostic techniques and interpretation

Dual energy X-ray absorptiometry (DXA), which is the most commonly used technique for evaluating bone mass, has limitations in Turner syndrome, as there is influence of body size on areal BMD. Smaller bones project less density on the measured surface than bigger ones with resulting lower T- and Z-scores in short individuals, a deficit which is less apparent when reduced bone size is considered (Bakalov et al., 2003; Gravholt, Lauridsen, Brixen, et al., 2002b). Peripheral QCT (quantitative computed tomography) provides measurement of 3-dimensional bone density without the influence of bone size, with assessment of trabecular and cortical bone separately. Studies of the variations and possible trends in bone density across the lifespan vary in methodology. Decrease in both cortical bone and trabecular bone occurs in adolescents and young adults with Turner syndrome (Holroyd et al., 2010; Soucek et al., 2011). However, high-resolution pQCT (hr-pQCT) has shown normal cortical bone in adolescents with Turner syndrome (Soucek, Schonau, Lebl, & Sumnik, 2015), and a prospective study of children with Turner syndrome hr-pQCT showed a decrease in BMD Z-score with time, but no increased risk of fracture at this age (Soucek et al., 2018). An earlier study of adults showed clearly reduced cortical porosity at both tibial and radial sites, as well as compromised trabecular integrity at both sites, leading to compromised trabecular microarchitecture and lower bone strength, both of which lead to a higher risk of low-impact fractures (Hansen, Brixen, & Gravholt, 2012). Current treatment with GH and age-appropriate pubertal induction may normalize BMD during adolescent years, but the available studies emphasize that adults with Turner syndrome may still have low BMD and an increased fracture risk.

In addition to bone density, bone microarchitecture is an important determinant of bone fragility and fractures. This can be influenced by remodeling (formation and degradation) controlled by osteoblasts and osteoclasts, respectively. In Turner syndrome, increased resorption with normal or decreased formation (imbalance of bone remodeling) may be observed (Faienza et al., 2015; Gravholt, Lauridsen, Brixen, et al., 2002b). Potential mechanisms resulting in bone fragility in Turner syndrome include estrogen deficiency, FSH excess, the effect of X-chromosome abnormality, and the comorbidities of Turner syndrome discussed separately.

6.4.4 | Impact of growth hormone and estrogen therapy

The positive effects of GH therapy on bone have been shown in several studies (Cleemann et al., 2011; Sas et al., 2001). The former study showed improvement in BMD using variable dose regimen of GH. In the latter, near normal Z-scores were found in those who had previously received GH. Most girls with Turner syndrome, particularly those with 45,X, have high FSH at the time of expected puberty. It has been suggested that high FSH levels in untreated Turner syndrome may drive osteoclastogenesis (Faienza et al., 2015), although these data have not yet been confirmed.

Estrogen replacement is important to optimize bone accretion in adolescents with Turner syndrome that has special emphasis on early initiation (reviewed by Backeljauw & Klein, 2019). Increased BMD was shown after 3 years of HRT with subcutaneous estradiol implants (Khastgir et al., 2003). Puberty itself, as well as the stage of puberty, had a positive impact on bone, irrespective of whether puberty was spontaneous or induced (Nadeem & Roche, 2014a). The impact of the dose of estradiol (2 vs. 4 mg) on bone and body composition was evaluated in a 5-year study, which found that BMD increased in both groups, with no difference between the treatment groups. However, lean body mass increased significantly more in the high dose group (Cleemann et al., 2017). Interestingly, the strongest determinant of bone density was the BMD at study entry. Thus, adequate and timely pubertal induction with estrogen therapy as well as timely and adequate GH treatment, as in their group of Turner syndrome patients, is sufficient for age appropriate bone accrual.

Although transdermal estradiol is preferred or hormone replacement in Turner syndrome, young women may not want to reveal the patch to their family, friends, roommate or when light clothes might disclose its location. Although less favorable (Herrmann & Seibel, 2010), some women simply prefer to use an oral contraceptive pill, which they feel is more practical.

6.4.5 | Impact of comorbidities on bone health

Comorbidities in women with Turner syndrome which may affect bone health include obesity, diabetes, and autoimmune disorders

(Gravholt, Juul, et al., 1998b), especially celiac disease, thyroid disease (such as hypothyroidism), vitamin D deficiency, and secondary hyperparathyroidism. In a study of 60 women with Turner syndrome, bone area, bone mineral content, and area-adjusted BMD were found to be universally reduced in Turner syndrome compared with 181 age-matched normal female controls (Gravholt, Lauridsen, Brixen, et al., 2002b). Bone markers showed increased resorption with unchanged or reduced bone formation, thus uncoupling bone remodeling in which endocrine, metabolic, chromosomal abnormalities, and other comorbidities may have contributed.

Screening for bone density is recommended every 5 years as adults (Gravholt, Andersen, et al., 2017b, tables 6 and 8). Improving bone health is an important health measure in adolescents and women with Turner syndrome. Studies of adults consistently report low BMD, whether measured with DXA or hr-pQCT, and epidemiological studies find increased fracture rates and risk of osteoporosis (Hansen et al., 2012). Further both longitudinal clinical research and mechanistic studies of bone turnover are necessary, both with regard to optimal HRT during adolescence and early adulthood, as well as throughout adulthood, including and beyond age of normal menopause. To be determined is the role of bisphosphonates or other agents to preserve bone and avoid fracture, and the best way to implement healthy lifestyle and regular weight-bearing exercise, which benefits women with Turner syndrome. Whether there is a "window of opportunity" for attaining maximal peak bone mass could be studied, as well as learning whether such a window of opportunity can be missed with too late pubertal induction and with too low doses of sex steroids.

6.5 | Overweight and obesity

In addition to discussions in this review about hypertension (Section 7.3) and diabetes (Sections 6.3 and 10.5), overweight/obesity and dyslipidemia are to be considered in the Turner syndrome population as they contribute to the cardiometabolic syndrome (Davis & Geffner, 2019).

6.5.1 | Prevalence and challenges

As reviewed in the Guidelines (Gravholt, Andersen, et al., 2017b, section 6.1), overweight/obesity in individuals with Turner syndrome appears to be more common than in the general population, although there are/is no data on actual prevalence. Overweight/obesity is a risk factor for thromboembolism when using estrogen, hypertension, diabetes, and other components of the "metabolic syndrome" (Gravholt, Andersen, et al., 2017b, section 6.1.3) and should be managed aggressively. Few discussions are as challenging for both the individual with Turner syndrome and the provider as weight maintenance and management. It often involves encouraging an adolescent or woman with Turner syndrome to alter how she prepares, plans for and consumes her meals and modifying daily routine to include or increase physical activity. This can often be perceived as a form of criticism or judgment provoking feelings of inadequacy, body shame or low self-esteem. These discussions should be approached with care to engage and encourage the woman with Turner syndrome to set attainable goals that promote weight loss. In our experience, women with Turner syndrome are keenly aware of the importance of avoiding weight gain; however, even those with good overall fitness express feelings of frustration. Given their short stature, even small changes in weight can have a marked effect on BMI and subsequently body image and self-esteem. When offering counseling about maintaining a healthy weight and lifestyle, body shape is not presented as the goal. Ideally, heart healthy exercise and nutrition are promoted, under the guidance and care of the primary care physician, cardiologist, and nutritionist. Women with Turner syndrome and overweight/obesity who would like to pursue pregnancy may be further motivated to achieve preconceptual weight loss.

6.5.2 | Weight management

Treatment for the adolescent or adult woman with Turner syndrome begins with family-centered prevention in childhood. Exploring the young woman and family's style of daily and leisure activities, meals, and the socioeconomic challenges they may face, as well as offering preventative counseling, may be more effective than recommending dietary changes and exercise after the individual is already overweight or obese. It is important to encourage the entire household to participate and become actively involved in implementing lifestyle modifications, as this will allow for a more supportive environment. Families should take measures to diminish access to unhealthy food choices and encourage a more active lifestyle in order to prevent excessive weight gain throughout the lifespan. Weight management programs are increasingly available at most major medical centers.

7 | CARDIOVASCULAR HEALTH ISSUES

7.1 | Congenital heart defects and vascular anomalies frequency and diagnosis

Congenital heart disease occurs in approximately 50% of individuals with Turner syndrome, primarily involving left-sided obstructive lesions such as BAV (30%), coronary anomalies (20%), aortic coarctation (15%), and an aortopathy that can lead to rare but often fatal dissection or rupture of the thoracic aorta (Ho et al., 2004; Kim et al., 2011). In addition, other thoracic vascular malformations, such as partial anomalous pulmonary venous connection, left superior vena cava, an elongated transverse aorta, and abnormalities of the head and neck arteries are also more frequent in Turner syndrome and may pose distinct risks for cardiovascular morbidity and mortality (Gutmark-Little, Hor, Cnota, Gottliebson, & Backeljauw, 2012; Olivieri et al., 2013). The incidence of congenital heart and vascular defects is higher in individuals with a 45,X karyotype compared to those with mosaicism or other X structural abnormalities (Bondy et al., 2013; Cameron-Pimblett et al., 2017; Klásková et al., 2015). However, a consistent association between karyotype and BAV remains to be established. In a 2018 study from the Netherlands, the frequencies of congenital cardiac abnormalities were not significantly different between various

karyotypes (Noordman et al., 2018). Thus, the guidelines for imaging should apply to all individuals with Turner syndrome regardless of karyotype.

Because of the high prevalence of congenital heart and vascular defects in Turner syndrome, noninvasive cardiac imaging is critical for diagnosis, management and risk assessment. The most common modalities include transthoracic echocardiography (TTE), computed tomography (CT), or magnetic resonance imaging (MRI). Magnetic resonance imaging and CT are more accurate than TTE in adults with Turner syndrome for the diagnosis of BAV and can detect malformations that are missed by TTE (Mortensen, Gopalan, Nørgaard, Andersen, & Gravholt, 2016). Magnetic resonance imaging and CT (Figure 1) are also more accurate for aortic size measurements and therefore more sensitive than TTE to detect changes in aortic size, particularly distal to the aortic root and in adults with Turner syndrome, who often have limited echocardiographic windows (Obara-Moszynska et al., 2018). Therefore, all individuals with Turner syndrome should undergo at least one complete set of head, neck, chest, abdomen, and pelvis images, at diagnosis or as soon as is feasible without the need for anesthesia.

Aortic coarctation is common in Turner syndrome and is frequently found in individuals who also have BAV and arch anomalies. Coarctation is associated with an increased likelihood of aortic dilation and dissection (Bambul Heck, Pabst von Ohain, Kaemmerer, Ewert, & Hager, 2017; Cools, Brown, & Gewillig, 2018; Eckhauser et al., 2015). Hypertension, a common consequence of aortic coarctation that may manifest in childhood, and altered compliance or distensibility of the aorta, which is prevalent in patients with coarctation, may both contribute to aortic disease (Hjerrild et al., 2010; Pees et al., 2018; Schoepp et al., 2018; Wen et al., 2018). Re-interventions due to re-coarctation are often necessary in adulthood. These procedures are most frequently safe and uneventful, but should be done with caution and in highly specialized centers to minimize the risk of complications (Cools et al., 2018; Roos-Hesselink et al., 2003). Clinicians should be aware that coarctation in Turner syndrome is a lifelong disease that requires routine cardiovascular evaluation and guidelines-based periodic surveillance with CT or MRI every 5 years in addition to TTE.

7.2 | Aortic dissection

In Turner syndrome, aortic dissection occurs in approximately 40 per 100,000 person-years compared to 6 per 100,000 person-years in the general population (Bondy, 2008). Most dissections originate in the ascending aorta (Type A), where they are more likely to cause death due to pericardial tamponade. Dissections in women with Turner syndrome occur at smaller absolute aortic diameters than in other genetically triggered aortopathies, but at similar ages (median age 29–35, range 4–64 years, Matura, Ho, Rosing, & Bondy, 2007). Adjustment of aortic diameters for body size using the aortic size index (ASI, maximum aortic diameter divided by body surface area) or Z-scores may more accurately predict dissection risk in most patients and is recommended as part of routine clinical practice (Corbitt et al., 2018; Prakash et al., 2017). However, these methods may be less accurate

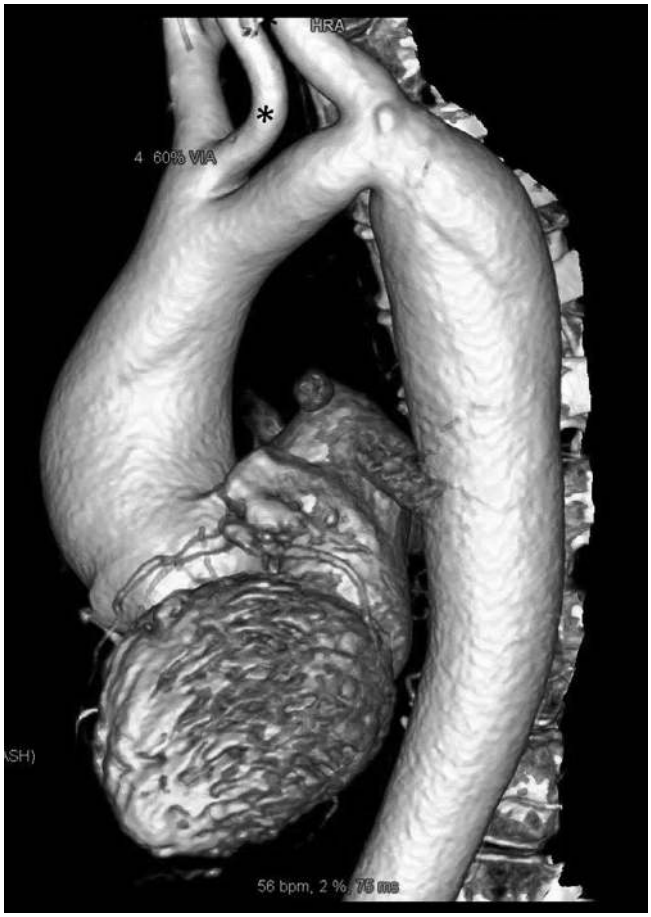

FIGURE 1 CT-scan of a 48-year-old woman with Turner syndrome (45,X) which shows (proximally to distally) a bicuspid aortic valve, aortic dilatation (4.1 cm), a minor aortic arch anomaly with origin of the left carotid artery from the innominate artery (*), an elongated and hypoplastic aortic arch, and a repaired coarctation of the aorta

when body surface area is less than 1.0 or greater than 2.5. Most individuals who develop aortic dissections have more than one of the following cardiovascular abnormalities: BAV, elongation of the transverse aorta, coarctation, hypertension, and/or an aortic aneurysm (Z > 3) (Carlson, Airhart, Lopez, & Silberbach, 2012; De Groote et al., 2015; Sybert, 1998; Turtle, Sule, Webb, & Bath, 2015).

The current clinical practice guidelines specify intervals for periodic surveillance of the aorta and indications to refer patients for prophylactic surgical repair, stratified by adjusted aortic dimensions and other clinical risk factors (Figure 2) (Silberbach et al., 2018). In limited observations, pregnancy appears to confer an additional risk for dissection (Bondy, 2014). Therefore, women contemplating pregnancy or assisted reproductive technologies should first undergo a complete cardiovascular evaluation and receive counseling about the increased cardiovascular risks of pregnancy (see Section 19).

7.3 | Hypertension

While thoracic aortic disease is fortunately rare and preventable, other cardiovascular conditions such as systemic hypertension,

ischemic heart disease, and cerebrovascular disease account for most of the threefold increased mortality and reduced lifespan of adult women with Turner syndrome. The prevalence of hypertension is as high as 60% in adults and may be independent of established risk factors such as aortic coarctation or renal disease (Brun et al., 2019; Nathwani, Unwin, Brook, & Hindmarsh, 2000). Diastolic hypertension may precede systolic hypertension in young adults with Turner syndrome independent of estrogen treatment, BMI, or dyslipidemia. Therefore, providers should maintain a high index of suspicion for the diagnosis and treatment of hypertension, even in young patients with isolated diastolic hypertension (Gravholt et al., 2006). Ambulatory blood pressure monitoring is superior to office or home blood pressure measurements to detect hypertension and is the most sensitive method for predicting hypertension-induced left ventricular hypertrophy. This monitoring approach should be considered for early detection of hypertension in patients who have other risk factors for heart disease or stroke. As technology advances, more readily available blood pressure monitoring may also aid in earlier diagnosis and management of hypertension in this population.

There is no evidence supporting specific antihypertensive medications in Turner syndrome. Angiotensin-converting-enzyme (ACE) inhibitors, diuretics, or angiotensin II receptor antagonists can be used as first line therapies, because they are generally well-tolerated and efficient. Calcium channel blockers can cause additional edema, which may reduce compliance. In women with Turner syndrome who have aortic aneurysms or dissections, beta-blockers or losartan may be used as first-line agents or added to other antihypertensive therapies, as recommended in current guidelines for patients with heritable thoracic aortic disease (Hiratzka et al., 2010). Lifestyle changes, exercise, weight loss, and reduced sodium intake are also important factors in treatment of hypertension and should always be included in the antihypertensive treatment strategy.

7.4 | Coronary artery disease

Coronary artery disease (CAD) causes significant morbidity and mortality in adult women with Turner syndrome (Fuchs et al., 2019). Hypertension, smoking, obesity, dyslipidemia, and T2D are major risk factors for stroke or myocardial infarction throughout life in Turner syndrome, as in the general population. Low estrogen levels due to inefficient estrogen substitution through adolescence and adult life may also contribute to cardiovascular risk in some women with Turner syndrome. Coronary artery disease appears earlier in women with Turner syndrome than in controls and the risk of coronary events and cardiovascular mortality is significantly increased (Schoepp et al., 2018). Whether the increased rate of cardiovascular events in Turner syndrome is entirely attributable to the burden of risk factors, or may also be related to Turner syndrome-specific causes, is unknown. Randomized studies of treatment targets or therapeutic strategies to reduce CAD are not specific to Turner syndrome. Therefore, guideline-directed lipid and glucose surveillance, nutritional and physical activity recommendations and medical and/or interventional therapies are recommended in Turner syndrome. In patients with impaired insulin sensitivity, the potential benefits of early statin therapy to prevent or delay cardiovascular events should be weighed against the risk of inducing T2D over time (Cederberg et al., 2015). Most importantly, clinicians should maintain a high index of suspicion for symptoms related to premature CAD. There is no data that justifies routine screening of CAD in women with Turner syndrome at this time, but it is important to be alert to symptoms and to realize that CAD can be found even in young adults with Turner syndrome.

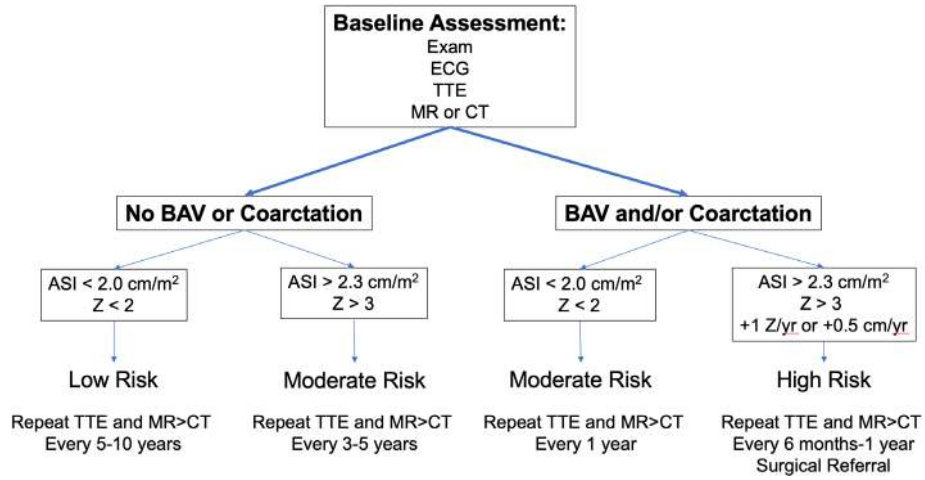

FIGURE 2 Schematic illustrating recommendations for assessment and surveillance of aortic disease in Turner syndrome. The presence of additional risk factors such as hypertension, a 45,X karyotype, rapid aortic dilatation (more than 1 Z-score/year or 0.5 cm/year), or aortic arch elongation, may prompt increases in surveillance frequency (adapted from Figure 1, Silberbach et al., 2018). ASI, aortic size index (maximum aortic diameter divided by body surface area); BAV, bicuspid aortic valve; CT, computed tomography angiogram; ECG, electrocardiogram; MR, magnetic resonance angiogram; Z, Z-score; MR > CT, MR preferred over CT when serial images are anticipated; TTE, transthoracic echocardiogram [Color figure can be viewed at wileyonlinelibrary.com]

7.5 | Electrocardiogram findings

Deaths without any obvious cardiac cause also occur with increased frequency in Turner syndrome, and cardiac arrhythmias related to a prolonged QT interval have been implicated in some cases (Nielsen, Nielsen, Trolle, Gravholt, & Andersen, 2017). The corrected QT interval is prolonged in 33% of children and 20% of adults with Turner syndrome, who may harbor an increased burden of rare gene variants associated with Long QT syndrome (Bondy & Bakalov, 2006; Trolle et al., 2013). The clinical relevance of these abnormalities is unresolved, and no data justifies a specific treatment strategy. If patients will be prescribed drugs that may prolong the QT interval, clinicians should assess the QT interval before drug initiation and continue electrocardiographic surveillance of patients with pre-existing QT prolongation.

In summary, the first encounter with an adolescent or an adult woman with Turner syndrome provides a critical opportunity for cardiovascular health assessment and risk stratification. This includes a thorough evaluation of cardiac structure and function with an ECG and TTE, supplemented by CT or MRI scans to detect aortic aneurysms, coarctation, and coronary or pulmonary vein abnormalities. Lifelong vigilance for CAD is also critical, because hypertension, hyperlipidemia, and diabetes are all markedly increased in Turner syndrome and are major causes of morbidity and premature mortality. A long-term plan for treatment, surveillance and follow up of cardiovascular disease should be tailored to the individual patient based on these initial findings. In order to provide pre-conceptual counseling, the Turner syndrome cardiac specialist should be aware of the woman's reproductive plans.

8 | NEUROCOGNITIVE AND BEHAVIORAL ISSUES, MENTAL HEALTH

8.1 | Overview

Women with Turner syndrome often demonstrate overall intellectual functioning within age-based expectations, with only 5–10% in the range of intellectual disability (Bender, Linden, & Robinson, 1994; Bispo et al., 2013), often associated with mosaicism for a ring X chromosome (Kubota et al., 2002; Swillen et al., 1993). However, overall measures of intellectual functioning may not accurately predict global functioning given the variability in the neuropsychological profiles of women with Turner syndrome (reviewed in Knickmeyer & Hooper, 2019). This profile appears to be largely stable over the course of the lifespan and impacts daily functioning, likely contributing to increased risk of mental health concerns, reduced QoL, and health outcomes. Thus, formal neuropsychological evaluation and mental health care are critical components of psychosocial care for women with Turner syndrome.

8.2 | Neuropsychological functioning and evaluation

The neuropsychological profile that is often observed in women with Turner syndrome is characterized by age-appropriate verbal abilities with core deficits in visuospatial skills, quantitative/math reasoning skills, social communication, executive functions, and fine motor skills and coordination (reviewed in Knickmeyer & Hooper, 2019; El-Mansoury, Barrenas, Bryman, Hanson, & Landin-Wilhelmsen, 2009). Historically, this constellation of strengths and weaknesses has been referred to as a nonverbal learning disability (NLD). NLD was initially defined as a developmental neuropsychological syndrome that is not specific to Turner syndrome and has been associated with other neurological or genetic syndromes (Rourke et al., 2002). As noted in the Guidelines, the term "NLD" is still considered to be in the scientifically "formative" stage and is not included in either the *Diagnostic and Statistical Manual of Mental Disorders*—Fifth Edition (DSM-5), nor the *International Classification of Disease and Related Disorders* (ICD-10) (American Psychiatric Association, 2013; Gravholt, Andersen, et al., 2017b, section 7.8). Within the academic literature, its definition and existence has been widely debated (Fine, Semrud-Clikeman, Bledsoe, & Musielak, 2013; Spreen, 2011). Our own view is that NLD is a useful construct to informally capture the typical neuropsychological profile of women with Turner syndrome, especially as NLD is a term often used by women with Turner syndrome and their families. However, when treatment is indicated, the complexity and heterogeneity of the neuropsychological profiles of many women with Turner syndrome is better characterized by specific and well-established psychiatric disorders (Hutaff-Lee, Bennett, Howell, & Tartaglia, 2019; Knickmeyer & Hooper, 2019) discussed in greater detail below, and summarized in Table 5.

From a neurological perspective, the discrepancy between verbal and spatial skills (verbal greater than spatial) that frequently characterizes the neuropsychological profile of women with Turner syndrome was initially interpreted as indicative of right hemisphere dysfunction. Early structural neuroimaging studies demonstrated a decrease in parietal-occipital gray matter, possibly more in the right than left hemisphere (Brown et al., 2002; Brown et al., 2004; Cutter et al., 2006; Marzelli, Hoeft, Hong, & Reiss, 2011). However, structural neuroimaging studies have also consistently demonstrated more diffuse and bilateral neuroanatomical differences (Bray, Dunkin, Hong, & Reiss, 2011; Knickmeyer, 2012; Knickmeyer & Hooper, 2019). Functional imaging studies have revealed atypical activation patterns in the parieto-occipital, frontoparietal, and sensorimotor regions (Hart, Davenport, Hooper, & Belger, 2006; Holzapfel, Barnea-Goraly, Eckert, Kesler, & Reiss, 2006; Kesler et al., 2004; Knickmeyer & Hooper, 2019; Villalon-Reina et al., 2013; Xie et al., 2015; Yamagata et al., 2012). These structural and functional differences may reflect the differential impact of multiple factors on brain development, including genetic vulnerabilities and gonadal steroid insufficiency due to loss of ovarian function, as well as the long-term systemic influence of chronic medical conditions and HRT (Knickmeyer & Davenport, 2011; Knickmeyer & Hooper, 2019). From a clinical perspective, MRI of the brain is not part of the standard surveillance for women with Turner syndrome in the absence of focal changes, seizures, or memory changes.

As might be expected in a condition affecting typical development, there are learning and behavioral difficulties that are typically identified in early childhood that can persist (Ross et al., 2002; Rovet, 2004). In structured conversations, these difficulties may not be immediately

TABLE 5 Core neuropsychological domains with associated diagnoses and treatment

Domain	Defining features	DSM5 diagnostic considerations	Treatment considerations
Cognitive	Age-appropriate verbal skills with comparably weaker spatial and visual-motor skills	Neurodevelopmental disorder associated with medical condition	• Special education services and accommodations • Assistance with functional living/vocational skills, • Psychotherapy • Medication
	Global developmental delay	Intellectual disability	
	Poor attentional regulation Organization and planning challenges Slower processing speed	Attention deficit hyperactivity disorder (ADHD)	
	Fine and gross motor difficulties (e.g., poor drawing and coordination)	Developmental coordination disorder	• Occupational therapy • Physical therapy
Academic	Math/financial management difficulties, especially with quantitative skills	Specific learning disability with impairment in mathematics (dyscalculia)	• Special education services and accommodations • Assistance with functional living/vocational skills
	Writing difficulties	Specific learning disability with impairment in writing	
	Reading comprehension difficulties	Specific learning disability with impairment in Reading	
Social communication	Reduced awareness and integration of nonverbal communication cues	Social (pragmatic) communication disorder, Autism Spectrum disorder	• Social skills groups • Individual psychotherapy • Speech and language therapy
	Difficulties interpreting ambiguous or nonliteral language		
	Difficulties initiating or maintaining peer relationships		
Emotional functioning	Anxiety, especially social anxiety	Anxiety disorder, unspecified, Social anxiety disorder	• Psychotherapy • Medication
	Depression	Depression, unspecified	

apparent, as women with Turner syndrome often have relative strengths in vocabulary and factual knowledge, as well as receptive language skills and auditory comprehension. Women may show a strong interest in performing arts, music, and language arts. Difficulties with visuospatial skills are more likely to manifest as trouble with driving and spatial navigation, as well as with mathematics (Hong, Dunkin, & Reiss, 2011). Many women with Turner syndrome have a history of math disability, which may require specialized instruction throughout their formal education, including academic accommodations through college (Hong et al., 2011; Murphy, Mazzocco, Gerner, & Henry, 2006). Ongoing assistance with financial management is often indicated, especially for those who have lower intellectual functioning. Importantly, not all women with Turner syndrome are challenged by all forms of math. In our experience, computational mathematics and biostatistics can be areas of academic and career success.

There may also be associated weaknesses in attentional regulation and aspects of executive function. Beginning in adolescence, women with Turner syndrome are more likely to be diagnosed with attention deficit hyperactivity disorder (ADHD) with approximately 25% meeting diagnostic criteria (McCauley, Feuillan, Kushner, & Ross, 2001; Russell et al., 2006). In our clinical experience with adult women, this is most likely to be the inattentive subtype of ADHD, although higher rates of hyperactivity have been reported in children and adolescents with Turner syndrome (Green et al., 2015). There are usually difficulties initiating tasks that are perceived to be challenging and disengagement on tasks that are uninteresting or overstimulating. Processing speed is also often reduced. As task complexity increases, there are also often difficulties with organization. In our clinical experience, there may be a tendency to focus on details rather than "the big picture", which can manifest as difficulties with prioritization and time management. This barrier to learning sometimes becomes more apparent in more advanced academic settings (e.g., college or graduate school) where women with Turner syndrome may have difficulties with reading comprehension (e.g., identifying the main idea, synthesizing complex and separate ideas as a whole), writing (e.g., identifying the most important elements to convey to others, choosing topics that are appropriate in scope or meet the conceptual demands of the assignment), and studying (e.g., identifying the most important elements to learn).

Despite these neurocognitive risk factors, women with Turner syndrome often achieve educational goals at a similar or increased level compared to the general population (Gravholt, Andersen, et al., 2017b, section 7.8; Næss et al., 2010). Research suggests that women with Turner syndrome may have lower occupational status than expected based on academic achievement and report less positive working experiences (Downey et al., 1991; Fjermestad, Næss, Bahr, & Gravholt, 2016). Clinically, we have observed that women with Turner syndrome are most successful in vocational environments that provide routine expectations, clear organizational hierarchies, supportive social interactions, and other accommodations (e.g., typing instead of handwriting). Career choices are broad. Women with Turner syndrome have doctorates in computational math and biostatistics, and advanced degrees in psychology. There are several physicians with Turner syndrome who serve as advocacy resources in the support group community as both patients and providers.

For these reasons, neuropsychological evaluations are recommended at key lifespan transitions to assess overall cognitive functioning and individual strengths and weaknesses to assist with treatment planning. In early adulthood, these evaluations are also helpful in establishing a baseline level of functioning from which to make future comparisons and identifying appropriate educational and psychosocial supports, including helping the family to understand the nature of any challenges. Involvement of allied health professionals (e.g., social work, occupational therapy, vocational rehabilitation) may be needed once the neuropsychological profile has been characterized to guide appropriate adjustments in the academic and occupational environments. Table 5 does not include specific diagnostic tools for each possible diagnosis, because the comprehensive neuropsychological evaluation could utilize different tools based on age and other factors. An exhaustive list of many available measures is beyond the scope of this review. Several measures are used in one evaluation to provide a profile of strengths and weaknesses. Repeat neuropsychological evaluations are recommended if there are behavioral changes, especially if these may be related to medical factors, changes in therapy, such as HRT, or, if there are concerns at any age about progressive cognitive decline (i.e., to determine whether there is evidence for a neurodegenerative condition).

8.3 | Social and emotional functioning and evaluation

Social communication challenges are often observed in women who have Turner syndrome, sometimes to a degree that warrants diagnosis of Social (Pragmatic) Communication Disorder. There may be reduced attention to nonverbal communication cues (e.g., eye contact, facial expression) but also difficulties interpreting ambiguous or non-literal language, especially in a fast-paced or novel environment (Lesniak-Karpiak, Mazzocco, & Ross, 2003). Women with Turner syndrome are often most comfortable interacting with familiar individuals in structured situations where social roles are clear or explicit. To care for the adolescent and adult with Turner syndrome, it should be appreciated that beginning in childhood, there may be difficulties initiating or sustaining peer relationships which can lead to social isolation in adulthood, when opportunities to interact with non-family members are often more limited and less structured. In our clinical experience, women with Turner syndrome are often motivated to relate to others, have some sensitivity to others' emotional experiences, and exhibit a capacity for reciprocal interactions, such that an autism spectrum disorder (ASD) diagnosis would be inappropriate. However, if there are more significant social communication concerns, as well as associated neurobehavioral symptoms of rigidity and restricted interests, then a formal ASD diagnosis should be considered and may be more likely in women who have comorbid Intellectual Disability.

The prevalence of psychiatric diagnoses was reported as 2–10% (Sybert & McCauley, 2004 citing data from 1990 and 2001). Using structured diagnostic interviews, the prevalence of DSM-IV diagnoses, in general, was not increased in women enrolled in a NIH study,

although mood disorders were more common (Cardoso et al., 2004). As acknowledged by the authors, these findings may be biased because the women were self-referred, more motivated, and less shy. The combination of learning and social communication challenges often leads to a prolonged transition and/or more limited functioning in adulthood, as well as emotional difficulties. Approximately half (52%) of women with Turner syndrome develop clinically significant anxiety or depression at some point in their lifetime (Cardoso et al., 2004; Schmidt et al., 2006), with later diagnosis of Turner syndrome (adolescence) possibly conferring a higher risk of depression (Reimann, Bernard Perman, Ho, Parks, & Comis, 2018). In our clinical experience, rates of anxiety and depression increase at the transition from adolescence to adulthood. Women with Turner syndrome may experience acute distress about finding and maintaining success in a vocational pursuit, as well as establishing intimate relationships. These concerns are often superimposed upon the responsibility of managing their chronic medical conditions. Adult women with Turner syndrome often have some awareness of their challenges, resulting in lower body image, self-esteem, and perceptions of social competence (Boman, Bryman, Halling, & Möller, 2001; Lagrou et al., 2006), which can contribute to the emergence of social anxiety, generalized anxiety, and depression. There may also be psychiatric disorders that are not necessarily secondary to psychosocial stressors. In our clinical experience, we have seen patients who have mood disorders (major depression and bipolar disorder), anxiety disorders (including panic disorder), and obsessive–compulsive disorder. Several have experienced traumatic events in childhood that have resulted in chronic post-traumatic stress disorder; others have had difficulties with attachment relationships leading to the development of character disorders, including Borderline Personality Disorder.

In the MGH Turner syndrome clinic, we have cared for women older than 30 years who developed hallucinations while hospitalized for a medical condition, each with previous untreated mental health issues (including depression and social isolation). They developed "psychosis" due to a surgical or medical condition and have improved without anti-psychotic medications. None of these women manifested signs or symptoms consistent with a primary psychotic disorder. We have not previously diagnosed schizophrenia in women with Turner syndrome. (Jung et al., 2014; Prior, Chue, & Tibbo, 2000).Future research could focus on these disorders, and on patients who manifest memory loss but who do not carry a diagnosis of dementia.

8.4 | Role of diagnostic evaluations and supportive therapies

Adult women with Turner syndrome often present with strong verbal abilities that support acquisition of academic and vocational skills important for functional independence. However, they also have a unique learning style that contributes to specific areas of difficulty and may become more pronounced as the demands on novel problem-solving, planning, and organization increase in adulthood. There may be a need for ongoing supports in aspects of daily living (e.g., managing finances, transportation, and navigation) and in an occupational setting. Social communication challenges, while often present in childhood and adolescence, may also become more pronounced in adulthood and result in social isolation. Adult women with Turner syndrome may experience some degree of anxiety and depression. Neuropsychological evaluations and mental health care are critical components of integrated care for women with Turner syndrome, especially as these factors may influence the ability to consistently engage in medical care. Additional longitudinal research is also needed to better understand how psychosocial functioning may fluctuate over the course of the lifespan so that practitioners can optimize QoL at all developmental stages.

For these reasons, mental health care should be a core consideration for adult women with Turner syndrome. In the Guidelines (Gravholt, Andersen, et al., 2017b, section 7.1), annual screening of emotional (e.g., symptoms of anxiety and depression) and behavioral functioning is recommended with referral to psychiatry for further evaluation if positive. Mental health interventions should be symptom driven. Potential interventions include psychopharmacology (antidepressants, anxiolytics, and mood stabilizers), cognitive behavioral therapy for anxiety and obsessive–compulsive symptoms, dialectic behavior therapy for personality issues, and family work for those for whose family members remain the primary social network and source of financial support. Participation in support groups including other women with Turner syndrome may also be helpful (Table 3).

9 | OTORHINOLARYNGOLOGIC ASPECTS

9.1 | Overview

Turner syndrome is associated with several features and complications involving the ear and, less often, nose and throat, which will be referred to as otorhinolaryngological aspects. A recent review describes treatment options and theories regarding the pathophysiology of hearing loss (Bonnard, Bark, & Hederstierna, 2019), whereas this section will focus on management.

External malformations of the ears and craniofacial morphologic differences are frequent findings (see also Section 11). Eustachian tube dysfunction is viewed as a precursor to middle ear disease, a predisposition factor to both conductive hearing loss and sensorineural hearing loss (SNHL) (Bois et al., 2018; Yehudai, Most, & Luntz, 2015). Karyotype is an important predictive factor, as complete lack of the X chromosome or absence of the short arm of the X chromosome increases the risk of development and severity of hearing loss (Bonnard et al., 2019; Cameron-Pimblett et al., 2017; Hultcrantz, 2003; King et al., 2007; Verver et al., 2011). Immune insufficiency of the T-cell line has been suggested to increase the risk of chronic otitis media. Hormone treatment has been hypothesized to influence cranial development and consequently middle ear function. Growth hormone, estradiol, and oxandrolone have not been shown to have a significant influence on hearing ability and middle ear function (Davenport et al., 2010; Hultcrantz, 2003; Ostberg, Beckman, Cadge, & Conway, 2004; Verver et al., 2014).

9.2 | Hearing loss

Among many older women with Turner syndrome, hearing loss is the chief complaint. Only approximately one-third of Turner syndrome patients have normal hearing (Bonnard, Hederstierna, Bark, & Hultcrantz, 2017; Verver et al., 2011). The hearing loss progresses with age and is present in nearly all women over 50 years of age (Beckman et al., 2004; King et al., 2007; Ros et al., 2014). The underlying reasons for hearing loss are multifactorial. Conductive hearing loss is commonly caused by recurrent otitis media, middle ear effusions, or pathology of the tympanic membrane, with prevalence varying between 0–44% based on age (Verver et al., 2014), although found to be less prevalent in adults (King et al., 2007; Sampaio et al., 2014). Middle ear disease has been noted with a similarly wide range (9–88%) reflecting age differences (Dhooge, De Vel, Verhoye, Lemmerling, & Vinck, 2005; King et al., 2007). A notable complication in Turner syndrome is the high prevalence of cholesteatoma (~4%), and is thought to be more common in patients with 45,X or 46,X isochromosome Xq and middle ear disease (Lim et al., 2014; Verver et al., 2011).

Approximately half of individuals with Turner syndrome, and at least 75% of the oldest women, develop syndromic SNHL (Bergamaschi et al., 2008; Hederstierna, Hultcrantz, & Rosenhall, 2009a; Hederstierna, Hultcrantz, & Rosenhall, 2009b). The degenerative process seems to start early in life with a midfrequency sensorineural dip in hearing on the audiogram observed in girls as early as the age of 6 years, although not always clinically apparent (Barrenäs, Nylén, & Hanson, 1999; Gawron, Wikiera, Rostkowska-Nadolska, Orendorz-Fraczkowska, & Noczyńska, 2008; Hederstierna et al., 2009a; Hultcrantz, 2003; Neslihan, Böke, Belgin, & Tuncbilek, 2000). Currently, no unequivocal risk factors for development of SNHL in Turner syndrome have been identified, although studies have reported a significant association between karyotype and SNHL (Barrenäs et al., 1999; Gawron et al., 2008; Oliveira, Ribeiro, Lago, & Alves, 2013; Verver et al., 2011). There is no specific correlation between audiogram and karyotype, and it is likely that the pathophysiology of SNHL in Turner syndrome is more complex than the specific X chromosome loss.

The study of vestibular function in Turner syndrome is limited to a single case report describing significant bilateral vestibular dysfunction (Baxter & Agrawal, 2014). Similarly, the study of structural alterations of the inner ear is limited to case reports (Bodet Agusti et al., 2012; Makishima et al., 2009; Windle-Taylor, Buchanan, & Michaels, 1982). A study of 27 individuals with Turner syndrome found no anomalies of the inner ear (Dhooge et al., 2005). Thus, inner ear imaging is not indicated unless cholesteatoma is suspected.

Recent genetic studies in the general population have found hearing ability strongly associated with DNA methylation levels of several genes (Wolber et al., 2014), although comparable studies investigating SNHL in Turner syndrome are not available. It is likely that genes or genomic mechanisms are involved in this differential DNA methylation and consequently influence ear function and hearing. Further discussion is found in Bonnard et al. (2019).

9.3 | Surveillance and treatment of hearing loss

The importance of identifying hearing loss at an early age cannot be underestimated because of the impact on social function and choice of education and occupation (Gravholt, Andersen, et al., 2017b, section 6.1). A baseline audiology exam at the time of diagnosis is essential, and although otitis media is less frequent with age, periodic audiology examinations throughout the lifespan (every 3–5 years) are recommended to detect SNHL (Gravholt, Andersen, et al., 2017b, table 8). The use of hearing aids is endorsed by the Guidelines (Gravholt, Andersen, et al., 2017b, section 6.1). In particular, a history of cholesteatoma in childhood should prompt more intense follow-up due to high recurrence rate and surgery may be needed.

There has been no systematic review of the use of hearing aids among women with Turner syndrome. In the general population, it is documented that there is an almost 9 year delay from hearing loss to adoption of hearing aids, and that they have a significant positive influence on quality of life QoL (Simpson, Matthews, Cassarly, & Dubno, 2018). It is widely observed by Turner syndrome physicians that some patients avoid hearing aids because of a personal wish to avoid revealing their syndrome. Many will adapt through lip reading, requesting repetition in conversation, or sitting in the front row in a classroom. The substantial cost of hearing aids and the tendency to lose or break fragile parts has a significant negative impact on use in some countries without a health care system based on equal access for all users. For example, the hearing aid adoption rate for patients with a need is 33% in the US compared with 53% in Denmark (European Hearing Instrument Manufacturers Association, 2016; Grundfast & Liu, 2016).

10 | AUTOIMMUNE DISORDERS

10.1 | Overview

Turner syndrome is associated with an increased risk of autoimmune disease, which increases with age (Jorgensen et al., 2010). Since these disorders may have no or minimal symptoms, adult women with Turner syndrome benefit from routine health maintenance visits to monitor autoimmune diseases. Thus, providers must be vigilant and offer routine laboratory screening, as well as monitor for the development of clinical findings associated with autoimmune disorders throughout the lifespan. In contrast with a young girl with Turner syndrome who meets routinely with her pediatrician and endocrinologist, adolescents and adults with Turner syndrome are more likely to receive intermittent care. The schedule and types of testing for all of these disorders is summarized in the Guidelines (Gravholt, Andersen, et al., 2017b, table 6).

Adult women with Turner syndrome have a twofold increased risk of developing any autoimmune disease compared with the general population (Jorgensen et al., 2010). By adulthood, over 50% will have positive autoantibodies with approximately 6% having more than one autoimmune disorder (Bakalov et al., 2012). Autoantibodies have been noted in 58% of girls and women with Turner syndrome

ages 6–60 years (Mortensen et al., 2009). Of these, 18% had more than one antibody; antithyroid peroxidase (TPO) and antibodies for celiac disease were the most common combination of antibodies detected.

10.2 | Mechanisms of disease risk

The mechanism behind the increased risk of autoimmune disease is unknown, although several possibilities have been studied. Increased pro-inflammatory and decreased anti-inflammatory cytokine levels, such as IL6/TGFβ1 and IL10/TGFβ2, respectively, have been detected which is consistent with the higher risk of inflammatory disorders found in this population (Bakalov et al., 2012). X chromosome monosomy and therefore haploinsufficiency for the genes in the pseudoautosomal region has been postulated as a possible explanation for this increased risk. Skewing of X chromosome inactivation has also been associated with an increased risk of autoimmunity (Bakalov et al., 2012). The presence of an isochromosome Xq has been linked specifically to inflammatory bowel disease (IBD) (Jorgensen et al., 2010) and the presence of anti-glutamic acid decarboxylase antibodies (Mortensen et al., 2009), and thus IBD and T1D should be considered when evaluating individuals with this karyotype; however, clinical management of these conditions should remain consistent regardless of karyotype. There may also be an association between ovarian failure itself and chronic lymphocytic thyroiditis (Bakalov et al., 2012; El-Mansoury et al., 2005).

Several genes associated with T cell regulation are located on the X chromosome. *FOXP3* is a transcription factor important in the development of regulatory CD4 T cells, and loss of this gene has been linked to the development of autoimmunity (Su et al., 2009). No differences in the percentage of regulatory T cells have been found between girls with Turner syndrome and controls, although girls with Turner syndrome who already had autoimmune disease had a significantly lower regulatory T cell percentage (Gawlik et al., 2018). *PTPN22*, *ZFAT* and *MYO9B* polymorphisms have been studied in pediatric and adult individuals with Turner syndrome in diverse populations (Bianco et al., 2010; Villanueva-Ortega et al., 2017). Although these areas of study help to enhance our knowledge and understanding of the possible mechanisms behind the increased risk of autoimmune disease in Turner syndrome, there is currently no clinical utility in testing for these cytokine, T cell, or genetic abnormalities.

10.3 | Thyroid disease

Autoimmune thyroid disease is the most common autoimmune disorder associated with Turner syndrome. By age 14–15 years, 36% of girls with Turner syndrome have positive anti-thyroid antibodies and 31% have subclinical hypothyroidism (Gawlik, Gawlik, Januszek-Trzciakowska, Patel, & Malecka- Tendera, E., 2011). The prevalence of anti-thyroid antibodies increases with age (El-Mansoury et al., 2005; Freriks et al., 2011; Mortensen et al., 2009), and one study estimates that the relative risk of hypothyroidism in Turner syndrome is six to sevenfold increased compared with the general population (Bakalov et al., 2012; Trolle, Mortensen, et al., 2012a). In adulthood, the annual incidence is approximately 3% (Mortensen et al., 2009), thus increasing the prevalence of hypothyroidism to about half of all women with Turner syndrome by the age of 50 years (El-Mansoury et al., 2005; Mortensen et al., 2009; Trolle, Mortensen, et al., 2012a). Graves' disease is also increased with an incidence of approximately 3% in adults with Turner syndrome, and it tends to present at a later age (Bakalov et al., 2012; Lucaccioni et al., 2015).

Overt signs of hypothyroidism are not always observed; thus, clinical symptomatology alone is unreliable to screen for thyroid dysfunction (Gawlik et al., 2011). Therefore, screening for thyroid dysfunction with thyroid stimulating hormone (TSH) and free T4 begins at the time of Turner syndrome diagnosis, and yearly thereafter throughout the lifespan. Antibodies to the thyroid should be measured once thyroid function tests are found to be abnormal. Treatment of hypothyroidism in Turner syndrome is similar to that in other populations and should thus follow clinical guidelines. Treatment is usually initiated as soon as TSH rises and TPO antibodies are positive, even before any symptoms may have become apparent. If TPO antibodies are negative in the face of rising TSH, a short observation period may be in order. Treatment is usually lifelong once initiated and should be monitored regularly (Gravholt, Andersen, et al., 2017b, section 6.1). Unlike hypothyroidism, hyperthyroidism due to Graves' disease presents with more classic clinical features of the disease; its course and treatment should mirror that recommended and seen in the general population.

10.4 | Gastrointestinal disease

Celiac disease is the second most common autoimmune disease described in women with Turner syndrome, present in approximately 8% (Gravholt, Andersen, et al., 2017b, table 2). There is a twofold increased risk of celiac disease in girls with Turner syndrome younger than 5 years of age (Marild, Stordal, Hagman, & Ludvigsson, 2016) which increases to a more than fivefold increase after the age of 10 years. The relative risk in adults, when compared to the general population, is increased by as much as 42-fold (Bakalov et al., 2012). Screening for celiac disease with transglutaminase antibodies begins at the time of diagnosis and is repeated every 2 years throughout adolescence, and with symptoms in adulthood. Despite its status as a known comorbidity in Turner syndrome, celiac disease may go undiagnosed unless providers are aware of its varied presentation. In late adolescence and adulthood, signs of celiac disease can include abdominal pain, bloating, flatulence, and steatorrhea, and individuals with these symptoms should be screened accordingly. The risk of IBD can be as frequent as 4% in adult women with Turner syndrome (Bakalov et al., 2012; Gravholt, Andersen, et al., 2017b, section 6.1; Trolle, Mortensen, et al., 2012a), with Crohn's disease seen more commonly than ulcerative colitis. This should be considered in an individual with unexplained weight loss, abdominal pain, and bloody stools as you would with the general population. Further discussion and recommendations for treatment of both disorders is found in Section 15.

10.5 | Type 1 diabetes and other disorders

There is a 10 to 11-fold increased risk of T1D with an observed frequency of 1% in adult women with Turner syndrome (Freriks et al., 2011). Anti-GAD antibodies were present in 4% of asymptomatic women with Turner syndrome (Mortensen et al., 2009). After age 10, it is important to screen at least annually for diabetes with a fasting blood sugar and a HbA1C, and more promptly when symptoms such as polyuria and polydipsia are noted.

Other autoimmune disorders such as juvenile rheumatoid arthritis, psoriasis, vitiligo, alopecia areata, and uveitis are familiar features of Turner syndrome (Bakalov et al., 2012; Gravholt, Andersen, et al., 2017b, section 6.1; Jorgensen et al., 2010). Their exact prevalence is unknown, but, in general, there is a fourfold increased susceptibility to male predominant autoimmune diseases such as T1D, ankylosing spondylitis, and reactive arthritis (Jorgensen et al., 2010; Lleo, Moroni, Caliari, & Invernizzi, 2012). Careful examination of the skin, hair, nails, and joints, as well as routine ophthalmologic evaluation, can help detect these possible disorders (See Sections 12 and 13).

11 | CRANIOFACIAL AND DENTAL

11.1 | Facial features and appearance

There is no single Turner syndrome "facies" because of the various karyotypes and variety in the type and degree of mosaicism (El-Mansoury et al., 2007; Freriks et al., 2007) (Figure 3). A subset of individuals with Turner syndrome have a distinctive craniofacial appearance that was noted in the original description (Turner, 1938) and which is often viewed as "classic Turner syndrome". The short neck with webbing, low posterior hairline, prominent auricles, inner canthal folds, ptosis, and down-slanted palpebral fissures have been attributed to the accumulation and resorption of fetal lymphedema in the head and neck region (Jones, Jones, & Del Campo, 2013). The facial appearance in some adults with Turner syndrome may give the appearance of older age because of estrogen insufficiency, loss of connective tissue elasticity, and greater skin wrinkling. In other women, a more youthful appearance is maintained.

Although individuals with a low (less than 20%) level of 45,X tend to have negligible facial differences from women in the general population, compared with those with typical 45,X who are more likely to have "Turner syndrome features", studies have shown inconsistent correlation between karyotype and phenotype. A recent prospective study from the Netherlands analyzed the karyotype in 118 women (84 girls) with Turner syndrome and compared three major phenotypic patterns. These were defined as lymphatic (at least three: lymphedema, neck webbing, low hairline, or hypoplastic/hyperconvex nails), skeletal (at least three: micrognathia, cubitus valgus, high palate, short fourth metacarpal or metatarsal bone, Madelung deformity, or scoliosis) and severe (6–12 features), which were not mutually exclusive (Noordman et al., 2018). Although the specific phenotype definitions might be debated, this study provides the strongest evidence of an association between 45,X and all three of these phenotypic patterns.

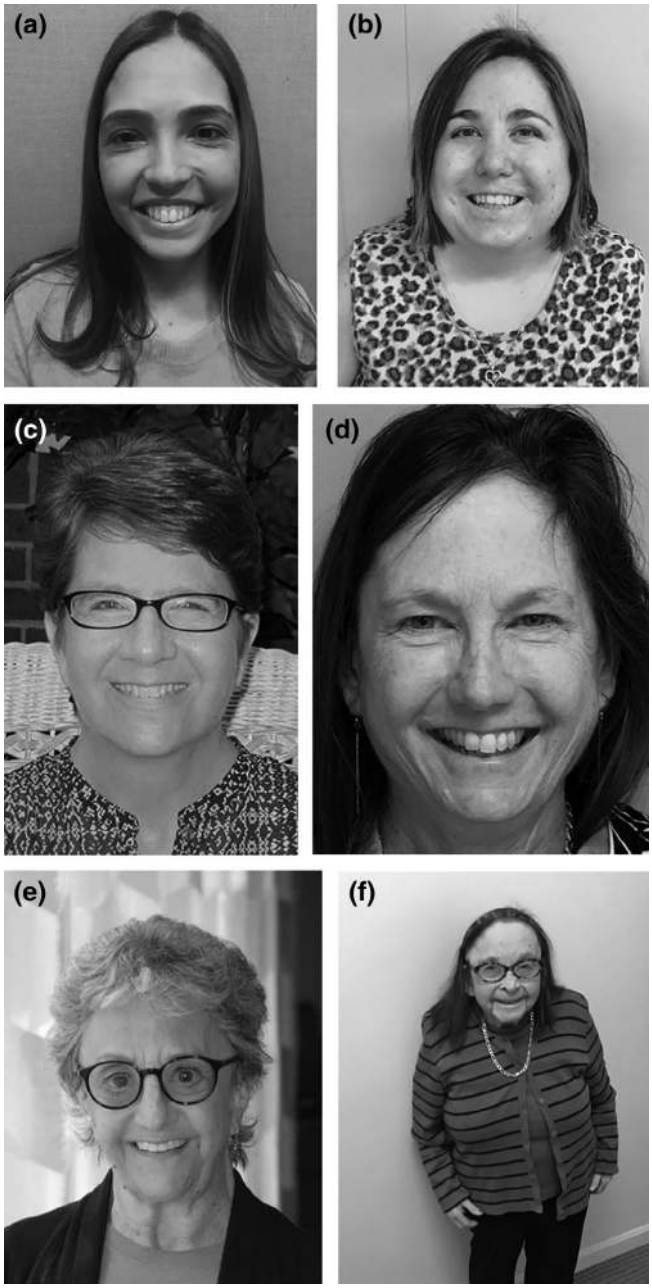

FIGURE 3 (a–f). Women with Turner syndrome, in ascending order of age (34, 40, 48, 54, 63 and 77 years) and their karyotypes: 45,X (individuals B, C, E, F); mosaicism for isochromosome Xq10 (60%) and 45,X(40%) (individual A), and mosaicism for 45,X (95%) and 46,X,idic(X)(p11.21)(5%) (individual D). Patient A is latino, all others are nonhispanic/northern European background

11.2 | Oral maxillofacial and dental structures

In general, there is underdevelopment of various facial structures, including flattened (increased) cranial base angle, bi-maxillary retrusion, high-arched narrow palate, micrognathia, and class II malocclusion (Ahiko, Baba, Tsuji, Horikawa, & Moriyama, 2019; Cazzolla et al., 2018; Svanberg, Norevall, Ekman, Wahlberg, & Bågesund, 2016). At least one study (Juloski et al., 2016) reported that GH treatment improved some of these structures. Dental problems include smaller primary and

permanent teeth, with emergence in the adult of changes in crown and root morphology and root resorption, and even tooth loss (Gravholt, Andersen, et al., 2017b, section 6.1). Malocclusion may include lateral cross-bite and anterior and lateral open-bite. Caries are reported as less frequent, though dental hygiene is poor. The treatment of orthodontic problems in adolescence may require dental extractions for dental crowding, use of a palate expander, and prolonged orthodontics. In adulthood, there is often a loss of correction and re-application of braces may be necessary for some women. Research is needed to evaluate the natural history of dental problems. Poor hygiene may be due to a combination of restricted mouth opening, and/or lack of motivation, often improved by electric tooth brushing. Although the Guidelines recommend "dental/orthodontic evaluation at diagnosis" (Gravholt, Andersen, et al., 2017b, section 6.1), this may be declined if a patient does not perceive need or in the absence of dental insurance coverage in the United States, which is usually independent from health insurance. In many European countries, dental care is part of a uniform health care system that allows free access during childhood and adolescence, enabling both pervasive dental care and orthodontics where necessary.

12 | EYE FEATURES AND VISION

12.1 | Type and frequency of eye abnormalities

Eye abnormalities in Turner syndrome include a diverse group with external ocular anomalies (ptosis, epicanthal folds, and hypertelorism), refractive errors (myopia or hyperopia, amblyopia), strabismus, and anterior segment abnormalities, especially cataracts; posterior ocular segment anomalies involving the optic nerve and retina are rare. Current reviews of adults with Turner syndrome lack specific data on eye problems. The most detailed information comes from Poland (Wikiera, Mulak, Koltowska-Haggstrom, & Noczynska, 2015) (82 patients, 2–30 years, mean 14.2 years) reporting a similar frequency of any impaired vision regardless of karyotype (approximately 40%). Strabismus was slightly less frequent (21%) than previously noted (33–45%) (Denniston & Butler, 2004). There was no specific pattern or a relationship to karyotype. A review of 274 patients (children and adults) with Turner syndrome described a number of different ocular abnormalities in individuals with Turner syndrome. Notably high were rates of amblyopia (almost 30%). Color vision abnormalities were also of relatively high prevalence (8%) (Denniston & Butler, 2004).

In addition to associated eye problems that are thought to be directly due to Turner syndrome, women may have a co-occurring diagnosis, especially X-linked ocular disorders which manifest in women with Turner syndrome because of the single sex chromosome. Most commonly reported is X-linked red-green color blindness, as well as X-linked retinitis pigmentosum (Jones et al., 2018; Zhou et al., 2018), X-linked juvenile retinoschisis (Jones et al., 2018) and X-linked congenital nystagmus. Dual diagnoses with eye problems have included Mendelian syndromes such as blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) and Axenfeld-Reiger syndrome, and a mitochondrial disorder Leber hereditary optic neuropathy (Jones et al., 2018). Growing awareness is essential in order to correctly diagnosis eye problems as more than "just Turner syndrome".

12.2 | Management

At the time of diagnosis, all individuals with Turner syndrome should have a formal ophthalmology examination to identify visual deficits, especially when diagnosis occurs later as an adult (Gravholt, Andersen, et al., 2017b, section 6.1.8). Management is the same as that for the general population with surveillance every 1–2 years to monitor progression of visual changes, the need for corrective eyeglasses, the development of cataracts, and glaucoma. Research is needed to determine whether there is a greater progression over time, impacted by the use or lack of hormones.

13 | INTEGUMENTARY SYSTEM AND LYMPHATICS

13.1 | Skin features

There is no single analysis of the skin of women with Turner syndrome, and thus, the following discussion is based on a review (Lowenstein, Kim, & Glick, 2004), numerous case reports and series, and an exhaustive literature review (Gravholt, Andersen, et al., 2017b, section 6.1), but not specifically focused on older patients. The most common skin features include increased skin ridge count, lymphedema, increased number of melanocytic nevi, nail dystrophy, vitiligo, and alopecia areata (Dogruk Kacar, Ozuguz, & Polat, 2014) (Figure 4). Less frequent, but familiar, are pilomatricomas (Handler et al., 2013), hypertrophic scars or keloids (Kedzia, Pawlaczyk, & Petriczko, 2014), and halo nevi (Brazzelli et al., 2004). Psoriasis has been reported in women with Turner syndrome, but a study of 594 women with Turner syndrome found prevalence was similar to that expected for the general population (Gravholt, Juul, et al., 1998b). Whorling pigmentary changes may be associated with mosaic karyotypes (Capaldi et al., 2005). Miscellaneous problems anecdotally noted, possibly due to hormonal changes, include more frequent dry skin and less frequent acne.

In the MGH Turner syndrome clinic, we have observed a high frequency of long eyelashes, occasionally as a double row (distichiasis). A few patients have noted the inability to create fingerprint passwords that they self-report as due to hypoplastic finger dermatoglyphics. We hypothesize that these clinically minor cutaneous features may represent "micro-anomalies" of lymphatic and tissue development.

Data on the prevalence of skin conditions could be improved by larger studies over the lifespan to provide the natural history, the effect of hormone therapy, and relative rates of these conditions in individuals with 45,X or mosaicism. Two national cohort studies have found an increased risk of melanoma with a standardized incidence ratio 2.2 in England and 3 in Sweden (Schoemaker, Swerdlow, Higgins, Wright, & Jacobs, 2008a and Ji et al., 2016, respectively). It is not clear whether the increased risk of melanoma is due to the increased number of nevi or other factors. However, neither the number of nevi nor risk for skin cancer is increased by the use of GH (Gravholt,

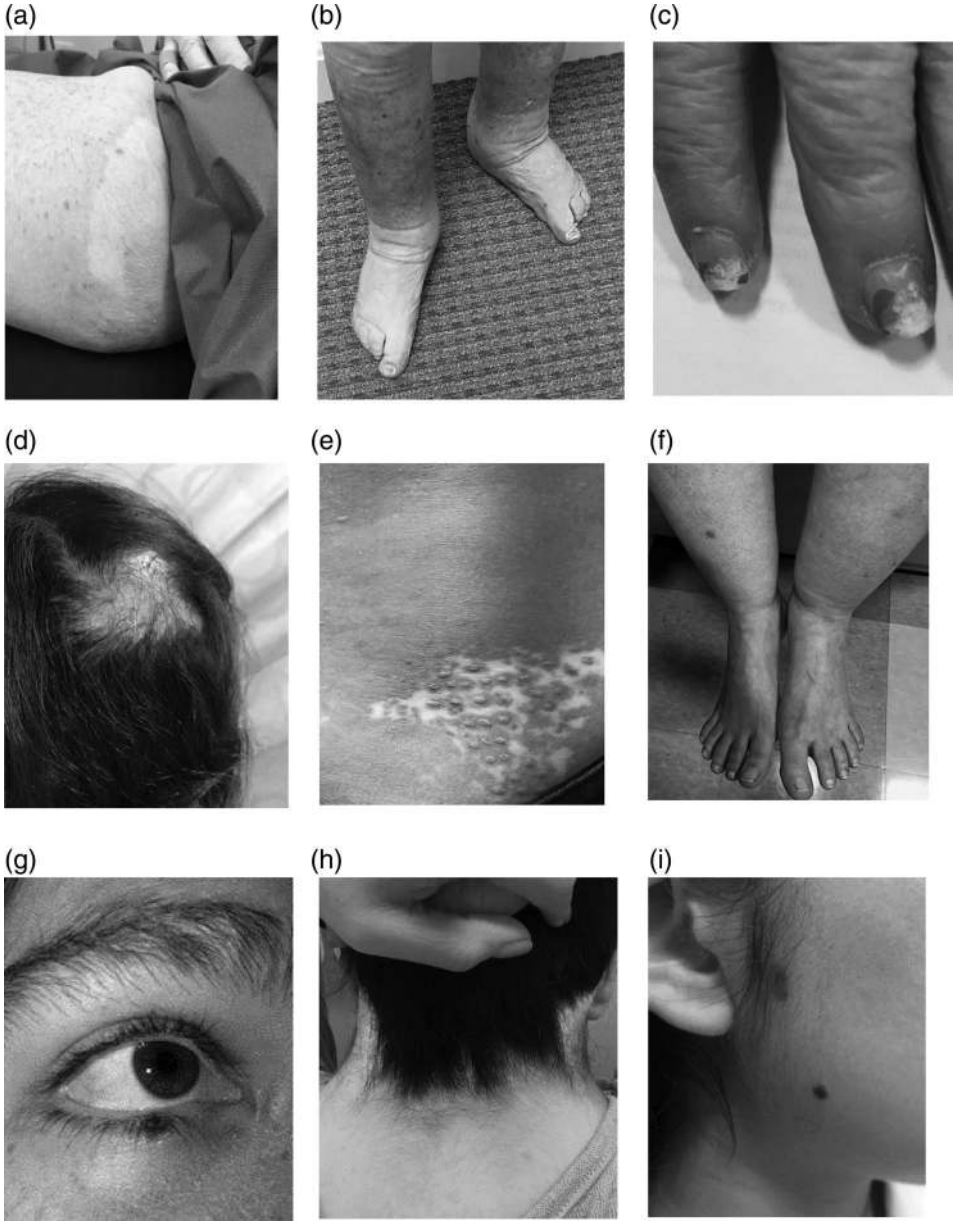

FIGURE 4 Assorted abnormalities of the skin, nails and hair in women with Turner syndrome (age and karyotype). (a) (48 years, 45,X) inverse psoriasis and vitiligo on right inner thigh, which is also present on left thigh (photo is oriented with perineal region on right and knee on left); (b) (77 years, 45,X) severe bilateral lower extremity lymphedema, sparing toes (c) (77 years 45,X) dystrophic, fragile fingernails with distal onycholysis and punctate leukonychia; (d, e) (32 years, mosaicism 45,X/isochromosome Xq, 10%/90%) scalp alopecia clinically thought to be lichen planopilaris, and vitiligo with partial repigmentation after miniature punch grafts complicated by cobblestoning in the right lumbar region; (f) (39 years, mosaicism with 67% 45,X and 33% marker chromosome) lymphedema of both calves; (g) (21 years, 45,X) thick, double eyelashes on lower eyelid, with a compound melanocytic nevus; (h) (34 years old, 45,X) low-set hairline and bilateral hypertrophic scars following surgery for reduction of neck webbing; (i) (25 years, nonmosaic 46 X, i(X) (q10)) compound melanocytic nevi right side of cheek

Andersen, et al., 2017b, section 6.1). Additionally, in contrast to normal control patients, onset of nevi in Turner syndrome appears to be later, and independent of sun exposure (Zvulunov, Wyatt, Laud, & Esterly, 1998).

13.2 | Management of skin problems

Women with Turner syndrome should have a skin exam at diagnosis, and annually thereafter, with self-examination of their nevi for possible malignant changes. Management of skin nevi is the same as that for the general population. Most Turner syndrome providers counsel conservatively regarding elective surgical procedures to avoid the formation of keloids (Lowenstein et al., 2004), but it is remarkable how variable the hypertrophic response can be. For example, ear piercing is usually discouraged because of the possibility of pea-sized firm keloids, but it is widely used without keloid formation. The most significant scars occur in the neck region following surgical reduction of neck webbing (Figure 4) or over surgical sites such as sternotomy, or other locations where there is tension at the suture line. Given the frequency of keloids, and the potentially serious cosmetic distress they can cause, it is surprising that there has not been a concerted research effort to understand their occurrence in Turner syndrome.

13.3 | Lymphedema frequency and description

Lymphedema is a common, (Loscalzo et al., 2005) but frequently undertreated, symptom in Turner syndrome. At birth, 76–95% of infants with Turner syndrome display dorsal foot and hand swelling (Atton et al., 2015; Welsh & Todd, 2006) that resolves during early childhood in ~37% (Rothbauer, Driver, & Callender, 2015). Approximately two-thirds of women with Turner syndrome reported lymphedema anytime during life (Rothbauer et al., 2015; Welsh & Todd, 2006), and evidence

indicates it persists into or recurs in adulthood in 80% (Atton et al., 2015; Welsh & Todd, 2006). Lymphoscintigraphic examination showed lymphatic dysfunction in 83% of 18 Turner syndrome patients (Bellini et al., 2009), suggesting that lymphedema incidence may be higher than reported, perhaps because lymphatic dysfunction does not always manifest as measurable swelling. Although lymphoscintigraphy can reveal lymphatic dysfunction in the absence of obvious swelling, other imaging methods not commonly used in Turner syndrome, such as near-infrared fluorescence lymphatic imaging, magnetic resonance lymphangiography, bioimpedence, and ultrasound can often detect cryptic lymphedema-associated fluid accumulation, vessel anomalies, and skin changes that lymphoscintigraphy may miss (Munn & Padera, 2014; Rasmussen et al., 2010).

In addition to extremity swelling, rare lymphatic complications such as lymphangiomas and hemangiolymphangiomas in organs and body cavities have been reported (Foldi & Foldi, 2006). While hypoplastic lymphatic vessels in the upper dermis/primary lymphatic capillaries have been reported in fetuses with Turner syndrome (von Kaisenberg et al., 2010; von Kaisenberg, Nicolaides, & Brand-Saberi, 1999), it is unknown whether lymphatic vessel anatomy and function change as women with Turner syndrome age.

Lymphedema impacts women with Turner syndrome in numerous ways. Swollen hands and feet may limit dexterity, physical activity/gait, and make shoe fitting difficult. In older women, there can be cellulitis (noted in 18–26% by Rothbauer et al., 2015; Atton et al., 2015), which increases the severity of lymphedema, creating a vicious cycle (Al-Niaimi & Cox, 2009) and placing patients at risk for developing sepsis. Stagnant lymph sends molecular signals to adipose cells to grow and divide (Wang & Oliver, 2010), so subdermal fat accumulation worsens with untreated lymphedema, and may contribute to obesity in Turner syndrome. Psychosocial effects (teasing by peers, poor body image) have not been objectively measured, but reported (Welsh & Todd, 2006). Recently, bone loss was reported in breast cancer-related lymphedema (Vural, Ayhan, Cakit, & Soran, 2018), suggesting that lymph dysfunction and osteoporosis in Turner syndrome may be associated. Because estrogens are beneficial to lymphatic health, HRT in Turner syndrome may minimize lymphedema (Morfoisse et al., 2018). Cardiovascular health in women with Turner syndrome may be improved by treating lymphatic dysfunction. Several liters of extracellular fluid, transiting through lymphatics, not venous vessels, must be returned as lymph to the vascular system each day (Foldi & Foldi, 2006; Guyton & Hall, 2000; Levick & Michel, 2010).

13.4 | Lymphedema treatment

Lymphedema and lymphatic dysfunction in Turner syndrome are undertreated. Over half of women with Turner syndrome and lymphedema do not use therapies such as compression garments, bandaging, or pumps, since there is a perception that treatment is not needed or unpleasant (Rothbauer et al., 2015). Between 51–65% of women with Turner syndrome (Rothbauer et al., 2015; Welsh & Todd, 2006) never received any treatment, and 39% reported having no knowledge about lymphedema (Rothbauer et al., 2015). Young adult women can be educated about lymphedema before the onset of brawny and fibrotic changes, but most tend to view this as a minor annoyance not requiring treatment. With early intervention, including manual lymphatic drainage, compression socks, stockings, and hosiery (which can be obtained without prescription), and when severe, pneumatic compression therapy, lymphedema outcome is improved (Koelmeyer et al., 2018; Stout Gergich et al., 2008). Providers should be aware, however, that the latter treatment, though effective, requires the patient to be seated for several hours a day, perpetuating a sedentary lifestyle that should avoided. Care of dystrophic nails and prevention of ingrowth and cellulitis is also part of lymphedema care.

14 | RENAL

14.1 | Type and frequency of renal anomalies

The type and frequency (25–40%) of renal anomalies in Turner syndrome has been well-studied (Gravholt, Andersen, et al., 2017b, section 6.1). A baseline renal ultrasound should be performed in any adolescent or adult who did not have one in childhood, or who is newly diagnosed. In descending order of frequency, there can be a horseshoe (~10%), or partially or totally duplicated kidney (5–10%) and rarely, nonvisualized multicystic/dysplasic or ectopic kidney, as well as collecting duct and ureteral anomalies including duplications (Hamza et al., 2016).

14.2 | Management of renal anomalies

In the absence of compelling natural history studies, the Guidelines (Gravholt, Andersen, et al., 2017b, section 6.1) did not recommend serial imaging or laboratory testing. Instead, increased awareness of the infrequent acquired problems such as obstructive uropathy and hydronephrosis is prudent. There is anecdotal experience that hypertension can occur secondary to renal scarring from recurrent infection or renal artery stenosis. Longitudinal studies of functional and imaging status will be needed to clarify the relationship to blood pressure.

15 | GASTROINTESTINAL AND LIVER DISEASE

15.1 | Overview

As noted in the Guidelines (Gravholt, Andersen, et al., 2017b, section 6.1, table 2), and in Section 10.4 of this article (Autoimmunity) celiac disease and IBD are relatively uncommon in Turner syndrome, but can be a source of gastrointestinal discomfort (such as abdominal pain and bloating). Presentation may be delayed until adulthood, so even if prior testing was considered reassuring, clinicians should have a low threshold to re-test adults of any age. In contrast, elevated liver enzymes are extremely common (50–80%), but usually asymptomatic except for the small percentage of patients who can present with symptoms of portal hypertension due to advanced cirrhosis. An association between isochromosome Xq and elevated liver enzymes has

been suggested (Calanchini et al., 2018). There has also been an association noted between elevated liver enzymes and aortic dilatation.

15.2 | Celiac disease

There is increased awareness in the Turner syndrome and general population about this immune-mediated disease of the small intestines, which is triggered by the ingestion of gluten-containing grains (wheat, barley and rye). It is treated by excluding all gluten-containing foods from the diet. Importantly, screening for celiac disease using tissue transglutaminase IgA antibodies should begin in early childhood, and be repeated every 2 years throughout childhood and with suggestive symptoms in adulthood (Gravholt, Andersen, et al., 2017b, table 6). In patients with positive serology, endoscopy with duodenal biopsy should be performed to confirm the diagnosis.

15.3 | Inflammatory bowel disease

In individuals with Turner syndrome and IBD (Elsheikh et al., 2002; Gravholt, Juul, et al., 1998b), Crohn's disease is slightly more common than ulcerative colitis. Although classical symptoms such as bloody diarrhea, abdominal pain, and weight loss may be present, growth retardation may be the only manifestation, which may delay the diagnosis of Turner syndrome. Among women with Turner syndrome, the median age of onset of inflammatory bowel disease has been reported as 16 years. Osteoporosis is a common complication, resulting from many factors including the inflammatory process itself, poor nutrition, corticosteroid therapy, as well as calcium and vitamin D deficiencies. The diagnosis of IBD should be considered in individuals with nonspecific complaints or poor growth in addition to those with abdominal complaints.

15.4 | Liver disease

Liver involvement in Turner syndrome can vary from asymptomatic mild elevation of liver function tests (LFTS) discovered during surveillance blood testing (Roulot, 2013) to pathology that is more serious. The most frequent cause is nonalcoholic fatty liver disease, related to excess weight and insulin resistance commonly seen in women with Turner syndrome. Other etiologies include vascular hepatic involvement as part of a more generalized vascular disorder. Autoimmunity may play a role in the cholangitis and ductopenia observed, as also seen in primary biliary cirrhosis.

Elevated LFTs including alkaline phosphatase, alanine/aspartase aminotransferase, and g-glutamyl transferase (ALT, AST, and GGT) are common, and generally remain elevated., Several studies have shown that increasing doses of oral estradiol decreases liver enzymes in a dose-dependent fashion. In other words, the higher the dose of estradiol (1–4 mg), the more liver enzymes decreases (Elsheikh, Hodgson, Wass, & Conway, 2001; Gravholt, Naeraa, Fisker, & Christiansen, 1997; Gravholt, Poulsen, Ott, Christiansen, & Vilstrup, 2007; Koulouri et al., 2008; Ostberg et al., 2005). The longer a patient with Turner syndrome is estrogen deficient, the more intrahepatocellular lipids are accumulated (Ostberg et al., 2005). Occasionally, patients may have isolated elevation in alkaline phosphatase and GTT with normal transaminases, in which case treatment with ursodeoxycholic acid can be considered. Bilirubin and synthetic function (as evidenced by prothrombin time and albumin levels) are usually normal. Women with Turner syndrome can progress to having non-alcoholic liver disease with steatosis, steatohepatitis, and steatofibrosis, which is often related to co-occurring metabolic disturbances including adiposity, diabetes, and dyslipidemia. The detection of elevated LFTs should not be misinterpreted as a toxic side effect of estrogen, which may lead some clinicians and patients to discontinue HRT. Instead, this is often a signal that HRT had been inconsistent or insufficient. With awareness of these elevations and the association with metabolic changes, excessive diagnostic testing can usually be avoided.

In some individuals with Turner syndrome, liver biopsy may demonstrate marked architectural changes including nodular regenerative hyperplasia and focal nodular hyperplasia (Roulot et al., 2013). A vascular basis has been postulated, and portal hypertension and esophageal varices may develop as potential life-threatening complications (Roulot et al., 2013). The most serious pathology is cirrhosis, which is six times more common than in the non-Turner syndrome population, especially in those with elevated LFTs.

Surveillance includes checking LFTs annually beginning at age 10 years, which is younger than previously suggested (Gravholt, Andersen, et al., 2017b, section 6.1). Vascular anomalies of the intestines and liver are uncommon, but should be considered in the presence of upper gastrointestinal bleeding and liver dysfunction. In patients with abnormal LFTs, further evaluation with Doppler ultrasound is helpful in identifying steatosis, cirrhosis, or nodules. The importance of appropriate estradiol treatment has to be emphasized, but otherwise management is the same as that for the general population. When non-alcoholic fatty liver is identified, weight loss and improved lifestyle are advised. In patients with bleeding, capsule endoscopy may be needed in addition to upper endoscopy and colonoscopy. Bleeding generally resolves with age, perhaps as the result of estrogen supplementation.

16 | CANCER

16.1 | Types of cancer, clinical reports

There is no conclusive proof that the absence or structural deficiency of the X chromosome in Turner syndrome *causes* cancer. Although case reports (including Alexiou et al., 2014; Hanaei, Habibi, Nejat, Sayarifard, & Vasei, 2015; Jones et al., 2018; Pier et al., 2014), case series (Larizza et al., 2016), and epidemiologic studies (Ji et al., 2016) provide support for an increase in certain types of cancer occurrence (showing a difference in *pattern*), the overall risk does not appear to be increased (see also Section 4.2). Thus, surveillance for cancer is not indicated.

The MGH Turner syndrome clinic follows 11 patients who have at least one form of cancer (six women with more than one type). All developed cancer as adults, except for a 3-year-old girl with

ganglioneuroblastoma who is thriving now as a young adult. The frequency (~5%) from a tertiary care hospital with a major cancer center does not represent prevalence, and since cancer was not diagnosed by systematic surveillance. Nevertheless, there appears to be an overrepresentation of central and peripheral nervous system tumors (7/11, 64%), as epidemiological evidence also suggests. From an Italian endocrinology clinic reporting on 87 women with Turner syndrome, there were 14 (~16%) with neoplasia (Larizza et al., 2016) including 3 (21%) with central nervous system tumors. Neuroblastoma and ganglioneuroblastoma are tumors of early childhood, and noted among girls with Turner syndrome (Blatt, Olshan, Lee, & Ross, 1997; Pinsker & Crudo, 2012). Despite the limitations and biases of clinic series, they provide clinical phenotyping superior to population-based studies.

Individuals with Turner syndrome and Y chromosome material with gonadoblastoma were discussed previously (Gravholt et al., 2000; Gravholt, Andersen, et al., 2017b, section 1.1). Because of malignant transformation, increased vigilance is necessary in females with Turner syndrome and Y chromosome material. On the other hand, epidemiological evidence has shown that this rare tumor is not the sole or partial cause for the increased overall mortality in Turner syndrome (Fuchs et al., 2019; Ji et al., 2016; Schoemaker et al., 2008b; Stochholm et al., 2006).

16.2 | Population-based studies of cancer

It has been suspected that lower rates of breast cancer in Turner syndrome can be attributed to the relative estrogen insufficiency (Section 4). Population-based analyses of over 5,000 females with Turner syndrome, linked to mortality data, show that overall cancer risk is not increased (Hasle et al., 1996; Ji et al., 2016; Schoemaker, Swerdlow, Higgins, Wright, & Jacobs, 2008a; Stochholm et al., 2006).

16.3 | Future directions

One hypothesis to explain the presence of cancer in women with 45,X may be extrapolated from the observation that cancer is more common in men who similarly have one X chromosome, and in whom tumor suppressor genes may escape X-inactivation (Dunford et al., 2017). Additional research is essential to follow the current population of women with Turner syndrome as they age. Cancer diagnosis has improved greatly, and among adult women is influenced by their access to care (Gravholt, Andersen, et al., 2017b, section 6.2). With increased availability of both clinical and research-based exome and genome sequencing, the ability to evaluate a person's somatic (tumor) and germline (peripheral blood) composition increases. The occurrence of cancer and mortality from cancer is not increased overall, but some specific tumors are seen more frequently. One could speculate that this is due to a combination of the genetic background and the lack of hormones, although there does not appear to be evidence for environmental factors such as exogenous hormones and lifetime environmental (UV radiation) exposure.

17 | MUSCULOSKELETAL AND PODIATRIC ISSUES

17.1 | Type and frequency of abnormalities

Skeletal abnormalities in Turner syndrome can be classified as those due to skeletal dysplasia, postural changes related to hypermobility/joint laxity, and osteoporosis due to bone loss. Although the Guidelines (Gravholt, Andersen, et al., 2017b, section 6.1) provide an extensive list of musculoskeletal abnormalities, most are mild differences rather than clinically important problems, a distinction that can reassure patients. Table 7 lists the familiar short sternum with broad "shield" chest (80%), pectus excavatum (20%), cubitus valgus (~80%), short neck (90%), Madelung deformity of the distal radius, disproportionately short lower extremities (nearly all), and short broad feet (65%) are characteristic structural bone defects which do not require treatment or special imaging. Joint laxity is common and may lead to mild–moderate postural scoliosis (10–60%), positional foot deformities (30%) and hyperextension of the great toe (~80%). Craniofacial skeletal anomalies are reviewed in Section 11 with defects of variable severity. Retrognathia, narrow palate, and short posterior cranial base that can be the cause of more-than-mild malocclusion and reduced mouth opening. Osteoporosis is a common problem due to complex multifactorial factors such as hormone use, activity level and vitamin D/calcium homeostasis (discussed in Section 6). The skeletal phenotype varies greatly among patients, and does not correlate to karyotype; detailed analysis among those with low-level mosaicism has not been studied.

Some musculoskeletal issues are most relevant during adolescence prior to physeal closure such as slipped capital femoral epiphysis (SCFE), scoliosis, and kyphosis. The only orthopedic emergency is SCFE that must be evaluated and treated aggressively by an orthopedic surgeon. Turner syndrome patients receiving growth hormone are much more likely to have SCFE as a complication compared to idiopathic growth hormone deficiency or idiopathic short stature patients (Darendeliler et al., 2007). In the adolescent, spinal abnormalities should be evaluated in relationship to the timing of growth. Young women with scoliosis receiving growth hormone, are more likely to have progressive scoliosis (Ricotti et al., 2011). In the adult woman, osteoporosis associated with kyphosis (40–75%), vertebral wedging, and scoliosis (10–60%) are extremely important which may progress and require surgery. Kyphosis and scoliosis are not progressive after vertebral apophyseal closure except in settings of weakness and osteopenia/osteoporosis with compression fractures. Some patients with severe cubitus valgus also need surgery.

17.2 | Abnormalities of the foot

The feet and toenails may be overlooked in women with Turner syndrome, but especially in the oldest women. Hallux valgus and pes planus can cause pain and may be best addressed with proper footwear; hallux valgus may require surgical evaluation if severe pain persists. Dystrophic nails that may be fragile and tear easily, or hyperconvex and thickened may be difficult to manage at home. Ingrown toenails that could lead to

cellulitis are to be avoided. Although a short fourth metacarpal (25–40%) is usually a minor anomaly, brachymetatarsia involving a very short fourth toes may cause discomfort with shoes. Abnormalities can be different in one extremity compared to the other and foot abnormalities may be independent of knee misalignment (Trzcińska, Olszewska, Wiśniewski, Milde, & Madej, 2011).

A systematic, longitudinal study about progressive bone deformities in Turner syndrome has not been performed. The Guidelines (Gravholt, Andersen, et al., 2017b, section 6.1) provides advice for girls during GH therapy, and recommendations for adult women is found within the discussion about osteopenia. Podiatric consultation may be valuable (Elsheikh et al., 2002). Physical therapy should be considered early to address pain associated with scoliosis and other musculoskeletal concerns such as stiffness, lack of flexibility, weakness and overuse due to joint laxity/hypermobility (Ricotti et al., 2011). Further research is needed to assess the specific musculoskeletal needs adult women with Turner syndrome may experience.

18 | SEXUALITY AND QUALITY OF LIFE

Although sexuality can encompass a range of topics, including intimacy, sexual activity, and sexual orientation, this discussion will focus primarily on sexual activity as it relates to Turner syndrome. Sexuality among women with Turner syndrome has been addressed as a specific topic in an increasing number of articles over time (Carel, Elie, Ecosse, Tauber, & Leger, 2006; Næss et al., 2010; Rolstad, Moller, Bryman, & Boman, 2007; Ros, Alobid, Balasch, Mullol, & Castelo-Branco, 2013), although intimacy is usually included in reviews of QoL, fertility, and HRT. A lack of data in this area of care was acknowledged in the Guidelines (Gravholt, Andersen, et al., 2017b, section 6.2), and this current review represents a deliberate expansion of that discussion. In addition to the medical literature, a compelling personal plea from the Turner syndrome community urged providers and patients to talk about sex more openly (Clifton, 2013). Concerns included a feeling that the subject of sex was “almost taboo”, a request for physicians to be “bold and delve a bit deeper”, and the insight that not all women with Turner syndrome would share the same viewpoints on sex and sexuality.

18.1 | Sexuality

Among women with Turner syndrome, it is reasonable to consider that medical factors may contribute to reduced sexual activity, although there has been no systematic study interrelating multiple factors known to affect sexuality. An observational study of 26 adults with Turner syndrome followed in an endocrinologic gynecology clinic in Barcelona reported that only 50% of Turner syndrome had been sexually active and that they had poorer arousal outcome when studied with the Female Sexual Function Index questionnaire compared to a normal control group treated with oral contraception and a second control group of females with congenital hypogonadism by other causes (Ros et al., 2013). Comparison of these two clinical groups noted differences between women with Turner syndrome and those with congenital hypogonadism. Women with congenital hypogonadism had even lower scores (i.e., less sexual desire), although not statistically significant, than the Turner syndrome group (Ros et al., 2013), perhaps indicating that hypogonadism is not the sole cause of concerns of sexual function among women with Turner syndrome.

Studies of European and North American women with Turner syndrome have noted that, they move away from their parents and have a sexual debut at a later age, if at all compared with the general population (Amundson et al., 2010; Carel et al., 2006; Næss et al., 2010; Rolstad et al., 2007). In a Norwegian study, only 48 of 80 (60%) women with Turner syndrome responded to a questionnaire, but approximately 50% of both women with Turner syndrome and age-matched controls were satisfied with their sexual life. Women with Turner syndrome had less confidence as a sexual partner, had fewer partners, and the late induction of puberty with exogenous estrogen was coupled with late sexual debut compared with controls (Næss et al., 2010). A follow-up study of the same cohort of 56 women showed similar findings. Women with Turner syndrome still reported fewer partners and felt less confident as a sexual partner (Fjermestad et al., 2016). Similarly, in a large French study of 566 young adult women with Turner syndrome (mean age = 22.6 years) who had been treated with GH, only 38% had intercourse (age of 20 years), while 63% had no sexual experience at all (Carel et al., 2006). A study from the NIH, with acknowledged referral bias, noted that many fewer individuals with Turner syndrome were or had been married (48% vs 78%), which was viewed as an indirect indicator of sexual activity (Gould et al., 2013). While reduced sexual activity may partly relate to the medical factors discussed above, greater difficulty establishing intimate relationships may also reflect broader difficulties with social communication, discussed elsewhere in this review.

In the clinical experience of the authors, and as noted previously (Sybert & McCauley, 2004), most individuals with Turner syndrome identify as women and heterosexual, but experience considerable anxiety and/or ambivalence about initiating romantic relationships. Of over 220 individuals followed in the MGH Turner syndrome clinic, gender identity approximates the normal population. It is possible that due to social and cultural factors within Turner syndrome communities, there will be expectations regarding sexual orientation, gender identity and/or gender expression.

18.2 | Recommendations for sexual education and function

For the adolescent with Turner syndrome, the initial discussion about intimacy and sexuality should take place with a parent or trusted adult at an appropriate time. Ideally, information should be provided no later than transition, and by the physician who has a sustained relationship with the young woman. Later in adulthood, ongoing discussion and care could be provided by a gynecologist or endocrinologist experienced in caring for women with ovarian insufficiency, with an awareness that women with Turner syndrome who are sexually active may not express a desire to change sexual function. Appreciating an

individual's social abilities or weaknesses (e.g., whether she is extremely shy, unable to interact with partners and date, etc.), Turner syndrome providers should counsel women who are not sexually active when they express an interest. Topical estrogen *per vaginum* or systemic androgen supplements may be beneficial, but currently, little information exists on their use in women with Turner syndrome (Trolle, Hjerrild, et al., 2012b; Zuckerman-Levin et al., 2009).

18.3 | Quality of life

Clinically, QoL measures are often used as a general indicator of psychosocial health. In Turner syndrome, QoL has been investigated in cross-sectional studies (Boman et al., 2001; Boman, Bryman, & Möller, 2004; Lasaite, Lasiene, & Lasas, 2010; Nadeem & Roche, 2014b), in four cohort studies (Carel et al., 2005; Carel et al., 2006; Fjermestad et al., 2016; Næss et al., 2010), in randomized clinical trials (Bannink, Raat, Mulder, & de Muinck Keizer-Schrama, 2006b; Freriks et al., 2015; Taback & Van, 2011; Zuckerman-Levin et al., 2009), and in a case–control study (Amundson et al., 2010). Most of these studies used the Short Form Health Survey (SF-36) questionnaire, but other questionnaires have been used, including the Psychological General Well-Being index, General Health Questionnaire, part of the Nottingham Health Profile, and adapted versions of the World Health Organization Quality of Life (WHOQOL) Assessment, making generalization difficult. Some studies comparing Turner syndrome with a normal sample form the population concluded that QoL was normal in females with Turner syndrome (Bannink, Raat, et al., 2006b; Carel et al., 2005; Taback & Van, 2011), while others reported that their QoL was reduced (Boman et al., 2001; Fjermestad et al., 2016; Lasaite et al., 2010; Nadeem & Roche, 2014b; Næss et al., 2010). A recent review concluded that it is necessary to develop Turner syndrome-specific tools in order to fully appreciate the intricacies of their QoL (Reis, de Assumpcao, Guerra-Junior, & de Lemos-Marini, 2018). Quality of life is likely influenced by multiple factors including age, height, pubertal development, infertility, sexuality, use of GH, age at diagnosis, physical aspects, socioeconomic status, education, reduced hearing, and the burden of morbidity.

18.4 | Body image

Body image is a multidimensional construct that includes self-perceptions and attitudes with relation to one's own body, and involves many related components, such as how appearance is evaluated by oneself. This develops from early in life and is based on shared experiences and interactions with parents, peers, social media, and society. Negative body image has been linked to a number of conditions, such as eating disorders, negative affect, social anxiety, and social inhibition (Avalos, Tylka, & Wood-Barcalow, 2005). Body image has only been sparingly examined in Turner syndrome. Bodily attitude scale has been rated similarly among women with Turner syndrome and an appropriate control group (Lagrou et al., 2006); furthermore, a less favorable body image may contribute to their lack of sexual intimacy and desire (Sutton et al., 2005). Some women with Turner syndrome also cited feeling less desirable due to short stature and/or infertility or lack of similar pubertal development to peers.

18.5 | Future research

Most of the current studies on sexuality and QoL in women with Turner syndrome are small in size and tend to have studied sexuality and QoL as an adjunct to other questions related to general health, instead of as a primary topic. It is clear that sexuality and QoL should be viewed holistically with regard to body image, medications like HRT, and assorted medical conditions. A bio-psycho-social framework should be used with consideration of social communication skills, emotional functioning, level of anxiety, socioeconomic status, and educational attainment. The importance of an integrated analysis of variables is illustrated by an ongoing study of sexuality and QoL in Klinefelter syndrome (47,XXY) at Aarhus University Hospital. Using a questionnaire to study health issues, socioeconomic indicators, sexuality, and treatment (especially testosterone replacement, and also other medications), Skakkebaek, Moore, Chang, Fedder, and Gravholt (2018) noted that sexuality of individuals with Klinefelter syndrome was affected by a number of co-variates such as socioeconomic status, medicinal use, physical activity, and BMI (Skakkebæk et al., 2018). Additionally, the Turner Syndrome Research Registry created by the TSSUS includes a module on sexuality with the intent of capturing more comprehensive, patient-driven research in this area (Prakash et al., 2019b). These data will further enrich the scientific community's understanding of sexuality in Turner syndrome in the coming years.

It is possible that as the treatment of young women with Turner syndrome is optimized from a medical and psychosocial point of view, then sexuality and QoL may improve. Currently, the young women with Turner syndrome who reach normal height due to GH treatment, which may add up to 15–18 cm to final height, and have age-appropriate pubertal development report normal health-related QoL. Satisfaction with breast development (and height) also has a positive influence on several health-related QoL scales (Bannink, Raat, et al., 2006b). Therefore, it seems that induced puberty at a physiologically appropriate age optimizes self-esteem, social adjustment, and initiation of the patient's sex life (Carel et al., 2006; Næss et al., 2010), although one study showed that both estrogen use and age of puberty did not influence sexual function in individuals with Turner syndrome (Sheaffer, Lange, & Bondy, 2008).

In addition to ongoing efforts to conduct research to obtain more data, providers should be reminded to include sexuality with current counseling about fertility and parenting. If a primary care physician, geneticist, or endocrinologist is not comfortable with discussing the necessary details, for example, lubrication, then referral to a gynecologist or endocrinologist should be made. Options may vary among different healthcare models worldwide. Importantly, when discussing sexuality with the adolescent or with an individual whose cognitive function or development is delayed, prior review with the parent or guardian is necessary. Some individuals may wish to include their partner if delivery of information by a physician would be more comfortable.

19 | FERTILITY AND PREGNANCY

19.1 | Overview

For many people, raising a child is an important chapter in life, and many women anticipate pregnancy. These feelings also apply often to women with Turner syndrome (Sutton et al., 2005), but for most, fertility is not straightforward. A few women with a mosaic karyotype, which includes a low level of 45,X, remain fertile, and are able to conceive naturally or after ovarian stimulation with or without cryopreservation of oocytes (Talaulikar, Conway, Pimblett, & Davies, 2019). However, most women with Turner syndrome need to pursue other options. Adoption is possible in some countries, dependent upon sociocultural attitudes. Guidelines to counsel women with Turner syndrome had been more cautious about undertaking pregnancy (Reindollar, 2011). More recently, the Guidelines (Gravholt, Andersen, et al., 2017b, section 3) have promoted a supportive medical environment based on longitudinal multidisciplinary preconception, intrapartum, and postpartum evaluation, and embracing shared-decision-making with respect for patient autonomy. As the literature has been extensively reviewed in the Guidelines (Gravholt, Andersen, et al., 2017b, section 3), and the European Society of Cardiology (ESC) cardiovascular disease in pregnancy guidelines (Regitz-Zagrosek et al., 2018, section 5.2.4), we focus on current surveillance and management strategies.

19.2 | Preconception counseling in Turner syndrome

The vast majority of women with Turner syndrome opt for oocyte donation. Fortunately, women with Turner syndrome are able to achieve pregnancy from oocyte donation at a rate comparable to women without Turner syndrome (Hagman et al., 2013b). Previous research revealing an increased risk of peripartum cardiovascular mortality (Bernard et al., 2016) led to the development of guidelines emphasizing thorough cardiovascular examination before attempted pregnancy and proper preparation of the uterus, both with regard to size and endometrial thickness (Cabanes et al., 2010; Gravholt, Andersen, et al., 2017b, section 3, table 8). Multidisciplinary programs for Turner syndrome assessment and preconception counseling were already in place, but grew in number as pregnancy in Turner syndrome was recognized as a high-risk condition.

Women with Turner syndrome who have a pre-existing cardiovascular condition including, but not limited to, hypertension, BAV, coarctation of the aorta or significant aortic dilation (Z-score > 2.5), carry the highest cardiac risk in pregnancy and should be counseled accordingly. The degree of disease (repaired or unrepaired, number of associated conditions, extent of disease) will influence the multidisciplinary preconception recommendation. Aortic dissection or rupture is the most feared and unpredictable outcome (intrapartum screening has not proven useful in predicting events). Pregnancy-induced hypertension, gestational diabetes, and preeclampsia are seen with increased frequency in comparison with normal pregnancies, but probably not in comparison with other recipients of oocyte donation (Hagman et al., 2010; Hagman et al., 2013a; Hagman, Loft, et al., 2013b). Other congenital heart or acquired cardiac conditions should be managed as recommended by those specific pregnancy guidelines, taking into account any unique Turner syndrome related contributions.

19.3 | Peripartum management in Turner syndrome

Once pregnancy is initiated, multidisciplinary follow up for women with Turner syndrome should occur each trimester as is possible. Home blood pressure monitoring, or at a minimum at each obstetric or cardiology visit, is useful. Most women without Turner syndrome with pre-existing hypertension and normal renal function have non-severe hypertension (140–159/90–109 mmHg) and are at low-risk for cardiovascular complications. Some are able to withdraw their medication in the first half of pregnancy because of the physiological fall in blood pressure in the setting of the placenta with low systemic vascular resistance. However, the rise in cardiac output and intravascular volume in the third trimester, combined with delivery of the placenta, can then pose in the immediate post-partum period an urgent rise in blood pressure for women with Turner syndrome and a history of hypertension. General adult recommendations for pregnant women could be implemented on a case-by-case basis in women with Turner syndrome, but with clear physiologic profiling of risk factors and the cardiovascular effects of pregnancy.

In general, cessation of teratogenic antihypertensives (such as ACE-inhibitors) and replacement with those allowed in pregnancy is a preferred conservative approach. If pre-eclampsia should develop, management with cardiovascular clinician input is important. In general, women at risk of pre-eclampsia can be treated with 75 mg aspirin from 12 weeks of gestation until delivery (National Collaborating Centre for Women's and Children's Health (UK), 2010), which is currently also recommended treatment for women with Turner syndrome (Webber et al., 2016). In France, a survey of 103 women with Turner syndrome and 170 pregnancies performed after implementation of new guidelines showed that pregnancy outcome was much improved with reduced frequencies of hypertension, preeclampsia, and prematurity and morbidity with no maternal deaths (Cadoret et al., 2018), compared with a similar survey some years earlier (Chevalier et al., 2011); the need to improve was acknowledged.

In the setting of BAV, in general, aortic regurgitant lesions are better tolerated than stenotic lesions. However, clear guidelines for pregnancy risk exist for congenital heart disease (Silversides et al., 2018). Unfortunately, the aorta itself carries some risk even in women without Turner syndrome, therefore the compounding effect of the Turner aorta cannot be predicted well in the setting of BAV with aortic dilation.

Aortic dilation relative to height is seen is Turner syndrome, and although aortic dissection is rare, it does occur nearly sixfold more often and at younger ages than in the general population. Therefore, in the setting of known BAV, aortic dilation, or coarctation of the aorta, concern still exists regarding aortic dissection risk. Pregnancy should be avoided when the aortic size index is >25 mm/m^2. Importantly, the entire aorta is potentially at risk; therefore, despite

ascending aortic or root surgery, the patient remains at risk of type B dissection.

Pregnancy can be well tolerated in non-Turner syndrome women after repair of coarctation of the aorta (WHO risk class II) (Silversides et al., 2018). Both women with unrepaired and repaired coarctation who have systemic hypertension, residual coarctation, associated BAV, aortic aneurysms or aortic dilation have an increased risk of complications including aortic dissection, pre-eclampsia, or heart failure. This population may be at even higher risk in the Turner syndrome population, and pregnancy would be a relative or absolute contraindication in some cases, with a requirement for multidisciplinary evaluation and clear recommendations to the patient and family.

Lastly, as cardiovascular mortality in pregnancy continues to be a global concern, acquired cardiovascular disease, especially in women with atherosclerotic cardiovascular disease risk factors or with advanced maternal age, must be recognized. Turner syndrome is associated with an increased risk of hypertension, diabetes, and atherosclerotic events (Regitz-Zagrosek et al., 2018). A recent study revealed an increased likelihood of coronary calcifications at a younger average age in women with Turner syndrome compared with non-Turner individuals (Schoepp et al., 2018). At a minimum, cardiovascular evaluation including blood pressure and diabetes management should be mandatory preconception care for women with Turner syndrome.

19.4 | Multidisciplinary pregnancy programs in Turner syndrome

Our institutions have developed multidisciplinary programs in which there is close collaboration between an endocrinologist, geneticist, cardiologist, fertility specialist, maternal-fetal medicine specialist, obstetrician, and social worker, although the exact composition may vary. In our experience, the formation of the teams was deliberate and varies in leadership, for example, the endocrinologist is the coordinator in Aarhus, whereas, there are three co-directors at MGH. Communication is essential among the team members to ensure that a consistent approach is followed and a similar message is communicated to patients, as the detailed evaluations occur usually over many months. Women with Turner syndrome and their partners have hopes and expectations, and are processing sensitive information. Care should be taken to ensure that the communication style of the provider matches the receptive language abilities of the patient, a nuance that can be overlooked if the woman has good expressive language. An approach to pregnancy emphasizing the need to coordinate care before, during, and after pregnancy was published recently and includes a checklist of possible examinations (Donadille, Bernard, & Christin-Maitre, 2019, table 2).

The need for additional outcome data from both European and other centers is essential, but there is cautious optimism with current results. One area for improvement in the care for women with Turner syndrome considering pregnancy is the creation of registries, which are available in some Nordic countries and France to provide long-term follow-up of the outcome of pregnancies for both mother and child (Hagman, Loft, et al., 2013b). This is currently lacking in the United States (Lin et al., 2016), but under development as a self-reporting patient registry (Prakash, Lugo-Ruiz, et al., 2019b). In addition to outcome data focusing on obstetric and fetal/neonatal morbidity, it will be important to extend ongoing population-based studies of aortic growth (Mortensen et al., 2019) to assess whether pregnancy has an effect. A recent prospective follow-up study showed that aortic growth rates in adult women with Turner syndrome overall are similar to healthy female controls. However, women with a BAV or repaired coarctation of the aorta appeared to dilate more rapidly. Interestingly, planned aortic root or valve surgery was a considerable cause of morbidity and mortality in this cohort (Mortensen et al., 2019).

19.5 | Ovarian cryopreservation

In the future, fertility preservation may be possible with cryopreservation of an entire ovary or parts of an ovary in young girls with Turner syndrome, perhaps as early as 2 years of age (Borgstrom et al., 2009; Gravholt, Andersen, et al., 2017b, section 3). Currently, such ovarian tissue cryopreservation programs are used among pre-adolescent girls and other women who have had cancer and are due to receive cytotoxic treatment (Anderson & Baird, 2019), from which successful pregnancies have been reported. Presently, there is insufficient evidence among women with Turner syndrome to recommend this as standard care (Gravholt, Andersen, et al., 2017b, section 3), but protocol development is ongoing at our own centers and others.

20 | OPTIMIZING MEDICAL CARE AND PERSONAL GROWTH

20.1 | Coordinated care in a multidisciplinary Turner syndrome clinic

Beyond the familiar medical problems of childhood, adult women with Turner syndrome must be monitored for both common medical problems (e.g., hypertension) and Turner syndrome-specific disorders (e.g., aortic dilatation and dissection). In addition to treating the medical issues, the management of an adult woman with Turner syndrome benefits from deliberate care coordination (Freriks et al., 2011; Trolle, Mortensen, et al., 2012a). This requires a team leader who might be the primary care physician (pediatrician, family doctor, and internist) skilled in these medical issues, or within a Turner syndrome clinic who serves as "coach" to a large team. For patients and providers, the recent Guidelines (Gravholt, Andersen, et al., 2017b; Silberbach et al., 2018) were created to bring consistency to care, but should not be viewed as rigid rules or self-enacting. In addition to the human dimension, technology can be utilized, which might apply to the entire program or specific areas requiring the most intensive review and coordination.

As an example of care coordination within the Turner syndrome program and outreach to the patient, communication about cardiovascular evaluations at the MGH Turner syndrome clinic has been enhanced in

recent years by taking advantage of the confidential staff messaging which is part of a proprietary electronic medical record (EMR) system. The cardiologist, usually the senior adult CHD specialist, may share with the patient's team members the consult note, interpretation and often, a screen shot of the aorta. Especially for adult women contemplating pregnancy, this facilitates the prompt evaluation they desire. Using telemedicine options can also enhance information delivery and care communication. The use of synchronous virtual visits for patients to review imaging studies allows patients to benefit from a Turner syndrome center without having to commute, and benefit from education regarding their cardiovascular disease from seeing their images and discussing with a physician rather than receiving a highly technical cardiovascular report, which can create anxiety.

There is a tension between communication methods which are compliant with patient privacy and those preferred by patients—particularly those with Turner syndrome. For example, the two-step log-in technique used at most institutions is secure, but more cumbersome for women with Turner syndrome. Like their peers, they prefer text messaging which is not compliant with hospital policies.

20.2 | The path to independence

Becoming an independent woman with Turner syndrome is a continuation of the transitional period into the third decade and beyond. Many young women with Turner syndrome follow familiar educational and social milestones from high school, often

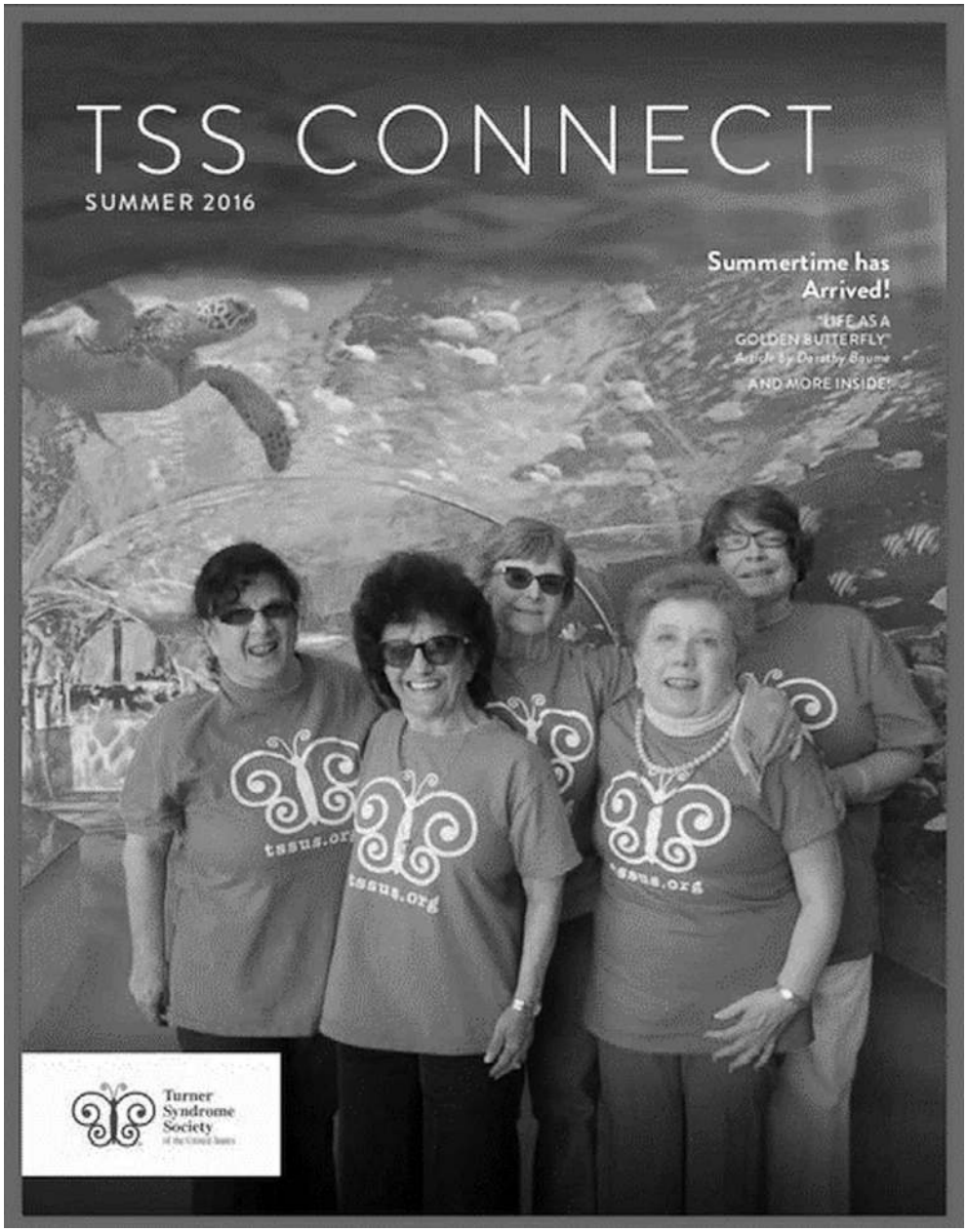

FIGURE 5 The oldest women with Turner syndrome, the "Golden Butterflies", celebrate their friendship at the 2016 annual TSSUS conference as shown on the cover of TSS Connect (summer issue, 2016, https://docs.wixstatic.com/ugd/8fb9de_2cdf3825b90341348369354ccf56ca9e.pdf)

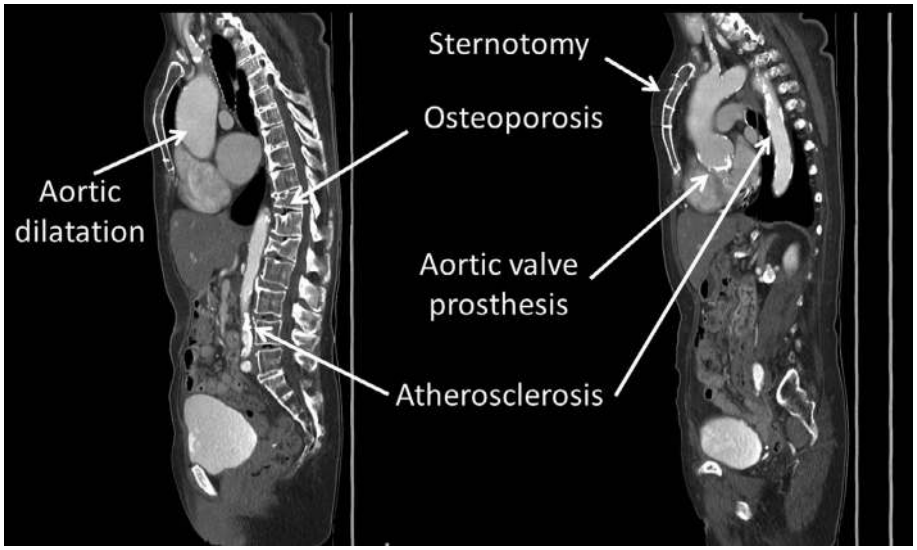

FIGURE 6 CT with contrast shows both cardiovascular and bone abnormalities. This woman had aortic valve replacement 25 years ago for a stenotic bicuspid valve, and was lost to follow-up for more than 10 years. Imaging was performed as surveillance and shows severe aortic dilatation (4 cm), severe atherosclerosis, osteoporosis resulting in vertebral collapse, fracture, increased lordosis, and flattening of the thoracic spine. (72-years-old, karyotype 45,X, type 2 diabetes. Height: 1.43 cms)

progressing to college or a two-year community college, and occasionally to advanced degrees. Ideally, women of all ages will be motivated to seek and obtain employment. For many women with Turner syndrome, there may be barriers to independence related to neuropsychologic challenges and mental health problems, which may delay or prevent independence. Reliance on parents for financial and healthcare support may be prolonged. Professional life and career "coaches" can be invaluable to provide direction and enhance confidence.

20.3 | Role of support groups (disease specific advocacy groups)

It is not uncommon for Turner syndrome specialists to hear that an adolescent or adult patient has never met another individual with Turner syndrome. With the explosion of information on the Internet, a simple query using any major search engine produces a profusion of photographs, videos, and educational figures. Not all are accurate or representative, but they do provide easy access to the subject matter. For some women, curiosity is tempered with hesitation and a wish to preserve their privacy. Those who are very shy or dealing with social interaction challenges common in Turner syndrome may be reluctant to meet others. Because of the wide spectrum of appearance and function associated with mosaicism, some individuals may not identify with Turner syndrome as a diagnostic category or label. Those who seek a more realistic opportunity for socializing and education are usually delighted to become members of the support groups for individuals, families, and friends of Turner syndrome (see references for list of websites). In particular, the national organization plays an important role in creating a social milieu, with education and access to research through its website, as well as through local and annual national meetings. In turn, Turner syndrome clinicians and bench scientists can meet girls and women in a more relaxed atmosphere than the typical clinic visit.

21 | TRANSITIONING FOR THE OLDEST ADULTS

21.1 | Definition, overview

An older adult is defined as older than 65 years, and within the Turner syndrome community, these women often refer to themselves as "Golden Butterflies" (Figure 5). In general, there is a trend to discourage use of the terms "seniors, elderly, aging, and geriatrics" in favor of positive aging ideology and terminology such as "older people" or "older adults" (Weisman, 2019). A recurring theme in this article has been the need for evidenced-based data, and even more so for the oldest individuals, for whom data is lacking. In the MGH Turner Syndrome clinic, we have followed four women over the age of 65 years (one of whom died of aortic dissection), while the clinic in Aarhus follows 10 women. Information is needed about common medical problems which could become more frequent (e.g., hypertension, hearing loss, osteoporosis, atherosclerosis), and rare features which could become problematic beyond the seventh decade (e.g., aortic dilatation/dissection, cancer) (Figure 6). Some issues have been addressed in previous sections on epidemiology, cardiovascular health, and cancer. With improved cardiovascular and hormonal health, we anticipate that the Turner syndrome patient population will grow older and suggest that providers consider this as a second transition period in their lifespan. Unknown is the potential cardiovascular risk posed by pregnancy, both during and after the pregnancy.

21.2 | Specific issues associated with aging

Non-medical life issues must be considered when caring for this age group. Depending on the adequacy of healthcare, older women with Turner syndrome may be vulnerable because of increasing morbidity at a time when medical insurance may not be adequate. Practical matters involving home care and personal health may be greater for those with severe short stature, reduced mobility, cardiac

limitations, and psychosocial constraints. Some older women have voiced concerns about the unknown medical aspects of Turner syndrome related to aging. Unknown is whether memory loss such as Alzheimer disease or due to cerebrovascular insufficiency could be more common. A solid support system is often lacking if a woman loses her partner, has no children, or has no close family or social support in close proximity. Physical challenges increase with the onset of decreased flexibility and weight management challenges. For example, the seemingly simple act of putting on and removing support hose for women with lymphedema can be physically demanding and could require assistance.

Driving is a skill that may have taken multiple attempts due to spatial learning disabilities. Once achieved, women with Turner syndrome are typically cautious drivers who may benefit from navigational devices. As with other older patients, safety may become a concern when there are motor vehicle collisions and the need to stop driving becomes a necessity. Strategies to approach this sensitive topic which results in a loss of autonomy can been extrapolated from general guidelines (Aronson, 2019).

Some older women with Turner syndrome (or their families) who have a vulnerable cardiovascular system, or who are simply forward-thinking, may want to discuss their end of life. This can be approached in a positive, sensitive manner, which focuses on the person's autonomy in how they want to live socially, financially, and medically (Prakash, San Roman, et al., 2019a). This recent article responded to women with Turner syndrome who had voiced questions at national meetings, and expressed a wish to contribute to science by donating their body for autopsy and research.

22 | CONCLUSION

Adolescents and adults with Turner syndrome represent a diverse group of individuals living with both typical and unique medical and psychosocial challenges. Often forgotten are the personality attributes which allow many to benefit from the "gifts" of Turner syndrome. As noted in individuals with Marfan syndrome (Pyeritz, 2018), and applicable to Turner syndrome, improved clinical history and an expanded phenotype with age means that there will be additional clinical problems to be monitored, and often a need for more Turner syndrome specialists. There is a pressing need for research to obtain more information about lifespan, clinical issues, mental health, and access to care. Our international group of authors tried to convey awareness of the differences faced by many women due to barriers of income, variations in healthcare systems, and specific health problems. We are convinced that the future should be brighter for adult women with Turner syndrome through increased awareness of medical and psychosocial problems, expansion of the knowledge base using multi-specialty research studies, and mobilization of Turner syndrome-specific clinics.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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APPENDIX: WEBSITES

GENERAL

Turner Syndrome Society of the United States, http://www.turnersyndrome.org/.

Turner Syndrome Global Alliance, http://tsgalliance.org/.

Turner Syndrome Foundation, Inc., www.TSFUSA.org.

Turner Foreningen i Danmark, www.turner-forening.dk/turner-syndrom.

National Library of Medicine Genetics Home Reference, https://ghr.nlm.nih.gov/condition/turner-syndrome.

Turner Syndrome Society of the United States (TSSUS): Clinical Practice Guidelines for the Care of Girls and Women with Turner syndrome (Gravholt, Andersen, et al., 2017b), and Brief Synopsis for Turner Syndrome Girls and Women and for their Parents/Caregivers/Families, http://www.turnersyndrome.org/.

UpToDate. Clinical manifestations and diagnosis of Turner syndrome (Philippe Backeljauw, MD), http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-turner-syndrome.

Turner Syndrome Global Alliance (TSGA) "Levels of Care" which currently apply to pediatric clinics, but could be extrapolated to include older women: https://drive.google.com/file/d/0B6KcRBfj-PzEVmx1WWxIOG4weII5Q2drLTJUY2YtSFJHUDNr/view.

TSGA Resources for Professionals, http://tsgalliance.org/httptsgalliance-orgconnect-to-resourcesfor-individuals-families/for-professionals/.

TRANSITIONING

American College of Physicians. Turner Syndrome. ACP High Value Care 2016, www.acponline.org.

The National Health Care Transition Center, AAP Got Transition Website, www.gottransition.org.

Endocrine Society: Transitions of Care (Turner syndrome), http://www.endocrinetransitions.org/turner-syndrome.

The University of North Carolina STARx Program, https://www.med.unc.edu/transition/transition-tools/.

Transition Readiness Assessment Questionnaire, https://www.etsu.edu/com/pediatrics/traq/.

Endocrine Society, Hormone Health Foundation, Turner syndrome Foundation and the ACP: Turner syndrome specific tool kit, https://www.endocrine.org/guidelines-and-clinical-practice/transitions/turner-syndrome.

CARDIOVASCULAR HEALTH

AHA Scientific Statement: Cardiovascular Health in Turner Syndrome, https://www.ahajournals.org/doi/pdf/10.1161/HCG.0000000000000048.