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FELLOWS FORUM

WILEY Congenital Heart Disease

Congenital heart disease and cardiac procedural outcomes in patients with trisomy 21 and Turner syndrome

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Abstract

Congenital heart disease (CHD) is present in approximately 50% of patients with trisomy 21 (T21) and Turner syndrome (TS). According to the American Academy of Pediatrics, every patient with these genetic disorders should have a postnatal echocardiogram. T21 is usually associated with atrioventricular (30%–60%), atrial (16%-21%), or ventricular septal defects (14%–27%). TS is usually associated with left-sided heart disease. However, the spectrum of CHD in these genetic disorders is wider than those mentioned lesions. More cardiac surgical procedures are offered to these patients and that has influenced positively their life expectancy for some CHD conditions. Single ventricular anatomy is associated with high mortality in these genetic disorders (49% in T21 and 83%–91% in TS). The goal of this article is to describe the spectrum of CHD, screening guidelines, and cardiac surgical outcomes in patients with T21 or TS with CHD.

KEYWORDS

congenital heart disease, outcomes, trisomy 21, Turner syndrome

1 | INTRODUCTION

Approximately 50% of the patients with trisomy 21 (T21) and Turner syndrome (TS) have congenital heart disease (CHD). The objective of this article is to describe the spectrum of CHD and cardiac surgical outcomes of patients with these genetic syndromes.

2 | TRISOMY 21

2.1 | Background

Down syndrome is a genetic disorder characterized by an extra chromosome 21, and it is related to multiple comorbidities and intellectual disability. According to the World Health Organization, the estimated worldwide incidence of T21 is 1 in 1000–1110 live births. Life expectancy has significantly evolved from 10 years in the 1900s to 80% reaching 50 years and beyond in the current era. However, there is a four to eightfold increase in mortality in patients with T21 compared with the normal population.[1] CHD is present in 35%–60%[2–6] of these patients, and it is one of the main causes of death (30%-35%).[7]

2.2 | Screening guidelines

According to the 2011 American Academy of Pediatrics (AAP) health care for individuals with Down syndrome article,[2] every patient with T21 should undergo a postnatal echocardiogram (ECHO) within the first month of life independently of having had a prenatal ECHO, and if it is abnormal, they should be referred to a pediatric cardiologist. It is important to have this ECHO done in a pediatric cardiology center where the technicians and cardiologists are trained in CHD. Multiple studies have suggested performing an initial screening within the first week of life, including physical exam, chest x-ray, and electrocardiogram (ECG), and if abnormal, to proceed with an ECHO.[8] However, without ECHO, the sensitivity of these screening tests for detecting major CHD ranges between 71% and 95%.[4,5,8]

2.3 | Neurodevelopmental outcome in patients with CHD and T21

T21 is associated with intellectual disability, from mild to severe, with language, expressive and receptive speech deficiencies. When comparing patients with T21 and CHD (T21-CHD) who underwent surgical procedure that required cardiac bypass within the first year of life with T21 patients without CHD (T21-nonCHD), T21-CHD infants/toddlers

had lower scores in expressive and receptive language[9] and gross motor skills[10] using the Bayley-III test.[9] T21-CHD preschoolers had lower scores, but not statistically significant, for auditory communication, expressive communication, visual motor and fine motor compared with T21-nonCHD group.[9] By school age, children within the T21-CHD group did not demonstrate any differences in math, reading, language capabilities, executive functioning, internalizing or externalizing symptoms when compared with T21-nonCHD patients.[9]

2.4 | Risk factors associated with development of T21 and CHD

There are discrepancies regarding gender and the risk of CHD in patients with T21, CHD being more frequently reported in females.[1,5,6,11] Other studies have suggested male predominance.[12] Prenatal factors associated with T21-CHD include maternal smoking (adjusted relative risk 1.57 [1.18–2.09]) and obesity (BMI $>$ 30 kg/m^2) with a 16%-34% increased risk.[6] Neither maternal hypertension (HTN) nor diabetes were associated with increased risk of developing CHD in fetuses with T21.[6]

2.5 | Spectrum of CHD in patients with T21

There is a wide spectrum of CHD in patients with T21. Atrioventricular septal defect (AVSD) is the most frequent CHD in patients with T21 (30%-60%),[4–6,9,11,12] followed by atrial (16%–21%),[4,6,8,12] and ventricular septal defect (VSD) (14%-27%),[4–6,8,9,12] tetralogy of Fallot (2%–11%),[5,8,12] patent arterial duct (6%),[5] coarctation of aorta (CoA) (0.3%),[8] and bicuspid aortic valve (BAV) (0.5%–2%).[5,8] Some of the CHD lesions could be isolated or combined with other types of CHD.

2.6 | Surgical procedures

Given the frequency of the lesions, it follows that complete AVSD repair is the most frequent cardiac procedure, followed by VSD repair.[3,7]

2.7 | Primary AVSD repair

Preoperatively, patients without T21 (non-T21) have more moderate to severe left atrioventricular valve regurgitation (T21 vs non-T21, 17% vs 38%, P = .05).[13] Centers vary regarding timing of primary AVSD repair in patients with T21. According to Lange et al.[14] and Atz et al.,[13] there is no difference regarding timing of AVSD repair between patients with and without T21; however, Fudge et al.,[3] reported primary AVSD repair at a younger age in T21 patients (median: T21 vs non-T21, 4.4 [3.2–7.1] vs 4.6 [3.1–8.5] months, P = .01). Other characteristics in patients with T21 compared with non-T21 patients regarding the time of repair included shorter height (median: T21 vs non-T21, 59 [56–62] vs 61 [56–67] cm, $P <$ .0001),[3] and lower weight[13] (median: T21 vs non-T21 4.9 [4.3–5.6] vs 5.1 [4.2–6.8] kg, P = .0004). There were no differences regarding cardiac bypass or cross-clamp times between the two groups.[3,13,14] Hospitalization length of stay (LOS) after repair was also similar in both groups[13] (median of 7 days, P = .9).[3] Patients with T21 needed longer postoperative mechanical ventilation times compared with non-T21 patients, (median: T21 vs non-T21, 3 vs 2 days, P = .012).[14] Patients with T21 had lower in-hospital mortality[15] (T21 vs non-T21, 1.9% vs 3.9%, P = .02); however, Lange et al.[14] reported no differences, and both groups had similar 6-month post procedural mortalities of 4%.[13,14]

2.8 | Risk of reoperation after AVSD repair

Higher frequency of reoperations was reported in patients with non-T21 (22.7%) compared with patients with T21 (11.1%), mainly left atrioventricular valve procedures (non-T21 vs T21, 5.3% vs 1.5%, P = .03),[15] despite no significant difference in postoperative left atrioventricular valve regurgitation degree.[6,13] This finding is thought to be secondary to more frequent anomalies in non-T21 patients, such as double orifice mitral valve and single papillary muscle.[1,14] Patients with non-T21 had higher freedom of reoperation (71%–81.4%) after successful biventricular repair or definitive univentricular palliation compared with T21-CHD patients (75%–94.6%),[15] but this has not always been statistically significant.[14]

2.9 | VSD repair

Patients with T21 and CHD are at risk of developing irreversible pulmonary vascular changes by 6 months.[7] Proposed reasons include failure of pulmonary artery resistance to regress after birth in patients with left to right shunting, lung hypoplasia, and obstructive airway disease causing hypercarbia, hypoxia, and pulmonary vasoconstriction.[16] According to Fudge et al., when comparing patients with and without T21, patients with T21 by the time of surgical repair were younger (median: T21 vs non-T21, 4.8 [3.2–7.1] vs 7.4 [3.8–25.2] months, $P <$ .0001), smaller (median: T21 vs non-T21 60 [56–65] vs 67 [59–87] cm, $P <$ .0001), and had lower weight (median: T21 vs non-T21, 4.9 [4.3–5.6] vs 5.1 [4.2–6.8] kg, $P <$ .0001).[3] Patients with T21 had longer cardiac bypass (median: T21 vs non-T21, 77 vs 72 min, $P <$ .0001) and cross-clamp times (median: T21 vs non-T21, 46 vs 41 min, $P <$ .0001).[3] Patients with T21 did not have differences in in-hospital mortality (T21 vs non-T21, 0.6% vs 0.5%, P = .7), but did have longer LOS (median: T21 and non-T21, 5 vs 4 days, $P <$ .0001).[3]

2.10 | Single ventricle in patients with T21

Patients who had undergone the single ventricle (SV) palliation, mainly had unbalanced AVSD.[1] The higher risk of elevated pulmonary vascular resistance in this population puts them at risk of increased postoperative mortality.[1] When comparing patients with CHD with and without T21 regarding in-hospital mortality after palliative procedures, it is higher in T21 patients after systemic to pulmonary shunt (T21 vs non-T21, 16.8% vs 10.8%, $P <$ .05), and bidirectional Glenn (T21 vs non-T21, 15.6% vs 2.1%, $P <$ .05), but lower after Fontan (T21 vs non-T21, 0% vs 2.3%, $P <$ .05).[1] Fudge et al. also published similar findings, reporting higher in-hospital mortality after stage 1 palliation (T21 vs non-T21, 72.9% vs 19.4%, $P <$ .0001), bidirectional Glenn (T21 vs non-T21, 18.8% vs 1.8%, $P <$ .0001), but Fontan was higher (T21 vs non-T21, 23.5% vs 1.6%, $P <$ .0001). The LOS was longer after

bidirectional Glenn procedure compared with non-T21 counterparts (median: T21 vs non-T21, 10 vs 6 days; $P = .0002$), but no differences were present after Stage 1 palliation (median: T21 vs non-T21, 27 vs 21 days, $P = .6$) and Fontan procedure (median in both groups: 9 days, $P = .3$).[3] Furukawa et al.,[17] reported that they performed more extracardiac fenestrated Fontan procedures in T21 patients (T21 vs non-T21, 50% vs 15%, $P = .031$); and after Fontan procedure, T21 patients had more use of postoperative nitric oxide (T21 vs non-T21, 50% vs 7.9%, $P < .001$), longer mechanical ventilation times (mean: T21 vs non-T21, 7.8 vs 2.6 days, $P = .039$), longer intensive care unit LOS (mean: T21 vs non-T21, 14 vs 5.2 days, $P = .009$), longer pleural drainage duration (mean: T21 vs non-T21, 17 vs 9.7 days, $P = .027$) and longer hospitalization (mean: T21 vs non-T21, 40.1 vs 27.7 days, $P = .007$). There were no differences between late or in-hospital deaths ($P = .5$). Colquitt et al.[18] and Campbell et al.[16] reported similar findings; 79% of patients with SV anatomy had pulmonary artery banding as their first palliation, with only 21% of the patients reaching definitive palliation (Fontan or 1.5 repair), with an overall SV mortality of 43%. However, SV patients with T21 had minimal mortality beyond 2 years if pulmonary vascular resistance was less than 3 WUm^2 during the first year of life.[18] Studies recommend offering pulmonary artery banding within the first 6 months of life to avoid irreversible vascular damage, even if the providers are undecided between taking biventricular or univentricular pathways.[18]

2.11 | Postoperative complications in patients with T21 and CHD

Postoperative complications include pulmonary infections secondary to subglottic stenosis, laryngo-, tracheal-, and bronchomalacia that put them at risk of failing extubation[1] and were identified as risk factors for early and late deaths.[7] Other complications, more frequent in patients with T21 compared with non-T21, included surgical site infections,[17] pulmonary HTN, development of chylothorax, and pacemaker placement after VSD repair.[3]

2.12 | Heart transplant in patients with T21

After some initial controversy, Sandra Jensen was the first patient with T21 who underwent heart and lung transplant in 1996.[19] She died 16 months later after a brain surgery. A 14-year experience from a single center in the United Kingdom described that they had a total of three T21 referrals for heart transplant, but none received it for reasons other than T21. There are not any available publications describing the outcomes of heart transplant in patients with T21. However, because of their immunological abnormalities, it is expected that they would be at risk of higher incidence of infection, malignancy, and autoimmune disease.[20]

2.13 | Conclusion

CHD is present in approximately 50% of patients with T21. AVSD repair is the most frequent cardiac surgery. After AVSD repair, T21 patients have lower frequency of reoperation and have similar in-hospital and long-term mortalities compared with non-T21 counterparts. T21 patients are at increased risk of irreversible pulmonary vascular changes within the first 6 months of life, so if complete repair is not possible at that age or still undecided, pulmonary artery band should be considered to protect pulmonary vasculature. Single ventricular anatomy in Down syndrome is associated with increased mortality. There is limited information about outcomes of heart transplant in patients with T21. More research is warranted in this topic.

3 | TURNER SYNDROME

3.1 | Background

Turner syndrome (TS), also known as Ullrich–Turner syndrome, is a genetic disorder characterized by an abnormal or absent second chromosome X.[21] It is estimated that TS is present in 3% of all female fetuses; however, only 10% survive.[22,23] Estimated prevalence is 1 of every 2000–2500 female live births.[24] CHD is present in 30%–50% of all patients with TS, mainly left sided heart disease; however, other lesions have been described.[21,25] The objective of this article is to describe the spectrum of CHD and outcomes in patients with TS.

3.2 | Screening and follow up

According to the American Academy of Pediatrics (AAP), all patients with TS should have an initial cardiology evaluation,[26] independently of history of normal fetal ECHO.[23,27] In cases of normal initial evaluation, pediatricians should closely monitor the cardiovascular exam (heart murmurs, blood pressure) and repeat cardiologic evaluation with cardiac imaging (ECHO or cardiac magnetic resonance imaging [MRI]) every 5–10 years, or sooner if transitioning to an adult clinic or planning pregnancy, to evaluate the presence of aortic dilation.[23,25,26] Routine ECG screening should be performed to evaluate prolonged QT interval.[25] Follow up evaluations should be at least yearly in patients who have BAV, HTN, or history of CoA with physical exam, ECG, and ECHO. If the aorta is dilated, follow up interval should be biannual to annual, depending on the size of ascending aorta and rate of its dilation using MRI or computed tomography angiography (CTA) if ECHO imaging quality is not adequate.[23]

3.3 | Etiology of CHD in patients with TS

Multiple theories about the etiology of CHD in patients with TS have been proposed, but none explains the whole spectrum of CHD in this population. The prevalence of CHD has been described to be higher in patients with chromosome X monosomy compared with mosaics or structural abnormalities in chromosome X.[25]

One theory regarding CoA development is that fetal lymphatic pressure and jugular lymphatic sac obstruction (apparent in fetuses as early as 10–12 weeks of gestational age) causes distention of the thoracic duct and external compression of the ascending aorta, reducing the blood flow through the developing heart and resulting in small left sided cardiac structures, as well as left superior vena cava due to back pressure from obstructed flow.[23,28] In surviving fetuses, the lymphatics mature and patients develop webbing of the neck.[23,25] It has been reported that

webbed neck is associated with the most severe CHD phenotype[28] and has a strong association with CoA and BAV;[26,27,29] however, there are patients with webbed neck who do not have CHD.[23] Other proposed theories include TGF-β2 deficiency resulting in fourth pharyngeal arch obstruction,[30,31] abnormal endothelial release of TGF-β1 influencing angiogenesis process of differentiation of neural crest cardiac cells,[30] or haplo-insufficiency for Xp (missing the short arm of the X chromosome) contributing to abnormal aortic valve and arch development.[23]

According to Bechtold et al.,[32] lymphatic flow obstruction and dilation increases the distance and causes incomplete fusion between the developing pulmonary veins and the left atrium causing partial anomalous pulmonary venous return (PAPVR).[32]

Marfan and TS have similar histological vascular changes such as cystic medial necrosis that has been found in 42%–72% of TS patients with aortic dilation who had dissection.[25,30] Other vascular abnormalities found in TS include reduced distensibility of branchial and carotid arteries,[23] decreased vascular endothelial growth factor and biglycan,[33] changes in vascular smooth muscle cells, elastin, and collagen fibers,[33] aortic and carotid wall thickening, increased TGF-β1 affecting SMAD signaling pathway and causing proliferation abnormalities of matrix proteins.[25,30,34] All these findings create concerns for increased vascular friability, risk of bleeding, and aneurysmal formation.[23,30]

3.4 | Diagnosis

Prenatal diagnosis is suspected in cases of increased nuchal translucency, cystic hygroma, anasarca, poly- or oligohydramnios, horseshoe kidney, growth retardation, or brachycephaly.[23] CHD findings concerning for TS include CoA or hypoplastic left heart syndrome (HLHS).[25,27] Postnatally, physical findings include lymphedema (secondary to increased lymphatic pressure causing vascular endothelial growth factor overexpression and increased vascular permeability),[23,32] webbed neck (tenting of the neck secondary to fetal cystic hygroma),[35] pedal edema with upturned toenails, cubitus valgus and widely spaced nipples. Lymphedema usually resolves by 2 years of age. TS diagnosis could be missed early in life and be diagnosed during childhood/teenage years during an evaluation of short stature or premature ovarian failure. All patients with prenatal or postnatal concerns for TS should have a karyotype, even if prenatal karyotype was performed.[27]

3.5 | Spectrum of CHD in patients with TS

CHD is present is 20%–50%[26,27] of patients with TS. The most frequent CHD are BAV (11%–50%),[27,33,36–38] CoA (11%–35%)[25–27,33,36,37,39] followed by HLHS, PAPVR, and elongation of transverse aortic arch.[23,40] Atrial and ventricular septal (1%–2%)[30] defects are usually small and not frequent in patients with TS, and if present, they do not usually require surgical repair.[23] There are other less commonly described types of CHD lesions in this population,[23] most of them in case reports, such as hypertrophic cardiomyopathy,[41] tetralogy of Fallot,[42,43] AVSD,[44] patent arterial duct, and aortic or pulmonary artery valve stenosis, among others.[30]

3.6 | Anomalous venous return

Anomalous venous return anomalies include pulmonary and systemic in patients with TS. Systemic venous return anomalies include left superior vena cava (7.8%–13%)[37,45] and interrupted inferior vena cava with azygous continuation (2%).[36]

PAPVR is found in 13%–15.7%[23,37,45] of patients with TS when using MRI as diagnostic imaging tool, but usually can be diagnosed by ECHO in 1.5%–3.7% of the cases.[46] PAPVR has been found to be one of the most missed cardiac diagnosis in the TS population, and is usually diagnosed later in life. Patients are asymptomatic until teenage years or adulthood.[23] Described PAPVR lesions in TS include left upper pulmonary vein draining into right atrium through a vertical vein or right upper or middle veins draining to the superior vena cava.[37] Kim et al.[37] study compared patient with TS with and without PAPVR (non-PAPVR) by cardiac MRI; however, right ventricular end diastolic and systolic volumes (RVEDV and RVESV) were reported as grams instead of ml, that is most likely a typo, so data are reported in ml in this review. Patients with TS with PAPVR had statistically significant higher RVEDV (median: PAPVR vs non-PAPVR, 133.4 [IQR 113.3–148.2] vs 92.7 [IQR 80.0–112.3] mL, $P = .0038$), RVESV (median: PAPVR vs non-PAPVR, 47.8 [IQR 38–57.9] vs 28.5 [IQR22.9–34.7] mL, $P = .0022$), end diastolic right heart mass (median: PAPVR vs non-PAPVR, 10.1 [IQR 7.3–12.9) vs 7.4 [IQR 6.1–9] g, $P = .0378$) and Qp : Qs ratio (median PAPVR vs non-PAPVR, 1.29 [IQR 1.14–1.54] vs 1.00 [IQR 0.99–1.03, $P = .0014$) than in patients without PAPVR.

Multiple studies[23,37,46] recommend the use of unsedated cardiac MRI/MRA as a screening method for patients with TS, not only to evaluate critical cardiovascular lesions, but also for long term morbidity of cardiac lesions missed by transthoracic ECHO.

3.7 | Aortic arch branching anomalies

Arch anomalies include elongation of transverse aortic arch, also known as pseudocoarctation (31.4%-50%),[23,37,45] aberrant right subclavian (8%)[45] or vertebral artery (4%),[45] and bovine arch (8%).[37,45] Elongation of the transverse arch is associated with BAV, CoA, and aortic sinus dilation.[37]

3.8 | Aortic dilation

Aortic dilation is present in 3%–30%[23,27,39] of patients, and it mainly affects the aortic root and ascending aorta.[25] According to Bondy et al., ascending aorta upper limit of normal in patients with TS should be an aortic size index (ASI) of 2 cm/m^2, and if meeting or exceeding 2.5 cm/m^2, surgical intervention should be considered.[23] Other proposed definitions for dilated ascending aorta include ascending to descending aorta ratio greater than 1.5,[39] that Bondy et al. do not agree using this criterion[23] with the concern that the descending aorta is also abnormal in this population.[38] Aortic dilation is associated with aortic dissection, most reported during adulthood with mean age of 30–35 years,[38] some cases in patients younger than 21 years had been reported.[26] When comparing aortic tricuspid (TAV) with bicuspid valve in patients with TS in adults (mean: TAV vs BAV: 26.6 vs 28.8 years,

$P = .22$), BAV patients had higher aortic peak flow velocity (mean: TAV vs BAV: 1.3 vs 1.6 m/s, $P < .0001$), annulus (mean: TAV vs BAV: 1.88 vs 2.07 cm, $P < .001$), sinuses (mean: TAV vs BAV: 2.61 vs 2.80 cm, $P < .003$), sinotubular junction (mean: TAV vs BAV: 2.11 vs 2.31 cm, $P < .001$), and ascending aortic diameters (mean: TAV vs BAV: 2.34 vs 2.62 cm, $P < .0005$).[38,47]

Hjerrild et al.[38] reported that ECHO has lower sensitivity diagnosing less than severe aortic dilation, and that cardiac MRI provides a better aortic evaluation. Prophylactic use of beta-blockers in the absence of HTN to prevent aortic dilation has failed to demonstrate any benefit.[25] It is still unclear whether beta-blockers or angiotensin II receptor blockers have any effect in slowing down aortic dilation progression.[23]

3.9 | Aortic dissection

Aortic dissection prevalence is 1.4%, with an incidence of 36/100 000 in TS patients per year, average of 30.7 (range 4–64) years.[23,25,48] This is younger than in the general population in whom the average age for dissection is 68 years.[34] It is reported to be the cause of 2%-8% deaths in patients with TS. Reported location of dissection include the ascending aorta (55%–85%), descending aorta (15%–37%), and both (8%).[23,30,34,48,49] Most patients who dissect will have symptoms such as chest, neck, back or abdominal pain, shortness of breath, nausea, vomiting, dizziness, or sudden death before presentation. Duration of symptoms does not correlate with chances of survival.[48] Carlson et al.[48] reported 37% survival after dissection. Risk factors found in up to 90% of the cases include HTN with/without left sided heart disease. Sixty-nine percent have a history of CHD such as CoA (47%), BAV (27%–95%), or both (18%). Ten to twenty percent of patients have no identifiable risk factors.[25,34,48] Because of the risk of dissection, these patients should have aggressive HTN management. Surgical intervention (replacement/angioplasty) has been suggested in TS patients with ascending aorta measurements of 4.5 cm or greater.[23]

3.10 | BAV

BAV is present in 1%–2% in the general population;[47] however, it is present in 11%–50% of patients with TS, usually secondary to fusion between right and left coronary cusps.[23,47] It is diagnosed by ECHO in 89% of cases.[47] Cardiac MRI has higher sensitivity, and has manifested an increase in frequency of diagnosis of BAV in TS.[47] BAV is an independent factor associated with aortic dilation, independent of its functional status.[47] Aortic valve monitoring should be performed to evaluate development of aortic stenosis (4%–16%), insufficiency (6%-45%), aortic dilation, and dissection.[25]

3.11 | Coarctation of aorta

CoA is the second most frequent CHD in patients with TS. It could be associated with other CHD lesions, most frequently BAV (20%–58%);[50] however, other lesions described include PAPVR, left superior vena cava, VSD, subaortic membrane, anomalous right subclavian artery, and restrictive cardiomyopathy.[33] Surgical CoA repair continues to be the standard treatment for this condition in infants less than 3 months old.[51] It is the most frequent cardiac surgical procedure in patients with TS and has an 11% operative morbidity.[50] Cramer et al. compared characteristics and outcomes of CoA repair in patients less than 16-year-old with and without TS. TS patients were younger (median: TS vs non-TS: 12 vs 70 days, $P = .001$), had lower weight (median: TS vs non-TS: 3.2 vs 5.3 kg, $P = .001$), longer cross-clamp time (median: TS vs non-TS: 22 vs 18 min, $P = .01$), and LOS (median: TS vs non-TS:9 vs 5 days, $P < .001$). Follow up of 8.8 ± 9 years after CoA repair showed that 12.5% of the patients had residual echocardiographic arch gradients over 19 mm Hg; 5% needed surgical reintervention. There were no reports of aortic dissection, dilation or aneurysm formation.[21] Surgical complications in TS include bleeding secondary to clamp injury on the friable aorta, sometimes resulting in reoperation and not related to age of repair,[52] dissection and aneurysm formation.[50] Factors that may explain prolonged LOS in TS patients include feeding intolerance, chest tube drainage and need of respiratory support.[21]

Kataoka et al.,[51] reported outcomes of balloon angioplasty in three cases of native CoA in TS (age: 3–17 years old), and after 3–4 years follow up, none had aneurysm formation or lesion recurrence. Balloon angioplasty risks include rupture, restenosis, dissection and aneurysm formation, with 20% reported aortic wall injury and 6.6% mortality rate.[50] Van den Hoven et al.[33] reported outcomes of 19 cases of percutaneous angioplasty in patients with TS, median age 16.9 (range: 7–60) years, with stent placement in 68% of the subjects. In his series, TS patients who had covered stent placement had descending aortic dissection, two confirmed and one suspected. Morbidity has been reported of 19% after balloon angioplasty and 9% after stent placement.[50] Patients with TS should be advised of the risk of dissection and death during and after percutaneous angioplasty procedure.

3.12 | Coronary arterial anomalies

Coronary arterial anomalies are more frequent in patients with TS (20%) compared with the general population (5%).[36] Those anomalies mainly involve the left coronary artery. They include absent left main coronary artery, left circumflex arising from the right coronary sinus,[36] coronary to pulmonary artery fistula or left coronary artery arising from pulmonary artery.[21] Anomalies related to right coronary artery include high origin above the aortic sinus.[36] Other reported coronary artery abnormalities include origin from descending aorta and coronary arteries dilation.[30] There is no correlation between coronary arterial anomalies and having 45 X mosaic or monosomy.[36] The etiology of coronary arterial anomalies in TS remains unclear.

Patients with TS have higher relative risk of coronary artery disease (2.1)[25] and increased risk of myocardial infarction around the fifth decade[30] due to comorbidities such as dyslipidemia, hypercoagulability, HTN, diabetes, and premature ovarian failure.[23,30]

3.13 | Single ventricular anatomy

Univentricular palliation in patients with TS is usually performed in patients who have HLHS. Cramer et al.[21] published a single center

experience in patients with HLHS who underwent single ventricular pathway. His study included initially 6 patients (2 who were later excluded). Four patients underwent Norwood procedure, three survived stage II procedure but 2 died later; the surviving patient was in palliative care. Lara et al.[53] used the Texas Birth Defect Registry and reported the outcome of 11 patients with HLHS, with only 1 patient surviving at the end of the study after stage 2 palliation (mortality: 6 cases before surgery, 3 after stage 1 palliation, 1 after state 2 palliation). Despite poor outcomes in patients with TS, SV palliation is still offered to this population. The reason of increased mortality in this population remains unclear.

3.14 | Heart transplant in patients with TS

There are currently no publications regarding heart transplant in patients with TS.

3.15 | Electrophysiologic abnormalities

Patients with TS have abnormal vagosympathetic tone causing resting tachycardia that starts in fetal life and continues through adulthood, accelerated conduction between atrial and atrioventricular node[54] and reduced heart rate variability. Other factors include T wave abnormalities, right axis deviation, not always secondary to PAPVR[23] and repolarization abnormalities causing prolonged QTc interval (33% children and 20% adults)[54] that was associated with sudden deaths.[30] Mutations in the following genes have been found in patients with TS: SCN5A, KCNH2, KCNE2.[54] BAV and medications (hormone replacement therapy, cholesterol, and blood pressure [BP] medications) have not been found to be the cause of prolonged QTc interval.[54] TS patients are at increased risk of atrial arrhythmias.[30] Based in these electrophysiologic abnormalities, the use of beta-blockers may have more than one benefit on this population.[54]

3.16 | Hypertension

Twenty-five to forty percent of adolescents and up to 60%[38] of adults with TS have HTN (elevated systolic BP), usually essential; however, 20% of the cases could be secondary to renal or cardiovascular abnormalities. These patients also have blunted decreases in BP during sleep.[30] In patients with premature ovarian failure with TS, estrogen deficiency has been associated with elevated BP. This improved after treatment with transdermal low doses of estrogen.[30] Proposed causes of HTN in these patients include elevated plasma renin levels and abnormal vagosympathetic tone.[25] Treatment options include beta-blockers, angiotensin converting enzyme inhibitor, or angiotensin receptor blockers (ARB). ARB antagonizes TGF-β1[30] and may benefit TS aortopathy; however, more research is warranted in this topic. Calcium channel blockers have been associated with worsening lymphedema, and should not be given to infants because of the risk of sudden death associated with this class of drugs.

3.17 | Growth hormone

There have been concerns of the use of growth hormone (GH) in patients with TS, as the dose given is higher to what is given to GH deficient patients. GH excess is associated with elevated heart rate and cardiac output, cardiac hypertrophy, cardiomyopathies, mitral and aortic insufficiency. GH treatment in GH deficient patients causes ventricular hypertrophy.[55] Matura et al. described outcomes of 67 TS patients who were treated with GH for average of 4–5 years. This study demonstrated that subjects who received GH were taller, and had normal proportional growth to their body size of ventricular dimensions without evidence of hypertrophy;[55] however, it did not describe a timeframe between GH treatment and ECHO. Bondy et al.[56] reviewed changes in aortic dimensions using cardiac MRI, after receiving GH treatment for 2 years, and reported no differences in ascending or descending aorta dimensions, and better (more normal) aortic to descending aorta ratios compared with patients with TS who did not receive GH. Factors influencing ascending aortic dimensions included weight, height and history of BAV; factors influencing descending aortic dimensions included age, height and history of CoA.[56] Van den berg et al.,[57] reported 6 month follow up by cardiac MRI after GH treatment, and demonstrated that TS patients did not demonstrate ventricular hypertrophy or dysfunction, but had smaller ventricular volumes without difference in cardiac output, as TS patients had higher resting heart rates when compared with healthy individuals. So far, studies have demonstrated that patients with TS who received GH did not have changes in BP,[58] ventricular or aortic dimensions, electrical abnormalities or increased risk of aortic dissection,[25] and that its use may be beneficial for aortic biophysical wall properties.[39] There is limited knowledge of long-term effects of GH in the cardiovascular system.

3.18 | Pregnancy

Spontaneous pregnancy has been reported in 2%–5% of patients with TS, usually in cases of mosaicism. Pregnancy is uncommon (<0.5%) in 45 X monosomy.[59] Most of the TS patients who achieved pregnancy had assisted reproductive therapy. According to the Practice Committee of the American Society for Reproductive Medicine,[60] "Turner syndrome is a relative contraindication for pregnancy, and patients should be encouraged to consider alternatives" and "cardiac MRI revealing any significant abnormality and/or aortic size index (ASI) greater than 2 cm/m^2 represents an absolute contraindication for attempting pregnancy in a women with Turner syndrome." However, according to Bondy et al.,[23] relative contraindication conditions for pregnancy include a history of repaired cardiovascular defect, systemic HTN, aortic dissection or dilation and BAV. A single-embryo is preferred in cases who elect assisted reproductive therapy.[60] TS patients who get pregnant are at increased risk of diabetes and preeclampsia.[23] Risk of death during pregnancy is 100 times higher in TS patients compared with female patients with normal karyotypes.[25] It is estimated that aortic dissection may complicate 2% of pregnancies in patients with TS, 53% happening during the third trimester.[25,48,49] Carlson et al.[34] reported outcomes of seven cases of aortic dissection related to assisted

reproductive technology without HTN or CHD (mean age: 26 [20–53] years), with 86% mortality, one death was reported one year later. Patients should have an ECG, ECHO, and/or cardiac MRI before considering pregnancy to evaluate the aortic root and arch. Once pregnant, patients should be followed in a tertiary center with close BP control, have regular ECHOs during each trimester and monthly during last trimester. Patients should be followed 15 days after delivery.[25] According to the Practice Committee of the American Society for Reproductive Medicine,[60] "women in stable condition who have ascending aortic size index (ASI) of less than 2 cm/m^2 may attempt vaginal delivery under epidural anesthesia" and "women exhibiting baseline or progressive aortic root dilation should have an elective cesarean delivery under epidural anesthesia before the onset of labor."

4 | CONCLUSIONS

Approximately 50% of patients with TS have CHD, mainly CoA and BAV. Every patient diagnosed with TS should have an initial ECHO, independent of normal fetal study. Throughout their lives, patients with TS should have close BP monitoring and management. In cases of normal cardiovascular exam, TS patients should have regular imaging studies (ECHO or cardiac MRI) to assess the aortic valve and arch. CoA surgical repair is the most frequent cardiac intervention. TS aortopathy has been associated with increased risk of bleeding and dissection during or after cardiac surgeries/balloon angioplasties. GH use in TS patients has not been associated with elevated BP, ventricular hypertrophy, aortic dilation or dissection. Single ventricular anatomy is associated with very poor outcomes in TS. Pregnancy has increased risk of HTN, diabetes and aortic dissection, so patients should be followed closely in a tertiary center with serial aortic imaging.

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CONFLICT OF INTEREST

None

AUTHOR CONTRIBUTIONS

Raysa Morales-Demori reviewed all papers cited in this article, designed the format and wrote this manuscript.

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REFERENCES

[1] Evans JM, Dharmar M, Meierhenry E, Marcin JP, Raff GW. Association between Down syndrome and in-hospital death among children undergoing surgery for congenital heart disease: a US population-based study. *Circ Cardiovasc Qual Outcomes*. 2014;7(3):445–452.

[2] Bull MJ. Health supervision for children with Down syndrome. *Pediatrics*. 2011;128(2):393–406.

[3] Fudge JC, Jr, Li S, Jaggers J, et al. Congenital heart surgery outcomes in Down syndrome: analysis of a national clinical database. *Pediatrics*. 2010;126(2):315–322.

[4] Tubman TR, Shields MD, Craig BG, Mulholland HC, Nevin NC. Congenital heart disease in Down's syndrome: two year prospective early screening study. *BMJ (Clinical Research Ed)*. 1991;302(6790):1425–1427.

[5] McElhinney DB, Straka M, Goldmuntz E, Zackai EH. Correlation between abnormal cardiac physical examination and echocardiographic findings in neonates with Down syndrome. *Am J Med Genet*. 2002;113(3):238–241.

[6] Bergstrom S, Carr H, Petersson G, et al. Trends in congenital heart defects in infants with Down syndrome. *Pediatrics*. 2016;138(1):e20160123.

[7] Malec E, Mroczek T, Pajak J, Januszewska K, Zdebska E. Results of surgical treatment of congenital heart defects in children with Down's syndrome. *Pediatr Cardiol*. 1999;20(5):351–354.

[8] Bogarapu S, Pinto NM, Etheridge SP, et al. Screening for congenital heart disease in infants with down syndrome: is universal echocardiography necessary?. *Pediatr Cardiol*. 2016;37(7):1222–1227.

[9] Alsaied T, Marino BS, Esbensen AJ, Anixt JS, Epstein JN, Cnota JF. Does congenital heart disease affect neurodevelopmental outcomes in children with down syndrome? *Congenit Heart Dis*. 2016;11(1):26–33.

[10] Visootsak J, Mahle WT, Kirshbom PM, et al. Neurodevelopmental outcomes in children with Down syndrome and congenital heart defects. *Am J Med Genet Part A*. 2011;155a(11):2688–2691.

[11] Sica CD, Cesa CC, Pellanda LC. Growth curves in Down syndrome with congenital heart disease. *Rev Assoc Med Brasil (1992)*. 2016;62(5):414–420.

[12] Freeman SB, Bean LH, Allen EG, et al. Ethnicity, sex, and the incidence of congenital heart defects: a report from the National Down Syndrome Project. *Genet Med*. 2008;10(3):173–180.

[13] Atz AM, Hawkins JA, Lu M, et al. Surgical management of complete atrioventricular septal defect: associations with surgical technique, age, and trisomy 21. *J Thoracic Cardiovasc Surg*. 2011;141(6):1371–1379.

[14] Lange R, Guenther T, Busch R, Hess J, Schreiber C. The presence of Down syndrome is not a risk factor in complete atrioventricular septal defect repair. *J Thoracic Cardiovasc Surg*. 2007;134(2):304–310.

[15] Formigari R, Di Donato RM, Gargiulo G, et al. Better surgical prognosis for patients with complete atrioventricular septal defect and Down's syndrome. *Ann Thoracic Surg*. 2004;78(2):666–672; discussion 72.

[16] Campbell RM, Adatia I, Gow RM, Webb GD, Williams WG, Freedom RM. Total cavopulmonary anastomosis (Fontan) in children with Down's syndrome. *Ann Thoracic Surg*. 1998;66(2):523–526.

[17] Furukawa T, Park IS, Yoshikawa T, et al. Outcome of univentricular repair in patients with Down syndrome. *J Thoracic Cardiovasc Surg*. 2013;146(6):1349–1352.

[18] Colquitt JL, Morris SA, Denfield SW, Fraser CD, Wang Y, Kyle WB. Survival in children with down syndrome undergoing single-ventricle palliation. *Ann Thoracic Surg*. 2016;101(5):1834–1841.

[19] Overby KJ, Fins JJ. Organ transplantation for individuals with neurodevelopmental disorders. *Cambridge Quart Healthcare Ethics: CQ*. 2016;25:(2):272–281.

[20] Leonard H, Eastham K, Dark J. Heart and heart-lung transplantation in Down's syndrome. The lack of supportive evidence means each case must be carefully assessed. *BMJ*. 2000;320(7238):816–817.

[21] Cramer JW, Bartz PJ, Simpson PM, Zangwill SD. The spectrum of congenital heart disease and outcomes after surgical repair among children with Turner syndrome: a single-center review. *Pediatr Cardiol*. 2014;35(2):253–260.

[22] Saenger P. Turner's syndrome. *N Engl J Med*. 1996;335(23):1749–1754.

[23] Bondy CA. Congenital cardiovascular disease in Turner syndrome. *Congenit Heart Dis*. 2008;3(1):2–15.

[24] Nielsen J, Wohlert M. Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. *Hum Genet*. 1991;87(1):81–83.

[25] Dulac Y, Pienkowski C, Abadir S, Tauber M, Acar P. Cardiovascular abnormalities in Turner's syndrome: what prevention? *Arch Cardiovasc Dis*. 2008;101(7–8):485–490.

[26] Frias JL, Davenport ML. Health supervision for children with Turner syndrome. *Pediatrics*. 2003;111(3):692–702.

[27] Saenger P, Wikland KA, Conway GS, et al. Recommendations for the diagnosis and management of Turner syndrome. *J Clin Endocrinol Metab*. 2001;86(7):3061–3069.

[28] Clark EB. Neck web and congenital heart defects: a pathogenic association in 45 X-O Turner syndrome?. *Teratology*. 1984;29(3):355–361.

[29] Loscalzo ML, Van PL, Ho VB, et al. Association between fetal lymphedema and congenital cardiovascular defects in Turner syndrome. *Pediatrics*. 2005;115(3):732–735.

[30] Mortensen KH, Andersen NH, Gravholt CH. Cardiovascular phenotype in Turner syndrome–integrating cardiology, genetics, and endocrinology. *Endocr Rev*. 2012;33(5):677–714.

[31] Miyabara S, Nakayama M, Suzumori K, Yonemitsu N, Sugihara H. Developmental analysis of cardiovascular system of 45,X fetuses with cystic hygroma. *Am J Med Genet*. 1997;68(2):135–141.

[32] Bechtold SM, Dalla Pozza R, Becker A, Meidert A, Dohlemann C, Schwarz HP. Partial anomalous pulmonary vein connection: an underestimated cardiovascular defect in Ullrich-Turner syndrome. *Eur J Pediatr*. 2004;163(3):158–162.

[33] van den Hoven AT, Duijnhouwer AL, Eicken A, et al. Adverse outcome of coarctation stenting in patients with Turner syndrome. *Catheter Cardiovasc Interv*. 2017;89(2):280–287.

[34] Carlson M, Silberbach M. Dissection of the aorta in Turner syndrome: two cases and review of 85 cases in the literature. *BMJ Case Rep*. 2009;200:bcr0620091998.

[35] McCarthy K, Bondy CA. Turner syndrome in childhood and adolescence. *Exp Rev Endocrinol Metab*. 2008;3(6):771–775.

[36] Viuff MH, Trolle C, Wen J, et al. Coronary artery anomalies in Turner syndrome. *J Cardiovasc Comput Tomogr*. 2016;10:480–484.

[37] Kim HK, Gottliebson W, Hor K, et al. Cardiovascular anomalies in Turner syndrome: spectrum, prevalence, and cardiac MRI findings in a pediatric and young adult population. *Am J Roentgenol*. 2011;196(2):454–460.

[38] Hjerrild BE, Mortensen KH, Sorensen KE, et al. Thoracic aortopathy in Turner syndrome and the influence of bicuspid aortic valves and blood pressure: a CMR study. *J Cardiovasc Magn Reson*. 2010;12:12.

[39] van den Berg J, Bannink EM, Wielopolski PA, Pattynama PM, de Muinck Keizer-Schrama SM, Helbing WA. Aortic distensibility and dimensions and the effects of growth hormone treatment in the turner syndrome. *Am J Cardiol*. 2006;97(11):1644–1649.

[40] Marin A, Weir-McCall JR, Webb DJ, van Beek EJ, Mirsadraee S. Imaging of cardiovascular risk in patients with Turner's syndrome. *Clin Radiol*. 2015;70(8):803–814.

[41] Conte MR, Bonfiglio G, Orzan F, et al. Hypertrophic obstructive cardiomyopathy in a patient with Turner syndrome. *Cardiologia (Rome, Italy)*. 1995;40(12):947–949.

[42] Vieira Nieto EL, Jaime L, Fonseca AM. Fetal turner syndrome and tetralogy of Fallot associated with elevated maternal serum alpha-fetoprotein levels. *Rev Brasil Ginecol Obstetr*. 1998;20(5):283–287.

[43] Madriago E, Nguyen T, McFerson M, et al. Frequency and outcomes of cardiac operations and catheter interventions in Turner syndrome. *Am J Cardiol*. 2012;110(4):580–585.

[44] Marino B, Digilio MC, Papa M, Giannotti A, Dallapiccola B. Turner's syndrome with atrioventricular canal. *Pediatr Cardiol*. 1991;12(4):245–246.

[45] Ho VB, Bakalov VK, Cooley M, et al. Major vascular anomalies in Turner syndrome: prevalence and magnetic resonance angiographic features. *Circulation*. 2004;110(12):1694–1700.

[46] Gutmark-Little I, Hor KN, Cnota J, Gottliebson WM, Backeljauw PF. Partial anomalous pulmonary venous return is common in Turner syndrome. *J Pediatr Endocrinol Metab*. 2012;25(5–6):435–440.

[47] Sachdev V, Matura LA, Sidenko S, et al. Aortic valve disease in Turner syndrome. *J Am Coll Cardiol*. 2008;51(19):1904–1909.

[48] Carlson M, Airhart N, Lopez L, Silberbach M. Moderate aortic enlargement and bicuspid aortic valve are associated with aortic dissection in Turner syndrome: report of the international turner syndrome aortic dissection registry. *Circulation*. 2012;126(18):2220–2226.

[49] Wong SC, Cheung M, Zacharin M. Aortic dilatation and dissection in Turner syndrome: what we know, what we are unclear about and what we should do in clinical practice?. *Int J Adolesc Med Health*. 2014;26(4):469–488.

[50] Zanjani KS, Thanopoulos BD, Peirone A, Alday L, Giannakoulas G. Usefulness of stenting in aortic coarctation in patients with the Turner syndrome. *Am J Cardiol*. 2010;106(9):1327–1331.

[51] Kataoka K, Ozawa A, Inage A, Benson LN. Transcatheter repair of native coarctation in children with Turner syndrome: three case reports and literature review. *Congenit Heart Dis*. 2006;1(6):315–320.

[52] Brandt B, 3rd, Heintz SE, Rose EF, Ehrenhaft JL, Clark EB. Repair of coarctation of the aorta in children with Turner syndrome. *Pediatr Cardiol*. 1984;5(3):175–177.

[53] Lara DA, Ethen MK, Canfield MA, Nembhard WN, Morris SA. A population-based analysis of mortality in patients with Turner syndrome and hypoplastic left heart syndrome using the Texas Birth Defects Registry. *Congenit Heart Dis*. 2016;9:548–558.

[54] Trolle C, Mortensen KH, Pedersen LN, et al. Long QT interval in Turner syndrome–a high prevalence of LQTS gene mutations. *PLoS One*. 2013;8(7):e69614.

[55] Matura LA, Sachdev V, Bakalov VK, Rosing DR, Bondy CA. Growth hormone treatment and left ventricular dimensions in Turner syndrome. *J Pediatr*. 2007;150(6):587–591.

[56] Bondy CA, Van PL, Bakalov VK, Ho VB. Growth hormone treatment and aortic dimensions in Turner syndrome. *J Clin Endocrinol Metab*. 2006;91(5):1785–1788.

[57] van den Berg J, Bannink EM, Wielopolski PA, et al. Cardiac status after childhood growth hormone treatment of Turner syndrome. *J Clin Endocrinol Metab*. 2008;93(7):2553–2558.

[58] Radetti G, Mazzanti L, Di Somma C, et al. Evaluation of function and structure of arterial wall in girls and young women with Turner syndrome. *J Endocrinol Investig*. 2015;38(9):963–970.

[59] Lim HH, Kil HR, Koo SH. Incidence, puberty, and fertility in 45,X/47,XXX mosaicism: Report of a patient and a literature review. *Am J Med Genet Part A*. 2017;173A:1961–1964.

[60] Increased maternal cardiovascular mortality associated with pregnancy in women with Turner syndrome. *Fertil Steril*. 2012;97(2):282–284.

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