

AHA SCIENTIFIC STATEMENT

Cardiovascular Health in Turner Syndrome

A Scientific Statement From the American Heart Association

ABSTRACT: Girls and women with Turner syndrome face a lifelong struggle with both congenital heart disease and acquired cardiovascular conditions. Bicuspid aortic valve is common, and many have left-sided heart obstructive disease of varying severity, from hypoplastic left-sided heart syndrome to minimal aortic stenosis or coarctation of the aorta. Significant enlargement of the thoracic aorta may progress to catastrophic aortic dissection and rupture. It is becoming increasingly apparent that a variety of other cardiovascular conditions, including early-onset hypertension, ischemic heart disease, and stroke, are the major factors reducing the life span of those with Turner syndrome. The presentations and management of cardiovascular conditions in Turner syndrome differ significantly from the general population. Therefore, an international working group reviewed the available evidence regarding the diagnosis and treatment of cardiovascular diseases in Turner syndrome. It is recognized that the suggestions for clinical practice stated here are only the beginning of a process that must also involve the establishment of quality indicators, structures and processes for implementation, and outcome studies.

Turner syndrome (TS) results from complete or partial absence of the second sex chromosome in either all or part of the cells of an individual. It is the most common chromosomal abnormality affecting females, occurring in 1 in 2500 live-born girls.¹ Characteristic clinical features include short stature, premature ovarian failure, and lymphedema. Early morbidity and mortality are increased in patients with TS compared with the general population and are related mainly to cardiovascular complications.² Congenital heart abnormalities occur in up to 50% of individuals, affecting mainly the left side of the heart and including bicuspid aortic valve (BAV), coarctation of the aorta, and thoracic aortic aneurysm. Mortality rates are 3-fold higher in women with TS compared with the general population, with the most common cause of death being cardiovascular disease.³ Prompt recognition of the signs and symptoms of aortic dissection (AoD) and rupture depends on the awareness that these often-fatal complications occur primarily in young adult women with TS.⁴⁻⁶

It is important for healthcare professionals to recognize that hypertension in children with TS and coronary artery disease, myocardial infarction, and stroke in adults with TS⁷ are exacerbated by an underlying predisposition to metabolic abnormalities, including dyslipidemia, type II diabetes mellitus, obesity, and hyperuricemia.⁸

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Given this broad spectrum of cardiovascular concerns, girls and women with TS require a continuum of care, counseling, and preventive management through their adult years. The specific management of many cardiovascular conditions, both congenital and acquired, is the same as in the general population. For these conditions, established guidelines should be followed. The purpose here is to highlight the instances in which there are unique cardiovascular risks involved in TS and to provide guidance for their monitoring and management.

WORKING GROUP

In July 2016, the Turner Resource Network hosted an international meeting of experts to make recommendations for the overall management of the numerous conditions affecting girls and women with TS, including cardiovascular health.⁹ Attendees included most of the current working group who also contributed to that meeting and presented the suggestions for clinical practice that are reproduced in this document. The working group recognized that further context, details, and justification were needed. The suggestions for clinical practice stated here are the result of a comprehensive review and discussion of >1200 publications* in the medical literature and represent a consensus view based on the literature and practice experience of the working group members. It is understood that these suggestions for clinical practice are only the beginning of a process that must also involve the establishment of quality indicators,¹¹ structures and processes for implementation, and outcome studies.

In nearly all cases, Turner-specific medical evidence is very limited, especially as it relates to the scientific literature on the aorta. Further clinical and basic research is imperative. The working group's suggestions for clinical practice should be considered from that perspective and not taken as dogma. We view this report as a first step toward improving the cardiovascular health of girls and women with TS. Our plan is to review and revise this work as new evidence accumulates.

CONGENITAL HEART DISEASE

Congenital heart defects occur in 23% to 50% of individuals with TS and are the most frequent cause of early mortality.^{12–14} The incidence is higher in individuals with 45X karyotypes compared with X mosaicism or other X structural abnormalities.^{15,16} Left-sided obstructive lesions are most common, with a prevalence of 15% to 30% for BAV and 7% to 18% for aortic coarctation.

*An EndNote X7 library is available at the website of the Turner Syndrome Society of the United States¹⁰ that contains the >1200 citations that helped to inform this work.

Because BAV is likely to occur 30 to 60 times more frequently in TS than in females with 46,XX, it is possible that BAV in a female may be an independent marker for TS. Cross-sectional imaging modalities have unveiled an increased incidence of additional vascular anomalies that might otherwise have gone undetected by transthoracic echocardiography (TTE), including partial anomalous pulmonary venous connection,¹⁷ left superior vena cava, an elongated transverse aorta, and dilatation of the head and neck arteries.^{18,19} Neck webbing and an increased anterior-posterior thoracic diameter have been shown to be strong predictors of arterial and venous anomalies in TS.^{20,21} Additional, but less frequent, anomalies include hypoplastic left-sided heart syndrome, mitral valve anomalies, interrupted inferior vena cava with azygous continuation, cardiac dextroposition, ventricular septal defect, atrioventricular septal defect, pulmonary valve abnormalities, and patent ductus arteriosus.^{22–24}

Congenital coronary arterial anomalies are prevalent in TS.²⁵ The left coronary artery is most often affected, with an absent left main coronary artery being the most frequent anomaly.²⁵ In addition, single cases of coronary arterial anomalies have been reported, which include coronary arterial dilatation, single coronary ostium, coronary arteries originating from the thoracic aorta, and coronary artery-to-pulmonary artery fistulas.^{22,26,27} Whether coronary arterial malformations increase mortality risk is unknown. The majority of the encountered coronary arterial anomalies in TS are benign or noninterarterial; however, it is important for the cardiothoracic surgeon to be aware of unusual coronary anatomy because it may necessitate modifications of the operative approach.

Suggestions for Clinical Practice

Diagnosis

- If TS is highly suspected or has been confirmed prenatally, a fetal echocardiogram should be performed. If congenital heart disease is confirmed, then follow-up care by a pediatric cardiologist is recommended to provide counseling on the anatomy and physiology of the specific defect, recommended site and mode of delivery, and postnatal multidisciplinary management plan.
- Diagnosis of a BAV or a left-sided obstructive lesion, whether prenatally or postnatally, in a female patient should prompt genetic evaluation for TS.
- All newly diagnosed individuals with TS should be evaluated by a cardiologist familiar with all aspects of cardiovascular disease seen in TS and undergo the following evaluation:
 - A comprehensive physical examination, including cardiac auscultation and assessment of femoral pulses and 4-extremity blood pressures (BPs), should be performed.

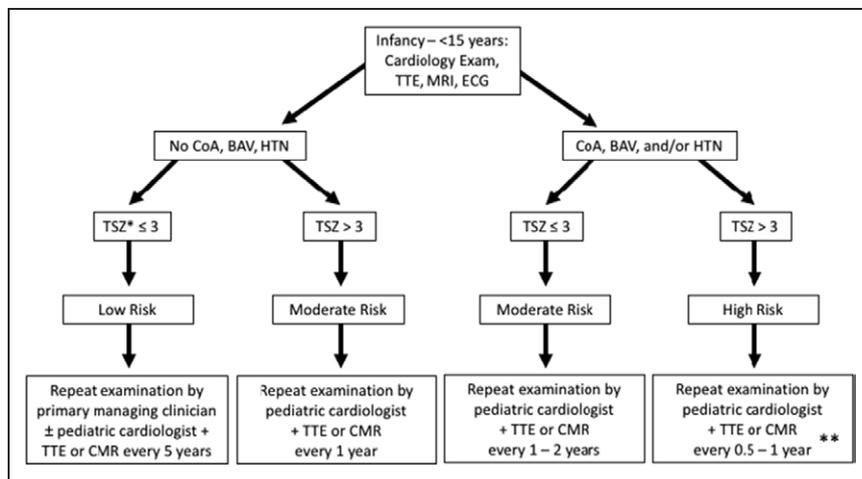


Figure 1. Suggested monitoring protocol for girls with Turner syndrome from infancy to 15 years of age.

BAV indicates bicuspid aortic valve; CMR, cardiac magnetic resonance; CoA, coarctation of the aorta; HTN, hypertension; MRI, magnetic resonance imaging; TSZ, Turner-specific z score; and TTE, transthoracic echocardiography. *Ascending aorta TSZ.²⁸ **It is important to remember that surveillance frequency may change with worse disease severity in terms of obstruction, regurgitation, or left ventricular hypertrophy. Modified from Gravholt et al.⁹ Copyright ©2017, European Society of Endocrinology.

- A complete TTE, even in the presence of a normal fetal echocardiogram and cardiac examination, should be performed because certain cardiac abnormalities may be clinically “silent” or may not be recognized on a fetal echocardiogram.
- Visualization of the coronary artery anatomy should be attempted at the first encounter, by TTE in newborns and infants, or by cardiac magnetic resonance (CMR) or computed tomography (CT) in the adult population.
- An ECG should be done to assess for potential conduction and repolarization abnormalities.
- A CMR can be performed, as soon as it is feasible, without the need for general anesthesia.

Management

- For individuals with TS with congenital heart defects, management of their cardiac disease should be determined by their cardiologist according to previously described guidelines with the assistance of a multidisciplinary team.
- For individuals with no structural heart disease, annual assessment of BP should be performed.
- Clinicians should be vigilant when monitoring girls and women with TS for hypertension, which should be treated according to the standards set for the general population (see the High Blood Pressure section).
- Periodic surveillance imaging is recommended for those with normal-appearing aortas (see the suggestions for clinical practice in the Cardiac Imaging section).
- Clinicians should refer to the most recent guidelines by the American Heart Association for the prevention of infective endocarditis.

CARDIAC IMAGING

Figures 1 and 2 provide monitoring protocols.

Because of the high prevalence of congenital and acquired cardiovascular disease in TS, noninvasive car-

diac imaging is critical for diagnosis, management, and risk assessment.^{1,29,30} The most common modalities include TTE, CMR, and CT.^{18,19,31–35} TTE is useful in the diagnosis of a BAV³⁶ and other congenital heart defects, as well as in the surveillance of aortic dilatation.³³ However, the high prevalence of undiagnosed abnormalities, such as elongation of the transverse aorta (defined as a relative increase in vertical distance from the top of the aortic arch to the origin of the innominate artery),³⁷ aortic coarctation, and partial anomalous pulmonary venous connection in TS, has led to increased use of CMR and CT as screening and surveillance tools.^{18,31,32,35} CMR has been shown to be more accurate than TTE in adults with TS for the diagnosis of BAV.¹⁹ CMR and CT are also more accurate for aortic size measurements and therefore more sensitive than TTE to changes in aortic size, particularly beyond the aortic root and in adults with TS, who often have limited echocardiographic windows.³⁸ Although serial surveillance with CT is an option, the risk of recurrent ionizing radiation should be recognized, and therefore, radiation should be used only when surveillance with CMR is not possible.

Cardiovascular disease is the major cause of death in TS, and death resulting from AoD is far in excess of that in the general population.^{2,3} Predictors of AoD risk in TS have not been well studied. In the aortopathy associated with Marfan syndrome, risk factors include the degree of aortic dilatation and aortic growth rate. BAV is commonly present when AoD occurs in TS and should be considered a risk factor.³⁹ Risk assessment in TS may also include measures of aortic stiffness, distensibility,⁴⁰ and tortuosity, but these are currently not part of standard clinical imaging protocols.^{41–43} The ascending aortic diameter divided by body surface area (BSA; the aortic size index [ASI]⁴³) may be useful in stratifying risk. The ASI has been the primary parameter used to assess AoD risk in TS and has known limitations in terms of the methodology for performing the measurement and for defining a dilated or aneurysmal aorta, particularly in children.^{42,44,45}

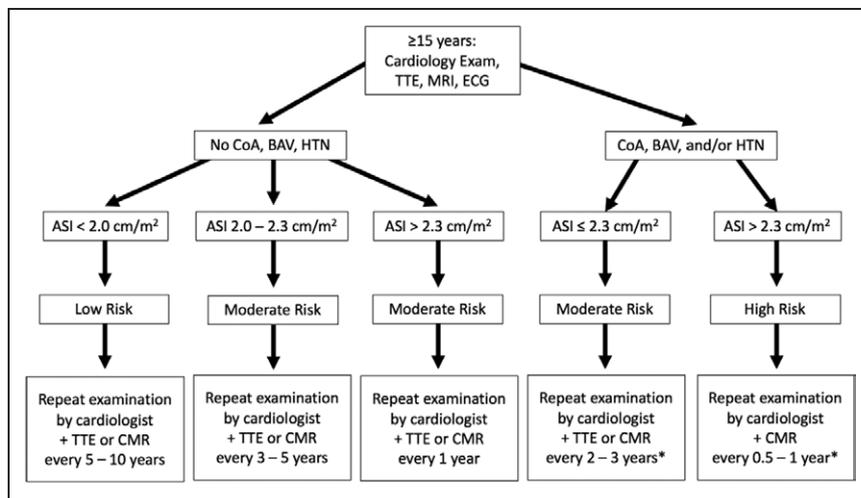


Figure 2. Suggested monitoring protocol for girls and women with Turner syndrome who are ≥ 15 years of age.

ASI indicates aortic size index; BAV, bicuspid aortic valve; CMR, cardiac magnetic resonance; CoA, coarctation of the aorta; HTN, hypertension; MRI, magnetic resonance imaging; and TTE, transthoracic echocardiography. *It is important to remember that surveillance frequency may change with worse disease severity in terms of obstruction, regurgitation, or left ventricular hypertrophy. Modified from Gravholt et al.⁹ Copyright ©2017, European Society of Endocrinology.

Published guidelines recommend aortic diameter measurements at specified locations perpendicular to the vessel wall.^{42,44,46–50} The optimal approach to aortic diameter measurements remains to be defined. Aortic diameters change over the cardiac cycle with the largest diameters observed in systole,^{51,52} and systolic diameters may best reflect vascular function.⁴² Conversely, diastolic diameters may be more reproducible.^{30,44,45,53} In addition, pediatric TTE quantification guidelines recommend that measurements be made from leading edge to leading edge, whereas adult guidelines recommend measurements from inner edge to inner edge. Recently published normative TTE data for TS and most CMR studies have used inner edge to inner edge in TS,^{18,28,31,54} which may therefore be preferable.

Furthermore, the aortic cross section may not be perfectly round along the entire aorta, particularly at the sinuses of Valsalva, where asymmetry can result in significantly varied measurements based on orientation along the axial plane.⁵⁵ Given these challenges, serial measurements must use the same modality and methodology to achieve the least possible measurement variability for the most reliable measurements of aortic size and growth.

Defining aortic dilatation is problematic because normal reference values must account for the effects of body size and age on the sizes of cardiovascular structures.^{42,56} In the context of the smaller body sizes of individuals with TS, absolute aortic dimensions may not be as useful in identifying a dilated aorta. Data in children without TS suggest that aortic dimensions should be normalized to the square root of the BSA, and many published TTE and CMR z-score databases use this approach.^{48,49,56,57} However, the outcome studies of ascending aortic size in TS normalize aortic dimensions to BSA¹⁹ (ASI) and define dilatation as $>2 \text{ cm}^2/\text{m}^2$ or >95 th percentile on the basis of nomograms of children in the general population.^{53,58,59}

An ascending ASI $>2.5 \text{ cm}^2/\text{m}^2$ has been used to predict risk of AoD for girls and women >15 years of age

(Figure 3).^{39,54} Because there has been no prospective longitudinal study of AoD related to ASI in TS, causation is unproven. Therefore, further research is essential to know whether ASI or other factors are the best predictors of risk. The position of the working group is that the ascending ASI is currently the best method to adjust absolute aortic measurements for body size for those >15 years of age, but this remains to be proven. Therefore, it is useful to note that a woman with the average BSA for TS (ie, 1.6 m^2 ; Figure 3) has an absolute ascending aortic diameter of $>4 \text{ cm}$ when the ascending ASI is $>2.5 \text{ cm}^2/\text{m}^2$. In addition, an ascending aorta ASI $>2.5 \text{ cm}^2/\text{m}^2$ for a woman with average BSA corresponds to an ascending aorta Turner-specific z score of >4 (discussed below).²⁸ Before the age of 15 years, ascending ASI is often $>2.5 \text{ cm}^2/\text{m}^2$ in healthy girls with TS (Figure 3), increasing the risk of false positives.⁴⁵ The age dependence of the ASI calculation is not specific to TS. Dividing by BSA is a simple way of indexing vascular dimensions and has been shown to be generally unreliable in children.⁵⁶

Other studies use the ratio of the ascending to descending aortic diameters, defining a ratio of >1.5 as dilatation,³² although this approach does not account for the fact that the descending aorta may not be normal. Given the limitations of the last 2 approaches (ASI and ascending/descending aorta ratio), a recent publication evaluated aortic diameters for healthy girls and women with TS (excluding subjects with a BAV), thereby providing normative z scores⁶⁰ based on a TS reference population.²⁸ The relationship between TS-specific z scores and z score referenced to the general pediatric/young adult population has been published.⁴⁵ TS-specific z scores are significantly lower than z scores based on a non-TS reference population.⁴⁵

Suggestions for Clinical Practice

- When an infant or child is diagnosed with TS, TTE should be performed at the time of the diagnosis,

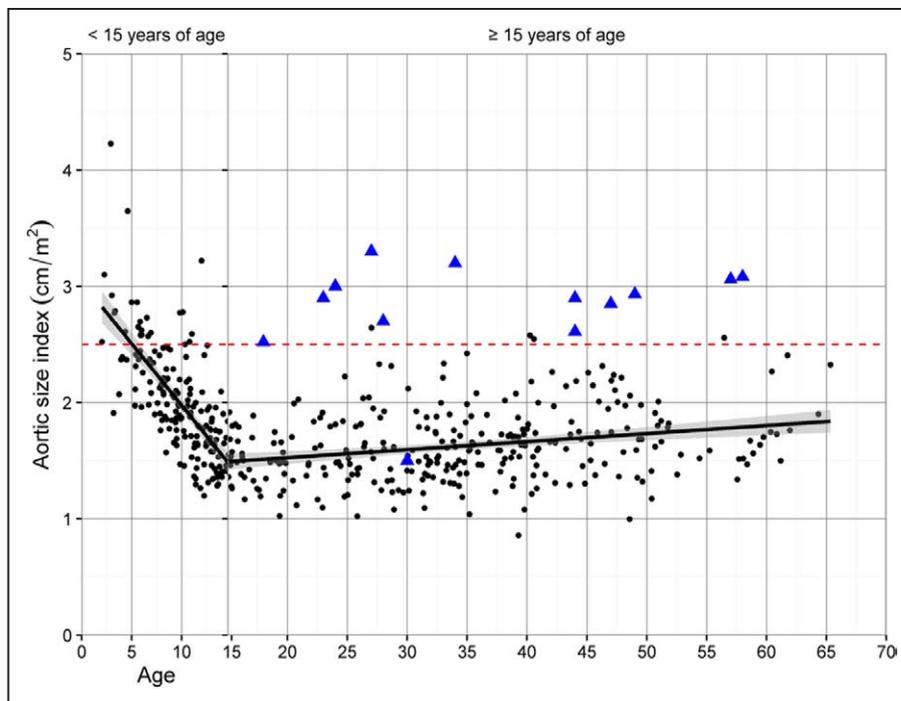


Figure 3. Relationship between ascending aortic size index (ASI) and age in individuals with Turner syndrome (TS) with or without aortic dissection (AoD).

Data were derived from references 39 and 54. Dots represent measurements determined by transthoracic echocardiography performed at study entry to the Healthy Heart Project during the annual meeting of the Turner Syndrome Society of the United States between 2003 and 2015 ($n=458$). For those who were ≥ 15 years of age ($n=212$), the mean body surface area (BSA) was 1.62 m^2 and the mean absolute aortic size was $2.6\pm 0.4\text{ cm}$. At the time the study was performed, none of these individuals had either a history of AoD or an elective operation for an aortic aneurysm. Note that subjects < 15 years of age with a negative history for AoD frequently have ascending ASI $> 2.5\text{ cm/m}^2$, making ASI unreliable as a predictor of AoD in this age group.⁴⁵ Triangles represent echocardiographically determined ascending aorta ASI obtained before presentation with AoD in 13 individuals with TS reported in 2 studies^{39,54} (absolute aortic size, $4.6\pm 0.7\text{ cm}$; ascending ASI, $2.8\pm 0.5\text{ cm/m}^2$). Dashed line represents an absolute ascending aortic diameter of 4.1 cm , ascending ASI of 2.5 cm/m^2 , and Turner-specific z score²⁸ of 4 based on the average BSA of 1.62 m^2 for the 290 women ≥ 15 years of age without aortic dissection (dots). Modified from Corbitt et al⁴⁵ with permission. Copyright © 2017, Wiley Periodicals, Inc.

even if the fetal echocardiogram or postnatal cardiac examination was normal.

- When an infant or child is diagnosed with TS, CMR should be performed as soon as it is feasible without the need for general anesthesia.
- When an adult is diagnosed with TS, cardiovascular screening with TTE and CMR at the time of diagnosis is the preferred approach.
- When an adult or child diagnosed with TS cannot tolerate a CMR study, cardiovascular screening with electrocardiographically gated CT is a reasonable option.
- In the absence of a BAV or other significant disease at the initial screening, TTE or CMR surveillance studies should be performed every 5 years in children, every 10 years in adults, or before anticipated pregnancy to evaluate the aorta.
- If aortic dilatation or other AoD risk factors are diagnosed, timing of surveillance imaging should be guided by the knowledge that AoD occurs at smaller diameters than in non-TS genetic aortopathies, and follow-up should be guided by a multidisciplinary team under the supervision of a cardiologist with knowledge, experience, or

special interest in the cardiovascular abnormalities in TS (see Figures 1 and 2 for suggested monitoring protocols).

MEDICAL AND OPERATIVE MANAGEMENT OF AORTIC ENLARGEMENT AND ANEURYSM THORACIC AoD IN TS

Gravholt et al⁵ reported that in TS AoD occurs in ≈ 40 per 100 000 person-years compared with 6 per 100 000 person-years in the general population. The majority of AoDs originate in the ascending aorta (type A), whereas a smaller percentage ($\approx 10\%$) originate in the descending thoracic aorta (type B).^{5,6,39,54} When AoD occurs, it is a catastrophic and often fatal event. It is important to note that for women with TS, AoD appears to occur at smaller ascending aortic diameters than in those with other genetic aortopathies.^{6,39,54} AoD in TS occurs at an age (median age, 29–35 years; range, 4–64 years) similar to that of others with genetic aortopathies.³⁹ Furthermore, in women with AoD, cardiovascular abnormalities such as BAV, coarctation of the aorta,

and hypertension are common.^{6,31,39,54} Limited evidence suggests that growth hormone therapy is not a risk factor for aortic enlargement.^{6,61} Aortic dilatation and enlargement of the brachiocephalic and carotid arteries may be present in TS even in the absence of structural heart disease, consistent with an underlying vasculopathy.^{31,40,62–64} Although pregnancy is a rare event in TS, it is believed that pregnancy confers an additional risk for AoD in women with TS, particularly in those undergoing assisted reproductive therapy (ART) who also have a BAV, other cardiovascular malformations, aortic enlargement, or hypertension.⁶⁵

Very limited data suggest that AoD usually (but not always) occurs at >15 years of age and appears to be more likely to occur with an ascending ASI ≥ 2.5 cm/m² (Figure 3).^{39,54}

The mid ascending aorta is often dilated in TS. A global aortopathy is, however, evident by dilatation potentially involving the aortic root, distal ascending aorta, and descending aorta, as well as the proximal head and neck arteries.^{18,31,66–68} Correspondingly, the risk of both Stanford type A and B AoD is increased.⁶ No evidence exists to define comparable segment-specific ASI thresholds beyond the mid ascending aorta. A pragmatic approach must therefore be adapted to proposed surgical thresholds, and imaging must include the entire thoracic aorta in all girls and women with TS.

Definition of Aortic Enlargement and Aortic Aneurysm

The aorta is considered enlarged when the vessel diameter is larger than expected on the basis of age, sex, and BSA. An aortic aneurysm is generally defined as a localized dilatation having at least a 50% increase in diameter compared with the expected normal diameter.⁴¹ When an aneurysm is diagnosed, medical or operative interventions may be necessary. Aortic enlargement of less than aneurysmal diameter may require changes in care such as limiting physical activity or additional monitoring. For growing girls and for women with TS who tend to have short stature, standardized scores (also called z scores) are typically used. In general, aortic enlargement has been defined as >2 SDs above the mean predicted diameter for a particular body size (or z score >2). Most measurements are obtained with 2-dimensional TTE according to endorsed standards.⁴² Specifically, the ascending aorta is measured from an image of the ascending aortic diameter at the level of the right pulmonary artery.⁴² TS-specific z scores have been established by Quezada et al²⁸ that are based on data suggesting that mild aortic enlargement occurs even in healthy individuals with TS who have no known risk factors for thoracic aortic enlargement.⁶⁹ Use of a Turner-specific z score^{28,60} may be preferable to the general, population-based z scores

because higher z scores derived from the non-Turner population could lead to overtreatment or stigmatization. Health professionals should be cognizant that TS-specific z scores are significantly lower than z scores derived from a general reference population.⁴⁵ For example, an ascending aorta TS-specific z score >3 is equivalent to a z score of >5 derived from the general reference population.

A TS-specific ascending aortic diameter z score of >3.0 generally fits the definition of an aneurysm, being at least 50% greater than the expected TS-specific mean normal diameter.

Using ASI has been proposed as a way to better predict risk for AoD in TS.^{5,6,39,43,69} ASI is not applicable to those <15 years of age because girls with TS usually have relatively larger aortic diameters when indexed to body size compared with older individuals with TS (≥ 15 years of age). The ascending ASI decreases with body growth until the mid teenage years and remains relatively stable thereafter, making it a useful index beyond the age of 15 years (Figure 3). Although body mass index is not a predictor of aortic size,²⁸ BSA calculations include body weight. Therefore, decisions based on either z-score calculations or ASI in short-statured but obese individuals or those who weigh very little relative to their height should be made with caution.⁷⁰ In these cases, an absolute ascending aorta diameter of 4 cm in someone ≥ 15 years of age may be more accurate than ASI when determining AoD risk.

Medical Management

The approach to managing individuals with TS with aortic dilatation is a pragmatic one, recognizing the absence of clinical trials to guide pharmacological therapy. Cystic medial degeneration similar to other aortopathies has been documented in resected aortic tissue of women with TS.⁵ Thus, using treatments that are typically a part of the treatment of Marfan syndrome or other genetic types of aortopathy may be reasonable. Because hypertension is common in TS, maintenance of normal BP may lessen the risk of aortic events.^{71,72} De Groote et al⁷² have proposed a practical algorithm for BP evaluation in adults. Because AoD appears to occur at a smaller absolute aortic dimension in TS than in other aneurysm disorders, it may be reasonable to begin prophylactic medical therapies earlier than what has been recommended for other conditions and to use ASI for the initiation of medication (see recommendations in the Medical Therapy section).

Operative Repair of Aortic Aneurysms and AoD

General technical concepts and perioperative care are not different from those for other patients with thoracic

aortic aneurysms and dissections. As with other aortopathies, the thresholds for considering elective operative repair are based on perceived risk for AoD. The diagnosis and management of AoD have been outlined in existing guidelines.⁴¹

Suggestions for Clinical Practice

Awareness of Risk for AoD

- Girls or women with TS and aortic enlargement and BAV should be counseled to seek prompt evaluation for any symptoms consistent with acute AoD such as unusual chest, neck, shoulder, back, or flank discomfort, particularly if it is sudden in onset and severe. They should be encouraged to provide information about their high-risk condition to healthcare providers.

Optimal Operative Management of Aortic Aneurysm in TS

- For women with TS who demonstrate an increase in either a TS-specific z score⁶⁰ of 1 or an increase in aortic diameter of >0.5 cm over a 1-year period, optimization of medical treatment and surgical consultation are recommended. The average aortic growth rate for adults with TS has been shown to be 0.1 to 0.4 mm/y.^{66,73}
- Operative management of the aortic root and ascending aorta is reasonable for women with TS who are ≥15 years of age, have an ascending ASI ≥2.5 cm/m², and have associated risk factors for AoD, including BAV and hypertension.
- Operative management for an aneurysm of the aortic root or ascending aorta may be considered for women with TS who are ≥15 years of age, have an ascending ASI ≥2.5 cm/m², and do not have associated risk factors for AoD.
- Operative management for an aneurysm of the aortic root or ascending aorta may be considered for girls with TS who are <15 years of age and for whom the ascending aorta TS-specific z score is ≥4.0, with or without associated risk factors for AoD (ie, BAV and hypertension).

Optimal Medical Management of Aortic Aneurysm in TS

- Medical treatment of hypertension is recommended.
- Medical treatment that includes a β-blocker, angiotensin receptor blocker, or both may be considered in patients with TS in whom the aorta is dilated.

ELECTROCARDIOGRAPHY

Differences between the ECG in TS and in the general population can be roughly categorized into morphological issues (bundle-branch block, T-wave changes,

P-wave changes) on the one hand and time intervals (PR interval, QT interval) on the other. The reported prevalence of these changes in girls and women with TS is ≈50%, which is higher than in control subjects without TS (30%).⁷⁴ Some changes such as P-wave and QTc dispersion and heart rate variability in TS can be attributed to an underlying autonomic effect.⁷⁵ Shortening of the PR interval (resulting from accelerated atrioventricular conduction) may be a consequence of excessive sympathetic drive.

The clinical relevance of these potential abnormalities may be 2-fold: Right-axis deviation in an individual with TS is correlated with the presence of partial anomalous pulmonary venous connection⁷⁶ and should trigger further diagnostic testing in those cases that are not already known, and QTc prolongation is associated with an increased risk for arrhythmias or even sudden cardiac death in the general population. It should be emphasized, however, that there is no published evidence to date for sudden cardiac death related to QTc prolongation in women with TS. Whether QTc prolongation should be considered an intrinsic feature of TS is unclear; a potential correlation with variants in the long-QT syndrome genes deserves further investigation.⁷⁷ Two observations suggest that prolonged QTc does not put girls and women with TS at risk: (1) No significant dysrhythmia has been documented in any girl or women with TS and prolonged QTc, and (2) in 1 TS study, QTc prolongation returned to normal in 40% of ambulatory ECGs⁷⁶ and returned to normal during exercise stress testing. Of note, QTc does not normalize during exercise in long-QT syndrome.⁷⁸

Additional uncertainties include the threshold at which to define QT prolongation (now set at 440 milliseconds in many studies, which may be too low) and the calculation method used to define QTc interval in TS.

In view of the increased intrinsic heart rate in many individuals with TS,⁷⁹ the Hodges formula may be preferred over the Bazett formula because it takes the higher heart rate into account.⁷⁷ Finally, caution may be warranted with the use of QTc-prolonging drugs in women with TS. Careful assessment of the QTc interval before the initiation of such agents and electrocardiographic surveillance at least in those with preexisting QTc prolongation should be considered, as illustrated in a recent case report.⁸⁰ Decisions should be made on a case-by-case basis, balancing the benefits of these drugs against their potential risks. Because the arrhythmia torsades de pointes is the cause of sudden cardiac death in those with prolonged QTc in the setting of long-QT syndrome, postmortem assessment of women with TS who die suddenly would indicate that prolonged QTc may be the cause by excluding more common causes such as AoD, stroke, myocardial infarction, or coronary malformations.

Suggestions for Clinical Practice

- Resting electrocardiographic recording with QTc measurement is reasonable in every individual with TS at the time of diagnosis.
- For QTc calculation, the Hodges formula [$QTc = QT + 0.00175 ([60/RR (R \text{ wave to R wave interval}) - 60)]$] may be preferred over the Bazett formula.
- Exercise testing and 24-hour Holter monitoring might be considered for risk estimation in women with TS with QTc prolongation.
- In individuals with prolonged QTc (QTc >460 milliseconds), the following applies:
 - An ECG should be performed 1 to 2 weeks after the initiation of QT-prolonging drugs.
 - It is reasonable to avoid drugs that lengthen the QTc.

COMPETITIVE SPORTS PARTICIPATION

A safe level of exercise is important for a healthy lifestyle in girls and women with TS. Evidence is lacking on the cardiovascular and aortic risks for competitive athletics with TS. However, many of the same principles stated in the American Heart Association/American College of Cardiology scientific statement “Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities”⁸¹ apply to girls and women with TS who have valvular, congenital heart, or aortic disease.^{82,83}

Given the propensity for obesity and the metabolic syndrome in TS, healthcare professionals should be mindful of the significant benefits of having a heart-healthy lifestyle in light of the low risk of AoD in absolute terms ($\approx 40:100\,000$ patient-years⁵) in this population. Therefore, consideration of the risk for AoD should be tempered by the importance of encouraging safe levels of physical activity in individuals with TS. In addition, there is no published evidence that contact sports represent a significant threat for AoD among girls and women with TS without significant aortic enlargement. Recreational (noncompetitive) exercise performed at low to moderate aerobic levels is considered to be low risk and beneficial for girls and women with TS unless significant cardiovascular or aortic disease is present (Figure 4⁸¹).

Because of short stature in TS, indexing the aortic size to the BSA (ascending ASI) may be a better predictor of aortic risk than aortic size alone. Consistent with information in earlier sections of this document, ascending ASI is age dependent for girls with TS who are <15 years of age (Figure 3). In girls with TS who are <15 years of age, an ascending ASI >2.5 cm/m² is relatively common, and as girls age, many “grow into” their aortas. Thus, for sports participation for girls <15 years of age, it is reasonable to use TS-spe-

cific z scores,²⁸ which are based solely on BSA, when determining eligibility for participation in competitive sports.⁸⁴ In women with TS who are ≥ 15 years of age, using the ascending ASI (or absolute aortic size) for determining eligibility and disqualification for sports participation is recommended. For certain women with TS and obesity, using absolute aortic diameter to guide sports participation and disqualification is reasonable.

Suggestions for Clinical Practice

- The function of the aortic valve and the presence of any other congenital heart defect or hypertension should be considered in determining participation recommendations for the athlete with TS and aortic dilatation.
- For girls and women with TS who are ≥ 15 years of age with a moderately dilated aorta (ascending ASI ≥ 2.0 cm/m²), avoidance of intense weight training should be considered.
- For girls with TS who are <15 years of age, it is reasonable to participate in all sports if the aortic size has a TS-specific z score of <2.5.
- For girls and women with TS who are ≥ 15 years of age, participation in all competitive sports is reasonable if the ascending ASI is <2.0 cm/m².
- For girls with TS who are <15 years of age with a mildly to moderately dilated aorta (TS-specific z score, 2.5–3), participation in low and moderate static and dynamic competitive sports (classes IA, IB, IC, IIA, IIB, and IIC and certain types of gymnastics with lower isometric demands)⁵⁵ may be considered.
- For girls and women with TS who are ≥ 15 years of age with a moderately dilated ascending aorta (ASI, 2.0–2.3 cm/m²), participation in low and moderate static and dynamic competitive sports (classes IA, IB, IC, IIA, IIB, and IIC and certain types of gymnastics with lower isometric demands) may be considered (Figure 4).
- Girls with TS who are <15 years of age with a TS-specific z score of >3 should not participate in any competitive sports.
- Girls or women with TS who are ≥ 15 years of age with an ascending ASI >2.3 cm/m² should not participate in any competitive sports.

TRANSITION

Transition is a process to optimize lifelong functioning and potential with high-quality, developmentally appropriate, and uninterrupted health care from adolescence to adulthood.⁸⁵ To be successful, this process should attend to the medical, psychosocial, educational, and vocational needs. Regional TS resource

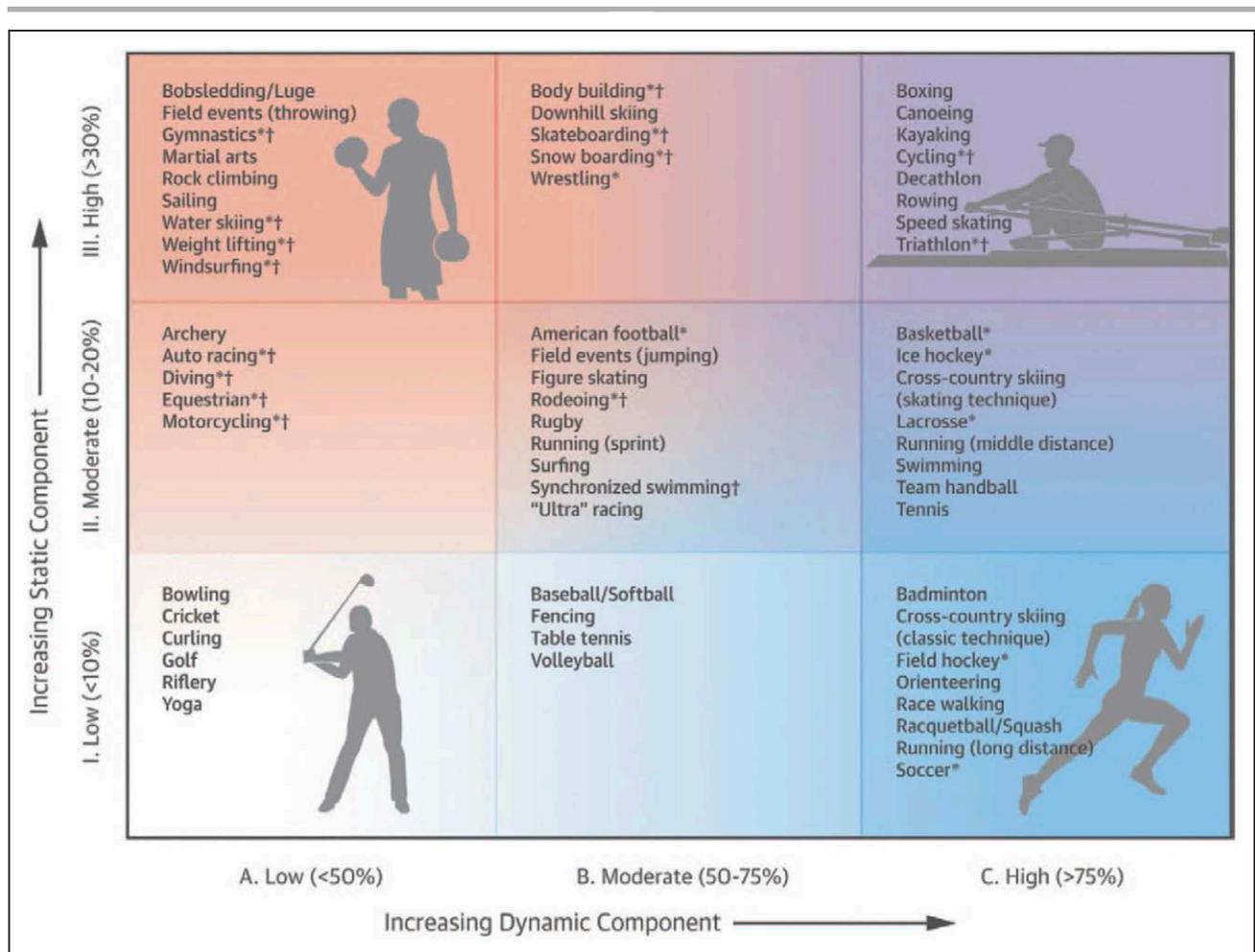


Figure 4. This classification is based on peak static and dynamic components achieved during competition; however, higher values may be reached during training.

The increasing dynamic component is defined in terms of the estimated percentage of maximal oxygen uptake (Vo_2max) achieved and results in an increasing cardiac output. The increasing static component is related to the estimated percentage of maximal voluntary contraction reached and results in an increasing blood pressure load. The lowest total cardiovascular demands (cardiac output and blood pressure) are shown in the palest color, with increasing dynamic load depicted by increasing blue intensity and increasing static load by increasing red intensity. Note the graded transition between categories, which should be individualized on the basis of player position and style of play. *Danger of bodily collision (see the Table for more details on collision risk). †Increased risk if syncope occurs. Modified with permission from Mitchell et al. Task Force 8: classification of sports. *J Am Coll Cardiol*. 2005;1364–1367. Copyright © 2005, Journal of the American College of Cardiology. Reproduced from Levine et al.⁸¹ Copyright © 2015, American Heart Association, Inc.

centers (team clinics) are being organized by the Turner Syndrome Global Alliance. The Turner Syndrome Global Alliance, through its overall transition program, is helping to identify cardiologists who care for adults who also have expertise in congenital heart defects.

Current guidelines recommend that the transition process start at the age of 12 years with a written transition plan by 14 years of age^{85–87} and with plans to transfer to adult congenital heart defect services by 18 years of age.⁸⁷ The transition process in this patient population should address the cardiovascular risks, associated congenital heart defects if applicable, and topics such as the educational and psychosocial needs. These topics are introduced gradually and reinforced in subsequent clinic visits and communications. Preparing the adolescent with TS for self-care and independence in adulthood is the goal.

Cardiovascular Health Care From Childhood to Adulthood

In addition to the congenital heart defects and aortopathy, girls with TS are at increased risk for obesity, abnormal triglycerides, diabetes mellitus, hypertension, stroke, and ischemic heart disease. The majority of the serious sequelae and increased mortality associated with these health risks are present in adults with TS.³ Therefore, for all adolescents, a detailed transition strategy emphasizing an understanding of the cardiac status and the importance of lifelong care and prevention is critical. Discussion with girls independently and with their families should start as early as 12 years of age and should be age and developmentally appropriate.^{85,86} The topics discussed⁸⁸ should be documented in the medical record and shared with the primary care provider and other subspecialists to ensure that the

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individual and family hear consistent information and that this information is reinforced by all providers. During this transition period, the importance of preparation for adulthood cardiovascular care is emphasized with the aim of ensuring guideline-driven care, regular medical visits, and a reduction in morbidity.

Suggestions for Clinical Practice

- Lifelong cardiac follow-up is recommended for all individuals with TS, even in the absence of cardiovascular disease.
- Medical care during adulthood should be guided by a multidisciplinary team that includes a cardiologist with knowledge, experience, or a special interest in the unique cardiovascular issues facing women with TS.
- A heart-healthy lifestyle is essential and should be discussed with adolescents and young adults given the increased risk of obesity, abnormal triglycerides, diabetes mellitus, hypertension, stroke, and ischemic heart disease.
- Cardiovascular health-specific discussions with emerging adults should include the following:
 - Any residual hemodynamic considerations
 - Symptoms to be aware of
 - Diagnostic tests and potential management
 - Risks associated with noncardiac surgery
 - Life and health insurance
 - Education and employment
 - Need for lifelong cardiac care
 - Endocarditis symptoms and prophylaxis
 - Contraception/pregnancy including risks
 - Medications (indications and side effects)
 - Exercise and healthy diet
 - End-of-life issues

CARDIOVASCULAR RISKS DURING PREGNANCY

The rapidly evolving field of ART is increasing the child-bearing potential for women with TS. Accordingly, it is imperative that reproductive health practitioners and obstetricians understand who might safely attempt pregnancy. Practitioners must become familiar with the special monitoring and management that women with TS might require during and after pregnancy. It should be noted that this document proposes that pregnancy can be undertaken safely by women with TS, even some individuals with known risk factors. The suggestions for clinical practice herein take a moderate stance on the advisability of pregnancy compared with the guidelines previously proposed by the American Society of Reproductive Medicine⁸⁹ that state that a significant cardiac malformation absolutely precludes pregnancy.

AoD During Pregnancy

Pregnancy in women with TS is associated with significant risks, including hypertensive disorders, preeclampsia, premature birth, low birth weight, and need for cesarean delivery.⁹⁰ Pregnancy in Marfan syndrome increases the risk of AoD or rupture.⁹¹ Case reports,⁶ but no controlled studies to date, suggest that pregnancy may increase the AoD risk in TS.

Structural changes in the intima and media have been described in pregnant women without aortic disease. Histopathology previously showed hypertrophy and hyperplasia of smooth muscle cells, fragmentation of reticular fibers, and less corrugated elastic fibers.⁹² These changes may be driven not only by the increase in cardiac output and circulating blood volume but also by hormonal changes. Whether the alterations in the aortic wall lead to an increased risk of AoD in pregnant women remains undetermined.^{6,39,65} There are case reports and AoD series that describe AoD during pregnancy, although low numbers and selection bias preclude any firm conclusions to be drawn. Patients derived from these reports may overrepresent those with unusual presentations of their disease.⁹³ In the GenTAC study (Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions) of 278 pregnancies in women with Marfan syndrome, an 8-fold increased risk of AoD was reported.⁹⁴ In addition, a population-based registry from Sweden reported a 25-fold increased risk of AoD related to pregnancy in TS.⁹⁵

ART may pose additional risk for significant complications beyond those of a spontaneous pregnancy.⁶⁵ Type A and B AoDs have been described during ART-associated pregnancy in TS.³⁹ A comprehensive registry that includes all cases of pregnancy in women with TS is essential to answer the question of AoD risk in pregnancy in women with TS.⁹⁶ In TS cases in which the aorta is dilated, there are no studies that consider the advisability of elective aortic surgery before pregnancy. In women with other conditions associated with AoD such as Marfan and Loeys-Dietz syndromes, a dilated aorta is an indication to perform pre-pregnancy surgery. However, after aortic surgery in these conditions, women are still considered at risk for distal AoD, especially those with Loeys-Dietz syndrome.⁹⁷ Similarly, it is assumed that the risk of AoD is still present after elective aortic root replacement in TS. Apart from the risk of AoD, women with TS may have other cardiovascular abnormalities such as aortic valve stenosis or coarctation of the aorta. If pre-pregnancy aortic root surgery will include aortic valve replacement with a mechanical valve, the woman with TS will be put at risk of a valve thrombosis or bleeding. In a recent article on mechanical valves, only 58% of the pregnancies were without severe complication.⁹⁸ If a bioprosthetic aortic valve is used, the risk of throm-

basis or bleeding is lower, but subsequent aortic valve interventions will be needed.⁹⁹ The guidelines for care in those with congenital heart defects are similar to those for women without TS.¹⁰⁰

Cardiovascular Risks Beyond the Aorta

In addition to the increased prevalence of congenital heart defects and potentially increased risk of AoD, women with TS are at increased risk for diabetes mellitus and hypertensive disorders of pregnancy, including preeclampsia.^{90,101,102} Preeclampsia and gestational hypertension in the general population are associated with several risk factors, including a family history of preeclampsia, nulliparity, older age, elevated body mass index, preexisting diabetes mellitus, chronic renal disease, antiphospholipid antibodies, multiple gestation, and preexisting hypertension.¹⁰³ Hypertension is more common in women with TS, which may contribute to the higher incidence of hypertensive complications during pregnancy. In addition, obstetric and fetal risks are higher, including a higher risk of miscarriage and fetal abnormalities.^{104,105}

ART in Individuals With TS

Specific considerations and recommendations for ART in women with TS have been published.⁹ In this document, aspects of ART that relate to cardiovascular health are addressed.

Most women with TS will not be able to conceive spontaneously or undergo ovarian stimulation because of reduced or absent ovarian capacity.¹⁰⁶ Women with mosaic TS are also likely to have reduced ovarian reserve. In women with normal ovarian reserve, stimulation has 3 potential adverse cardiovascular consequences: a prothrombotic effect,¹⁰⁷ a hemodynamic effect,^{108–110} and the occurrence of ovarian hyperstimulation syndrome, which exacerbates these prothrombotic and hemodynamic changes and is further complicated by increased capillary permeability causing marked fluid shifts.¹¹¹ The risk of ovarian hyperstimulation syndrome is very low in women with TS and can be further reduced or even avoided altogether by altering the stimulation regimen used and avoiding the use of exogenous human chorionic gonadotropin.¹¹²

Because the majority of women with TS have no ovarian reserve, they will need to take estrogen to prepare the endometrium and subsequently the combination of estrogen and progesterone to maintain pregnancy. Hormone replacement therapy has prothrombotic effects and consequences.^{113,114} However, hormone replacement therapy has not been studied specifically in TS. Prothrombotic effects are limited in the context of endometrial preparation and can be reduced by giving the estrogen component via the transdermal route.¹¹³ Overall, the impact of the short-term exposure to exog-

enous estrogen is limited and minor compared with the prothrombotic effect of pregnancy.

No clear evidence is available on an association between ART and aortic dimension or AoD. Assisted conception seems to further increase the risk of hypertensive and cardiovascular complications compared with spontaneous conception. Associated older age at conception and a higher percentage of multiple pregnancies may contribute to these risks of assisted conception.⁶⁵

Medical Treatment During Pregnancy

Medical treatment, specifically in terms of cardiovascular health, comprises antihypertensive treatment and prophylactic medication to prevent (further) aortic dilatation. Antihypertensive treatment recommendations are similar to those for pregnant women without TS. There is no clear evidence for prophylactic medication during pregnancy in women with TS who have aortic dilatation. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated in pregnancy because of potential detrimental fetal effects. β -Blockers may be considered and do not cause fetal abnormalities; however, some effect on fetal birth weight has been described.^{115,116} This recommendation holds for any woman with aortic dilatation. The National Institute for Health and Care Excellence recommends 75 to 81 mg aspirin daily from 12 weeks of gestation until delivery for women at risk of preeclampsia.¹¹⁷ This recommendation is based on data showing a benefit with aspirin use in patients with ≥ 2 moderate risk factors.⁷ Oocyte donation is not given as a specific risk factor, but consideration should be given to prescribing aspirin in such pregnancies in a woman with TS.

Mode of Delivery in Women With a Dilated Aorta and TS

A delivery plan should be made by a multidisciplinary team consisting of at least an obstetrician, cardiologist, and anesthesiologist, all with expertise in pregnancy in the context of maternal heart disease or aortopathy. Vaginal delivery is the preferred mode of delivery in most women, according to the available literature. In the Registry of Pregnancy and Cardiac Disease, cesarean delivery was not superior to a vaginal delivery for the mother, whereas an increase in adverse fetal events was seen.¹¹⁶ According to expert opinion, in women with a severely dilated aorta, a cesarean delivery is reasonable, although it also leads to hemodynamic changes. A cesarean delivery is recommended for women with a history of AoD. The short stature in TS predisposes for disproportion of the pelvis; cesarean delivery may be required for this reason.¹⁰⁵

Suggestions for Clinical Practice

Imaging, Counseling, and Treatment in Women With TS Before Pregnancy or ART

- Imaging of the thoracic aorta and heart with TTE and CT/CMR should be performed within 2 years before pregnancy or ART in all women with TS.
- Exercise testing before pregnancy can be useful to reveal exercise-induced hypertension, especially in women with a history of coarctation of the aorta.
- All women with TS should be counseled about the increased cardiovascular risk of pregnancy.
- Women with aortic dilatation, BAV, elongation of the transverse aorta, coarctation of the aorta, or hypertension should be advised that pregnancy carries a high risk of AoD.
- Other options for motherhood such as adoption or using a gestational carrier should be discussed during preconception counseling.
- It is recommended that ART and spontaneous conception be avoided in women with TS with an ascending ASI of >2.5 cm/m² or (history of) AoD.
- It is recommended that ART or spontaneous conception be avoided in women with TS with an ascending ASI of 2.0 to 2.5 cm/m² and associated risk factors for AoD, which include BAV, elongation of the transverse aorta, coarctation of the aorta, and hypertension.
- If women with an ASI >2.5 cm/m² or a history of AoD do become pregnant, they should be followed up very closely at a specialized center and should deliver by cesarean delivery.
- Angiotensin inhibition (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) is contraindicated during pregnancy.

Monitoring, Therapeutic Management, and Delivery of Pregnant Women With TS

- During pregnancy, individuals with TS should be treated in specialized centers by a multidisciplinary team with knowledge of TS.
- In women with TS without aortic dilatation or other risk factors (hypertension, BAV, coarctation, elongation of the transverse arch, previous AoD, or surgery), it is reasonable to perform a TTE and clinical assessment at least once at ≈ 20 weeks of gestation.
- Women with TS with an ascending ASI >2.0 cm/m² or any risk factor (hypertension, BAV, coarctation, elongation of the transverse arch, previous AoD, or surgery) should be monitored frequently, including TTE at 4- to 8-week intervals during pregnancy and once during the first month after

delivery, with subsequent imaging depending on the severity of aortic enlargement.

- CMR (without gadolinium) should be performed during pregnancy in the following circumstances: when there is concern of disease of the distal ascending aorta, aortic arch, or descending aorta; in cases of insufficient image quality of the ascending aorta; or when aortic dimensions are increasing.
- In pregnant women with TS, strict BP control is recommended.
- During pregnancy, prophylactic aortic surgery may be considered in the case of a dilated aorta (ASI ≥ 2.5 cm/m²) with a rapid increase in diameter (>3 mm).
- The use of low-dose aspirin (75–81 mg) may be considered in pregnant women with TS.
- A vaginal delivery is reasonable in women with TS with an ascending ASI <2.0 cm/m².
- In women with TS with an ascending ASI of 2.0–2.5 cm/m², the following applies:
 - A vaginal delivery with epidural anesthesia and expedited second stage is reasonable.
 - A cesarean delivery may be considered.
- If women with TS with an ascending ASI >2.5 cm/m² become pregnant, a cesarean delivery is recommended.
- In women with TS with a history of AoD, a cesarean delivery is recommended.
- In case of an acute ascending AoD before the fetus is viable, it is recommended that emergency aortic surgery be performed with the understanding that fetal viability may be at risk.
- In case of an acute ascending AoD and a viable fetus, performing a cesarean delivery first, followed by urgent aortic surgery, should be considered.
- Aortic surgery in the pregnant patient should be performed under the following conditions: near normothermia, pulsatile perfusion or high pump flow, and avoidance of vasoconstrictors.
- In women with TS with an ascending ASI of >2.0 cm/m², postpartum monitoring is indicated for at least 48 hours.

HIGH BP

High BP is one of the most important modifiable risk factors for the cardiovascular risks in TS: AoD, stroke, and myocardial infarction. Although individuals with TS are frequently found to have hypertension, little has been documented about measurement, definitions, and management of hypertension specifically for women with TS. The subject has only recently been reviewed.⁷²

Epidemiology and Pathogenesis

The prevalence of hypertension in individuals with TS is 20% to 40% in childhood⁷¹ and up to 60% in adulthood. Hypertension may appear at early ages and continue through adulthood. Hypertension may be the result of renal anomalies that are frequently seen in TS or may be idiopathic.⁷¹ Hypertension can persist after coarctation repair even in those without residual descending aortic pressure gradients. The intrinsic shape of the aorta in individuals with TS without coarctation may be a factor in the pathogenesis of hypertension for some.¹¹⁸ Obesity, metabolic derangements, the lack of estrogen, the renin-angiotensin system, and abnormal vascular wall and vessel resistance have been identified as pathogenetic factors in hypertension in TS.¹¹⁸ In addition to well-known end-organ damage in multiple systems, hypertension is a risk factor for aortopathy (specifically AoD) in individuals with TS, although AoD can occur without this risk factor.⁶

Identifying Hypertension and the Value of Ambulatory BP Monitoring

Several guidelines for the measurement and ascertainment of hypertension in infants, children, adolescents, and adults are available, but no guideline specifically addresses individuals with TS. De Groote et al⁷² suggest a practical approach to hypertension identification and management for girls and women with TS, including an algorithm for BP evaluation in adult women.

Left ventricular hypertrophy (increased left ventricular mass) has been identified in TS even in those who are normotensive.¹¹⁹ This could be an end-organ effect of hypertension that is masked during resting BP assessment, or it may relate to loss of diurnal variation (lack of nighttime dipping). Ambulatory BP monitoring (ABPM) has proved to be useful in demonstrating abnormal diurnal variation in BP values in women with TS.^{120,121} In addition, because the vasculopathy of TS is characterized by increased vessel stiffness,⁴⁰ random resting BP measurement may not accurately reflect ongoing hypertensive stresses occurring throughout the day. Because other conditions associated with elevated arterial stiffness such as chronic kidney disease¹²² are known to have a high prevalence of masked hypertension (normal in clinic and high on ABPM), women with TS may also be at increased risk of this abnormal BP pattern. ABPM is the best method to rule out masked hypertension and is the most sensitive method for predicting hypertension-induced left ventricular hypertrophy.¹²³ ABPM may be particularly valuable in those who are overweight or have prehypertension, conditions associated with a higher prevalence of masked hypertension.

Management

Recognition and treatment of hypertension in TS are similar to that in other individuals and include encouraging healthy lifestyle choices and aggressive management of obesity. Therefore, in all children, hypertension is diagnosed on the basis of percentile rank determined by sex, age, and height.¹²⁴ Adult guidelines suggest that BPs <130/80 mm Hg are desirable with >120 mm Hg considered borderline.⁷² It is essential to diagnose secondary causes of high BP such as renal anomalies, obstructive uropathy, coarctation, sleep apnea, and hyperaldosteronism. Medication therapy is often used for women with TS with hypertension and includes the entire pharmacological armamentarium typically used for hypertension in patients without TS.⁷² However, it is reasonable to treat high BP in TS with certain antihypertensive drugs such as β -blockers or angiotensin receptor blockers that are effective in slowing the rate of aortic dilatation in other genetic aortopathies such as Marfan syndrome.¹²⁵

Women with TS have been recognized to have cellular and endothelial dysfunction that may be unique to the genotype and involves a variety of abnormal feedback and BP control mechanisms. Clues are emerging that give promise of better and more effective treatments. Individuals with TS have an aortopathy characterized by increased vascular stiffness and greater arterial medial thickness, suggesting a potential connection between abnormal vascular compliance/distensibility and childhood onset of essential hypertension. Paternal origin of the X chromosome appears to be associated with decreased aortic compliance.¹⁰⁸ New directions in biomarker detection and directed pharmacological therapy to specific pathogenic derangements are needed. Ultimately, the need to develop evidence-based treatments in the relatively small cohort of individuals with TS will require collaborative, multicenter efforts.

Suggestions for Clinical Practice

- Normal BP values should be defined on the basis of accepted guidelines for the general population.
- The diagnosis of hypertension should be considered in individuals with TS throughout the life span.
- ABPM should be considered in adults and children with normal resting BP, especially in the presence of unexplained left ventricular hypertrophy.
- Antihypertensive medication adequate to control hypertension with a greater emphasis on β -blockers or angiotensin receptor blockers, which may also be efficacious in decreasing aortic growth velocity, is reasonable.

LIPIDS AND THROMBOSIS

Adult women with TS have a high prevalence of ischemic heart disease and stroke.³ The cardiovascular morbidity and mortality in adult life are significantly higher in women with TS compared with the general population.² Lean, normotensive woman with TS may never develop ischemic heart disease, whereas hypertensive patients with type 2 diabetes mellitus, obesity, and insufficient estrogen substitution are more likely to develop stroke or a myocardial infarction throughout life.¹²⁶ Therefore, it is important to assess the risk factors of a patient with TS in a multidisciplinary setup and to motivate the patient to exercise, to maintain normal weight, and to abstain from smoking.¹²⁷ There is not a specific dyslipidemia associated with TS,¹²⁸ but many patients develop an unhealthy lipid profile as a result of obesity, diabetes mellitus, or poor estrogen substitution.^{129,130} There is no need for early lipid screening and intervention in childhood; instead, surveillance of risk factors such as obesity, diabetes mellitus, and hypertension is strongly advised. A multidisciplinary approach is important in patients with a high-risk profile, which often includes a cardiologist, an endocrinologist, and a dietitian. Attaining and maintaining a healthy weight through dietary and exercise modification should always be the primary approach. Medical treatment with statins should be implemented, if needed, as indicated by current guidelines.

Suggestions for Clinical Practice

- Lipids should be assessed in early adulthood (17–21 years) to rule out rare disorders in lipid metabolism. Additional assessment will depend on the general health of the patient (diabetes mellitus, hypertension, obesity, family history).
- Considerations for treating dyslipidemia should be based on current guidelines for the general population.

Stroke occurs in excess of the general population,³ but whether this is simply related to the increased risk of hypertension or other TS-specific causes is unknown. Disturbances of thrombosis and fibrinolysis may increase the risk of thromboembolic stroke. The risk of thrombotic disease has not yet been formally addressed in outcome studies, but an increased risk of thrombus formation, even in the absence of a functional or morphological cardiovascular substrate, has been suggested.¹³¹ Clotting factors and clotting times may be normal for cohorts with TS when assessed in total, but on the individual level, many will have procoagulant levels of clotting and fibrinolytic factors.⁷ Fibrinogen has been found to be elevated in 65% of females with TS, and proteins C and S were reduced in a large fraction.⁷ Conversely, clotting factors, fibrino-

lytic factors, fibrinogen levels, and clotting times have also been reported to be within the normal range in other cohorts with TS,^{128,132} although high-normal values have been reported for some procoagulant factors.^{133,134} The most common mutations associated with thrombus formation are more frequently reported in TS.^{133,134} One study showed that factor V Leiden G1691A gene polymorphism heterozygosity is more prevalent in individuals with TS (13%) than in the general population (2%).¹³³

Most patients with TS need hormone replacement therapy to induce puberty, to maintain female secondary sex characteristics, to obtain peak bone mass, and to normalize uterine growth,⁹ and this treatment does not seem to be an issue in relation to venous thrombosis. The goal is to mimic physiological estrogen levels, and there are no studies that support that treatment with physiological doses increases the risk of thrombosis.¹³⁵ Therefore, screening for thromboembolic risk should be performed only in girls with a personal or family history of thromboembolism, and hormone replacement therapy can continue until the risk overshadows the benefits, which is around the usual age of menopause.¹³⁶ In summary, the clotting system appears to be excessively activated in some women with TS, but outcome data are lacking, and the common denominator has not yet been found. For this reason, no general recommendation can be issued, but certain awareness about thromboembolic disease in TS will help identify the few women with TS with coagulation disorders.

Suggestion for Clinical Practice

- No general recommendation can be issued for thromboembolic disease in TS. Awareness about the risk of thromboembolic disease in TS will help identify women with TS with coagulation disorders.

GENETICS OF HEART DISEASE

TS is characterized mainly by obstructive left-sided congenital heart defects that are rare in the general female population and should increase clinical suspicion for TS.¹ Congenital heart defects that are commonly diagnosed in TS include coarctation of the aorta, BAV, mitral valve anomalies, hypoplastic left-sided heart syndrome, and partial anomalous pulmonary venous connection.^{17,19} Genetic testing for TS should be considered in female patients with any of these abnormalities. Regardless of the indication for genetic testing or specific result, genetic counseling by a geneticist or genetic counselor should be provided before and after any genetic test.¹³⁷

A standard 20-cell karyotype remains the investigation of choice for molecular diagnosis of TS. Any adult woman with suspected TS who has no documented karyotype should be retested. If mosaicism is strongly suspected but not demonstrated with a standard karyotype, additional metaphases may be counted or fluorescence in situ hybridization studies performed.^{138–141} Although a karyotype is preferred, TS will be detected on a comparative genomic hybridization microarray¹⁴² (which is routinely performed in children with congenital heart defects). However, if diagnosed by comparative genomic hybridization microarray, a karyotype should subsequently be performed. 45,X/46,XX or 45,X/47,XXX mosaicism is associated with a milder cardiovascular phenotype, including less prevalent and less severe congenital heart defects and lymphatic abnormalities.^{143,144} However, there is insufficient evidence to withhold routine surveillance from those with even low levels of mosaicism.

Suggestions for Clinical Practice

- The diagnosis of a BAV or an obstructive left-sided congenital heart defect in a female fetus, child, or adult should prompt a genetic evaluation for TS.
- The diagnosis of TS should be considered in any female with short stature and at least 1 additional characteristic clinical feature (ie, thyroid dysfunction, ovarian failure, Madelung deformity, renal anomalies, or hearing impairment) who also has an associated congenital heart defect.
- All individuals with suspected TS should have a standard 20-cell karyotype analysis because it will identify at least 10% mosaicism with 95% confidence in peripheral blood.
- Guidelines for surveillance and clinical management of cardiovascular disease should be applied equally to all patients with TS, regardless of karyotype.

FUTURE DIRECTIONS

Although the past 2 decades have seen significant advancements in our understanding of TS, many fundamental questions remain unanswered, and those that have been answered have also served to raise more questions. From the developmental origins of the cardiovascular manifestations seen in TS to the best approaches to clinical care for these girls and women, the field is wide open for clinical and basic researchers to make novel and meaningful discoveries. Given the broad scope of medical problems associated with TS, delineating key domains lacking evidence is essential. Therefore, the working group has identified research priorities in the field of TS (Table).

Table. Cardiovascular Research Priorities in TS

Molecular and developmental
Understand the biological and genetic determinants of aortopathy and congenital heart disease in TS.
Understand the impact of endogenous and exogenous hormones, including pregnancy and fertility treatments and growth hormone replacement, on aortic growth and the risk of aortic dissection.
Determine the extent of arterial pathology beyond the aorta.
Identify the role of tissue-specific mosaicism in the isolated cardiovascular phenotype.
Investigate the influence of the second sex chromosome on cardiovascular risk in the general population through the paradigm of TS.
Identify genetic profiles or serum biomarkers that will stratify individual risk.
Medical and surgical
Characterize and reduce the risk for aortic dissection with aortic enlargement in TS, including the use of specific biomarkers and functional imaging tools.
Develop new medical therapies that reduce the risk of cardiovascular complications in patients with TS (with or without aortic dilation).
Optimize risk stratification strategies and identify the ideal criteria for elective aortic surgery.
Elucidate the pathogenesis of increased cardiovascular morbidity and mortality in women with TS compared with the general population and determine the contributions of atherosclerotic disease, dyslipidemia, hypertension, and obesity.
Delineate the risk of stroke in TS.
Understand the pathophysiology of the QTc prolongation and what it means clinically for patients with TS.
Understand the role of estrogen replacement in early stroke risk.
Imaging protocols
Characterize the most accurate tool to define aortic enlargement and aneurysm (ie, TS-specific z score vs ASI vs absolute measurement).
Characterize the most accurate approach to measure the aortic diameter (eg, leading edge to leading edge vs inner edge to inner edge or measurements taken during systole vs diastole).
Pregnancy
Use the ROPAC registry to characterize the risk of pregnancy associated with TS (eg, aortic dissection, fetal growth restriction, preeclampsia).
Investigate the additional risk of ART.

ART indicates assisted reproductive therapy; ASI, aortic size index; ROPAC, Registry of Pregnancy and Cardiac Disease; and TS, Turner syndrome.

A better understanding of cardiovascular health in TS must overcome 2 fundamental challenges: A vast array of cardiovascular diseases significantly affect girls and women with TS, and TS is a rare condition, making the recruitment of large numbers of subjects for clinical studies difficult. Accordingly, significant advances will require collaboration across all the cardiovascular subspecialties and will need to engage research centers throughout the world. Clinical registries, such as the Turner Syndrome Research Registry, sponsored by the Turner Syndrome Society of the United States, and the Registry of Pregnancy and Cardiac Disease, sponsored by the European Society of Cardiology, that can recruit large numbers of potential research subjects, will be crit-

ical to the success of these projects. The topical areas of interest in terms of cardiovascular disease in TS include genetic and developmental factors affecting congenital and acquired disease, pathophysiological mediators and mitigators, clinical outcomes in operated and unoperated states, therapeutic strategies to improve clinical outcomes, and clinical management strategies to improve quality of life and attainment of full potential.

ARTICLE INFORMATION

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity or owns \$10000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.
†Significant.

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†Significant.

REFERENCES

- Sybert VP, McCauley E. Turner's syndrome. *N Engl J Med*. 2004;351:1227–1238. doi: 10.1056/NEJMra030360
- Stochholm K, Juul S, Juul K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. *J Clin Endocrinol Metab*. 2006;91:3897–3902. doi: 10.1210/jc.2006-0558
- Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA; United Kingdom Clinical Cytogenetics Group. Mortality in women with Turner syndrome in Great Britain: a national cohort study. *J Clin Endocrinol Metab*. 2008;93:4735–4742. doi: 10.1210/jc.2008-1049
- Lin AE, Lippe BM, Geffner ME, Gomes A, Lois JF, Barton CW, Rosenthal A, Friedman WF. Aortic dilation, dissection, and rupture in patients with Turner syndrome. *J Pediatr*. 1986;109:820–826.
- Gravholt CH, Landin-Wilhelmsen K, Stochholm K, Hjerrild BE, Ledet T, Djurhuus CB, Sylven L, Baandrup U, Kristensen BØ, Christiansen JS. Clinical and epidemiological description of aortic dissection in Turner's syndrome. *Cardiol Young*. 2006;16:430–436. doi: 10.1017/S1047951106000928
- Carlson M, Silberbach M. Dissection of the aorta in Turner syndrome: two cases and review of 85 cases in the literature. *J Med Genet*. 2007;44:745–749. doi: 10.1136/jmg.2007.052019
- Calcaterra V, Gamba G, Montani N, de Silvestri A, Terulla V, Lanati G, Larizza D. Thrombophilic screening in Turner syndrome. *J Endocrinol Invest*. 2011;34:676–679. doi: 10.3275/7724
- Gravholt CH, Juul S, Naeraa RW, Hansen J. Morbidity in Turner syndrome. *J Clin Epidemiol*. 1998;51:147–158.
- Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, Lin AE, Mauras N, Quigley CA, Rubin K, Sandberg DE, Sas T CJ, Sil-

- berbach M, Soderstrom-Anttila V, Stochholm K, van Alfen-van derVelden JA, Woelfle J, Backeljauw PF; International Turner Syndrome Consensus Group. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur J Endocrinol*. 2017;177:G1–G70.
10. Turner Syndrome Society of the United States website. <http://www.turnersyndrome.org/>. Accessed August 18, 2018.
 11. Gurvitz M, Marelli A, Mangione-Smith R, Jenkins K. Building quality indicators to improve care for adults with congenital heart disease. *J Am Coll Cardiol*. 2013;62:2244–2253. doi: 10.1016/j.jacc.2013.07.099
 12. Mazzanti L, Cacciari E. Congenital heart disease in patients with Turner's syndrome: Italian Study Group for Turner Syndrome (ISGTS). *J Pediatr*. 1998;133:688–692.
 13. Sybert VP. Cardiovascular malformations and complications in Turner syndrome. *Pediatrics*. 1998;101:E11.
 14. Vökl TM, Degenhardt K, Koch A, Simm D, Dörr HG, Singer H. Cardiovascular anomalies in children and young adults with Ullrich-Turner syndrome the Erlangen experience. *Clin Cardiol*. 2005;28:88–92.
 15. Göttsche CO, Krag-Olsen B, Nielsen J, Sørensen KE, Kristensen BO. Prevalence of cardiovascular malformations and association with karyotypes in Turner's syndrome. *Arch Dis Child*. 1994;71:433–436.
 16. Mazzanti L, Prandstraller D, Tassinari D, Rubino I, Santucci S, Picchio FM, Forabosco A, Cacciari E. Heart disease in Turner's syndrome. *Helv Paediatr Acta*. 1988;43:25–31.
 17. van den Hoven AT, Chelu RG, Duijnhouwer AL, Demulier L, Devos D, Nieman K, Witsenburg M, van den Bosch AE, Loeys BL, van Hagen IM, Roos-Hesselink JW. Partial anomalous pulmonary venous return in Turner syndrome. *Eur J Radiol*. 2017;95:141–146. doi: 10.1016/j.ejrad.2017.07.024
 18. Kim HK, Gottliebson W, Hor K, Backeljauw P, Gutmark-Little I, Salisbury SR, Racadio JM, Helton-Skally K, Fleck R. Cardiovascular anomalies in Turner syndrome: spectrum, prevalence, and cardiac MRI findings in a pediatric and young adult population. *AJR Am J Roentgenol*. 2011;196:454–460. doi: 10.2214/AJR.10.4973
 19. Ho VB, Bakalov VK, Cooley M, Van PL, Hood MN, Burklow TR, Bondy CA. Major vascular anomalies in Turner syndrome: prevalence and magnetic resonance angiographic features. *Circulation*. 2004;110:1694–1700. doi: 10.1161/01.CIR.0000142290.35842.B0
 20. Clark EB. Neck web and congenital heart defects: a pathogenic association in 45 X-0 Turner syndrome? *Teratology*. 1984;29:355–361. doi: 10.1002/tera.1420290305
 21. Loscalzo ML, Van PL, Ho VB, Bakalov VK, Rosing DR, Malone CA, Dietz HC, Bondy CA. Association between fetal lymphedema and congenital cardiovascular defects in Turner syndrome. *Pediatrics*. 2005;115:732–735. doi: 10.1542/peds.2004-1369
 22. Horne D, Morris SA, Colquitt JL, Molossi SM, McKenzie ED. Incidental finding of right coronary artery to pulmonary artery fistula during surgical repair of aortic arch atresia in Turner syndrome. *World J Pediatr Congenit Heart Surg*. 2017;8:646–649.
 23. Gravholt CH. Turner syndrome in adulthood. *Horm Res*. 2005;64(suppl 2):86–93. doi: 10.1159/000087763
 24. 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;35:253–260. doi: 10.1007/s00246-013-0766-5
 25. Viuff MH, Trolle C, Wen J, Jensen JM, Nørgaard BL, Gutmark EJ, Gutmark-Little I, Mortensen KH, Gravholt CH, Andersen NH. Coronary artery anomalies in Turner syndrome. *J Cardiovasc Comput Tomogr*. 2016;10:480–484. doi: 10.1016/j.jcct.2016.08.004
 26. Oohara K, Yamazaki T, Sakaguchi K, Nakayama M, Kobayashi A. Acute aortic dissection, aortic insufficiency, and a single coronary artery in a patient with Turner's syndrome. *J Cardiovasc Surg (Torino)*. 1995;36:273–275.
 27. Luckraz H, Mohammed A, Youhana A. A prominent collateral coronary artery. *Ann Thorac Surg*. 2006;81:1518. doi: 10.1016/j.athoracsur.2004.04.069
 28. Quezada E, Lapidus J, Shaughnessy R, Chen Z, Silberbach M. Aortic dimensions in Turner syndrome. *Am J Med Genet A*. 2015;167A:2527–2532. doi: 10.1002/ajmg.a.37208
 29. Bondy CA; Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. *J Clin Endocrinol Metab*. 2007;92:10–25. doi: 10.1210/jc.2006-1374
 30. 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;70:803–814. doi: 10.1016/j.crad.2015.03.009
 31. Mortensen KH, Hjerrild BE, Andersen NH, Sørensen KE, Hørlyck A, Pedersen EM, Lundorf E, Christiansen JS, Gravholt CH. Abnormalities of the major intrathoracic arteries in Turner syndrome as revealed by magnetic resonance imaging. *Cardiol Young*. 2010;20:191–200. doi: 10.1017/S1047951110000041
 32. Ostberg JE, Brookes JA, McCarthy C, Halcox J, Conway GS. A comparison of echocardiography and magnetic resonance imaging in cardiovascular screening of adults with Turner syndrome. *J Clin Endocrinol Metab*. 2004;89:5966–5971. doi: 10.1210/jc.2004-1090
 33. Lanzarini L, Larizza D, Prete G, Calcaterra V, Meloni G, Sammarchi L, Klersy C. Aortic dimensions in Turner's syndrome: two-dimensional echocardiography versus magnetic resonance imaging. *J Cardiovasc Med (Hagerstown)*. 2007;8:428–437. doi: 10.2459/01.JCM.0000269716.33435.d3
 34. Mortensen KH, Gravholt CH, Hjerrild BE, Stochholm K, Andersen NH. Left ventricular hypertrophy in Turner syndrome: a prospective echocardiographic study. *Echocardiography*. 2012;29:1022–1030. doi: 10.1111/j.1540-8175.2012.01754.x
 35. Gutmark-Little I, Backeljauw PF. Cardiac magnetic resonance imaging in Turner syndrome. *Clin Endocrinol (Oxf)*. 2013;78:646–658. doi: 10.1111/cen.12157
 36. Miller MJ, Geffner ME, Lippe BM, Itami RM, Kaplan SA, DiSessa TG, Isabel-Jones JB, Friedman WF. Echocardiography reveals a high incidence of bicuspid aortic valve in Turner syndrome. *J Pediatr*. 1983;102:47–50.
 37. Madhwal S, Rajagopal V, Bhatt DL, Bajzer CT, Whitlow P, Kapadia SR. Predictors of difficult carotid stenting as determined by aortic arch angiography. *J Invasive Cardiol*. 2008;20:200–204.
 38. Nejatian A, Yu J, Geva T, White MT, Prakash A. Aortic measurements in patients with aortopathy are larger and more reproducible by cardiac magnetic resonance compared with echocardiography. *Pediatr Cardiol*. 2015;36:1761–1773. doi: 10.1007/s00246-015-1231-4
 39. 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;126:2220–2226. doi: 10.1161/CIRCULATIONAHA.111.088633
 40. Lawson SA, Urbina EM, Gutmark-Little I, Khoury PR, Gao Z, Backeljauw PF. Vasculopathy in the young Turner syndrome population. *J Clin Endocrinol Metab*. 2014;99:E2039–E2045. doi: 10.1210/jc.2014-1140
 41. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, Eagle KA, Hermann LK, Isselbacher EM, Kazerooni EA, Kousshous NT, Lytle BW, Milewicz DM, Reich DL, Sen S, Shinn JA, Svensson LG, Williams DM. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Catheter Cardiovasc Interv*. 2010;76:E43–E86.
 42. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, Lai WW, Geva T. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *J Am Soc Echocardiogr*. 2010;23:465–95; quiz 576. doi: 10.1016/j.echo.2010.03.019
 43. Davies RR, Gallo A, Coady MA, Tellides G, Botta DM, Burke B, Coe MP, Kopf GS, Elefteriades JA. Novel measurement of relative aortic size predicts rupture of thoracic aortic aneurysms. *Ann Thorac Surg*. 2006;81:169–177. doi: 10.1016/j.athoracsur.2005.06.026
 44. Mongeon FP, Marcotte F, Terrone DG. Multimodality noninvasive imaging of thoracic aortic aneurysms: time to standardize? *Can J Cardiol*. 2016;32:48–59. doi: 10.1016/j.cjca.2015.09.025
 45. Corbitt H, Maslen C, Prakash S, Morris SA, Silberbach M. Allometric considerations when assessing aortic aneurysms in Turner syndrome: implications for activity recommendations and medical decision-making. *Am J Med Genet A*. 2018;176:277–282. doi: 10.1002/ajmg.a.38584
 46. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14. doi: 10.1016/j.echo.2014.10.003

47. Goldstein SA, Evangelista A, Abbara S, Arai A, Asch FM, Badano LP, Bollen MA, Connolly HM, Cuéllar-Calàbria H, Czerny M, Devereux RB, Erbel RA, Fattori R, Isselbacher EM, Lindsay JM, McCulloch M, Michelena HI, Nienaber CA, Oh JK, Pepi M, Taylor AJ, Weinsaft JW, Zamorano JL, Dietz H, Eagle K, Elefteriades J, Jondeau G, Rousseau H, Schepens M. Multimodality imaging of diseases of the thoracic aorta in adults: from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:119–182. doi: 10.1016/j.echo.2014.11.015
48. Kaiser T, Kellenberger CJ, Albisetti M, Bergsträsser E, Valsangiacomo Buechel ER. Normal values for aortic diameters in children and adolescents: assessment in vivo by contrast-enhanced CMR-angiography. *J Cardiovasc Magn Reson*. 2008;10:56. doi: 10.1186/1532-429X-10-56
49. Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER, Vogel-Claussen J, Turkbey EB, Williams R, Plein S, Tee M, Eng J, Bluemke DA. Normal values for cardiovascular magnetic resonance in adults and children. *J Cardiovasc Magn Reson*. 2015;17:29. doi: 10.1186/s12968-015-0111-7
50. Turkbey EB, Jain A, Johnson C, Redheuil A, Arai AE, Gomes AS, Carr J, Hundley WG, Teixido-Tura G, Eng J, Lima JA, Bluemke DA. Determinants and normal values of ascending aortic diameter by age, gender, and race/ethnicity in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Magn Reson Imaging*. 2014;39:360–368. doi: 10.1002/jmri.24183
51. Sheil ML, Jenkins O, Sholler GF. Echocardiographic assessment of aortic root dimensions in normal children based on measurement of a new ratio of aortic size independent of growth. *Am J Cardiol*. 1995;75:711–715. doi: 10.1016/S0002-9149(99)80659-6
52. Bossone E, Yuriditsky E, Desale S, Ferrara F, Friz O, Asch FM. Normal values and differences in ascending aortic diameter in a healthy population of adults as measured by the pediatric versus adult American Society of Echocardiography guidelines. *J Am Soc Echocardiogr*. 2016;29:166–172. doi: 10.1016/j.echo.2015.09.010
53. Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. *Am J Cardiol*. 1989;64:507–512.
54. Matura LA, Ho VB, Rosing DR, Bondy CA. Aortic dilatation and dissection in Turner syndrome. *Circulation*. 2007;116:1663–1670. doi: 10.1161/CIRCULATIONAHA.106.685487
55. Meijboom LJ, Groenink M, van der Wall EE, Romkes H, Stoker J, Mulder BJ. Aortic root asymmetry in Marfan patients; evaluation by magnetic resonance imaging and comparison with standard echocardiography. *Int J Card Imaging*. 2000;16:161–168
56. Sluysmans T, Colan SD. Theoretical and empirical derivation of cardiovascular allometric relationships in children. *J Appl Physiol (1985)*. 2005;99:445–457. doi: 10.1152/jappphysiol.01144.2004
57. Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. *J Am Soc Echocardiogr*. 2008;21:922–934. doi: 10.1016/j.echo.2008.02.006
58. Lanzarini L, Larizza D, Prete G, Calcaterra V, Klersy C. Prospective evaluation of aortic dimensions in Turner syndrome: a 2-dimensional echocardiographic study. *J Am Soc Echocardiogr*. 2007;20:307–313. doi: 10.1016/j.echo.2006.08.028
59. Sachdev V, Matura LA, Sidenko S, Ho VB, Arai AE, Rosing DR, Bondy CA. Aortic valve disease in Turner syndrome. *J Am Coll Cardiol*. 2008;51:1904–1909. doi: 10.1016/j.jacc.2008.02.035
60. Quezada E, Lapidus J, Shaughnessy R, Chen Z, Silberbach M. Aortic dimensions in Turner syndrome. <http://www.parameterz.com/refs/quezada-ajmg-2015>. Accessed August 18, 2018.
61. Bondy CA, Van PL, Bakalov VK, Ho VB. Growth hormone treatment and aortic dimensions in Turner syndrome. *J Clin Endocrinol Metab*. 2006;91:1785–1788. doi: 10.1210/jc.2005-2625
62. Ostberg JE, Donald AE, Halcox JP, Storry C, McCarthy C, Conway GS. Vasculopathy in Turner syndrome: arterial dilatation and intimal thickening without endothelial dysfunction. *J Clin Endocrinol Metab*. 2005;90:5161–5166. doi: 10.1210/jc.2005-0677
63. Chalard F, Ferey S, Teinturier C, Kalifa G. Aortic dilatation in Turner syndrome: the role of MRI in early recognition. *Pediatr Radiol*. 2005;35:323–326. doi: 10.1007/s00247-004-1359-5
64. Baguet JP, Douchin S, Pierre H, Rossignol AM, Bost M, Mallion JM. Structural and functional abnormalities of large arteries in the Turner syndrome. *Heart*. 2005;91:1442–1446. doi: 10.1136/hrt.2004.048371
65. Hadnott TN, Gould HN, Gharib AM, Bondy CA. Outcomes of spontaneous and assisted pregnancies in Turner syndrome: the U.S. National Institutes of Health experience. *Fertil Steril*. 2011;95:2251–2256. doi: 10.1016/j.fertnstert.2011.03.085
66. Mortensen KH, Hjerrild BE, Stochholm K, Andersen NH, Sørensen KE, Lundorf E, Hørlyck A, Pedersen EM, Christiansen JS, Gravholt CH. Dilatation of the ascending aorta in Turner syndrome: a prospective cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson*. 2011;13:24. doi: 10.1186/1532-429X-13-24
67. Hjerrild BE, Mortensen KH, Sørensen KE, Pedersen EM, Andersen NH, Lundorf E, Hansen KW, Hørlyck A, Hager A, Christiansen JS, Gravholt CH. 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. doi: 10.1186/1532-429X-12-12
68. Cleemann L, Mortensen KH, Holm K, Smedegaard H, Skouby SO, Wieslander SB, Leffers AM, Leth-Espensen P, Pedersen EM, Gravholt CH. Aortic dimensions in girls and young women with Turner syndrome: a magnetic resonance imaging study. *Pediatr Cardiol*. 2010;31:497–504. doi: 10.1007/s00246-009-9626-8
69. Lopez L, Arheart KL, Colan SD, Stein NS, Lopez-Mitnik G, Lin AE, Reller MD, Ventura R, Silberbach M. Turner syndrome is an independent risk factor for aortic dilation in the young. *Pediatrics*. 2008;121:e1622–1627.
70. Braley KT, Tang X, Makil ES, Borroughs-Ray D, Collins RT. The impact of body weight on the diagnosis of aortic dilation: misdiagnosis in overweight and underweight groups. *Echocardiography*. 2017;34:1029–1034. doi: 10.1111/echo.13565
71. Los E, Quezada E, Chen Z, Lapidus J, Silberbach M. Pilot study of blood pressure in girls with Turner syndrome: an awareness gap, clinical associations, and new hypotheses. *Hypertension*. 2016;68:133–136. doi: 10.1161/HYPERTENSIONAHA.115.07065
72. De Groote K, Demulier L, De Backer J, De Wolf D, De Schepper J, T'sjoen G, De Backer T. Arterial hypertension in Turner syndrome: a review of the literature and a practical approach for diagnosis and treatment. *J Hypertens*. 2015;33:1342–1351. doi: 10.1097/HJH.0000000000000599
73. Mortensen KH, Erlandsen M, Andersen NH, Gravholt CH. Prediction of aortic dilation in Turner syndrome: the use of serial cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2013;15:47. doi: 10.1186/1532-429X-15-47
74. Bondy CA, Van PL, Bakalov VK, Sachdev V, Malone CA, Ho VB, Rosing DR. Prolongation of the cardiac QTc interval in Turner syndrome. *Medicine (Baltimore)*. 2006;85:75–81. doi: 10.1097/01.md.0000205629.16302.bc
75. Sozen AB, Cefle K, Kudat H, Ozturk S, Ofiaz H, Pamukcu B, Akkaya V, Isguzen P, Palanduz S, Ozcan M, Goren T, Guven O. Atrial and ventricular arrhythmogenic potential in Turner syndrome. *Pacing Clin Electrophysiol*. 2008;31:1140–1145. doi: 10.1111/j.1540-8159.2008.01154.x
76. Bondy CA, Ceniceros I, Van PL, Bakalov VK, Rosing DR. Prolonged rate-corrected QT interval and other electrocardiogram abnormalities in girls with Turner syndrome. *Pediatrics*. 2006;118:e1220–e1225. doi: 10.1542/peds.2006-0776
77. Trolle C, Mortensen KH, Pedersen LN, Berglund A, Jensen HK, Andersen NH, Gravholt CH. Long QT interval in Turner syndrome: a high prevalence of LQTS gene mutations. *PLoS One*. 2013;8:e69614. doi: 10.1371/journal.pone.0069614
78. Dalla Pozza R, Bechtold S, Urschel S, Netz H, Schwarz HP. QTc interval prolongation in children with Turner syndrome: the results of exercise testing and 24-h ECG. *Eur J Pediatr*. 2009;168:59–64. doi: 10.1007/s00431-008-0709-y
79. Gravholt CH, Hansen KW, Erlandsen M, Ebbehøj E, Christiansen JS. Nocturnal hypertension and impaired sympathovagal tone in Turner syndrome. *J Hypertens*. 2006;24:353–360. doi: 10.1097/01.hjh.0000200509.17947.0f
80. Nielsen DG, Nielsen JC, Trolle C, Gravholt CH, Andersen NH. Prolonged QT interval and cardiac arrest after a single dose of amiodarone in a woman with Turner's syndrome. *Clin Case Rep*. 2017;5:154–158. doi: 10.1002/ccr3.802
81. Levine BD, Baggish AL, Kovacs RJ, Link MS, Maron MS, Mitchell JH; on behalf of the American Heart Association Electrocardiography and Arrhythmias Committee of Council on Clinical Cardiology, Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, American College of Cardiology. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 1: Classification of Sports: Dynamic, Static, and Impact: a scientific statement from the American Heart Association and American College of Cardiology. *Circulation*. 2015;132:e262–e266. doi: 10.1161/CIR.0000000000000237

82. Braverman AC, Harris KM, Kovacs RJ, Maron BJ; on behalf of the American Heart Association Electrocardiography and Arrhythmias Committee of Council on Clinical Cardiology, Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and American College of Cardiology. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 7: Aortic Diseases, Including Marfan Syndrome: a scientific statement from the American Heart Association and American College of Cardiology. *Circulation*. 2015;132:e303–e309. doi: 10.1161/CIR.0000000000000243
83. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O’Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published corrections appear in *Circulation*. 2014;129:e651 and *Circulation*. 2014;130:e120]. *Circulation*. 2014;129:e521–e643. doi: 10.1161/CIR.0000000000000031
84. Maron BJ, Zipes DP, Kovacs RJ; on behalf of the American Heart Association Electrocardiography and Arrhythmias Committee of Council on Clinical Cardiology, Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and American College of Cardiology. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: preamble, principles, and general considerations: a scientific statement from the American Heart Association and American College of Cardiology. *Circulation*. 2015;132:e256–e261. doi: 10.1161/CIR.0000000000000236
85. American Academy of Pediatrics, American Academy of Family Physicians, American College of Physicians, Transitions Clinical Report Authoring Group, Cooley WC, Sagerman PJ. Supporting the health care transition from adolescence to adulthood in the medical home. *Pediatrics*. 2011;128:182–200. doi: 10.1542/peds.2011-0969
86. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). *Circulation*. 2008;118:e714–e833. doi: 10.1161/CIRCULATIONAHA.108.190690
87. Baumgartner H, Budts W, Chessa M, Deanfield J, Eicken A, Holm J, Islerin L, Meijboom F, Stein J, Szatmari A, Trindade PT, Walker F; Working Group on Grown-up Congenital Heart Disease of the European Society of Cardiology. Recommendations for organization of care for adults with congenital heart disease and for training in the subspecialty of ‘grown-up congenital heart disease’ in Europe: a position paper of the Working Group on Grown-up Congenital Heart Disease of the European Society of Cardiology. *Eur Heart J*. 2014;35:686–690. doi: 10.1093/eurheartj/ehf572
88. Sable C, Foster E, Uzark K, Bjornsen K, Canobbio MM, Connolly HM, Graham TP, Gurvitz MZ, Kovacs A, Meadows AK, Reid GJ, Reiss JG, Rosenbaum KN, Sagerman PJ, Saidi A, Schonberg R, Shah S, Tong E, Williams RG; on behalf of the American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Best practices in managing transition to adulthood for adolescents with congenital heart disease: the transition process and medical and psychosocial issues: a scientific statement from the American Heart Association. *Circulation*. 2011;123:1454–1485. doi: 10.1161/CIR.0b013e3182107c56
89. Practice Committee of American Society For Reproductive Medicine. Increased maternal cardiovascular mortality associated with pregnancy in women with Turner syndrome. *Fertil Steril*. 2012;97:282–284.
90. Hagman A, Loft A, Wennerholm UB, Pinborg A, Bergh C, Aittomäki K, Nygren KG, Bente Romundstad L, Hazekamp J, Söderström-Anttila V. Obstetric and neonatal outcome after oocyte donation in 106 women with Turner syndrome: a Nordic cohort study. *Hum Reprod*. 2013;28:1598–1609. doi: 10.1093/humrep/det082
91. Kamel H, Roman MJ, Pitcher A, Devereux RB. Pregnancy and the risk of aortic dissection or rupture: a cohort-cross-over analysis. *Circulation*. 2016;134:527–533. doi: 10.1161/CIRCULATIONAHA.116.021594
92. Manalo-Estrella P, Barker AE. Histopathologic findings in human aortic media associated with pregnancy. *Arch Pathol*. 1967;83:336–341.
93. Oskoui R, Lindsay J Jr. Aortic dissection in women < 40 years of age and the unimportance of pregnancy. *Am J Cardiol*. 1994;73:821–823.
94. Roman MJ, Pugh NL, Hendershot TP, Devereux RB, Dietz H, Holmes K, Eagle KA, LeMaire SA, Milewicz DM, Morris SA, Pyeritz RE, Ravekes WJ, Shohet RV, Silberbach M; for the GenTAC Investigators. Aortic complications associated with pregnancy in Marfan syndrome: the NHLBI National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC). *J Am Heart Assoc*. 2016;5:e004052. doi: 10.1161/JAHA.116.004052
95. Nasiell J, Lindqvist PG. Aortic dissection in pregnancy: the incidence of a life-threatening disease. *Eur J Obstet Gynecol Reprod Biol*. 2010;149:120–121. doi: 10.1016/j.ejogrb.2009.10.029
96. Lin AE, Karnis MF, Calderwood L, Crenshaw M, Bhatt A, Souter I, Silberbach M, Reindollar RH. Proposal for a national registry to monitor women with Turner syndrome seeking assisted reproductive technology. *Fertil Steril*. 2016;105:1446–1448. doi: 10.1016/j.fertnstert.2016.01.042
97. Braverman AC, Moon MR, Geraghty P, Willing M, Bach C, Kouchoukos NT. Pregnancy after aortic root replacement in Loays-Dietz syndrome: high risk of aortic dissection. *Am J Med Genet A*. 2016;170:2177–2180. doi: 10.1002/ajmg.a.37694
98. van Hagen IM, Roos-Hesselink JW, Ruys TP, Merz WM, Goland S, Gabriel H, Lelonek M, Trojnarska O, Al Mahmeed WA, Balint HO, Ashour Z, Baumgartner H, Boersma E, Johnson MR, Hall R; on behalf of the ROPAC Investigators and the EURObservational Research Programme (EORP) Team. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation*. 2015;132:132–142. doi: 10.1161/CIRCULATIONAHA.115.015242
99. Kaza AK, Pigula FA. Are bioprosthetic valves appropriate for aortic valve replacement in young patients? *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2016;19:63–67. doi: 10.1053/j.pcsu.2015.12.005
100. European Society of Gynecology (ESG); Association for European Paediatric Cardiology (AEPIC); German Society for Gender Medicine (DGesGM), Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JS, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AH, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L, Bax J, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Baumgartner H, Deaton C, Aguiar C, Al-Attar N, Garcia AA, Antoniou A, Coman I, Elkayam U, Gomez-Sanchez MA, Gotcheva N, Hilfiker-Kleiner D, Kiss RG, Kitsiou A, Konings KTS, Lip GYH, Manolis A, Mebaaza A, Mintale I, Morice MC, Mulder BJ, Pasquet A, Price S, Priori SG, Salvador MJ, Shotan A, Silversides CK, Skouby SO, Stein JI, Tornos P, Vejlstrup N, Walker F, Warnes C. ESC guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:3147–3197.
101. Alvaro Mercadal B, Imbert R, Demeestere I, Englert Y, Delbaere A. Pregnancy outcome after oocyte donation in patients with Turner’s syndrome and partial X monosomy. *Hum Reprod*. 2011;26:2061–2068. doi: 10.1093/humrep/der166
102. Chevalier N, Letur H, Lelannou D, Ohl J, Cornet D, Chalas-Boissonnas C, Frydman R, Catteau-Jonard S, Greck-Chassain T, Papaxanthos-Roche A, Dulucq MC, Couet ML, Cédric-Durnerin I, Pouly JL, Fénelon P; French Study Group for Oocyte Donation. Materno-fetal cardiovascular complications in Turner syndrome after oocyte donation: insufficient prepregnancy screening and pregnancy follow-up are associated with poor outcome. *J Clin Endocrinol Metab*. 2011;96:E260–E267. doi: 10.1210/jc.2010-0925
103. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet*. 2010;376:631–644. doi: 10.1016/S0140-6736(10)60279-6
104. Bernard V, Donadille B, Zenaty D, Courtillot C, Salenave S, Brac de la Perrière A, Albarel F, Fèvre A, Kerlan V, Brue T, Delemer B, Borson-Chazot F, Carel JC, Chanson P, Léger J, Touraine P, Christin-Maitre S; CMERC Center for Rare Disease. Spontaneous fertility and pregnancy outcomes amongst 480 women with Turner syndrome. *Hum Reprod*. 2016;31:782–788. doi: 10.1093/humrep/dew012

105. Bryman I, Sylvén L, Berntorp K, Innala E, Bergström I, Hanson C, Oxholm M, Landin-Wilhelmsen K. Pregnancy rate and outcome in Swedish women with Turner syndrome. *Fertil Steril*. 2011;95:2507–2510. doi: 10.1016/j.fertnstert.2010.12.039
106. Hovatta O. Ovarian function and in vitro fertilization (IVF) in Turner syndrome. *Pediatr Endocrinol Rev*. 2012;9(suppl 2):713–717.
107. Chan WS, Dixon ME. The “ART” of thromboembolism: a review of assisted reproductive technology and thromboembolic complications. *Thromb Res*. 2008;121:713–726. doi: 10.1016/j.thromres.2007.05.023
108. Manau D, Fábregues F, Arroyo V, Jiménez W, Vanrell JA, Balasch J. Hemodynamic changes induced by urinary human chorionic gonadotropin and recombinant luteinizing hormone used for inducing final follicular maturation and luteinization. *Fertil Steril*. 2002;78:1261–1267.
109. Manau D, Balasch J, Arroyo V, Jiménez W, Fábregues F, Casamitjana R, Creus M, Vanrell JA. Circulatory dysfunction in asymptomatic in vitro fertilization patients: relationship with hyperestrogenemia and activity of endogenous vasodilators. *J Clin Endocrinol Metab*. 1998;83:1489–1493. doi: 10.1210/jcem.83.5.4796
110. Manau D, Arroyo V, Jiménez W, Fábregues F, Vanrell JA, Balasch J. Chronology of hemodynamic changes in asymptomatic in vitro fertilization patients and relationship with ovarian steroids and cytokines. *Fertil Steril*. 2002;77:1178–1183.
111. Balasch J, Arroyo V, Fábregues F, Saló J, Jiménez W, Paré JC, Vanrell JA. Neurohormonal and hemodynamic changes in severe cases of the ovarian hyperstimulation syndrome. *Ann Intern Med*. 1994;121:27–33.
112. Nelson SM. Venous thrombosis during assisted reproduction: novel risk reduction strategies. *Thromb Res*. 2013;131(suppl 1):S1–S3. doi: 10.1016/S0049-3848(13)00023-6
113. Lowe GD, Upton MN, Rumley A, McConnachie A, O'Reilly DS, Watt GC. Different effects of oral and transdermal hormone replacement therapies on factor IX, APC resistance, t-PA, PAI and C-reactive protein: a cross-sectional population survey. *Thromb Haemost*. 2001;86:550–556.
114. Lowe G, Woodward M, Vessey M, Rumley A, Gough P, Daly E. Thrombotic variables and risk of idiopathic venous thromboembolism in women aged 45–64 years: relationships to hormone replacement therapy. *Thromb Haemost*. 2000;83:530–535.
115. Ersbøll AS, Hedegaard M, Søndergaard L, Ersbøll M, Johansen M. Treatment with oral beta-blockers during pregnancy complicated by maternal heart disease increases the risk of fetal growth restriction. *BJOG*. 2014;121:618–626. doi: 10.1111/1471-0528.12522
116. Ruys TP, Maggioni A, Johnson MR, Sliwa K, Tavazzi L, Schwerzmann M, Nihoyannopoulos P, Kozelj M, Marelli A, Elkayam U, Hall R, Roos-Hesselink JW. Cardiac medication during pregnancy, data from the ROPAC. *Int J Cardiol*. 2014;177:124–128. doi: 10.1016/j.ijcard.2014.09.013
117. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management. <https://www.nice.org.uk/guidance/cg107/chapter/1-Guidance#management-of-pregnancy-with-pre-eclampsia>. Accessed August 18, 2018.
118. De Groote K, Devos D, Van Herck K, Demulier L, Buysse W, De Schepper J, De Wolf D. Abnormal aortic arch morphology in Turner syndrome patients is a risk factor for hypertension. *Heart Vessels*. 2015;30:618–625. doi: 10.1007/s00380-014-0529-0
119. Sozen AB, Cefle K, Kudat H, Ozturk S, Oflaz H, Akkaya V, Palanduz S, Demirel S, Ozcan M, Goren T, Guven O. Left ventricular thickness is increased in nonhypertensive Turner's syndrome. *Echocardiography*. 2009;26:943–949. doi: 10.1111/j.1540-8175.2009.00902.x
120. Fudge EB, Constantacos C, Fudge JC, Davenport M. Improving detection of hypertension in girls with Turner syndrome using ambulatory blood pressure monitoring. *Horm Res Paediatr*. 2014;81:25–31. doi: 10.1159/000355510
121. Akyürek N, Atabek ME, Eklioglu BS, Alp H. Ambulatory blood pressure and subclinical cardiovascular disease in children with Turner syndrome. *Pediatr Cardiol*. 2014;35:57–62. doi: 10.1007/s00246-013-0740-2
122. Briese S, Claus M, Querfeld U. Arterial stiffness in children after renal transplantation. *Pediatr Nephrol*. 2008;23:2241–2245. doi: 10.1007/s00467-008-0894-y
123. Narayan O, Cameron JD. Ambulatory blood pressure monitoring and dipping status in predicting left ventricular hypertrophy. *J Hypertens*. 2014;32:1962–1963. doi: 10.1097/HJH.0000000000000285
124. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK, Gidding SS, Goodwin C, Leu MG, Powers ME, Rea C, Samuels J, Simasek M, Thaker VV, Urbina EM, Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140:e20173035. doi: 10.1542/peds.2017-3035
125. Lacro RV, Dietz HC, Sleeper LA, Yetman AT, Bradley TJ, Colan SD, Pearson GD, Selamet Tierney ES, Levine JC, Atz AM, Benson DW, Braverman AC, Chen S, De Backer J, Gelb BD, Grossfeld PD, Klein GL, Lai WW, Liou A, Loeys BL, Markham LW, Olson AK, Paridon SM, Pemberton VL, Pierpont ME, Peyerit RE, Radojewski E, Roman MJ, Sharkey AM, Stylianou MP, Wechsler SB, Young LT, Mahony L; Pediatric Heart Network Investigators. Atenolol versus losartan in children and young adults with Marfan's syndrome. *N Engl J Med*. 2014;371:2061–2071. doi: 10.1056/NEJMoa1404731
126. Mortensen KH, Andersen NH, Hjerrild BE, Hørlyck A, Stochholm K, Højbjerg Gravholt C. Carotid intima-media thickness is increased in Turner syndrome: multifactorial pathogenesis depending on age, blood pressure, cholesterol and oestrogen treatment. *Clin Endocrinol (Oxf)*. 2012;77:844–851. doi: 10.1111/j.1365-2265.2012.04337.x
127. Freriks K, Timmermans J, Beerendonk CC, Verhaak CM, Netea-Maier RT, Otten BJ, Braat DD, Smeets DF, Kunst DH, Hermus AR, Timmers HJ. Standardized multidisciplinary evaluation yields significant previously undiagnosed morbidity in adult women with Turner syndrome. *J Clin Endocrinol Metab*. 2011;96:E1517–E1526. doi: 10.1210/jc.2011-0346
128. Landin-Wilhelmsen K, Bryman I, Wilhelmsen L. Cardiac malformations and hypertension, but not metabolic risk factors, are common in Turner syndrome. *J Clin Endocrinol Metab*. 2001;86:4166–4170. doi: 10.1210/jcem.86.9.7818
129. Van PL, Bakalov VK, Bondy CA. Monosomy for the X-chromosome is associated with an atherogenic lipid profile. *J Clin Endocrinol Metab*. 2006;91:2867–2870. doi: 10.1210/jc.2006-0503
130. Gravholt CH, Christian Klausen I, Weeke J, Sandahl Christiansen J. Lp(a) and lipids in adult Turner's syndrome: impact of treatment with 17beta-estradiol and norethisterone. *Atherosclerosis*. 2000;150:201–208.
131. Mortensen KH, Andersen NH, Gravholt CH. Cardiovascular phenotype in Turner syndrome: integrating cardiology, genetics, and endocrinology. *Endocr Rev*. 2012;33:677–714. doi: 10.1210/er.2011-1059
132. Lanes R, Gunczler P, Palacios A, Villarroel O. Serum lipids, lipoprotein lp(a), and plasminogen activator inhibitor-1 in patients with Turner's syndrome before and during growth hormone and estrogen therapy. *Fertil Steril*. 1997;68:473–477.
133. Gravholt CH, Mortensen KH, Andersen NH, Ibsen L, Ingerslev J, Hjerrild BE. Coagulation and fibrinolytic disturbances are related to carotid intima thickness and arterial blood pressure in Turner syndrome. *Clin Endocrinol (Oxf)*. 2012;76:649–656. doi: 10.1111/j.1365-2265.2011.04190.x
134. Kopacek Zilz C, Keller Brenner J, Elneave RH. Portal vein thrombosis and high factor VIII in Turner syndrome. *Horm Res*. 2006;66:89–93. doi: 10.1159/000093693
135. Cintron D, Rodriguez-Gutierrez R, Serrano V, Latotue-Albino P, Erwin PJ, Murad MH. Effect of estrogen replacement therapy on bone and cardiovascular outcomes in women with Turner syndrome: a systematic review and meta-analysis. *Endocrine*. 2017;55:366–375. doi: 10.1007/s12020-016-1046-y
136. Stuenkel CA, Davis SR, Gompel A, Lumsden MA, Murad MH, Pinkerton JV, Santen RJ. Treatment of Symptoms of the Menopause: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100:3975–4011. doi: 10.1210/jc.2015-2236
137. Davenport ML. Approach to the patient with Turner syndrome. *J Clin Endocrinol Metab*. 2010;95:1487–1495. doi: 10.1210/jc.2009-0926
138. Hook EB. Exclusion of chromosomal mosaicism: tables of 90%, 95% and 99% confidence limits and comments on use. *Am J Hum Genet*. 1977;29:94–97.
139. Wiktor AE, Van Dyke DL. Detection of low level sex chromosome mosaicism in Ullrich-Turner syndrome patients. *Am J Med Genet A*. 2005;138A:259–261. doi: 10.1002/ajmg.a.30954
140. Wolff DJ, Van Dyke DL, Powell CM; Working Group of the ACMG Laboratory Quality Assurance Committee. Laboratory guideline for Turner syndrome. *Genet Med*. 2010;12:52–55. doi: 10.1097/GIM.0b013e3181c684b2
141. Addendum: laboratory guideline for Turner syndrome. *Genet Med*. 2016;18:107.

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142. Prakash S, Guo D, Maslen CL, Silberbach M, Milewicz D, Bondy CA; GenTAC Investigators. Single-nucleotide polymorphism array genotyping is equivalent to metaphase cytogenetics for diagnosis of Turner syndrome. *Genet Med*. 2014;16:53–59. doi: 10.1038/gim.2013.77
143. El-Mansoury M, Barrenäs ML, Bryman I, Hanson C, Larsson C, Wilhelmsen L, Landin-Wilhelmsen K. Chromosomal mosaicism mitigates stigmata and cardiovascular risk factors in Turner syndrome. *Clin Endocrinol (Oxf)*. 2007;66:744–751. doi: 10.1111/j.1365-2265.2007.02807.x
144. Denes AM, Landin-Wilhelmsen K, Wettergren Y, Bryman I, Hanson C. The proportion of diploid 46,XX cells increases with time in women with Turner syndrome—a 10-year follow-up study. *Genet Test Mol Biomarkers*. 2015;19:82–87. doi: 10.1089/gtmb.2014.0240