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Turner syndrome–issues to consider for transition to adulthood

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Abstract

Background: Turner syndrome (TS) is associated with a spectrum of health problems across the age span, which requires particular attention during the transition period in these adolescents.

Areas of agreement: The majority of girls with TS require oestrogen replacement from puberty onwards, which is important for adequate feminization, uterine development and maintenance of bone health. There is a lifetime increased risk from autoimmune conditions like hypothyroidism, coeliac disease, hearing loss and aortic dilatation with the potential to lead to aortic dissection. A systematic and holistic approach to provision of health care in TS is needed.

Areas of controversy: Several unanswered questions remain, including the choice of hormone replacement therapy in the young person with TS and in adulthood; the optimal mode of cardiovascular assessment; the best management and assessment prior to and during pregnancy.

Areas timely for developing research: The optimal model of care and transition to adult services in TS requires attention. Further research is needed in relation to cardiovascular risk assessment, pregnancy management and hormone replacement therapy in TS.

Key words: Turner syndrome, transition, hormone replacement therapy, puberty, pregnancy, aortic dissection, aortic dilatation

Background

Turner syndrome (TS) is a condition in phenotypic girls and women with a lack of one or part of one sex chromosome and affects ~1/2500 live female births.[1] While short stature, hypogonadism and typical dysmorphic features are commonly recognized clinical features, a range of medical problems can exist across the age span (Table 1). Paediatric management has often focussed on the use of recombinant human growth hormone (rhGH) to improve linear growth and the timely use of sex steroid to mimic normal pubertal development. Medical issues like aortic dilatation (AD) and dissection, bone health, hearing loss, liver dysfunction, autoimmune conditions and cancer risks may have a major impact on the life of these girls and women. With the advent of modern techniques of assisted reproduction technologies, many TS women are seeking the opportunity for childbearing. However, associated medical problems such as AD and autoimmune conditions (e.g. undiagnosed hypothyroidism) may contribute to significant risks in these pregnancies.[2,3] It is, therefore, imperative that a comprehensive health assessment in girls with TS is performed at the time of transition and continues to be addressed in adulthood by clinicians cognizant with the unique and inter-related issues encountered by these women. Careful counselling of these young individuals and their families at this critical period is also imperative.

It is accepted that the diagnosis of TS is reached with standard banded karyotype, counting 15–30 cells. If low-level mosaicism is suspected, increasing the number of cell count to 100 cells may be necessary, which allows for detection of 3% mosaicism at 95% confidence levels.[4] Only ~50% of TS individuals have a 45, X karyotype and 40% will have a structural abnormality of the second X chromosome. Approximately 30% of TS will have a mosaic peripheral blood karyotype, where a 45,X cell line coexists with one non-45, X cell line.[5,6] Importantly, 10% of women with TS have mosaicisms for a cell line with a normal or abnormal Y chromosome. The risk of gonadoblastoma in these individuals is estimated to be ~30% and early gonadectomy is recommended.[7] The majority of TS with mosaic karyotype will not have the classical features of TS, and a low threshold for investigations is encouraged to avoid late diagnosis. In many genetic laboratories, DNA microarrays are increasingly used to make the diagnosis of TS. The accuracy of detection of low-level mosaicism and Y chromosome material is still unclear.[8]

Current expert consensus recommends performing karyotype in girls with any of the following: short stature, delayed puberty, webbed neck, lymphoedema, inner ear problems and coarctation of aorta (CoA).[9] The prevalence of TS in girls presenting with short stature is between 2 and 4%, and its prevalence in girls presenting with CoA is at least 5%.[10,11] Delayed diagnosis of TS in adolescence and beyond is still seen in ~20% of diagnosed cases. This clinical review aims to summarize the important health issues that need to be considered by a clinician preparing a young person with TS for transition to adult care.

Pubertal development in TS

TS is associated with hypergonadotropic hypogonadism, as a consequence of premature ovarian failure. Approximately 30% of girls with TS enter puberty spontaneously, but only ~4% reach menarche and only 1% are fertile. Almost 90% will require hormone replacement therapy either to initiate and/or to ensure progress in puberty, maintain secondary sexual development and promote bone health.[12] The pattern of gonadotrophins (Gn) secretion in TS is similar to that observed in normal pre-pubertal girls, but serum concentrations are consistently higher at all pre-pubertal ages. Assessment of ovarian function in childhood using Gn may be unhelpful due to the relative quiescence of the hypothalamic pituitary gonadal axis. Concentration of antimullerian hormone (AMH), produced by granulosa cell, has been found to remain stable from mid-childhood to early adulthood and can be used to evaluate ovarian function throughout the age range. AMH may help predict those girls who will achieve spontaneous onset of puberty and normal pubertal progress as well as the presence of healthy follicles.[13,14]

Sex steroid replacement in TS

The optimal regimen for sex steroid replacement for induction of puberty in TS remains a controversial

Table 1 Clinical features in Turner syndrome

	Neonate and childhood	Adolescence and adult age

Specific physical features	Neonate:
	- Redundant nuchal skin
	- Puffiness of the hands and feet
	Childhood:
	- Short stature
	- Short neck
	- Characteristic facies with micrognathia
	- Abnormal upper-to-lower segment ratio
	- Orthopaedic stigma:
	  - Short metacarpals
	  - Madelung deformity
	  - Scoliosis
	  - Genu valgum
	  - Cubitus valgus
		Short stature

Lymphatic system	Foetus failed to survive: obstructed jugular lymphatics with nuchal cystic hygromas due to cardiovascular failure Neonate: peripheral lymphedema and webbed neck (residual of the cystic hygroma)	Lymphedema may occur at any age and be exacerbated by treatments as growth hormone or oestrogens
Bone	Congenital hip dislocation Scoliosis and kyphosis	Scoliosis and kyphosis Osteopenia and osteoporosis due to lack of oestrogen production
ENT	Otitis media due to an abnormal relationship between the eustachian tube and middle ear Progressive sensorineural hearing loss	Progressive sensorineural hearing loss
Renal	Congenital urinary system malformations: - Horseshoe kidneys - Malrotations - Other positional abnormalities Urinary tract infections	Risk to develop hypertension and frequent urinary tract infections

Table continues

Table 1 Continued

	Neonate and childhood	Adolescence and adult age
Eyes	Abnormalities of the external ocular adnexa: - Epicanthal folds - Ptosis - Hypertelorism - Upward slanting palpebral fissures Strabismus and hyperopia, high risk of amblyopia	
Cardiovascular system	Congenital heart disease: - Bicuspid aortic valves - Coarctation of aorta - Aortic dilatation - Partial anomalous pulmonary connection - Persistent left superior vena cava	High risk of aortic dissection or rupture due to aortic dilation Generalized dilation of major vessels including the brachial and carotid arteries as well as the aorta Electrocardiographic conduction and repolarization abnormalities: right axis deviation, T-wave abnormalities, accelerated AV conduction and QTc prolongation Systemic hypertension
Growth	Mild intra-uterine growth retardation Slow growth during infancy Delayed onset of the childhood component of growth Growth failure during childhood	Absence of a pubertal growth spurt Short stature
Mental development	Normal intelligence with selective impairment in non-verbal perceptual motor and visuospatial skills Attention deficit disorder	Increased risk of social isolation, immaturity and anxiety Higher levels of shyness and social anxiety and reduced self-esteem
Puberty and pregnancy	Lack of spontaneous pubertal development onset	Hypergonadothrophic hypogonadism due to primary ovarian failure Absent or partial pubertal development Infertility Increased rate of maternal complications in TS who achieved pregnancy (dilatation and dissection of the aorta, diabetes, hypothyroidism)
Gastrointestinal system and liver	Coeliac disease	Inflammatory bowel diseases Liver enzymes raised High risk of steatosis, steatofibrosis and steatohepatitis Marked architectural changes due to portal hypertension
Autoimmunity and endocrine	Autoimmune thyroiditis Coeliac disease Diabetes mellitus	Alopecia Vitiligo Obesity and diabetes mellitus

Table 2 Development and maintenance of puberty in TS—local approach

Age (years)	Aim of therapy								
12+	Pubertal induction (suggested doses):								
		Year 1			Year 2			Year 3	
	Oral ethinyloestradiol (μg)	2			4			6/8/10[a]	
	Patch 17β-oestradiol (μg)	6.25		12.5	25		50[a]	50	
15+	Completion of puberty (suggested doses):								
		Year 4 onwards							
	Oral ethinyloestradiol (μg)	20–30[a]							
	Patch 17β-oestradiol (μg)	50–100[a]							

[a]Norethisterone 5 mg daily for the first 5 days of each calendar month when ethinyloestradiol reaches 10 μg daily, or when breakthrough bleeding occurs, whichever is the sooner.

issue. The timing of introduction of oestrogen, the type, dose and route of oestrogen administration may impact on health outcomes. The main goals of sex steroid replacement in puberty are to ensure (i) adequate breast development, (ii) pubertal growth spurt, (iii) adequate uterine development and (iv) bone accrual for adequate peak bone mass. Our current clinical practice for pubertal induction is summarized in Table 2. For a more comprehensive review on aspects on the area of sex steroid replacement in TS, the reader is referred to two recent excellent reviews of the topic.[15,16]

Generally, oestrogen is initiated around the age of 12–13 years if there are no signs of breast development or progression in pubertal status. The combined effect of rhGH and low doses of oestrogens seems to influence height velocity in a favourable way, while supra-physiological oestrogen doses given too early might limit the GH-dependent gain in final height.[17,18] Oestrogen is gradually increased over a 2–3 year period to mimic the physiological rise in levels to ensure adequate breast development and pubertal growth spurt. Delaying sex steroid treatment until the completion of linear growth, a practice common previously, undervalues the psychosocial importance of age-appropriate pubertal maturation and may be deleterious to bone development and other aspects of the child's health.[19] Healthy pre-pubertal girls, in fact, secrete low but measurable amount of oestradiol.[20,21] Given the effects of oestrogen on various target organs, it is thought that delaying sex steroid replacement to >12 years may lead to unfavourable clinical outcome. A recent randomized placebo trial of ultra-low-dose oral ethinyl oestradiol introduced as young as 5 years show that it may lead to more physiological onset of pubertal development, more favourable augmentation of rhGH growth and benefits for cognition.[22,23] This is not conventional practise and further research is needed.

Optimizing uterine growth is fundamental in improving success rates of pregnancy in the future. The window of opportunity (during puberty and post-pubertal/pre-conception) and outcome in TS is unclear. In the UK, oral ethinyl oestradiol commencing at 2 μg daily at age 12–13 years is commonly used. This leads to satisfactory pubertal induction and maintenance, but may fail to induce a fully mature uterus in about half of the affected population without spontaneous pubertal onset.[12] The ethinyl component of ethinyl oestradiol also induces prorenin substrate product at a much higher rate than natural oestrogen and may lead to an increase in blood pressure in a cohort of patient where hypertension is relatively common.[24]

There are also possible advantages of transdermal oestrogen over oral oestrogen including a more physiologic delivery, decreased first past metabolism and higher systemic IGF1 levels with possible consequent improvement in metabolism and body composition.[25–27] While studies in adult hypopituitary and postmenopausal women treated with oral 17β-oestradiol showed reduction in IGF1 levels, with

consequent reduction in lipid oxidation, whole-body protein synthesis, lean mass and increase in fat mass,[28,29] less is known about the effects of oral oestrogen in childhood and puberty. In girls with short stature, oral 17β-oestradiol leads to reduction in IGF1 levels following short-term rhGH injections as part of the IGF generation test.[30] However, a pilot, randomized controlled trial of oral conjugated oestrogen vs. transdermal 17β-oestradiol for pubertal induction in 12 girls with TS showed no differences in systemic IGF1 levels. Transdermal 17β-oestradiol however led to better bone accrual and increased uterine growth compared with oral conjugated oestrogen.[31]

Table 3 summarizes the currently published studies of pubertal induction with oestrogen on uterine development in TS. The summary highlights the heterogeneity of the current published studies (number of cases, study design, oestrogen regime). It is, however, noteworthy that most were commenced on oestrogen relatively late. One recent randomized controlled trial show that transdermal 17β-oestradiol used to induce puberty in TS was superior to oral conjugated oestrogen with regards to uterine development.[31] A study in 25 adult women (including 7 with TS) with primary hypogonadism showed that women managed with transdermal oestrogen containing 17β-oestradiol (Estraderm patches) showed a trend towards increase in uterine volumes compared with an oral contraceptive pill containing ethinyl oestradiol (Loestrin 30).[39] These early studies point to the possible benefit of transdermal oestrogen for pubertal induction and replacement therapy, and there may still be an opportunity to optimize uterine volume post puberty, although the magnitude of this is currently unknown.

At the end of this period of increasing doses of oestrogen, progesterone is added at least every 3 months to allow endometrial shedding, although some girls may prefer a monthly bleed. In the UK, common forms of oestrogen replacement post induction of puberty are the oral contraceptive pill, oral oestrogen/oral progesterone, combined transdermal patch and transdermal patch/oral oestrogen.[40] Decisions of ongoing oestrogen replacement need to be carefully discussed with the young person and family during transition and management may need to be individualized.

From a cardiovascular point of view, oral oestrogen replacement may be associated with a higher risk of hypertension, stroke, venous thromboembolism (VTE) and coronary heart disease in predisposed women.[41] In comparison with a 12-month oral regimen (ethinylestradiol 30.0 μg and norethisterone 1.5 mg daily for Weeks 1–3, followed by 7 'pill-free' days), physiological replacement with transdermal oestrogen (transdermal oestradiol 100 μg daily for Week 1 and 150 μg for Weeks 2–4 plus oral or vaginal passaries of progesterone 200 mg twice daily in Weeks 3–4) resulted in lower blood pressure, better renal function (plasma angiotensin II and serum creatinine concentrations) and less activation of the renin-angiotensin system in women with premature ovarian failure.[42] These differences potentially have major consequences for the future long-term cardiovascular risk in TS. Oral oestrogens are unable to reach the systemic circulation directly and are usually first metabolized by intestine and liver. Thus, the liver is exposed to a higher dose of oestrogen than the rest of the body, stimulating the production of hepatic proteins as renin substrate, which may exacerbate hypertension and triggering changes between antithrombotic mechanisms and pro-coagulant factors.[12] Although VTE can occur at any time, the risk is highest in the first year of treatment. Both the risk for VTE and education regarding thrombosis prevention should be discussed with the young person and her family. Transdermal oestradiol and micronized progesterone are preferable for girls with TS who have an increased risk of VTE, but these need to be balanced against the possibility of poor adherence with transdermal treatment.

Bone health

As discussed earlier, appropriate timing of introduction of oestrogen for induction of puberty in TS is needed for achievement of peak bone mass. Oestrogen stimulates endocortical formation with resultant narrowing of the medullary cavity. Bone health is thought to be variably affected in TS, although older studies using dual energy absorptiometry (DXA) evaluation have not adjusted for the relative short stature of these individuals. Thus, TS individuals are

Table 3 Effects of pubertal induction regimen on uterine outcomes and on bone development

Reference	Study design	Number of subjects	Mean/Median age starting oestrogen	Form of oestrogen and dose	Outcome
Effect of pubertal induction regimen on uterine outcome					
Nabhan *et al.*[31]	Randomized controlled trial	12 (6 in each group)	14 years	Oral CE: 0.3 increasing to 0.625 mg/day Transdermal E (TE): 0.025 increasing to 0.0375 mg/day	↑ uterine length in TE (66% mature uterus in TE, 0% mature uterus in oral CE)
Kim *et al.*[32]	Retrospective	9 10	14.5 years 15.9 years	Oral EV: 0.5–2 mg increasing Oral EV: 1–2 mg increasing	Oral EV 1 mg ↑ uterine size (50% mature uterus in 1 mg group, 22% mature uterus in 0.5 mg group)
Cleemann *et al.*[33]	Cross-sectional	41	13 years	Oral E: 0.1–1.75 mg increasing	↓uterine volume
Bannink *et al.*[34]	Prospective non-randomized	56	12.7 years	Oral E: 5 µg/kg/day increasing to 10 µg/kg/day	↓uterine volume Mature adult shaped fundo-cervical ratio uterus in 79.5%
Piippo *et al.*[35]	Prospective, non-randomized	23	13.6 years	Gel E: 0.1 mg/day increasing to 1.5 mg/day	Normal uterine size
Doerr *et al.*[36]	Prospective, non-randomized	75	14.7 years	Oral EE Oral CE Oral EV OCP	↓uterine volume, but no group details. Only 45 X0/46 XX individuals with normal uterine length and volume
McDonnell *et al.*[37]	Prospective, non-randomized	13	14.6 years	Oral CE 0.25 mg increasing to 2 mg	Normal uterine volume
Snajderova *et al.*[38]	Cross-sectional	57	14.6 years	Oral E 5 µg/kg/day increasing to 15–20 µg/kg/day	63% hypoplastic uterus
Paterson *et al.*[12]	Retrospective	14 (Tanner 5)	10–21.6 years	EE 1 µg/day increasing to 30 µg/day	Normal uterine length but only 50% mature adult configuration
Effect of pubertal induction regimen on bone development					
Nabhan *et al.*[31]	Randomized controlled trial	12 (6 in each group)	14 years	Oral CE: 0.3 increasing to 0.625 mg/day Transdermal E (TE): 0.025 increasing to 0.0375 mg/day	↑ absolute spine BMC, BMD and BMD *Z*-score in TE
Kim *et al.*[32]	Retrospective	9 10	14.5 years 15.9 years	Oral EV: 0.5–2 mg increasing Oral EV: 1–2 mg increasing	No differences in BMD between groups

CE, conjugated oestrogen; E, 17β-oestradiol; EV, oestradiol valerate; EE, ethinyloestradiol; OCP, oral contraceptive pill.

often reported to have low bone mass when age matched but not height matched. In addition, some older reports may have included individuals who had very late introduction of oestrogen for pubertal induction. Table 3 summarizes the currently published studies of pubertal induction with oestrogen on bone development.

For adequate maintenance of bone health in adulthood, the conventional use of the oral contraceptive pill (OCP) may be contraindicated and may lead to ongoing bone loss as the woman with TS will be oestrogen deficient for 7 days out of the 30-day cycle. In some countries, there is now an OCP which allows for only two oestrogen-free days. The degree of possible bone loss in TS on either of these regimes is unknown. Identifying and managing other associated clinical conditions that may predispose to further insults to bone health in TS including coeliac disease (CD), inflammatory bowel disease (IBD) and thyroid dysfunction is also important.

A recent study revealed that TS adolescents (mean 13 years) may have lower size adjusted bone mineral apparent density (BMAD) at femoral neck but not at lumbar spine and lower cortical volumetric bone density on peripheral quantitative computer tomography. Most TS individuals under 13 years of age are unlikely to have completed puberty, whereas the majority of the reference group of girls would have achieved menarche at that age with a significant increase in bone mass accrual.[43] A more recent study in adults (mean age 30 years) showed that trabecular microarchitecture however may be abnormal in TS.[44] Currently, it is unclear whether the bone abnormalities in TS are related to adequacy of oestrogen replacement or whether it is also a non-progressive phenotype of the skeletal dysplasia associated with the syndrome. Longitudinal studies of bone mass in adults with TS especially in relation to HRT regimes are now needed.

Pregnancy and fertility

Spontaneous pregnancies are very rare (2%) in women with TS. The likelihood of functional ovarian tissue and fertility in women with TS relies on the presence of 46,XX germ cells in the ovaries and is therefore more likely in women with mosaicism. Advances in reproductive medicine, involving *In Vitro* Fertilization—Embryo Transfer (IVF-ET), have increased the possibility of childbearing in infertile women with TS, but pregnancy remains particularly challenging due to the high prevalence of serious, life-threatening cardiovascular complications such as aortic dissection (AoD).

Despite recent advances, there is an excess of foetal malformations, spontaneous abortion, intrauterine growth restriction, low birth weight, prematurity and perinatal death in the offspring of mothers with TS irrespective of the method of conception, due to chromosomal and uterine abnormalities. However, a recent report of 106 TS women has provided more favourable neonatal outcome data, with a preterm birth rate of 8% and a low birth weight rate of ~9% in singletons.[45] Major birth defects were found in 4% of the children, not different from pregnancies after conventional IVF and better than previously reported. The perinatal mortality was 2%, including a set of extremely preterm twins. Maternal risks were high in this group, particularly in the development of hypertensive disorders. Heterologous IVF-ET, using oocyte donation, is the most used reproductive technique and it represents the only way to become pregnant for the vast majority of such women in whom ovarian failure is likely to be established at the time of starting a family. A review of 23 women with TS following ovum donation reported a miscarriage rate of 44% and take home baby rate of 18% per transfer.[46] In a further cohort of 30 women following oocyte donation, 26% of clinical pregnancies ended in miscarriage, much lower than the miscarriage rate of 45% using the patient's own gametes.[47]

Women with mosaic TS may also benefit from cryopreservation of patient's own oocytes for fertility preservation before decline in ovarian function. A report regarding 57 TS girls has informed the selection criteria among girls with TS who would be candidates and should be offered sampling and storing of ovarian tissue for cryopreservation.[48] This report concluded that at the age of 13–14 years, girls with TS should be counselled about fertility options and, in those with mosaic karyotype and spontaneous puberty in the absence of any elevation in follicle stimulating hormone (FSH) or reduction in AMH, the

discussion should include cryopreservation. Harvesting of oocytes or ovarian tissue from girls with TS for storage is technically possible, but these techniques remain experimental and have as yet not been associated with reported pregnancies published in the literature as far as we are aware.

Cardiovascular health

Congenital heart disease (CHD) is a common association of TS and reported in up to 50%.[49] Bicuspid aortic valves (BAV), CoA and AD significantly contribute to the risk of AoD, although in 10% of reported cases no risk factors were reported. Hypertension is also relatively common and may require careful evaluation with 24 h blood pressure monitoring. AoD in TS, 6 times commoner than in healthy individuals, occurs frequently in the third decade as opposed to the seventh decade, although paediatric cases are seen. Symptoms are often non-specific including chest pain, non-specific gastrointestinal symptoms and musculoskeletal complaints but also change in phonation due to compression on recurrent laryngeal nerves, highlighting the importance of early recognition by TS individuals and medical staff. A recent comprehensive review on AD and dissection in TS includes a thorough review of the 122 published cases of AoD in these individuals.[50] As discussed in the previous section, pregnancy is a critical period. The risk of mortality from AoD alone during pregnancy in TS is in excess of 100 times the population risk.[51] The highest risk period during pregnancy is the third trimester although several cases reported have dissected within the first 2 weeks postpartum BAV, the commonest cardiovascular system (CVS) pathology, is seen in ~20% of individuals, although magnetic resonance imaging (MRI) reveal a spectrum of other abnormal aortic valves. CoA presenting with neonatal collapse, often but not universally associated with low birth weight and pedal oedema seen in ~4–12% of infants, may be the most well-recognized cardiac pathology. CoA may also present later in life with uncontrolled hypertension, or limb claudication diagnosed only on MRI.[52]

Ongoing CVS monitoring of all individuals with TS throughout adult life and during pregnancy is recommended. Careful re-evaluation using MRI or detailed echocardiogram should be performed in adolescence before transfer to adult care to allow for appropriate counselling of risk. MRI should be used in adults and older adolescents with broad chests as adequate views are often not obtained with echocardiogram. Evaluation with MRI for evaluation of aortic arch dimensions may be better with MRI. Given that most girls with TS are relatively short even with rhGH therapy, aortic dimensions need to adjust for body surface area called aortic sized index (ASI). There is now sufficient evidence that TS with ASI of >2.0 and >2.5 cm/m^2 is at high risk and very high risk of AoD, respectively.[53] New data propose a mathematical model incorporating aortic dimensions and other clinical factors to identify TS individuals at greatest risk for AoD, although this is not validated against the clinical outcome of AoD.[54]

Despite the recognized importance of CVS monitoring, the majority of TS individuals do not currently have CVS monitoring. One study reported that only 40% of those undergoing oocyte donation had any form of CVS evaluation.[55] A single-centre approach with involvement of one endocrinologist and cardiologist on the other hand showed that ~70% of TS women had evaluation with echocardiogram and MRI.[56] Despite the recognition of ongoing monitoring, several controversies exist in particular to CVS issues especially during pregnancy. Two international expert consensus differ in recommendations of CVS risk contraindicating pregnancy in TS (Table 4),[57,58] and it is in this respect that further research and local consistencies in advice is needed.

We believe that TS individuals should be reviewed by cardiologists with experience in assessment of these girls and women, ideally by the Congenital Heart Disease Team. In a recent study, 40% of women with TS had abnormal cardiovascular findings which may preclude pregnancy when assessed by cardiologist with expertise in TS after having had normal assessments by previous cardiologists not familiar with TS.[55]

Other health and psychosocial issues

Autoimmune and inflammatory conditions are commoner in TS. Hypothyroidism occurs in up to 30%,

Table 4 International expert consensus in recommendations of CVS risk contraindicating pregnancy in TS

Consensus	Recommendations	Criteria
American Society for Reproductive Medicine (2012)	Absolute contraindication	Any significant cardiac abnormality and/or ASI >2 cm/m^2
French College of Obstetricians and Gynaecologists (2010)	Contraindication	History of aortic surgery Previous aortic dissection Aortic dilatation (ASI >2.5 cm/m^2 or absolute dimensions >3.5 cm) Coarctation of aorta Uncontrolled hypertension despite medical treatment

whereas thyrotoxicosis occurs in ~1.6%. Diabetes mellitus is also more common, which may be associated with obesity and metabolic syndrome. Abnormal glucose homeostasis in TS may be due to a combination of reduced insulin response to glucose load, reduced insulin sensitivity and reduced beta cell function, suggesting that it is maybe a specific disorder unique to TS. Coeliac disease is seen in ~2–10% of TS although usually asymptomatic. An increased risk of IBD is also seen in TS, especially those with i(Xq) lineage.[3,59,60]

Abnormal liver function with raised ALT and GGT is thought to be related to hepatic steatosis and also small intrahepatic vascular anomalies. It was previously thought that oestrogen therapy may have a contributing role, but recent studies in fact show that mild improvement may be seen with oestrogen therapy.[61] Regular screening for thyroid disease, liver dysfunction and CD is recommended and imperative pre-conception.

Otitis media, middle ear effusions often requiring grommets insertion and subsequent cholesteatoma[62] are recognized complications of paediatric girls with TS. ENT surgeons, general practitioners, general paediatricians and physicians should consider the diagnosis of TS in a girl or woman with a history of ongoing ENT problems like recurrent otitis media, recurrent grommets insertion and cholesteatoma. Less well recognized is the progressive hearing loss, usually in the high frequency region, especially after the age of 30 years. The rate of decline in TS women aged 30–60 years is equivalent to those of 70–80 years in non-TS women.[9]

Women with TS appear to be at increased risk of cancers especially CNS tumours, bladder and urethral cancers. The increased risk of CNS tumours appears to be from non-malignant tumours like meningioma. Currently, there is no information on the relationship of risk with hormone therapy.[63]

While most girls and women with TS have normal intellect, ~10% may require special education and assistance. The majority, however, have specific learning difficulties involving non-verbal, perceptual, motor and visuospatial skills, which translates to difficulties in such aspects such as mathematics, driving, multitasking and social functioning especially reading social cues. Impaired peer relationship, higher anxiety, inflexibility, low self-esteem and preoccupation with keeping things in order are often reported.[64]

An approach for provision of coordinated care

Provision of health care to the adolescent and adult with TS needs to be holistic and should address both the medical and non-medical aspects of the patient. Access to clinicians and allied health professionals aware of the complex and inter-related issues impacting on health of these individuals is needed. Support for TS individuals and families from TS support groups should be strongly encouraged and provides families with a source of valuable information. Often families may not wish to be involved with support groups at diagnosis, but this should be discussed again during adolescence as the young person may wish to be involved with other individuals with

TS. Specific needs of the TS young person and adult should be individualized with access to nurse specialist, psychologist and educational support. During the period of transition, addressing and paying attention to aspects relating to navigational planning and visuomotor integration may be necessary for a range of important day-to-day aspects of life such as driving training, choosing future career options and also organizing aspects of individual health care like medication and attendance in clinic. Psychosocial support is often lacking, but it should be an important part of clinical care of these girls and women. Group psychological intervention may improve self-esteem and generic skills in these young people.[64]

A comprehensive health evaluation should be performed in late adolescence prior to transition. These investigations should identify important health issues prior to transition to adult care (Table 5). In addition, crucial investigations from careful cardiovascular evaluation will allow appropriate risk of AoD, especially during pregnancies. We believe that these issues should be discussed in adolescence by the treating paediatric team rather than deferring such discussions to the adult clinic, given the possibility of loss to follow-up during the transition period. However, there may be a case to conduct such investigations (e.g. cardiac MRI) once the young person is in the adult setting to ensure consistency of information and reporting given the need for future repeat evaluations. Discussion of such important issues may need to be individualized to the developmental maturity of each young person with TS. Close working relationship with adult clinicians and other paediatric subspecialties who may be involved in the care of the young person and adult with TS is needed to ensure consistencies in advice of some of the more unclear aspects of management of these individuals. Young adults with TS should be managed in dedicated TS clinics or by clinicians aware of the complex health issues encountered by these individuals and with

Table 5 Suggested assessment in Turner syndrome prior to pubertal induction and transition

	Childhood	Young person—prior to transition
Auxology	Height, weight	Height/weight
	Pubertal assessment (from 10 years)	Pubertal assessment
Growth hormone monitoring	IGF1 and bone age (if on growth hormone therapy)	Thyroid function
	Thyroid function	
Ovarian reserve	FSH, AMH (at diagnosis)	Pelvic ultrasound
	Pelvic ultrasound (prior to pubertal induction)	Counsel young person and family regarding fertility
Cardiovascular	Cardiac assessment and echocardiogram (diagnosis)	Cardiac assessment, echocardiogram ± MRI
	Blood pressure (every clinic)	Blood pressure
Bone	Examine for scoliosis (before commencing growth hormone and annually)	DXA scan
Autoimmune	Thyroid peroxidase antibody (diagnosis)	Thyroid function
	Thyroid function (diagnosis and then annually if on growth hormone)	Coeliac screen
	Coeliac screen (12 years)	
ENT	Hearing test (diagnosis)	Hearing test
	ENT referral if appropriate	
Renal	Renal ultrasound (diagnosis)	–
	Urine culture if any renal abnormalities	
Liver	Liver function (12 years)	Liver function
Metabolic	–	Fasting glucose, lipids, HbA1C
Psychosocial	Review school performance	Vocational advice

access to other health professionals. Numerous clinicians will be involved in the health-care provision of these young people and adults, but the primary managing clinician in adult care should always involve an endocrinologist in the clinical care via the multidisciplinary clinic setting.

Conclusion

With the range of varied issues encountered by the young person and adult with TS, transition is a complex process. This requires multidisciplinary care with a systematic approach to screen for associated medical conditions but individualized to address the needs of each young person with TS. Medical and non-medical aspects of TS girls and women need to be addressed in ongoing health-care provision by clinicians familiar with the spectrum of problems encountered by these women. Families and the young person should be made aware of the TS support group. Engaging TS women with ongoing follow-up in adulthood and regular health surveillance remains a challenging area.

Conflict of Interest statement

The authors have no potential conflicts of interest.

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