

Turner Syndrome Management Guidelines
Australasian Paediatric Endocrine Group – November 2003
by George Werther, with advice from Margaret Zacharin

Introduction

Turner syndrome affects around one in 2500 female live births, the majority of which carry mosaicism in at least some tissues. Thus, the phenotypic features vary significantly among affected individuals. Consequently, while short stature and gonadal dysgenesis are almost universal in Turner syndrome, many other organ systems are affected to varying degrees and at different stages of life. A multi-disciplinary approach to management is therefore essential, and should be based on knowledge and awareness of the likely and potential adverse outcomes in each organ system. These Guidelines are designed to provide the basis of management protocols at key stages of development from birth to adulthood. The information has been drawn from various sources, both from medical/scientific consensus forums and from Turner support groups and their publications, as cited in the reference list. While most of the guidelines are evidence-based, some recommendations are based on consensus or opinions from experienced professionals or affected women with Turner syndrome.

Diagnosis

While the diagnosis of Turner syndrome may be made in utero or in the newborn period, it may be delayed into late childhood, adolescence, or even adulthood because of failure to recognise the significance of *poor growth* or *pubertal delay*. These two features are highly characteristic, but the majority of girls with Turner syndrome do not have the classical spectrum of phenotypic features including neck webbing and marked cubitus valgus. The ultimate diagnosis is however usually straightforward. Deletion of the whole (45X) or part of one X chromosome will invariably be the basis of the definitive diagnosis. Examination of at least 50 cells is required to exclude low level mosaicism.

While the most common forms of mosaicism are 45X/46XX and 45X/46Xiq, the spectrum of Turner syndrome includes karyotypes with Y chromosome material present (eg. 45X/46XY). While most individuals who are found to have Y chromosomal material are phenotypically female, a mixed picture of gonadal dysgenesis, short stature and a male phenotype can occasionally occur; probing for Y chromosome material should be undertaken if there is any evidence of virilisation or when a marker chromosome is found. Gonadal material in such cases is potentially neoplastic and should be removed when recognised, if possible before the age of puberty.

Diagnosis is sometimes made in utero during antenatal screening based on ultrasound findings such as increased nuchal translucency, cystic hygroma, coarctation of the aorta, renal anomalies or polyhydramnios. None of these is diagnostic however, and karyotyping must be performed and repeated post-natally. Prenatal karyotyping can be highly misleading, often showing poor correlation with phenotype, such that fetuses with mosaicism including 45X/46XX may be phenotypically normal females at birth. Similarly, 45X/46XY and similar karyotypes containing Y chromosome may be considered prenatally to indicate ambiguous genitalia, whereas most of these fetuses/infants have a normal male phenotype.

Post-natal diagnosis should be considered, and based on karyotype in any girl with unexplained growth failure or pubertal delay. Other findings which may point to Turner syndrome, and should thus lead to karyotyping, include newborn oedema of feet or hands, nuchal folds, coarctation of the aorta or hypoplastic left heart, low hairline, low set ears, cubitus valgus, nail dysplasia and multiple pigmented naevi. Congenital dislocation of the hip is an association. Elevated circulating FSH levels in girls in infancy or adolescence indicate gonadal failure and may point to Turner syndrome.

Management in Infancy

The diagnosis of Turner syndrome is increasingly made in the newborn period or in early life, and may be associated with several problems. These can include sleeping disorder, related to high activity levels, as well as apparent immaturity in various areas. Feeding difficulties sometimes require specific intervention due to physical problems such as the high arched palate, requiring special teats or Rosti (cleft palate) feeding bottles and advice from an infant feeding consultant or speech therapist.

Management during Childhood and Adolescence

A multidisciplinary team should oversee management of girls with Turner syndrome from diagnosis through to adult life. The attached Table summarises the key mandatory monitoring and interventions and their recommended timing and frequency, as well as an indication of their importance. They are discussed briefly in the following section, together with a number of optional interventions.

Cardiovascular assessment

Left-sided obstructive cardiac anomalies occur in 30% of girls with Turner syndrome, with bicuspid aortic valve accounting for up to half of these, and coarctation in up to 30% of these. Aortic dilatation, occurring in 5%, is associated with the major risk of rupture, and is more likely in the presence of left sided cardiac anomalies together with hypertension.

Cardiac assessment by a cardiologist should occur at diagnosis, including physical examination and echocardiogram and/or MR angiography (superior for aortic valve visualisation), even if prenatal echocardiogram was normal. If cardiac structural abnormalities are found, antibiotic prophylaxis should be considered.

Blood pressure should be measured annually, including arm and leg if coarctation is suspected, and measured routinely at all visits, since hypertension is common even in the absence of cardiac or renal anomalies. The right arm should be used, to avoid effects of coarctation repair and minimal narrowing.

Formal cardiologic examination with echocardiography should be repeated in adolescence or earlier and more frequently if aortic root enlargement is detected. This should be repeated every five years throughout life.

Renal assessment

Urinary tract anomalies occur in 30% of patients with Turner syndrome, commonly rotational abnormalities and double collecting systems. Risks include hypertension, urinary infection and hydronephrosis.

Ultrasound should be performed at diagnosis, and repeated following interventions if abnormalities are detected. Follow-up ultrasound and urine cultures should then be performed in affected individuals every 5 years.

Thyroid Function

Primary hypothyroidism occurs in 10-30% of individuals with Turner syndrome, usually associated with thyroid antibodies, which should be measured with free T4 and TSH at diagnosis and annually thereafter. Isochromosome Xq karyotype is an association.

Hearing

Progressive sensorineural hearing loss occurs in 50-90% of women with Turner syndrome, detectable by age 6, with overt hearing loss sometimes appearing in childhood.

Conductive hearing loss secondary to recurrent otitis media is also common, with peak incidence of otitis between ages 1 to 6, when aggressive treatment is necessary to prevent deafness, mastoiditis and cholesteatoma. Audiological assessment should be performed in mid-childhood. Speech problems are common, and may be secondary to hearing disorders. Referral to an ENT specialist and speech pathologist should be undertaken.

Clinical evidence of hearing loss often only appears in adulthood, so that review is necessary throughout life.

Low-set ears may also be associated with malformations requiring plastic surgical referral. Note that keloid formation is more common in Turner syndrome.

Lymphoedema and Neck webbing

Lymphoedema is common in infancy, affecting hands and feet, but may recur with introduction of growth hormone or oestrogen therapy. Support stockings may be required, but the value of surgery is unproven.

Neck webbing requires plastic surgical referral, though keloid formation is a risk and hair growth within the z-plasty can be a cause of a major problem with fistula /sinus formation. Generally therefore, such intervention should be carefully considered if careful hair styling can do the trick.

Vision

Strabismus, amblyopia and ptosis are all common and should be assessed annually and ophthalmology referral made if necessary.

Dental

Crowding and malocclusion result from the small mandible, and dental assessment should be made at mid-childhood

Glucose intolerance

Although glucose intolerance associated with insulin resistance and defective insulin secretion is more common, and exacerbated by growth hormone and oxandrolone, frank diabetes is rare in childhood and adolescence, but Type 2 diabetes is more common in adulthood

Gastrointestinal disease

Anti-gliadin or endomysial antibodies occur in more than 5% of girls with Turner syndrome, and may be indicative of coeliac disease. Antibody screening should be performed in mid-childhood,

with gastroenterological referral if antibodies are positive, regardless of the presence or absence of symptoms. Repeat screening every two years is recommended.

Inflammatory bowel disease is 2-3 times more common in Turner syndrome than in the normal population, particularly Crohn's disease. This is linked to isochromosome Xq karyotype, similar to thyroid autoimmune disease.

These diagnoses should be considered in any girl with Turner syndrome with poor weight gain or gastrointestinal symptoms.

Hepatic enzyme dysfunction occurs in 40-80% of Turner subjects, leading to an increased risk (up to X5) of cirrhosis in adulthood. Etiology is unknown, but may relate to oestrogen deficiency.

Short stature and bone health

The invariable growth failure of Turner syndrome has intrauterine, childhood and pubertal components, each contributing to poor growth outcome, with adult heights around 20cm below average women. Parental height will however modify final height outcome.

Height should be assessed at each visit and plotted on a Turner-specific growth chart.

Scoliosis is reported in 10-25% of affected girls and should be monitored by an orthopaedist.

Growth hormone (GH) therapy should be considered in all girls with Turner syndrome whose height is below the 95th centile for Turner syndrome and are not exhibiting significant catch-up on these charts. This usually occurs around age 3-4.

The advantages and disadvantages of GH therapy should be discussed with parents and the girl when she is old enough to comprehend.

Briefly, GH accelerates growth in Turner syndrome, with earlier onset of treatment and higher doses giving better outcomes. Approved doses in Australia are from 4.7-9.3 mg/m²/week (0.16-0.32mg/kg/week), with most girls commencing on 0.23 mg/kg/week. Final height increments range from 5-15cm according to these factors in various studies.

Growth hormone also contributes to achievement of peak bone mass in combination with oestrogen.

There may be recurrence or exacerbation of lymphoedema, as well as enlargement of naevi, with induction of GH therapy.

Monitoring of IGF-I levels should be performed if high doses are used, due to unknown long-term effects of consequently elevated IGF-I levels.

If treatment is commenced later than age 10-12, addition of low dose androgen has in the past been considered in order to enhance initial growth. The non-aromatizable oxandrolone may be preferred in order to avoid conversion to oestrogen which accelerates bone maturation. On balance however, such androgens should be avoided if possible due to their potential masculinising effects and with the potential risk of hepatotoxicity with a 17 alkylated androgen.

While on GH therapy, girls with Turner syndrome should be reviewed 3 monthly for auxological assessment and treatment continued while growth crosses increasing Turner height centiles.

Pubertal Induction

Over 90% of girls with Turner syndrome have gonadal failure, but up to 30% will undergo spontaneous puberty and 2-5% have spontaneous menses. The majority however will require either pubertal induction and/or later maintenance oestrogen therapy.

Oestrogen is essential for the physical changes of puberty including breast development, uterine and pelvic growth, and the psychological, social, emotional and sexual evolution of puberty.

Oestrogen is also essential for the achievement of peak bone mineralisation. But, since oestrogen also potently accelerates fusion of bony epiphyses, the timing of its commencement must be coordinated with GH therapy in order to achieve maximum growth potential, while not unduly delaying the onset of puberty. If GH therapy is commenced early using adequate doses, then pubertal onset can be achieved at near normal age without compromising gains in final height achieved with GH. There is also synergy between GH and oestrogen in the achievement of peak bone mass.

In general, oestrogen should be commenced around age 12-13, but generally no later than age 14. Gonadotrophin levels should be determined prior to introduction of oestrogens in order to confirm gonadal failure (elevated FSH). If FSH is normal, consider pelvic ultrasound to determine whether follicles are visible, as a predictor of gonadal status.

Adequate uterine size is only achieved if oestrogen is commenced by age 15. Perform pelvic ultrasound to determine uterine size prior to commencing oestrogen therapy.

Bone density, adjusted for height and timing of puberty, should be performed in late puberty to ensure adequate bone mineralisation has taken place if puberty has been delayed. If bone density is low, it should be repeated in 1-2 years, as delayed puberty will have a significant effect on comparison with an age matched group.

Low dose oestrogen therapy should be commenced using a natural oestrogen, preferably oestradiol valerate (Progynova). Piperazine oestrone sulphate (Ogen) may have poorer clinical efficacy with respect to breast development, and is not the oestrogen of choice. Similarly, ethinyl oestradiol (as in contraceptive pills) has 40-times renin substrate induction capacity due to the ethinyl radical, increasing hypertensive risk.

Progynova should be given at a quarter of the adult dose, namely 0.5-1mg alternate days, increasing the dose at 6-12 monthly intervals to complete feminisation over 2-3 years. .

A progestin, eg Medroxyprogesterone acetate, should be added (5mg daily for 12-14 days each month) when vaginal spotting occurs or after 24 months of oestrogen therapy in order to establish regular withdrawal bleeding.

Transdermal oestrogen patches have been used successfully in a number of small series, though some young women dislike using visible patches.

Advice regarding avoidance of sexually transmitted diseases should be given.

In those with spontaneous puberty, appropriate contraception should be recommended.

Psychosocial and educational issues

Psychosexual issues are complex, influenced by both the genetic and hormonal deficiencies, as well as by psychological and body image factors related to stature and disturbed physical development. Nevertheless, girls with Turner syndrome do not show ambiguous gender identification any more frequently than the normal population.

There are some well-documented disturbances in personality and social adjustment in some girls, including limited emotional arousal, unassertiveness, and over-compliance, as well as reduced

likelihood to establish independence or sexual relationships. However, most of these features are in common with short normal girls.

A range of programs designed to improve body image and self-confidence have been described. These include group and individual therapies, dance therapy etc.

There is no evidence of global intellectual delay in Turner syndrome, but there are well-documented specific deficits in non-verbal visio-spatial processing, leading to poorer performance than verbal outcomes on intellectual testing. School, academic and vocational training performance may thus be affected, particularly in mathematics and areas requiring fine co-ordination, with signs of specific learning deficits. These deficits are by no means universal. Educational and vocational training must therefore be tailored to account for these difficulties, if present, since they are likely to persist throughout life.

Transition to Adult Management

The transition process needs to be carefully planned and discussed with the young woman, and her family if appropriate. While a multidisciplinary approach is similarly ideal in adult women with Turner syndrome, this may be less available in practice. An appropriate primary physician should be identified, usually a gynaecologist with a particular interest, or a reproductive endocrinologist. The range of other specialists to be involved includes: cardiologist, nephrologist, ENT specialist, dentist, fertility specialist, psychologist, nurse specialist, social worker.

Adult Management

Although these Guidelines are focussed on children and adolescents with Turner syndrome, management issues in adults will be briefly summarised. Some 10% of Turner women are first diagnosed as adults

An initial comprehensive assessment by the managing physician should pay particular attention to pre-existing problems, particularly:

- *cardiac, hearing, dental and skeletal* problems.

Initial and annual clinical evaluation should include assessment of the following:

- *blood pressure, cardiac auscultation, thyroid size and function, breast examination, pap smear.*

Particular issues requiring monitoring in adults include the following, which may only become evident in adulthood:

Cardiovascular Health

Hypertension is common and should be treated vigorously, since it contributes to aortic dissection risk. Cardiovascular complications are the major contributor to premature death in Turner syndrome.

Echocardiograms or other imaging (MR angiography) should be performed 5 yearly to monitor the aortic root, especially if assisted pregnancy is contemplated, when aortic dissection risk increases. Since Turner women are shorter than average, aortic root diameter norms are inappropriate, and a proposed Turner-specific nomogram has been developed.

Oestrogen replacement reduces the risk of atherosclerosis.

Thyroid dysfunction

Autoimmune thyroid disease increases in frequency with age in Turner syndrome, with 50% antibody positivity and 25-30% hypothyroid as adults. Thyroid autoantibodies should be measured every 5 years, and if positive, TSH should be measured annually.

Hearing

Up to 15% of adults with Turner syndrome experience clinical hearing loss (conductive +/- sensorineural), with 50-90% having significant measurable sensorineural loss, especially beyond 35 years of age. Follow-up should be 3-5 yearly or less frequently if no sensorineural loss in the presence of a low risk karyotype [45X or 45X, I(Xq)].

Gastrointestinal disease

As in childhood, inflammatory bowel disease and Crohn's disease are more common, and should be considered if symptoms occur. Liver enzymes should be measured.

Obesity, Diabetes, and Dyslipidaemia

These are all increased risks, with Type 2 diabetes 2-4 times more common in Turner adults than normal women. Appropriate lifestyle advice, including diet and exercise, should be given. Two-yearly fasting glucose (+/-OGTT), lipids, and renal function should be performed.

If there is a known urinary tract anomaly, urinary infection screening should be performed every two years.

Bone Health

Fracture risk increases over 45 years of age. Bone density should initially be performed every 3-5 years. Adequate dietary calcium (1.2g/day), exercise and oestrogen replacement is essential. Scoliosis, if present should be monitored by an orthopaedic specialist.

Hormone Replacement Therapy

Cyclical oestrogen and progesterone therapy should be prescribed, using low doses sufficient to prevent symptoms and signs of oestrogen deficiency. Oestradiol valerate, not ethinyl oestradiol (see earlier comments regarding hypertensive risk) in a continuous, rather than interrupted regimen (as in cyclical contraceptive pills), together with cycles of progestogen to ensure adequate endometrial shedding. If the o/c is used for purposes of HRT rather than contraception, there are 7 lactose pills every cycle which result in bone loss for 25% of each month when there is no ovarian function. Transdermal oestrogen has a theoretical advantage of avoiding first pass hepatic effects, and reducing triglycerides and hypertensive risk, but there are little comparative data.

Fertility and assisted pregnancy

Since pregnancy increases many of the risk factors in Turner syndrome, comprehensive medical, cardiac and gynaecological assessment prior to becoming pregnant is essential.

In women with functional ovaries, the risks of miscarriage and major chromosomal and phenotypic abnormalities in offspring should be considered, and pregnancies should not be delayed due to the risk of premature ovarian failure.

Oocyte or embryo donation needs careful planning via a specialist team, initially ensuring adequate preparation of the uterus via optimal oestrogen and progestogen therapy. Cephalo-pelvic disproportion is a frequent complication, often necessitating caesarean section. IVF assisted pregnancy outcome compares favourably with those of other infertile couples, the most generally quoted figure being a 19% per cycle take home baby rate. Early miscarriage rate has been higher than average but this may relate to smaller uterine size of past E2 regimes and may improve with present management.

Support Groups

A very important role is fulfilled by the various Turner syndrome support groups. In Australia there are two major groups:

Turner Syndrome Association of Australia Ltd., PO Box 112, French's Forest NSW 1640. Tel (02) 9452-4196. Email: turnersyn@one.net.au

Victorian Turner Syndrome Association Inc., 31 Price St., Essendon Vic 3040. Tel (03) 9337-4074.

References

Saenger P, Albertsson Wikland, Conway GS et al. 2001 Recommendations for the Diagnosis and Management of Turner Syndrome. *J Clin Endocrinol Metab* 86:3061-3069

Rosenfeld RG, Tesch L-G, Rodriguez-Rigau LJ, et al. 1994 Recommendations for diagnosis, treatment and management of individuals with Turner syndrome. *The Endocrinologist* 4:351–358.

Rosenfeld RG, Attie KM, Frane J, et al. 1998 Growth hormone therapy of Turner's syndrome: beneficial effect on adult height. *J Pediatr* 132:319–324.

Ross JL, Roeltgen D, Feuillan P, Kushner H, Cutler GB Jr. 1998 Effects of estrogen on nonverbal processing speed and motor function in girls with Turner's syndrome. *J Clin Endocrinol Metab* 83:3198–3204

Ostberg JE and Conway GS. 2003. Adulthood in Women with Turner Syndrome. *Hormone Research* 59:211-221.

Zacharin M. 2000. Use of Androgens and Oestrogens in Adolescents – a Review of Hormone Replacement Treatment. *J Ped Endo Metab.* 13:3-11

Bonamico M, Pasquino AM, Mariani P et al. 2002. Prevalence and Clinical Picture of Celiac Disease in Turner Syndrome. *J Clin Endocrinol Metab.* 87:5495-5498.

Zacharin M (ed). *Turner Syndrome (Hormones and Me)* (adapted from original version by Richard Stanhope) Serono Symposia 2002

Turner Syndrome Lifelong Guidance and Support. Turner Syndrome Support Society (UK) 2002.

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TURNER SYNDROME: OUTLINE OF ESSENTIAL MANAGEMENT STEPS

	Diagnosis	Annual	Every 5 yrs	Age 6-8	Adolescence	All visits	Adult
Cardiac	Cardiologist Examination Echo Aortic root ?CT ?antibiotics prophylaxis	Blood Pressure (arm and leg) F/U Echo if aortic root dilatation			Cardiologist Examination Echo Aortic root		Cardiac review with echo of aortic root every 5 years esp pre pregnancy
Renal	Ultrasound		Ultrasound and urine culture if structural anomalies		Ultrasound and urine culture if structural anomalies		Hb, U+E, creatinine MSU every 2 years
Blood Pressure						Check	Monitor & treat hypertension
Thyroid function	TSH/Free T4 Thyroid antibodies	TSH/Free T4					Thyroid size TSH annually
Hearing and ears	?Plastic referral NB. Keloid	Speech pathology in early life		Audiology ?Speech path ?ENT		Check for otitis media age 1-8	ENT 3-5 yrly Or 10 yearly if no audiol
Lymph-oedema Webbing	Common at birth Plastic referral					Check for dysplastic naevi	Note keloid potential pre surgery
Vision (Squint, ptosis)		Review ?amblyopia ?Refer Opth					
Dental				Refer to dentist re occlusion			
G-I disease Nutrition	Feeding support in infancy			Endomysial antibodies ?gastro ref	Repeat endomysial antibodies		LFTs Endomysial antibodies two-yearly
Short stature	Height and weight on Turner charts			Offer GH therapy by this age	Consider age to add oestrogen	Plot Ht/Wt. Review 3 monthly on GH therapy	
Pubertal induction					Check FSH/LH Bone age, pelvic u/sound Commence low dose oestrogen by age 13		Cyclical oestrogen and progestin Annual breast exam and Pap smear
Obesity, glucose tolerance						Weight Nutrition and exercise advice	Fasting glucose, lipids, every 2 years Low fat diet Exercise
Bone health	Exclude congenital dislocation of hip	Check for scoliosis and refer if indicated.			Bone density in late puberty		Bone density 3-5 yearly. Calcium 1.2g/day Exercise
Psycho-social and education	Assessment of overall function Referral to Support groups and psychologist				Vocational guidance	Review school performance and social issues	Vocational guidance