REVIEW ARTICLE

MEDICAL PROGRESS

Turner's Syndrome

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TURNER'S SYNDROME, A DISORDER IN FEMALES CHARACTERIZED BY THE absence of all or part of a normal second sex chromosome, leads to a constellation of physical findings that often includes congenital lymphedema, short stature, and gonadal dysgenesis.[1-3] Turner's syndrome occurs in 1 in 2500 to 1 in 3000 live-born girls. Approximately half have monosomy X (45,X), and 5 to 10 percent have a duplication (isochromosome) of the long arm of one X (46,X,i(Xq)). Most of the rest have mosaicism for 45,X, with one or more additional cell lineages (Table 1).

In the past decade, more has been learned about the natural history of Turner's syndrome, and recent molecular studies have identified some genes that may be involved in the clinical expression of the condition. This review summarizes current knowledge and makes recommendations for care on the basis of the medical literature and on our own experience with 532 live-born children and adults with karyotypically confirmed Turner's syndrome (Table 1).[4]

DIAGNOSIS

When Turner's syndrome is diagnosed prenatally, the diagnosis is usually based on the finding of fetal edema on ultrasonography; abnormal levels of human chorionic gonadotropin, unconjugated estriol, and alpha-fetoprotein on screening of maternal serum (triple screening); or abnormal results of fetal karyotyping performed because of advanced maternal age. Affected fetuses often abort spontaneously. A 45,X fetus identified prenatally and surviving to birth has a prognosis similar to that of a child in whom Turner's syndrome is diagnosed postnatally. In contrast, approximately 90 percent of fetuses in whom 45,X/46,XX or 45,X/46,XY mosaicism is diagnosed incidentally during the course of screening for advanced maternal age or maternal triple screening will likely have a normal phenotype, female or male, respectively, at birth. The risk of eventual gonadal failure in these children with mosaicism is unknown.[5,6] In contrast, a child in whom 45,X/46,XX or 45,X/46,XY mosaicism is diagnosed after birth is usually identified because of phenotypic features suggestive of Turner's syndrome; such children have a prognosis similar to that for 45,X children.[5]

One fifth to one third of affected girls receive a diagnosis as newborns because of puffy hands and feet or redundant nuchal skin (Fig. 1), the residual effect of cystic hygromas in utero. Turner's syndrome should be suspected in any newborn girl with edema or hypoplastic left heart or coarctation of the aorta, since the frequency of both conditions is increased among children with Turner's syndrome. Approximately one third of girls with Turner's syndrome receive the diagnosis in midchildhood on investigation of short stature. With the exception of familial short stature or constitutional delay, Turner's syndrome is the most common cause of short stature in otherwise healthy girls. In most other patients with Turner's syndrome, the condition is diagnosed either in adolescence when they fail to enter puberty or in adulthood because of recurrent pregnancy loss. The diagnosis should be excluded in any teenage girl with primary or secondary amenorrhea, especially if she is short.

Table 1. Major Clinical Features of Turner's Syndrome.*

Karyotype	No. of Patients	Mental Retardation	Cardiac Disease†	Renal Malformation‡	Edema	Menses	Height§	
		number/total number (percent)					*cm*	*no.*
All	532	55/500 (11)	169/319 (53)	147/373 (39)	165/461 (36)	64/288 (22)	148±7.1	149
45,X	241 (45)	19/230 (8)	94/154 (61)	84/181 (46)	141/217 (65)	13/128 (10)	147.3±6.0	64
46,X,i(Xq)	35 (7)	6/33 (18)	10/20 (50)	8/22 (36)	4/30 (13)	4/22 (18)	145.6±4.7	9
45,X/46,X,i(Xq)	40 (8)	3/34 (9)	7/24 (29)	10/38 (26)	0/26	4/26 (15)	143.4±7.9	14
45,X/46,X,+ring	32 (6)	10/30 (33)	14/22 (64)	6/27 (22)	3/27 (11)	2/16 (12)	145.7±4.9	7
45,X/46,X,+mar	5 (1)	4/5 (80)	1/2 (50)	1/3 (33)	1/4 (25)	0/1	—	
45,X/46,XY or 46,X,Yvar/Ydel	37 (7)	0/32	14/22 (64)	12/27 (44)	3/32 (9)	0/13	148.8±5.9	12
45,X/46,XX/47,XXX	17 (3)	0/24	1/10 (10)	3/12 (25)	1/17 (6)	5/9 (56)	144.9±7.7	6
45,X/47,XXX								
45,X/46,XX	70 (13)	5/65 (8)	17/43 (40)	17/44 (39)	9/61 (15)	14/35 (40)	149.7±7.5	22
46,X,Xp (short-arm deletions)	13 (2)	1/13 (8)	0/4	0/5	1/12 (8)	6/7 (86)	153±5.0	5
46,X,Xq (interstitial long-arm deletions)	9 (2)	0/9	ND	2/4 (50)	0/6	5/7 (71)¶	163±16.6	6
Other	33 (6)	7/32 (22)	11/18 (61)	4/20 (20)	2/29 (7)	6/20 (30)	149.9±7.4	15

* Data were obtained from patients in our Seattle clinic. Denominators reflect the number of patients for whom we have complete information for each feature. Plus–minus values are means ±SD. ND denotes no data.
† The category includes both structural malformations and hypertension. Patients with normal physical examinations who did not undergo echocardiography are omitted.
‡ The analysis includes patients with either renal-ultrasound or intravenous-pyelographic information.
§ The analysis does not include patients who received a diagnosis in adult life on the basis of recurrent pregnancy loss (four women; mean height, 167 cm). The analysis excludes patients who had received growth-promoting agents (oxandrolone, human growth hormone, or both).
¶ Secondary amenorrhea developed in all five patients with spontaneous menarche.

Karyotyping of a blood sample is definitive in most cases. Detection of mosaicism depends on the proportion of cells present from the additional cell lineages. In routine karyotyping, 20 cells are counted, since this number is sufficient to detect mosaicism at a level of about 5 percent.

Mosaicism for a second, normal 46,XX cell population occurs in approximately 15 percent of girls with Turner's syndrome. Extensive searching for 46,XX cells in a girl with a 45,X karyotype is not necessary, since the detection of a normal cell lineage in fewer than 5 percent of cells does not change the prognosis or the management. Conversely, if the diagnosis of Turner's syndrome is suspected clinically but the result of routine testing is normal, increasing the number of cells counted to 100 and performing a skin biopsy for karyotyping of fibroblasts are indicated to rule out mosaicism for an abnormal cell lineage.

Girls with mosaicism for a cell population with a Y chromosome are at increased risk for gonadoblastoma (risk, 7 to 30 percent) in their streak gonads.[7] Although the use of flow cytometry or DNA hybridization to search for Y-chromosome material has been suggested for all girls with a 45,X karyotype,[8] clinical evidence indicates that such an approach is merited only in those with masculinization or mosaicism for an unidentified marker. The use of polymerase-chain-reaction testing for Y-chromosome sequences has a high false positive rate.[9]

Which chromosomal regions and genes account for the physical characteristics of Turner's syndrome remains uncertain (Fig 2).[10-12] It has been hypothesized that the physical manifestations of Turner's syndrome are due either to the absence of two normal sex chromosomes before X-chromosome inactivation or to haploinsufficiency of genes in the pseudoautosomal regions of the X or Y chromosome, as well as to aneuploidy itself.[13,14] Both the short arm and the long arm of the X chromosome contain genes important for ovarian function, and aneuploidy alone may lead to a reduction in the number and survival of oocytes.

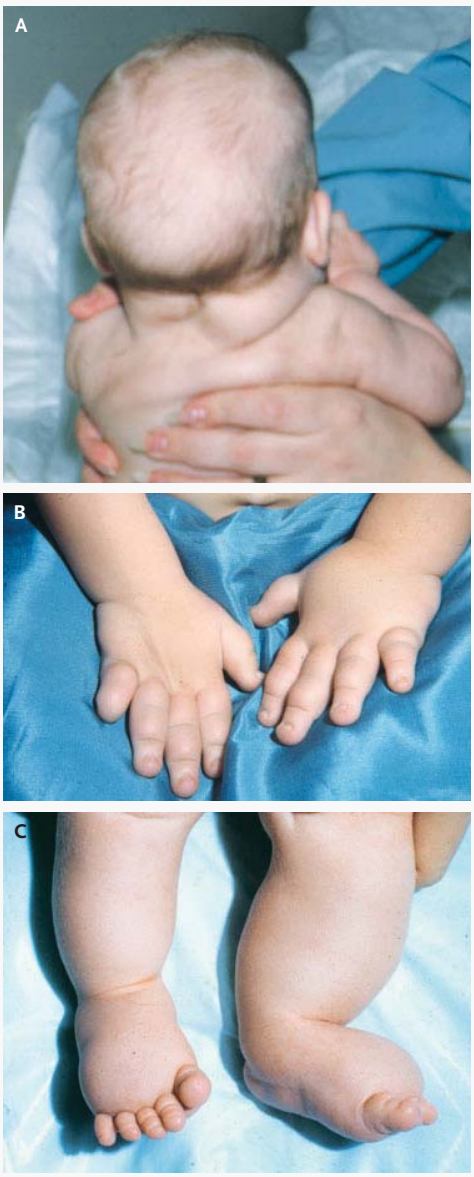

Figure 1. Redundant Nuchal Skin (Panel A) and Puffiness of the Hands (Panel B) and Feet (Panel C) in Turner's Syndrome.

Loss of interstitial or terminal long-arm material of the X chromosome (Xq) can result in short stature and primary or secondary ovarian failure.[15] Deletions distal to Xq21 appear to have no effect on stature. In general, loss of the short arm (Xp) results in the full phenotype. Very distal Xp deletions are compatible with, but do not ensure, normal ovarian function.[11,12] Loss of this region usually confers short stature and the typical skeletal changes, in part as a result of haploinsufficiency of the short stature–homeobox (*SHOX*) gene, located in the pseudoautosomal region of Y and Xp.[16] The *SHOX* gene is probably not the only gene responsible for the skeletal features. Aneuploidy itself may contribute to growth failure.[14] Loss of a region at Xp22.3 appears to be associated with the neurocognitive problems in Turner's syndrome.[17] Loss of the testis-determining factor (*SRY*) gene locus on the short arm of the Y chromosome (e.g., 46,X,del(Yp)) also leads to the phenotype of Turner's syndrome, even without a 45,X cell population. A region on Xp11.4 has been proposed as critical for the development of lymphedema.[18]

There are some correlations between karyotype and phenotype (Table 1). Infants with a 45,X karyotype are the most likely to have congenital lymphedema. Patients with a karyotype of 45,X/46,XX or 45,X/47,XXX are the most likely to have spontaneous menarche and fertility.[4,19] As a group, women with mosaicism for 45,X/46,XX are marginally taller than other women with Turner's syndrome. The presence of an isochromosome Xq suggests an increased risk for hypothyroidism and inflammatory bowel disease.[3,4,20] The presence of a ring or marker chromosome confers an increased risk of mental retardation and atypical phenotypic features. Nonetheless, phenotypic predictions for a given patient that are based on karyotype are unreliable in patients with Turner's syndrome. Women with a 45,X karyotype have conceived; women with a 45,X/46,XX karyotype and a preponderance of 46,XX cells may have all the findings of the disorder.

MANAGEMENT

GROWTH

The mean birth length of infants with Turner's syndrome falls within the low end of the normal range. A decrease in growth velocity occurs as early as 18 months of age.[21] Many patients will not be the shortest child in kindergarten but will have had a significant decrease in linear growth rate by third or fourth grade. Some present only when the normal pubertal growth spurt fails to occur. It is easy to misinterpret the absence of puberty and small size of these patients as due to constitutional delay; 104 of 150 patients who came to our attention as teenagers had had evidence of growth failure earlier in childhood that had been overlooked.[4]

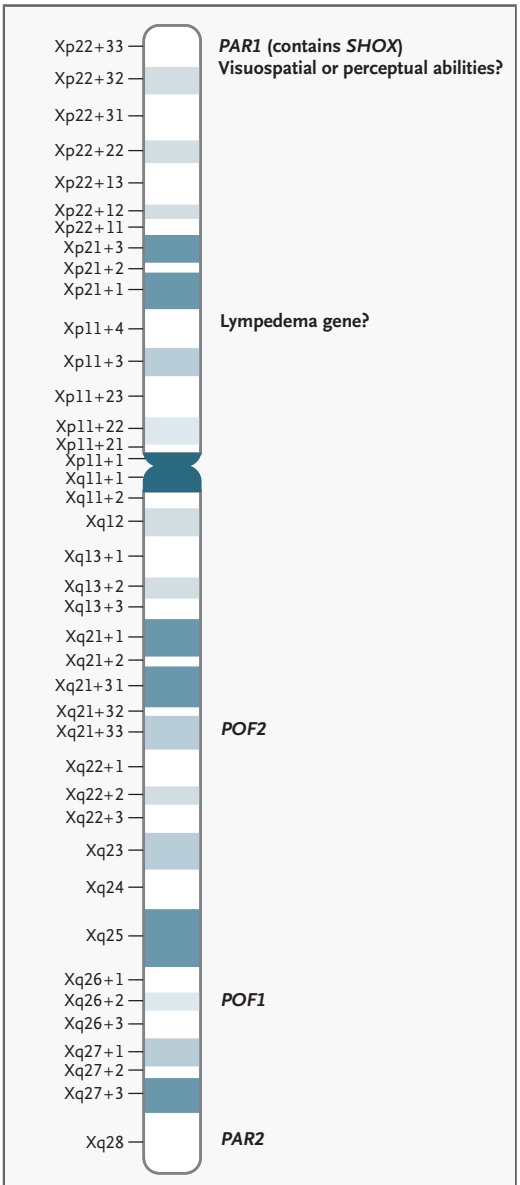

Figure 2. The Banding Pattern on the X Chromosome, the Location of Pseudoautosomal Regions (*PAR1* and *PAR2*), and the Putative Locations of Regions and Genes Responsible, in Part, for the Phenotypic Features of Turner's Syndrome.

POF2 denotes the premature ovarian failure gene, an unidentified gene hypothesized to be responsible for ovarian failure on the basis of the study of translocations. The *POF1* gene is homologous to the diaphanous gene (*DIAPH2*) in the fruit fly. *SHOX* is located within *PAR1*.

A study of the efficacy of recombinant human growth hormone in patients with Turner's syndrome was initiated in 1983 in the United States[22] and led to approval of this agent by the Food and Drug Administration in 1997. Treatment with recombinant human growth hormone is now standard in many centers, though physiologically significant alterations in growth hormone secretion have not been identified in patients with Turner's syndrome. Studies that followed treated patients to their final height[23-36] have based therapeutic success on one of three measures: the mean final height of the treated group, as compared with a historical mean height of 143.2 cm[37]; the height achieved by each subject, as compared with her projected height on the basis of her centile on the Lyon curve (a growth chart specific to patients with Turner's syndrome)[37] at the onset of treatment with recombinant human growth hormone; and the subject's predicted height, which was derived from midparental height.[38] Only one published, nonrandomized study has included a concurrent control group.[30] Two studies that include randomized control groups have been initiated — one in Canada and one at the National Institutes of Health. Only interim results in abstract form are available for the former[39]; the latter is ongoing.

Comparisons of the final heights of girls treated with recombinant human growth hormone with projected or predicted heights range from no gain to an increase of as much as 11.9 cm.[22-36] Differences in ages at the commencement of treatment and differences in the doses and duration of therapy complicate analysis. The use of historical controls whose measurements led to the Lyon growth curves may not be valid for contemporary populations. For example, the mean adult height in 149 of our untreated patients is currently 148 cm, 4.8 cm taller than the mean adult height of the Lyon curve. Although one study suggested that all treated girls reached or exceeded their predicted adult height,[22] other studies have not.[33,38-41] The ideal dosing regimens and duration of treatment have not been established.[36,42] It has been estimated that the cost of recombinant human growth hormone per centimeter of final gain in height is approximately $29,000.[42]

The short-term safety of treatment with recombinant human growth hormone in patients with

Turner's syndrome appears to be acceptable. Increased insulin resistance and increased blood pressure have occurred during therapy and resolve on its cessation.[43] The long-term effects of recombinant human growth hormone treatment on cardiovascular status,[44] especially on aortic-root diameter, and the lifetime risk of type 2 diabetes are unknown. No systematic studies have examined whether treatment with recombinant human growth hormone improves the psychosocial outcomes and the quality of life of patients with Turner's syndrome.

Our view is that recombinant human growth hormone should be considered for every girl with Turner's syndrome. Parents and children should be told of the limitations of current knowledge about treatment and be given realistic expectations with respect to the resulting gain in height, so that they can make informed decisions.[28] Most adults with Turner's syndrome cope successfully with their small stature.[45]

Weight management is an issue in patients with Turner's syndrome. Obesity is neither inherent nor unavoidable.[46] Affected girls should be encouraged to engage in physical activities such as swimming, walking, and bicycling beginning in childhood and continuing throughout their lives.

DEVELOPMENTAL AND BEHAVIORAL CONCERNS

Most people with Turner's syndrome have normal intelligence. Approximately 10 percent of patients (Table 1), irrespective of karyotype, will have substantial developmental delays, need special education, and require ongoing assistance in adult life. The risk of mental retardation is highest among patients with a marker chromosome (66 percent) or a ring (X) chromosome (30 percent).[4]

Approximately 70 percent of patients with Turner's syndrome have learning disabilities affecting nonverbal perceptual motor and visuospatial skills.[47-49] These deficits appear to be more common among patients with a 45,X karyotype than among those with a 45,X/46,XX karyotype.[50] Better verbal and executive skills may be associated with inheritance of a paternally derived X chromosome,[51] although these findings have not been corroborated. Findings on magnetic resonance imaging and positron-emission tomography have suggested the presence of nonspecific differences between patients with Turner's syndrome and controls, particularly in the right posterior regions of the brain.[52,53] How these differences may relate to neurocognitive findings is unknown.

A meta-analysis of 13 studies involving 226 patients with Turner's syndrome and 142 controls identified deficits in visuospatial organization, social cognition, nonverbal problem-solving, and psychomotor functioning in the patients.[49] Deficits in nonverbal memory,[54] executive function,[55,56] and attentional abilities[47] are common. As with nonverbal learning disabilities,[57] these deficits translate into problems with diverse activities such as mathematics,[58,59] driving, multitasking, and social functioning.[49,56] Spatial and math deficits appear early; problems with reading comprehension emerge as more complex academic demands are made. Attention-deficit–hyperactivity disorder is relatively common.[60] Early cognitive testing and appropriate accommodations, such as tutoring; enrollment in small, structured classes; and the use of untimed testing, may be indicated.

Girls with Turner's syndrome have typical female-sex identification. Most affected women report being heterosexual, although they are less likely than their peers to have sexual relationships and do so at an older age.[45,61] Prevalence rates of coexisting psychiatric diagnoses range from 2 to 10 percent,[4,62] which are actually lower than the rate of 14 percent among the general population.[63]

Younger patients may have impaired peer relationships and anxiety and may be preoccupied with keeping things in order and inflexible regarding changes in their routine.[64-66] They have relatively poor self-esteem, particularly in the social arena, as compared with both girls with short stature from other causes and girls with normal height.[60,66,67]

During adolescence, immaturity, social isolation, and anxiety are common.[60,64] People with Turner's syndrome may misread social cues, facial expressions, and body language,[47,65,68] contributing to awkwardness in social interactions; special training in recognizing social cues may be helpful.

Successful transition of these patients into the working world requires age-appropriate, not size-appropriate, expectations. During driver's training, many adolescents will require attention to be paid to their impaired navigational planning, visuomotor integration, and spatial and directional abilities. Most adults with Turner's syndrome report satisfaction with their lifestyle[45,69]; they have fewer

social contacts than their peers but do not perceive themselves to be isolated.[45] They react with appropriate depression and feelings of loss related to their physical limitations and usually cope well; their sense of self appears to be directly related to their health status.[45]

Women with Turner's syndrome are often employed at occupational levels below that predicted on the basis of their education and training. They may fail at jobs requiring a rapid response and multitasking, reflecting the effect of nonverbal learning disabilities.[70] Nonetheless, many have successful professional careers.

CARDIOVASCULAR CONCERNS

The prevalence of congenital heart disease among patients with Turner's syndrome ranges from 17 to 45 percent, with no clear phenotype–genotype correlations.[3,71,72] Death from cardiac causes is a serious concern.[4,73] Coarctation of the aorta and bicuspid aortic valve are the most common structural malformations, followed by other left-sided defects. Hypertension, mitral-valve prolapse, and conduction defects also occur. Hypertension in the absence of structural cardiac malformations is usually not associated with arteriosclerotic heart disease or renal disease.[4] The risk of hyperlipidemia and coronary artery disease in patients with Turner's syndrome is unclear.

Echocardiography is a mandatory part of the diagnostic workup for Turner's syndrome, since a physical examination may be inadequate to detect a bicuspid aortic valve.[71] Use of magnetic resonance imaging as a screening tool for Turner's syndrome has not been standardized.

There have been more than 80 reports of aortic dissection in patients with Turner's syndrome.[71,74-76] Coarctation of the aorta (unrepaired or repaired), bicuspid aortic valve, hypertension, or a combination of these findings, which are risk factors for aortic dissection, were present in 93 percent of these patients. The normal range of aortic-root diameters has not been established in patients with Turner's syndrome. The need for and frequency of repeated echocardiography for the assessment of the aortic-root diameter in those without structural cardiac abnormalities is unknown and should be individualized (Table 2).[71,76]

ENDOCRINE CONCERNS

Hypothyroidism occurs in 15 to 30 percent of women with Turner's syndrome.[4,20,77] The mean age at onset is in the third decade, though 5 to 10 percent of cases occur before adolescence. Acute thyroiditis is uncommon. Screening of thyroid function, including measurement of thyrotropin levels, should begin at about 10 years of age in asymptomatic patients. We do not monitor antithyroid antibody status, since the presence of these antibodies does not alter management.

Gonadal dysgenesis is a cardinal feature of Turner's syndrome; 90 percent of patients will require hormone-replacement therapy to initiate puberty and complete growth. In utero, the ovaries have a decreased number of primordial follicles; these appear to undergo premature apoptosis[78] and are usually absent by adult life. The uterus may be small owing to a lack of estrogen; structural uterine abnormalities are rare. Dyspareunia sometimes occurs because of a small vagina or an atrophic vaginal lining.

The presence of normal gonadotropin levels in the first three to six months of life suggests that residual ovarian function exists but does not ensure that the initiation and progression of puberty will be normal. Gonadotropins are suppressed in childhood, even in those with gonadal dysgenesis. In many girls with Turner's syndrome, pubic and axillary hair will develop spontaneously, but changes of adrenarche are not indicative of ovarian function. Some girls have enough residual ovarian function for breast budding or vaginal spotting to occur, but secondary amenorrhea will develop. A minority will maintain ovulatory cycles for a time. Two fifths of girls with 45,X/46,XX mosaicism will have spontaneous menarche; however, ovarian failure usually ensues.[4] If the status of ovarian function in adolescence is unclear, measurement of follicle-stimulating hormone, luteinizing hormone, and estradiol levels can help determine the need for hormone-replacement therapy.

Hormone-replacement therapy should be initiated at about the age of 14 years.[4,79] Earlier treatment may result in a decrement in final height. Psychosocial issues and the patient's maturity and wishes also need to be considered. Girls who have received recombinant human growth hormone and who have completed most of their growth, as judged on the basis of bone age or growth velocity, may start hormone-replacement therapy at the age of 12 years if they wish.

There is no single formula for the use of hormone-replacement therapy.[80] Several strategies are outlined in Table 3. After the first year, the use

Table 2. Recommendations for Care.

Procedure	Timing of Evaluation			
	At Diagnosis	Childhood	Adolescence	Adulthood
Physical examination*	Yes	As indicated by age	Yearly	Yearly
Echocardiography	Yes	Every 3–5 yr†	Every 3–5 yr†	Every 3–5 yr†
Renal ultrasonography	Yes	—	—	—
Thyroid-function test	Yes	Repeat only if indicated by findings	Yearly	Yearly
Hearing test	Yes (baseline)	Optional	Optional	Yearly
Ophthalmologic evaluation	Early referral to ophthalmologist if strabismus or ptosis present	—	—	—
Lipid screening	—	—	—	Optional
Liver-function test	—	—	—	Optional
Screening for diabetes	Only if indicated by clinical findings	Only if indicated by clinical findings	Only if indicated by clinical findings	Optional
Evaluation for ovarian failure‡	Yes	—	Yes	Yes
Evaluation of growth issues§	Yes	Yes	Yes	—
Evaluation for psychosocial issues¶	Yes	Yes	Yes	Yes
Weight-control measures	As needed	As needed	As needed	As needed

* Physical examination should include measurement of blood pressure, growth, weight, and vision and an evaluation for scoliosis.
† Recommendations are current (best-guess) estimates with few data to support the use of this approach in patients without cardiac disease. If structural cardiac malformations are present, recommendations need to be individualized.
‡ Measurement of gonadotropins may be helpful, as discussed in the text. Any discussion of gonadal dysgenesis, the need for hormone-replacement therapy, sexual function, and fertility should be age-appropriate.
§ The use of recombinant human growth hormone should be discussed.
¶ Schooling issues and the need for job and driver's training and other steps to independence should be discussed at appropriate ages.

of a cycling regimen with a progestational agent is mandatory to minimize the risk of endometrial hyperplasia and uterine adenocarcinoma.

The effects of hormone-replacement-therapy on liver function, on bone density, and on the risk of hypertension, cancer, and obesity in patients with Turner's syndrome are uncertain. Although there have been very few reports of frank liver disease in women with Turner's syndrome, elevated liver enzymes have been reported,[81] and the use of different forms of estrogen replacement may ameliorate or exacerbate this problem.[82] There are currently insufficient data to make specific recommendations. There has not been an increased occurrence of breast cancer among patients with Turner's syndrome.[83]

Spontaneous fertility is rare among patients with Turner's syndrome and is most likely in women with mosaicism for a normal 46,XX cell lineage, a 47,XXX cell lineage, or very distal Xp deletions.[19] These women have an increased risk of spontaneous pregnancy loss, twins, and aneuploidy in fetuses that are carried to term.[4,19,84] Efforts to cryopreserve ovarian tissue are fairly new, and the applicability of such techniques to preserve fertility in women with Turner's syndrome may be compromised by a high rate of aneuploid gametes.

Physicians should discuss infertility issues and reproductive options with their patients and reassure them about their sexual function. It is important to acknowledge the sense of loss associated with infertility, on the part of both the patient and her parents. Pregnancy, by means of gamete intrafallopian transfer with donor eggs, has been attempted in women with Turner's syndrome, with a success rate equal to that in other infertile women. However, there have been five case reports of aortic dissection in women with Turner's syndrome

Table 3. Ovarian Hormone Replacement.

Variable	Comment
Induction	Start one of the following at the age of 12 years if the child has previously been treated with recombinant human growth hormone; and at the age of 14 if she has not.
Estrogen	Conjugated estrogens (Premarin), 0.3 mg daily; ethinyl estradiol, 2–5 μg daily; or 17β-estradiol, 1 patch nightly.
	After 6 months, if the response is poor as measured by the Tanner breast stage, increase the dose. After 1 year, begin cyclical treatment on days 1–21, 1–25, or 1–28, adding progestin.
Progesterone	Medroxyprogesterone acetate, 10 mg on days 1–12, 15–21, 15–25, or 15–28, or norethindrone, 0.7–1.0 mg on days 1–12, 15–21, 15–25, or 15–28.
Maintenance therapy	Use any of above cycling regimens. The dose of conjugated estrogens can be increased to 1.25 mg, or that of ethinyl estradiol to 10 to 20 μg if needed. Continuous treatment can be used with daily estrogen, low-dose progestin, or low-dose oral contraceptives to increase patient compliance. Use of the transdermal patch for induction is relatively new; it can also be used for maintenance therapy in combination with progestin in an appropriate cycling regimen.
Menopause	There are no data regarding the benefits or risks of continuing or stopping hormone-replacement therapy in women with Turner's syndrome at the usual age of menopause. Decisions need to be made on an individual basis.

who have undergone gamete intrafallopian transfer. Two of these cases may represent duplicate reports; inadequate details were provided to be certain. In a collected series,[85] 101 of 146 women with Turner's syndrome in whom gamete intrafallopian transfer was attempted became pregnant; none had aortic dissection. One woman had an aortic dissection before the procedure. Among 93 reports of women with Turner's syndrome who have become pregnant spontaneously, there have been no occurrences of aortic dissection.[4]

The prevalence of insulin resistance and type 2 diabetes may be increased in patients with Turner's syndrome. Among 257 patients in several large series, 18 (7 percent) had diabetes requiring treatment.[4] Diabetes has developed in 11 of our 372 patients older than five years of age for whom we have information (type 1 in 3 and type 2 in 8).[4] The majority of patients with Turner's syndrome and diabetes have adult-onset diabetes, and most are overweight. There is conflicting evidence regarding the effect of hormone-replacement therapy on glucose homeostasis in patients with Turner's syndrome and none regarding the long-term effects of recombinant human growth hormone.

OPHTHALMOLOGIC AND OTOLOGIC CONCERNS

Clinically significant strabismus occurred in 18 percent of our patients with Turner's syndrome, and ptosis in 13 percent.[4] Cataracts and nystagmus also occur more commonly in patients with Turner's syndrome. Red–green colorblindness is found with the same frequency as in normal males.[4,86] There should be a low threshold for referral to ophthalmologists for these patients.

The majority of infants and children with Turner's syndrome have recurrent otitis media, which is probably due to a combination of small, dysfunctional eustachian tubes and palatal dysfunction. This can be a major problem in early childhood, causing substantial complications and many sleepless nights. The frequency of ear infections decreases with age and growth of facial structures. Palatal dysfunction in these patients may be exacerbated by the removal of adenoids. Such surgery should be undertaken only after a careful evaluation of the patient's speech and palatal configuration.

Progressive sensorineural hearing loss is a major feature of Turner's syndrome in adults. Ninety percent of 44 adults with Turner's syndrome had sensorineural hearing loss. The loss was clinically significant in two thirds, and 27 percent required hearing aids.[87] Five percent of children and 17 percent of adults in our clinic require hearing aids. The biologic basis is not known.

GASTROINTESTINAL MANIFESTATIONS

Feeding problems, gastroesophageal reflux, and failure to thrive occur in both breast-fed and bottle-fed infants with Turner's syndrome, possibly as a result of anatomical differences in the oropharynx as well as oral motor immaturity.[88] There have been rare reports of a variety of symptomatic vascular malformations of the gastrointestinal tract.

More common are instances of inflammatory bowel disease. In a series of 135 adults with Turner's syndrome, 2 had Crohn's disease, 2 had ulcerative colitis, and 2 had chronic diarrhea of unknown cause.[89] More than half of patients with Turner's syndrome and inflammatory bowel disease who have been described in the literature have had an i(Xq) cell lineage. There may be an increased incidence of celiac disease among patients with Turner's syndrome; preliminary screening studies have shown elevated levels of IgA–antiendomysium and IgA–antigliadin antibodies in 2 to 10 percent of patients who were screened but symptomatic disease in only a few.[3,90,91] The incidence of gallbladder disease may be higher than expected and is not associated with diabetes or obesity.[4]

RENAL MANIFESTATIONS

Structural renal malformations, including horseshoe kidney and duplication of the collecting system, are found in up to 40 percent of patients with Turner's syndrome.[4,92] Whereas most structural malformations do not cause renal dysfunction, silent hydronephrosis resulting from obstruction of a duplicated collecting system may occur (present in 10 percent of our patients). Screening renal ultrasonography is necessary for all patients with Turner's syndrome.

MUSCULOSKELETAL CHARACTERISTICS

Turner's syndrome is characterized by skeletal dysplasia, with short stature, mild epiphyseal dysplasia, and typical bony alterations. Dislocation of the patellae and chronic knee pain are common. Malformation of the ulnar head causes the typical increased carrying angle of the arm and may cause limited range of motion. Chondrodysplasia of the distal radial epiphysis (Madelung's deformity), typical of the Leri–Weill syndrome — the skeletal dysplasia associated with *SHOX* haploinsufficiency — is a rare complication. Congenital dislocation of the hip is common (occurring in 5 percent of patients), as is clinically significant scoliosis (occurring in 10 percent).[4]

It is unclear whether patients with Turner's syndrome have an increased risk of osteoporosis or fractures.[93-96] Their bones appear osteopenic on radiographic evaluation, and their regional bone mass is often, but not always, below that of age-matched, but not height-matched, controls.[95] No longitudinal studies have been done to establish whether the reduced bone mass is a nonprogressive feature of a general skeletal dysplasia or is analogous to the accelerated bone loss seen in postmenopausal women primarily as a result of estrogen deficiency. Both hormone-replacement therapy and recombinant human growth hormone treatment may improve regional bone mass.[95,97] However, one study found no differences among patients treated with growth hormone, estrogen replacement, or both and an age-matched group of untreated patients with Turner's syndrome.[97]

DERMATOLOGIC CONCERNS

It may take several years for the congenital puffiness of the hands and feet to resolve in patients with Turner's syndrome. In rare cases, pedal edema persists or recurs in late childhood, at the time of ovarian hormone-replacement treatment, or later. There is an increased number of typical melanocytic nevi that are not clinically or histologically unusual, with no recognized increase in the risk of malignant melanoma.[83]

The risk of keloid formation may be more apparent than real because the neck and upper chest, which are the typical areas for operative procedures in these patients, are more likely to have such scarring.[98] Premature fine wrinkling of facial skin, similar to that seen in smokers, occurs commonly in women with Turner's syndrome in their late 30s and early 40s. It is not associated with smoking or excessive sun exposure.

NEOPLASIA

A review of 597 women with Turner's syndrome in the Danish Cytogenetic Register found no increase in the relative risk of cancer, although there were more cases of colon cancer than expected.[83] In another review of 400 women, neither colon cancer nor nervous system cancer was increased.[99] No history of gonadoblastoma or dysgerminoma was reported in 29 patients with Turner's syndrome and a Y chromosome, but it was not known whether they had undergone prophylactic gonadectomy. One of these patients with a 45,X/46,XY karyotype had adenocarcinoma of a gonadal streak. Two of our 37 patients with Y-chromosome material have had gonadoblastoma. Until better data regarding risk are available, prophylactic gonadectomy is indicated if a Y chromosome is present. Endometrial carcinoma has occurred exclusively in patients who received unopposed estrogen treatment or prolonged treatment with diethylstilbestrol.[4]

LIFE EXPECTANCY

Patients with Turner's syndrome appear to have a decreased life expectancy, primarily as a result of complications of heart disease and diabetes.[100] In our series of 532 live-born patients, 30 have died, 13 from heart disease (mean age at death, 27.9±25.5 years; range, birth to 80.2 years).[4]

SUMMARY

Most children with Turner's syndrome are under the care of specialists. It has been proposed that adults should also be followed in multidisciplinary specialty clinics.[3] We believe, on the basis of our own experience, that most affected women can best be served by their primary care practitioners, with the use of informed judgment about the need for referral to specialists. Although these women have substantial health concerns, their care for the most part falls under the standard repertoire of primary care, and continued follow-up in specialty care centers may inhibit their integration into society and foster a sense of ill-being. Support groups for patients with Turner's syndrome and their families (listed in the Appendix) can be a source of valuable information.

We are indebted to the members of the Puget Sound Turner Syndrome Society for their faith in our work and their support; to the Welch's Fund for initial seed money; to Dr. Judith G. Hall, who was instrumental in establishing the clinic; to Dr. Christine Disteche for help with Figure 2; and to numerous colleagues for their contributions.

APPENDIX

There are several support groups for patients with Turner's syndrome and their families:

The Turner's Syndrome Society of the United States, 14450 TC Jester, Suite 260, Houston, TX 77014; telephone 800-365-9944 or 832-249-9988; fax 832-249-9987; e-mail tssus@turner-syndrome-us.org; or see www.turner-syndrome-us.org;

The Turner Syndrome Society of Canada, 21 Blackthorn Avenue, Toronto, ON M6N 3H4, Canada; telephone 800-465-6744 or 416-781-2086; fax 416-781-7245; or see www.TurnerSyndrome.ca;

The Turner Syndrome Society of Quebec (in French), telephone 888-9TURNER or 450-655-8771; or see www.turnerquebec.qe.ca; and

The Turner Syndrome Society of UK, 12 Irving Quadrant, Hardgate, Clydebank G81 6AZ, United Kingdom; telephone +44(0)1389-380385; fax +44(0)1389-380384; e-mail Turner.Syndrome@tss.org.uk; or see www.tss.org.uk/contact.html.

Free growth charts for patients with Turner's syndrome are available through the Turner Syndrome Society. Publications are also available at cost through the Turner Syndrome Society, including *Turner syndrome: A guide for families*, by P.A. Reiser and L.E. Underwood (1992), and *Turner syndrome: A guide for physicians*, by R.G. Rosenfeld (1992). The Turner Syndrome Society also has videotapes of their annual conferences available for a fee.

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