

Mini-Review

Healthcare for Adolescents with Turner Syndrome

Shahryar K. Kavoussi, MD, MPH, Gregory M. Christman, MD, and Yolanda R. Smith, MD, MS
Department of Obstetrics and Gynecology, University of Michigan Health System, Ann Arbor, Michigan, USA

Abstract. This review paper highlights important health-care issues for adolescents with Turner Syndrome. Turner Syndrome potentially affects multiple organ systems including: cardiovascular, renal, endocrine, neurologic, gastrointestinal, skin, skeletal, auditory, and reproductive systems. Congenital and acquired cardiac defects remain the most significant health problem faced by women with Turner Syndrome.

Key Words. Turner Syndrome—Gonadal dysgenesis—Ovarian failure—Chromosomal anomaly—Adolescent—Healthcare—Hormone therapy—Pregnancy—Fertility

Introduction

Turner syndrome (TS), also known as ovarian/gonadal dysgenesis, is the most common anomaly of the sex chromosomes. It affects approximately 3% of all female conceptuses and is found in approximately 15% of analyzed abortus material. Although most embryos with a 45X genetic makeup will abort and only 1 in 100 progresses to term, it has been estimated that TS affects 1 in 2500 newborn females, resulting in a worldwide prevalence of 1.5 million women with TS.^{1,2}

Genetically, TS is characterized most commonly by a monosomy 45X karyotype.³ The X-chromosome is of maternal origin in approximately two thirds of TS patients and of paternal origin in the remaining one third.^{4,5} The remainder of karyotypes may have an abnormal X chromosome or are mosaic, such as those that share a 46XX or 46 XY cell line. Mosaic

TS patients typically have a less pronounced phenotypic expression.⁶

Henry Turner first described this syndrome in 1938 among seven young women with sexual infantilism, congenital webbed necks, short stature, and cubitus valgus.⁷ TS has since been found to affect a wide spectrum of organ systems to varying degrees. Additional clinical features of TS may include cardiovascular, endocrine, renal, gastrointestinal, skin, bone, hearing, and neurologic defects. The multiple organ systems potentially affected in girls with TS may have dramatic implications on the overall health status of adolescents with this syndrome, and these health issues should be addressed in a comprehensive, systematic manner. In addition, the reproductive health implications of ovarian dysgenesis, including hormone therapy both for development of secondary sexual characteristics and for increasing bone mineral density, as well as issues surrounding fertility, are growing areas of interest. A summary of health maintenance issues for adolescents and young adults is presented in Table 1.

Cardiovascular System

Cardiovascular disease, particularly congenital heart disease and aortic dissection, is a main concern in patients with TS and accounts for the increased early mortality among this patient population.⁹ The most common congenital cardiovascular abnormality diagnosed in patients with TS is a bicuspid aortic valve. This may be found in isolation or in association with coarctation of the aorta.¹⁰

Careful clinical assessment and echocardiogram are mandatory in the evaluation of TS patients.¹¹ The National Cooperative Growth Study, a registry of 955 girls with TS, reported abnormal cardiac findings in 28% when physical examination and imaging evaluations were included.¹² Furthermore, a recent 3D magnetic resonance angiography study of the thoracic great vessels in 85 women with TS identified

Address correspondence to: Yolanda R. Smith, MD, MS, Department of Obstetrics and Gynecology, University of Michigan Health Systems, 1500 E. Medical Center Drive, Room L4224, Women's Hospital, Ann Arbor, Michigan 48109-0276; E-mail: ysmith@umich.edu

Table 1. Health Maintenance Issues in Women with Turner's Syndrome

	Adolescence	Young Adulthood
Heart	<ul style="list-style-type: none"> • Echocardiogram • If abnormal, Cardiology consult • If normal, repeat every 3–5 years 	<ul style="list-style-type: none"> • Echocardiogram • Repeat every 3–5 years
Blood Pressure	<ul style="list-style-type: none"> • Evaluate at each visit • Treat hypertension aggressively 	<ul style="list-style-type: none"> • Evaluate at each visit • Treat hypertension aggressively
Kidneys	<ul style="list-style-type: none"> • Renal ultrasound at diagnosis • Check urinalysis yearly only if renal/collecting system anomalies present • Treat urinary tract infections aggressively 	<ul style="list-style-type: none"> • Treat urinary tract infections aggressively • Check urinalysis yearly only if renal/collecting system anomalies present
Thyroid	<ul style="list-style-type: none"> • TSH yearly 	<ul style="list-style-type: none"> • TSH yearly
Glucose Tolerance	<ul style="list-style-type: none"> • Fasting glucose not recommended for routine screening 	<ul style="list-style-type: none"> • Fasting glucose every 1–2 years
Cholesterol	<ul style="list-style-type: none"> • Fasting lipid profile once during adolescence 	<ul style="list-style-type: none"> • Fasting lipid profile every 1–2 years
Cognition	<ul style="list-style-type: none"> • Early assessment of strengths and weaknesses • Educational interventions as needed • Vocational planning 	<ul style="list-style-type: none"> • Educational interventions as needed • Vocational planning
Gastrointestinal	<ul style="list-style-type: none"> • Check liver function enzymes yearly 	<ul style="list-style-type: none"> • Check liver function enzymes yearly
Skin	<ul style="list-style-type: none"> • Evaluate yearly • Sunscreen education • Minimize potential scars 	<ul style="list-style-type: none"> • Evaluate yearly • Sunscreen education • Minimize potential scars
Bone	<ul style="list-style-type: none"> • Estrogen therapy • Calcium 1200 mg / day Vitamin D • Weight-bearing exercise • DEXA scan (baseline in late adolescence) • Screen for scoliosis • **Avoid bisphosphonates (long half-life) as pregnancy is possible with donor oocyte IVF 	<ul style="list-style-type: none"> • Continue estrogen, calcium, and vitamin D intake • Continue weight-bearing exercise • Periodic DEXA scans depending on treatment and baseline DEXA • **Avoid bisphosphonates
Hearing	<ul style="list-style-type: none"> • Treat otitis media aggressively • Periodic hearing examinations 	<ul style="list-style-type: none"> • Periodic hearing examinations
Growth Hormone Therapy	<ul style="list-style-type: none"> • Start between the ages of 2–5 years • Discontinue when approaching targeted final height (bone age = 15 years) 	<ul style="list-style-type: none"> • Not indicated
Estrogen Therapy	<ul style="list-style-type: none"> • Start one year before anticipated completion of GH therapy • Start with low dose CEE 0.3 mg q.o.d. or estradiol 0.5 mg q.o.d. • Evaluate periodically (i.e. every 3 months) • Incrementally increase frequency and dose • Once breasts developed, maintenance dose of either conjugated equine estrogens 0.9–1.25 mg daily or estradiol 2 mg daily with cyclic progestin or low dose oral/patch contraceptive 	<ul style="list-style-type: none"> • Continue maintenance dose hormone therapy
Reproductive health	<ul style="list-style-type: none"> • Sexual education • Pap smear per ACOG guidelines⁸ • STD screening • Discuss fertility issues • For those with ovarian function, discuss contraception 	<ul style="list-style-type: none"> • Sexual education • Pap smear per ACOG guidelines • STD screening • Discuss fertility issues • For those with ovarian function, discuss contraception and risk of early ovarian failure

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unsuspected structural anomalies, with deviations of the aortic arch in 49% of subjects and coarctation of the aorta in 7%.¹³

In addition, women with TS may develop various cardiac problems. The risk of aortic root dilatation is reported at 8% to 28%,¹⁴ and may develop even in women with no known underlying cardiac pathology. This is the major reason for the need to continue cardiac monitoring even with prior normal evaluations. In addition, subsequent calcification of the

aortic valve may lead to stenosis or regurgitation. Ischemic cardiac disease and hypertension are other conditions that may develop over time.¹⁰

When a patient is diagnosed with TS, the ideal cardiac evaluation consists of an echocardiogram and cardiology consultation. If no cardiovascular abnormality is found initially, then repeat evaluations are recommended every three to five years. Annual cardiac evaluations, including blood pressure measurement, are recommended.¹⁵ The risk of hypertension

is three-fold in TS patients when compared to the general population.¹⁶ Adequate blood pressure control is imperative for preventing aortic root dilation.

In a comparison of echocardiography and magnetic resonance imaging (MRI) to detect cardiovascular anomalies, the two imaging modalities were found to be complementary in terms of information provided, leading to the conclusion that obtaining both imaging studies is ideal. MRI may be of most value for patients with a bicuspid aortic valve, those desiring oocyte donation to carry a pregnancy, and for situations in which echocardiography is ambiguous. If MRI is not available, then echocardiography should be universal.¹⁷

Patients with left-sided cardiac anomalies are at an increased risk for endocarditis. Therefore, prophylactic antibiotics are strongly recommended for TS patients who are to undergo procedures putting them at risk for blood borne bacterial contamination.^{18,19}

Patients who desire fertility via assisted reproductive technology using donor oocytes and embryo transfer are at an increased risk of cardiovascular complications such as aortic dissection and exacerbation of hypertension.²⁰ In a large survey of TS patients undergoing donor oocyte treatment, a 2% or higher risk of maternal mortality was estimated. The study also showed that only half of the patients had been screened adequately for cardiovascular abnormalities prior to treatment.²¹

Renal System

Women with TS have a nine-fold higher risk of congenital renal anomalies than the general population,¹⁶ and the vast majority of these defects may be detected by renal ultrasound. The National Cooperative Growth Study reported abnormal renal findings in 20% of girls with TS.¹² Examples of such anomalies include horseshoe kidneys and collecting duct abnormalities. Routine screening for renal abnormalities by ultrasound is recommended. In a study of Turkish patients with TS, ultrasonographic evaluation showed that structural malformations of the kidney were more commonly found among patients with a 45X karyotype, while collecting duct anomalies were more common among mosaic/structural forms of TS.²²

Potential risks of renal system abnormalities include pyelonephritis and obstruction, thus aggressive treatment of urinary tract infections is recommended. In addition, vascular disease of the renal system increases the likelihood of hypertension.¹⁰

If a TS patient has a single kidney, precautions should be taken to minimize the risk of injury to the solitary organ, including the avoidance of behaviors associated with the potential for significant physical contact. It may be advisable to obtain a screening

urinalysis at routine visits, even if there is a relatively low suspicion for urinary tract infection.

Associated Endocrinopathies

Several endocrinopathies have been found to be more common among patients with TS than in the general population. TS patients have a higher prevalence of autoimmune thyroid disease in general, and hypothyroidism in particular.²³ Serum anti-thyroglobulin and anti-microsomal antibodies are more common in TS patients.²⁴ Type II diabetes mellitus,¹⁶ insulin resistance,⁴ and impaired glucose tolerance²⁵ are also more frequent findings in TS patients. Dyslipidemias²⁶ have been associated with TS, and may be corrected while a patient is on growth hormone therapy.^{27,28} However, estrogen therapy has not been shown to have a beneficial lipid effect in women with TS.²⁹

Health maintenance care for adolescents with TS includes a yearly TSH. Glucose testing is only recommended for adolescents with risk factors such as obesity or family history of diabetes, but a fasting lipid profile should be measured at least once during adolescence.^{18,30} In addition, clinic visits provide the opportunity to monitor vital signs, with particular attention to blood pressure, as well as monitoring and charting of height and weight.

Neurologic and Psychologic Manifestations

Turner's syndrome has effects on brain development and function; however, these are not as well characterized as phenotypic features of the syndrome. Although girls with TS are fully competent in terms of verbal abilities and intelligence, they may reveal a very subtle to easily recognizable impairment with non-verbal cognitive abilities using specialized testing.³¹⁻³³ The literature primarily reports concerns in visual-spatial functions.^{31,34-39} Other reported neurocognitive deficits include potential difficulty with number processing and simple arithmetic, social cognition, working memory, attention, motor function, and executive function.^{36,37,40-44} In addition, social adjustment problems have been reported in the areas of delayed maturity, relationships, and self-esteem.^{31,45,46}

Neuroimaging studies have attempted to localize areas within the brain responsible for the neurocognitive profile of girls with TS. Morphologic studies demonstrate a reduction in parietal and occipital volume, areas related to visual-spatial functioning.^{43,47-51} This is consistent with results of positron emission tomography studies reporting decreased baseline glucose metabolism, indicative of lowered metabolism, in these specific brain areas.^{52,53} In addition, a recent study

demonstrated alterations in the amygdala (involved in emotional processing) and hippocampal (involved in memory) volumes.⁵⁴ Furthermore, functional MRI studies have demonstrated altered brain activation patterns in women with TS during tests of executive function, working memory, and visuospatial function.^{55–57} Recently, Molko et al identified microstructural changes in fiber tract orientation, which may alter connections between different brain regions and may account for the identified specific cognitive deficits.⁵⁸

These deficits can have a recognizable effect on the activities of daily living for adolescents with TS. For example, due to difficulties with visual-spatial relations, driving an automobile may be more challenging. In addition, compared to those without TS, TS patients have fewer social interactions.³¹ Trouble with face recognition may be a factor in the reduced social interaction. Some specific recommendations to maximize neurocognitive functioning include: early assessment of cognitive strengths and weaknesses, use of tutoring, specific instructions in organization, study and time management skills, computer learning, providing information in a verbal format, small structured classrooms for attentional issues, occupational training for motor skills issues, and vocational/educational planning.^{31,59}

Gastrointestinal System

Patients with TS are more likely to develop gastrointestinal disorders such as Crohn's disease, ulcerative colitis,⁶⁰ and liver dysfunction.⁶¹ Although it is controversial, some studies have suggested that estrogen therapy may actually improve liver function enzyme abnormalities.⁶² Intestinal telangiectasia is found more frequently among women with TS, and progesterone administration may have a beneficial effect.⁶² Liver function enzymes were followed every 6 months by Larizza et al, and elevated enzymes were generally found not to be progressive when checked at that frequency.⁶³

Skin

Lymphedema is a commonly recognized skin manifestation among TS patients. However, these young women also have an increased incidence of benign nevi. Even though benign nevi are more common among TS patients, there is not an associated increased risk of cutaneous melanoma.⁶⁴ The formation of keloids has been thought to be more common, making it important to limit excision of benign nevi. The possible increased risk of keloids should be considered in any discussions concerning elective surgery or body piercing. In addition, there may be an increase in vitiligo and alopecia areata.⁶⁵

Skeletal

Girls with TS have an increased risk of scoliosis, with approximately 10% of patients affected. This most commonly presents in adolescence and screening for this skeletal disorder should be included in the physical examination.^{18,66} Women with TS are at an increased risk for developing osteopenia and osteoporosis. Appropriate estrogen treatment, calcium, vitamin D, avoidance of smoking, and weight-bearing exercise are recommended.⁶⁷ Animal studies have suggested that bisphosphonates cross the placenta, and very little is known about the effects of these pharmacologic agents on the human fetus.⁶⁸ Therefore, since women with TS have the potential for pregnancy with assisted reproductive technologies, it is prudent to avoid bisphosphonates because of the long biological half-life, incorporation into bone, and the potential for incorporation into fetal bone as the maternal skeleton is mobilized as a source of calcium in pregnancy.

Auditory

Girls with TS have a predisposition to otitis media, and chronic or recurrent infections may result in future conductive hearing loss. In addition, sensorineural hearing loss is extremely common in women with TS, affecting up to 90% of individuals. This is a progressive hearing loss and may begin in childhood. The school work and social interactions of adolescents may potentially be affected by hearing loss.^{69,70} Therefore, healthcare providers should aggressively treat otitis media, and should institute early hearing assessments.

Hormone Therapy for Puberty and Further Development

Because TS patients have ovarian dysgenesis and short stature, hormonal treatment has attracted much attention over the years. Growth hormone and sex steroids, in particular, have been studied and have been applied to various facets of puberty and development. The effectiveness of hormonal treatment is evaluated by monitoring sexual development, linear growth, and bone age over time.

Growth Hormone Therapy

Short stature is a hallmark of Turner's syndrome with an associated mean loss of 20 cm associated with X chromosome aneuploidy.⁷¹ Growth hormone (GH) has been shown to have a positive effect on linear growth during childhood and puberty. In addition, there has been an increase in final height attained.⁷² These findings were also shown in large multicenter

studies demonstrating the beneficial effects of growth hormone administration in TS patients.^{73,74} Without intervention, the mean adult height of TS patients is 4 feet 8 inches.⁷⁵ With GH therapy, women with Turner's syndrome will achieve on average a 2.8-in increase in final adult height with a 95% confidence interval of 2.3–3.3 inches.⁷⁶ Despite compelling evidence that GH therapy achieves increased height in patients with TS, the impact of this increase in height on quality of life has not yet been addressed.

To assist with growth, recommendations have been made to begin growth hormone therapy if a TS patient's height is found to be below the fifth percentile of the growth curve for females. The need to initiate growth hormone therapy usually occurs between the ages of 2 to 5. The regimen is to be continued until bone age is greater than 15 years and growth slows to less than 2 cm a year.⁷⁷ The alteration in final adult height seen in women with Turner's syndrome is appreciably lower than the benefit seen in women with GH deficiency or constitutional delay. This appears to be related to a relative tissue resistance to the growth promoting effects of IGF-I.⁷⁸

Various studies have had different conclusions regarding the matter of growth hormone therapy for improving bone mineral density (BMD). Although short stature may be a confounding factor that can potentially falsely indicate decreased BMD, osteopenia and osteoporosis are concerns in patients with TS due to the hypogonadal environment resulting from ovarian dysgenesis.

Efforts are underway to clarify the long-term effects of growth hormone administration on BMD. Some studies have shown an improvement in BMD with exogenous growth hormone.^{79,80} Others have reported a decrease in BMD,^{81,82} and others have shown no difference.^{83,84,85} After finding a decreased BMD with treatment, Bakalov et al reevaluated the effect of growth hormone on cortical BMD with more subjects and evaluated additional skeletal sites.⁸³ This reevaluation showed no difference with treatment.

Estrogen Therapy

Although some patients with TS spontaneously initiate full development of secondary sexual characteristics, development typically will cease early and many have no development at all. Exogenous estrogen therapy has been employed in order to promote the development of secondary sex characteristics. Estrogen therapy may have positive effects on breast development, uterine growth, BMD, and in combination with cyclic progestins, can facilitate cyclic menstruation.

The age at which to commence exogenous estrogen therapy is somewhat controversial. Some sources recommend starting estrogen therapy between the ages of 12 to 15 years, and others recommend later

hormone initiation in order to minimize the possibility of premature closure of the epiphyseal plates.^{77,86} If a TS patient is receiving GH therapy, estrogen treatment should not be started if the bone age is less than 11 or 12 years. When the patient is near final height, estrogen may be started, and this corresponds to approximately one year before cessation of GH therapy.^{86–88} Hogler et al showed that the absence of puberty can lead to a prepubertal decrease in BMD as well as osteopenia, and they suggested that prepubertal estrogen administration may have a role in treating patients, with the consideration that a potential reduction in final height may be the risk involved in such early therapy.⁸⁹

In order to maximally promote the development of secondary sexual characteristics, low doses of daily estradiol may initially be administered for 6–12 months. Thereafter, incremental increases in dose are recommended. Normal breast development occurs most readily with a hormone regimen that mimics the typical pubertal transition.

There are various protocols for estrogen therapy; in general, a starting dose of conjugated equine estrogens 0.3 mg or estradiol 0.5 mg is recommended. Revisits at 3-month intervals provide the opportunity to monitor breast and body shape development and to adjust the dosage, if necessary. After breast and uterine development, maintenance doses of conjugated equine estrogens 0.9–1.25 mg or estradiol 2 mg a day may be prescribed and cyclic progestin may be added to facilitate menses.^{77,86} Likewise, a low dose oral contraceptive pill or patch may be utilized for hormone therapy. In addition, percutaneous estrogen gel has been shown to be efficacious in inducing puberty in TS patients. Once adequate breast and uterine development are initiated, a maintenance dose of estrogen is given, and cyclic or continuous progestins are recommended thereafter to prevent endometrial hyperplasia or breakthrough bleeding.⁹⁰

Current estradiol protocols have facilitated pubertal induction and maintenance; however, it has been difficult to develop a fully mature uterus in many TS girls.⁹¹ In a study of 57 women treated with estrogen from puberty induction, uterine length and shape seen on pelvic ultrasound in relation to estrogen treatment was analyzed. With treatment, 37% had an adequate uterine length and 50% had a normal uterine shape as calculated by a fundal-cervical ratio. It was concluded that a higher daily postmenarchal dose of estrogen was associated with a more mature uterus.⁹²

Fertility among Turner's Syndrome Patients

While to adolescents the development of secondary sexual characteristics is of primary importance, concerns and interests regarding fertility potential should

be addressed as well. Furthermore, although the majority of adolescents will not be at risk for an unplanned pregnancy, it is important that these young women receive education concerning prevention of other risks associated with sexual activity, including sexually transmitted diseases.

The majority of TS patients undergo ovarian failure prior to or around the time of puberty. They have “streak gonads” as a result of accelerated atresia of ovarian follicles, and as a result, are infertile.^{93,94} For the vast majority of TS patients, the recommended fertility option is in vitro fertilization with donor oocytes. If the patient plans to carry the pregnancy, a thorough evaluation of various organ systems should be done to assess the risk of potential pregnancy-related complications.

During pregnancy, there is at least a 2% risk of aortic dissection, and the risk of death increases 100-fold. Although aortic dilation is a risk, dissection may occur in those without aortic root dilation on imaging studies. Therefore, TS is a relative contraindication to pregnancy.¹⁵

Spontaneous pregnancy among women with TS is reported in at least 2% of cases,⁹⁵ particularly in those with a mosaic chromosomal makeup, such as 45X/46XX, or in those in whom ovarian function-preserving genes (Xq13-q26) are intact.⁹⁶ An observational study of pregnancies among six TS patients that conceived showed that six pregnancies resulted in abortion and eight resulted in live-born infants. Half of the live-born infants in this study manifested malformations. A literature review, performed by the same group, of 160 pregnancies among 74 TS patients revealed a 29% spontaneous abortion rate, a 7% perinatal death rate, a 20% malformation rate, and 38% of these infants were born healthy.⁹⁶ Therefore, these are high risk pregnancies that warrant close fetal surveillance.

In a study of fertility and outcomes of pregnancy among 410 Danish TS patients, 7.6% of these patients achieved a spontaneous pregnancy. Among this study population, spontaneous pregnancies and subsequent live births were achieved only by those with 45X/46XX mosaicism or those with 46XX and a structural abnormality of the second X chromosome.⁹⁷

Surveillance during pregnancy includes treatment of hypertension and serial echocardiograms and cardiology consultation. Clinically stable patients with an aortic root diameter less than 4 cm may attempt spontaneous vaginal delivery under epidural anesthesia. However, if the patient has dilation of the aortic root, a cesarean section should be planned under epidural prior to the initiation of labor.¹⁵ There is, nonetheless, a high rate of cesarean section among TS patients, mainly attributable to a disproportionately high rate of cephalopelvic disproportion.²⁰

If a TS patient is a potential candidate for a planned pregnancy from donor oocyte in vitro fertilization, assessment of the cardiovascular and renal systems, thyroid function, and glucose tolerance should be performed.²⁰ Screening for cardiovascular anomalies is strongly recommended. If a significant malformation is found, this is an absolute contraindication to pregnancy. Even with a normal cardiovascular evaluation, TS patients should be counseled regarding the high risk nature of pregnancy and the rare possibility of a catastrophic cardiac event leading to mortality.

The first report of a successful pregnancy and delivery in a patient with Turner's syndrome was reported in 1988.⁹⁸ Endometrial preparation for TS patients undergoing donor oocyte in vitro fertilization (IVF) often require higher doses of estrogen due to studies that suggest a suboptimal response with conventional protocols.⁹⁹ The per cycle pregnancy rate for TS patients receiving oocyte donation is approximately 30%, which is similar to that of other patient populations that undergo the same fertility treatment. The miscarriage rate among TS patients, however, is higher, in the range of 40–50%. This higher degree of pregnancy loss may be due to hypoplastic uteri and possibly the aforementioned decreased endometrial receptivity to estrogen protocols.²⁰

Foudila et al reported the experience of a donor oocyte program in which 20 clinical pregnancies were achieved in 18 TS patients. Thirteen of these pregnancies were the result of 28 fresh cycles, and the remaining seven were the product of 25 frozen embryo transfers. The fresh embryo transfer clinical pregnancy and implantation rates were 46% and 30%, respectively. The frozen embryo transfer rates were 28% and 19%. Forty percent of these pregnancies resulted in miscarriage. Due to the higher risk of hypertension exacerbation and the potential severity of complications such as aortic dissection, single embryo transfer is strongly recommended.¹⁰⁰

Future Directions for Fertility

Due to the rapid development of novel technologies and discoveries, there may someday be the potential for TS patients to become pregnant with their own oocytes. A future possibility includes oocyte or ovarian tissue cryopreservation. Hreinsson et al detected the presence of primordial follicles in the ovarian tissue of adolescent girls with TS. They found that younger age, lower FSH, and a mosaic chromosomal makeup were all correlated with a higher follicle density.¹⁰¹ If the oocytes retrieved from such patients have a normal chromosomal complement, then cryopreservation may hold great promise as a means to preserve fertility.^{88,101}

In addition, the recent finding that oocytes may be generated from germinal stem cells located in bone marrow will undoubtedly lead to further investigation.¹⁰² If stem cells in the hematopoietic system do indeed have the ability to replenish oocytes, then this concept may be explored in many subpopulations of patients at risk of premature ovarian failure, including those with TS.

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