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Reproductive Issues in Women with Turner Syndrome

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Synopsis

Turner syndrome is one of the most common chromosomal abnormalities affecting female infants. The severity of clinical manifestations generally varies and affects multiple organ systems. Women with Turner syndrome have a threefold increase in mortality, which becomes even more pronounced in pregnancy. There are several reproductive options available for women with Turner syndrome, including adoption or surrogacy, assisted reproductive techniques, and in rare cases spontaneous pregnancy. There are well-documented risks for women with Turner syndrome during pregnancy, including specific risks of aortic pathology, hepatic disease, thyroid disease, type 2 diabetes, and Cesarean section delivery. Several professional societies have published guidelines to aid in the care of women with Turner syndrome prior to and during pregnancy. It is important for providers who care for these women to be familiar with the specific risks and recommendations in caring for women with Turner syndrome of reproductive age.

Keywords

Turner syndrome; Fertility; Reproduction; Pregnancy risks; Society recommendations; Pre-pregnancy counseling

Introduction

Turner syndrome, defined as typical features in a phenotypic female with partial or complete loss of the second sex chromosome, is one of the most common chromosomal abnormalities, with an annual incidence of 1:2500 live born female infants (1), (2). Approximately 50% of affected women are missing an entire X chromosome and have a karyotype of 45,X. About 25% have a partial deletion of one X chromosome, while about 20% have varying degrees of mosaicism, most commonly a 45,X/46,XX karyotype (3). A small group of affected women carries an XY cell line.

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The authors have nothing to disclose.

In general, the phenotypic severity of Turner syndrome varies with the extent of X chromosome loss. Clinical manifestations of Turner syndrome (**FIGURE 1**) may be categorized as abnormalities affecting multiple organ systems, including the skeletal, cardiovascular and lymphatic, endocrine, gastrointestinal, renal, and the central nervous system (**TABLE 1**). Major morbidities may occur during adult life, and these result in a threefold increase in mortality (4). Particularly relevant to the discussion of reproductive function is the increased prevalence of aortic root dilatation and aortic dissection, which occur in 32% and 1-2% of affected women, respectively (5), (6). Dissection occurs at an average age of 31.5 years, making it particularly relevant to women in their reproductive years (7).

Ovarian Development in Females with Turner Syndrome

In the normal developing human, the number of non-growing ovarian follicles increases through the first half of gestation, reaching an average maximum of 300,000 per ovary at 18-22 weeks of gestation (8). Oogonia enter meiosis, which is arrested at prophase I, forming oocytes. Oocytes are incorporated into primordial follicles starting at 14-20 weeks of gestation. Throughout the second half of gestation, the number of non-growing follicles remains fairly constant, and by birth the number of follicles averages 295,000 per ovary. This number then decreases over pre-pubertal life, reaching about 180,000 per ovary by the age at menarche, and then declines further in an accelerating fashion until menopause (**FIGURE 2**).

During the first trimester, ovarian development in fetuses with Turner syndrome is initially normal. Examination of ovaries at 14 to 18 weeks gestation has revealed normal gonadal development (9). Shortly thereafter, however, oocyte loss is accelerated in many girls with Turner syndrome, with oocyte depletion being nearly complete prenatally or by the first few months after birth. In fetuses with 46,XX karyotypes, oogonia were seen as early as 18 weeks, ovaries from 20 weeks onward were found to have primordial follicles, and preantral and antral follicles were seen at 26 weeks. In contrast, some ovaries from fetuses with 45,X karyotypes had oogonia, but no follicles were visualized (10). There is evidence that some girls with Turner syndrome continue to have oocytes and functional follicles after birth. In a study to assess for the presence of ovarian follicles in adolescents with Turner syndrome, ¼ to 1 ovary was removed laparoscopically from nine adolescent girls with Turner syndrome and histologically analyzed. Eight of the nine ovaries had follicles, with higher numbers of follicles in younger adolescents and girls with mosaicism. Follicular density inversely correlated with FSH level (11).

Pubertal maturation in Turner syndrome

Gonadotropins and ovarian hormone production

In 46,XX fetal development, the hypothalamic-pituitary-gonadal axis becomes active in late gestation. At birth, there is a surge of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (9). In newborns with Turner syndrome, an exaggerated FSH surge has been documented, suggesting the onset of ovarian failure. Elevated FSH levels during infancy decline between the ages of 4-11 years as they do in normal girls, although average FSH

concentrations in children with Turner syndrome are generally higher than normal (9). After the age of 11 years, FSH concentrations in girls with Turner syndrome again rise sharply to levels much higher than those typically seen in normal puberty (12). Using an ultrasensitive assay, pre-pubertal girls with Turner syndrome were found to have lower estradiol levels when compared with age-matched girls without Turner syndrome.

Chromosomal analysis was performed on a group of 40 patients diagnosed with Turner syndrome with variable degrees of mosaicism. Six of these patients had spontaneous menarche, with the remainder having primary amenorrhea. Cytogenetic analyses showed that in those with mosaicism, the presence of at least 10% euploid cells is predictive of spontaneous pubertal development (13).

Ovarian and uterine growth

Uterine development is altered in girls with Turner syndrome. A cohort of 38 patients with Turner syndrome was followed longitudinally, and serial pelvic ultrasounds were performed to document ovarian and uterine size before and during the expected time of puberty. Twenty-seven to forty-six percent of patients had ultrasonographically detectable ovaries; in these patients, the authors documented an initial increase in ovarian size at a skeletal age of approximately nine years, and this increase became more pronounced after 14 years of age, suggesting continued estrogen production in these patients. Seventy-six percent of the patients with mosaic Turner syndrome had two detectable ovaries and larger ovarian volumes, compared to girls with 45,X karyotypes, of whom only 26% had ovaries detected by ultrasonography. Girls with mosaicism more frequently had spontaneous thelarche (50%) and menarche (38.5%) than those with 45,X karyotypes. Uterine size was only assessed in patients who were not prescribed estrogen therapy, and increased in all patients with Turner syndrome; however, girls with mosaicism had larger increases in uterine size than girls with 45,X karyotypes. Even though all Turner syndrome patients had increased uterine size, these measurements were still significantly lower than those from the control group (14).

Menstrual function

Menarche is infrequent in girls with Turner syndrome. However, one recent report noted that as many as 40-50% of girls with Turner syndrome may have some observed pubertal development. Rates are higher in girls with mosaic karyotypes, but up to 25% of girls with 45,X karyotypes have some signs of spontaneous puberty. Up to 10% of girls with Turner syndrome achieve menarche (15). In another study, 522 subjects with Turner syndrome were observed for spontaneous puberty, and spontaneous menarche occurred in 84 (16.1%) subjects (16). During follow up, 30 patients were found to have regular menses nine years after the onset of menarche, 12 patients developed secondary amenorrhea 1-3 years after the onset of menarche, and 19 patients developed oligomenorrhea. Of the remaining patients, long-term data were not available in ten, and 13 were lost to follow up. Spontaneous menarche was more common in patients with mosaicism than in those with 45,X karyotypes, leading the investigators to conclude that the additional X chromosome likely has a significant influence on the progression of puberty. Additionally, a serum FSH level less than 10 mIU/mL at age 12 years is predictive of the onset of spontaneous menarche and regular cycles (17).

As the majority of patients with Turner syndrome (>80%) do not undergo spontaneous puberty or menarche, estrogen therapy is typically required to initiate pubertal development (16). The age at which estrogen is initiated varies but is generally around age 12 years. Estrogen is initiated in very low doses, generally 1/10 to 1/8 the adult dose, and slowly increased to full replacement doses over a period of two years to promote normal breast and uterine growth. After two years of treatment or once breakthrough bleeding occurs, a progestin is typically added to allow for regular menstrual cycles. With the assistance of hormone therapy, girls with Turner syndrome may have regular monthly menses throughout life until hormone therapy is discontinued at the typical time of menopause (2).

Pregnancy in Turner syndrome

Spontaneous pregnancy can be seen in a small percentage of individuals with Turner syndrome and generally is more likely in women with mosaicism and those who report spontaneous puberty and regular menses (18,19). There are, however, reports of individuals with 45,X karyotypes spontaneously conceiving and delivering healthy infants, indicating that although women with mosaicism are more likely to conceive spontaneously, women with monosomy may also be fertile. Over 90% of women with Turner syndrome who have spontaneous pregnancies have a mosaic karyotype (18-21). In a study of 482 women with Turner syndrome, 57 women (12%) reported a total number of 124 pregnancies, occurring either spontaneously or through IVF. Twenty-seven women (47%) became pregnant using their own oocytes – of these, 23 women (85%) conceived spontaneously, and four (15%) with the use of either in vitro fertilization or insemination. Thirty women (53%) became pregnant as a result of oocyte donation. Ninety-two percent of the women who achieved pregnancy via autologous oocyte transfer were found to have a mosaic karyotype (19).

Assisted reproductive technology

In rare incidences, individuals with Turner syndrome are able to conceive spontaneously and deliver. For the vast majority of women with Turner syndrome, however, infertility is inevitable. In the past, all women with Turner syndrome were advised to avoid pregnancy entirely due to risks of complications. However, recent studies have shown that in selected cases women with Turner syndrome are able to become pregnant successfully and deliver healthy infants. There are several options for women with Turner syndrome who desire to have children: adoption and surrogate gestational carriers have been the two most traditionally recommended options, although more recently additional alternatives have been developed that allow women with Turner syndrome to carry and deliver children themselves.

The most commonly sought fertility option is in vitro fertilization (IVF) with donor oocytes (22). In this option, a donor oocyte is obtained and fertilized, with the resulting embryo being transferred into the uterus of the individual with Turner syndrome – donor IVF. Oocyte donation programs cite pregnancy success rates of 24-47%, which are consistent with pregnancy rates in women undergoing IVF who do not have Turner syndrome (23). Khastgir et al. cite an implantation rate of 17.1% per embryo transferred at a facility in London (24). Miscarriages are most often due to the presence of a hypoplastic or bicornuate uterus and a thinner endometrial lining than that typically seen in pregnant women without

Turner syndrome (24). Due to the comparatively small uterine size of women with Turner syndrome, even after hormonal preparation to ensure adequate uterine growth, is it recommended that only one embryo be transferred per IVF cycle to prevent undue complications, many of which will be discussed later in this review. Hormone replacement therapy is continued during the IVF process for up to 12 weeks, until the placenta is able to produce sufficient amounts of estrogens and progestins to maintain the pregnancy (25).

More recently, there have been reports of women with Turner syndrome who have functional ovaries undergoing IVF using their own oocytes – autologous IVF. In this option if a woman with Turner syndrome is thought to be a good candidate, she undergoes FSH-stimulation to promote follicle growth. Her own individual follicles are then removed and cryopreserved, later undergoing in vitro fertilization and implantation. Predictors for successful autologous IVF include a mosaic peripheral blood karyotype, normal serum FSH and AMH levels, and spontaneous puberty. Negative predictors for successful autologous IVF are monosomy or a structurally anomalous X chromosome, elevated FSH levels, low AMH levels, and lack of spontaneous puberty (22), (15), (26).

Timing for oocyte retrieval is controversial. Although some girls do have spontaneous puberty, the vast majority does not, and those who start puberty spontaneously often do not complete puberty or have premature ovarian failure in the teenage years. It may be better to obtain oocytes for cryopreservation before ovarian failure begins. Additionally, there have been several case reports of adolescents and adults with Turner syndrome undergoing ovarian stimulation followed by both oocyte and ovarian tissue cryopreservation for later IVF (27), (28), (29). However, there is currently no evidence regarding the safety of ovarian stimulation regimens in pre-pubertal females, and it is unknown what effect these treatments may have on overall pubertal development or adult height. An alternative is laparoscopic ovarian wedge resection with subsequent cryopreservation. This approach has succeeded in a 16 year old girl with mosaic Turner syndrome (30).

Pregnancy outcomes

Pregnancy outcomes in women with Turner syndrome have been studied closely. In 2011 Bryman et al. reported an overall delivery rate of live babies in 54%, with a rate of 44% in pregnancies that resulted from autologous oocytes, either spontaneous pregnancies or with IVF assistance, and a rate of 74% in pregnancies resulting from oocyte donation (19). In the 68 live births, only 5 infants (7.4%) were found to have complications or birth defects, including cerebral palsy, neuropsychological disorder, coarctation of the aorta, cleft lip and palate, and congenital tumor. The infants were non-dysmorphic and without chromosomal anomalies. Tarani et al. cited a 20% rate of birth defects in children born to women with Turner syndrome, and a higher incidence of chromosomal abnormalities, including trisomy 21 (31). In a Belgian study, 24 women with Turner syndrome were followed from conception to delivery. Pregnancies were monitored for complications in both mothers and infants, and the authors documented a miscarriage rate of 23%. However, when considering loss of biochemical pregnancies as well, the rate of early pregnancy losses approached 44% (32). A recent study of 103 women with Turner syndrome who underwent oocyte donation with IVF reported reassuring neonatal outcomes with life-birth per embryo transfer rates

ranging from 30.5-33.3%, preterm birth rate of 8%, low birth weight in 8.8%, and major birth defects in 3.8%, with overall perinatal mortality of 2.3%. These numbers are reassuring due to their similarity to neonatal complication rates in normal pregnancies (6).

Risks and complications of pregnancy

Cardiovascular disorders

Despite improved expectations for fertility in individuals with Turner syndrome, pregnancy-related mortality remains higher than in the general population, approximately 2% compared to 0.013% in normal women (33). One of the most significant risks is worsening of cardiovascular disease during pregnancy. Coarctation of the aorta and bicuspid aortic valve are the two most common cardiovascular manifestations in Turner syndrome, with prevalence rates of 11% and 16%, respectively (2). Other cardiovascular abnormalities include elongated transverse aortic arch, partial anomalous pulmonary connection, and persistent left superior vena cava (34). In addition, women with Turner syndrome also have dilated vasculature when compared to those with 46,XX karyotypes, particularly dilatation of the aortic root (2). Women with Turner syndrome are at increased risk for aortic dissection or rupture related to the increased cardiovascular stress that occurs during pregnancy. Another reason that single oocyte transfer is recommended for women undergoing IVF (see above) is that the stress on the cardiovascular system increases with multiple gestations. There is also some evidence that the changes to the aorta persist even after pregnancy and can be exacerbated by subsequent pregnancies (35). Due to these risks, it is imperative to perform careful pre-conception counseling and screening in all women with Turner syndrome who are considering pregnancy. Specific factors that increase the risk of aortic dissection or rupture during pregnancy include aortic size index (ASI) of >2.0 cm/m², history of surgery to repair cardiovascular defects, bicuspid aortic valve, current aortic dilatation, and systemic hypertension (2,36). Despite careful screening and intra-pregnancy monitoring, aortic dissection and rupture can still occur, and the risk for this is highest in the third trimester of pregnancy or postpartum (37). Women with any of these risk factors should be offered alternatives to pregnancy, including adoption and surrogacy.

Hypertension and its sequelae, including pre-eclampsia and eclampsia, are major risks for cardiovascular complications during pregnancy. Pregnancy-induced hypertension is defined as two elevated blood pressure readings $\geq 140/90$ mm Hg occurring after 20 weeks of gestation, measured at least 4 hours apart or on two separate occasions, and pre-eclampsia is defined as elevated blood pressure in combination with proteinuria. The incidence of any pregnancy-associated hypertensive disorder in women with Turner syndrome is variable and has been reported to range from 35% to 67% (6,38). Severe hypertensive syndromes such as pre-eclampsia, eclampsia, and HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) have been documented in 50% of women with Turner syndrome and hypertension during pregnancy. In a study of 21 women with Turner syndrome, Bodri et al. documented pregnancy-associated hypertensive disorders in 5 patients – two with pregnancy-induced hypertension, two with pre-eclampsia, and one with HELLP syndrome (38). One hypothesis for the increased incidence of pre-eclampsia is endothelial dysfunction resulting from a mismatch between pro-angiogenic factors, such as vascular endothelial

growth factor, and anti-angiogenic factors including soluble fms-like tyrosine kinase 1 (39). There is some thought that the higher incidence of intra-uterine growth restriction and pre-term births seen in the infants of women with Turner syndrome could be related to pregnancy-associated hypertension. Therefore, careful blood pressure screening both before and during pregnancy is indicated.

Hepatic disease

Non-pregnant women with Turner syndrome are more likely to have abnormal liver function tests, including elevated concentrations of transaminases and alkaline phosphatase, as well as an increased incidence of regenerative nodular hyperplasia and portal hypertension (2). In 1998, a review of the Danish Cytogenetic Central Register revealed a relative risk of 5.69 for cirrhosis in women with Turner syndrome compared to the general population (40). A more recent study of 218 women with Turner syndrome in Sweden noted elevated concentrations of liver enzymes in 36% of patients at baseline, with an additional 23% developing abnormalities at the five year follow up evaluation (41). Six percent of the original cohort of women normalized their transaminase levels at follow up. Six of the women with abnormal liver enzyme concentrations underwent liver biopsy, and pathology was consistent with cholangitis and hepatitis C in one subject each, with steatosis and normal biopsies in two patients each.

With an increased incidence at baseline, there is concern that pregnancy may contribute to worsening liver disease. A retrospective cohort study of 106 European women with Turner syndrome revealed that two women (1.9%) had elevated liver enzyme concentrations at baseline (6). During pregnancy, six women were found to have intrahepatic cholestasis, and one woman developed HELLP syndrome requiring early Cesarean-section delivery. Although it is clear that hepatic disease is more common in women with Turner syndrome than in the general population, further studies are required before the magnitude of risk during pregnancy can be determined.

Thyroid disease

Thyroid dysfunction is common in women with Turner syndrome, with a prevalence approaching 24%. However, the incidence of hypothyroidism appears to increase during pregnancy (2), with reported rates ranging from 7.7%-43.8%, (6,42). Comparatively, in normal women the incidence of thyroid dysfunction in pregnancy is around 1-2% (43). To prevent complications from uncontrolled or undiagnosed maternal hypothyroidism, all women with Turner syndrome should have annual thyroid function testing, including TSH, either total or free thyroxine, and anti-thyroid antibodies (6).

Diabetes and glucose metabolism

It is well known that women with Turner syndrome are at a higher risk of glucose intolerance and diabetes when compared to normal women (2). In one study of 26 adult women with Turner syndrome who underwent oral glucose tolerance testing, 38.4% had abnormal glucose tolerance, and 7.7% were diagnosed with type 2 diabetes (44). In a study of 57 pregnancies in Swedish women with Turner syndrome with previously normal glucose tolerance, 5% were found to have gestational diabetes (19). One hundred ten women with

Turner syndrome who became pregnant via oocyte donation were followed for nearly 20 years, and 9.4% of pregnancies were complicated by gestational diabetes (6). The increased incidence of diabetes in women with Turner syndrome is thought to be related to impaired first-phase insulin secretion caused by pancreatic beta cell dysfunction, and this effect appears to be amplified during sex hormone administration. Gravholt et al. reported 26 women with Turner syndrome who underwent oral glucose tolerance testing prior to and after receiving six months of sex hormone replacement therapy (40). A majority of the women had impaired first-phase insulin secretion at baseline as well as lower basal insulin levels; these effects were intensified after six months of sex hormone therapy. Because pregnancy is a condition in which sex hormone levels are significantly elevated, pregnant women with Turner syndrome are more likely to develop diabetes. Hence, these women should be screened diligently prior to and during pregnancy to ensure gestational diabetes is promptly diagnosed.

Cesarean section delivery

Due to their short stature and narrow pelvic diameter, women with Turner syndrome have a higher rate of Cesarean section (C-section) deliveries than normal women (2). Bryman et al. evaluated 124 pregnancies in 57 Swedish women with Turner syndrome and documented C-section rates of 63% in women who became pregnant using their own oocytes and 80% after oocyte donation, compared to a C-section rate of 16% in the general population (19). Hagman et al. evaluated 117 pregnancies in 106 women with Turner syndrome. They found that C-sections, either planned or emergent, were performed in 82% of all deliveries; 34.4% of these were emergent. The most common reasons for non-emergent C-sections were cephalo-pelvic disproportion and breech presentation. Induction of labor was attempted in 34% of the women. However, 72.2% of these attempts required unplanned C-section due to slow labor or failure to progress. Only 21% of women were able to deliver via spontaneous vaginal delivery. (6). Risks of C-section delivery include pelvic fetal head impaction, hemorrhage, uterine atony, damage to bladder or bowel, and complications from anesthesia (45). As women with Turner syndrome have a significantly higher rate of C-section delivery than those without Turner syndrome, the risks of C-section delivery should be discussed thoroughly during pre-pregnancy counseling.

Pre-pregnancy counseling

Due to the pregnancy risks specific to women with Turner syndrome, all women of reproductive age who have been diagnosed with Turner syndrome should be provided with comprehensive pre-pregnancy counseling. Although uncommon, women with Turner syndrome have been reported to spontaneously conceive. Therefore, all women should be provided with adequate information regarding the importance of contraception (18,20). The risks of increased overall mortality, cardiovascular disease (including aortic dissection, hypertension, pre-eclampsia and eclampsia), liver disease, hypothyroidism, diabetes, and the increased chance of Cesarean delivery should all be discussed as part of the pre-pregnancy visit. Due to the risks of pregnancy, all women with Turner syndrome should be informed of alternative methods to expand their families, including adoption or surrogacy. These options should be especially stressed in women who have relative contraindications for pregnancy (2).

Professional society recommendations

Several professional organizations and expert groups have developed consensus guidelines and position statements regarding pregnancy in women with Turner syndrome, with relatively similar recommendations, (36), (46), (2), (**TABLE 2**) and many other authors have put forward additional suggestions (22), (33), (47). All women carrying the diagnosis of Turner syndrome are at risk during pregnancy, and there is no distinction between those with 45,X karyotypes and those with partial X chromosome deletions or mosaic karyotypes. A careful, complete pre-pregnancy medical evaluation is mandated, including meticulous cardiovascular assessment with cardiac imaging using echocardiography and cardiac MRI. Consultation with specialists in cardiovascular disease, endocrinology, and high-risk obstetrics is required to ensure the best chance for a successful pregnancy and delivery of a healthy infant. Pregnancy is considered contraindicated in the presence of significant hypertension or structural cardiac disease, including bicuspid aortic valve, aortic coarctation, and aortic dilatation at baseline. Mothers require detailed pre-pregnancy counseling about the increased risk for aortic dilatation and aortic dissection and the increased risk for C-section. If assisted reproductive technology is required, a single embryo should be transferred to avoid the increased risks of multiple gestation. Throughout pregnancy, close follow up with subspecialty care is needed, including periodic echocardiography or MRI, and monitoring of thyroid dysfunction, glucose metabolism, hepatic function, and blood pressure. At delivery, if there is no evidence of aortic dilatation, vaginal delivery may be attempted. However, if the aortic size index or absolute aortic diameter is increased, the infant should be delivered by C-section, without allowing the mother to labor.

Conclusions

Turner syndrome is one of the most common chromosomal abnormalities, with clinical manifestations affecting multiple organ systems. As children with Turner syndrome transition into adulthood it is important for practitioners to be familiar with screening guidelines and health concerns, particularly in regards to fertility and pregnancy. There are unique health issues to consider in women with Turner syndrome who desire fertility, including stature, cardiovascular risk, and disorders of the endocrine system, including thyroid disease and type 2 diabetes. It is imperative that providers who care for women with Turner syndrome be familiar with the current guidelines in order to provide the highest level of care.

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Key Points

- Turner syndrome is one of the most common chromosomal abnormalities in female infants.
- Clinical manifestations of Turner syndrome include abnormalities of the following organ systems: skeletal, cardiovascular and lymphatic, endocrine, gastrointestinal, renal, and the central nervous system.
- Ovarian function sufficient to result in puberty is uncommon, and subsequent fertility is even less common in women with Turner syndrome. However, there are several options for women who desire to expand their families.
- Due to the unique pregnancy risks and complications in women with Turner syndrome it is important to be familiar with the current guidelines for pre-conception counseling and monitoring during gestation.

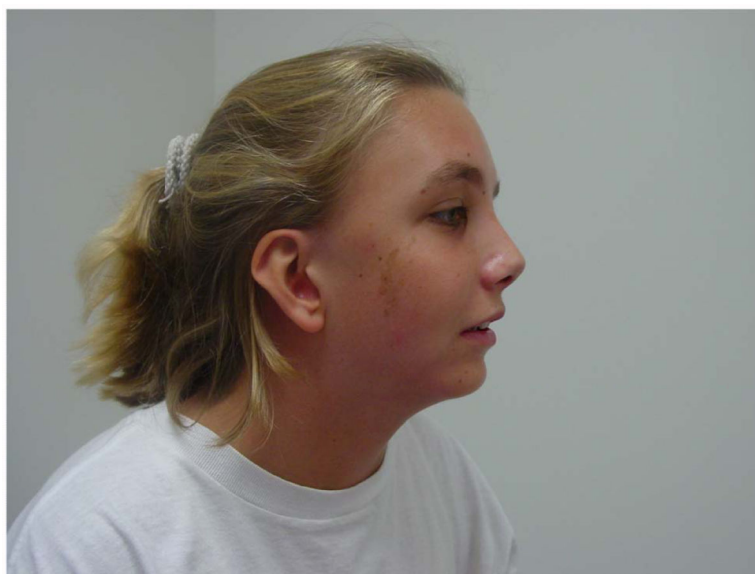


Figure 1. Adolescent with Turner syndrome. Note the phenotypic features, including ptosis, down slanting palpebral fissures, micrognathia, low set and posteriorly rotated ears, low posterior hairline, and pigmented nevi. Figure courtesy of Erica Eugster, M.D.

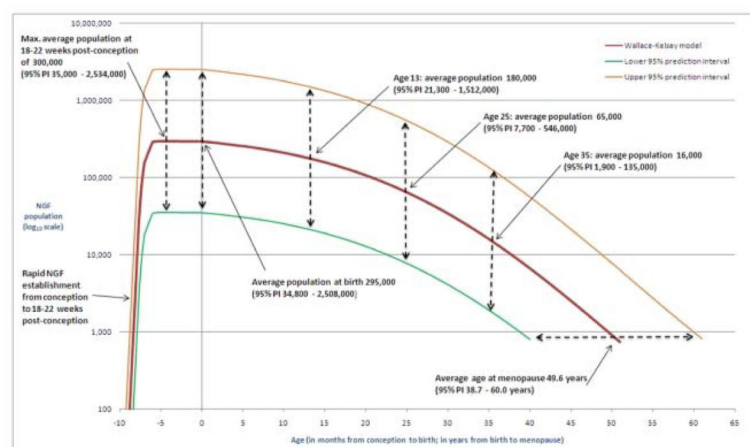


Figure 2.

Changes in ovarian follicle number across the life span in normal subjects. These data were derived from eight histological studies of ovaries from subjects ranging from seven weeks post-conception to 51 years. Note the rapid proliferation up to 18-22 weeks post-conception and the gradually increasing rate of decline until menopause. Figure courtesy of Wallace and Kelsey, 2010. (8) NGF, Non-growing follicles; PI, Prediction interval

Table 1

Phenotypic features of Turner syndrome

Skeletal system	
Short stature	
Broad chest	
Scoliosis	
Cubitus valgum	
Short 4 th metacarpal	
Madelung deformity of the wrist	
Genu valgum	
Cardiovascular and Lymphatic systems	
Bicuspid aortic valve	
Coarctation of the aorta	
Hypertension	
Aortic root dilatation	
Aortic dissection	
Lymphedema of hands and feet	
Pterygium colli	
Low posterior hairline	
Low-set and posteriorly rotated ears	
Down slanting palpebral fissures	
Endocrine system	
Primary ovarian failure	
Hashimoto thyroiditis	
Glucose intolerance	
Type 2 diabetes mellitus	
Gastrointestinal system	
Celiac disease	
Central nervous system	
Sensorineural hearing loss	
Attention deficit-hyperactivity disorder	
Learning disability	
Decreased visuospatial skills and executive function	
Renal system	
Duplicated renal collecting system	
Horseshoe kidney	
Other	
Arched palate	
Micrognathia	
Otitis media	

Conductive hearing loss
Pigmented nevi
Hyperconvex fingernails

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Table 2

Position and consensus statements on pregnancy in women with Turner syndrome

Organization	Contraindication to pregnancy	Pre-conception	ART	Monitoring during gestation	Delivery
American Society for Reproductive Medicine, 2012 (36)	Pregnancy is absolutely contraindicated if any cardiac defects on MRI, including ASI > 2 cm/m ² . Pregnancy is relatively contraindicated, even if no cardiovascular defects	Maternal counseling, including Cardiology and High-Risk OB. Encourage other options for children. Cardiac MRI	Single embryo transfer	Careful observation. Periodic echocardiography or MRI. Treat HTN. Monitor for gestational diabetes, hypertension, hepatic failure	ASI < 2 cm/m ² : OK for vaginal delivery ASI > 2 cm/m ² : C-section with epidural anesthesia before labor
French Joint Practice Committee, 2010 (46)	Contraindicated if any past or current aortic disease, uncontrolled hypertension, or portal hypertension with esophageal varices. Not contraindicated if isolated BAV	Maternal counseling, including Cardiology, Endocrinology, and others. Blood pressure. Echocardiography. Cardiac/aortic MRA	Single embryo transfer	Echocardiography at end of 1 st and 2 nd trimesters and monthly during 3 rd trimester, confirm suspected aortic dilatation with MRI. Treat HTN with beta blockade. Echocardiography 5-8 days post-partum	ASI < 2.5 cm/m ² : OK for assisted vaginal delivery ASI > 2.5 cm/m ² : Hospitalize, accelerate fetal lung maturity, C-section
Turner Syndrome Consensus Study Group, 2007 (2)	Relatively contraindicated if: Surgically repaired cardiovascular disease, BAV, aortic dilatation, hypertension. Counsel against pregnancy if these conditions present	Maternal counseling. Echocardiography. EKG. Cardiac MRI	Single embryo transfer	Care by Cardiology and High-risk OB at a tertiary care facility. Monitor for gestational diabetes, hypothyroidism, hypertension	Vaginal delivery allowable under "optimal conditions"

ART, Assisted reproductive technology; ASI, Aortic size index; BAV, Bicuspid aortic valve; C-section, Cesarean section; EKG, Electrocardiogram; HTN, Hypertension; MRA, Magnetic resonance angiography; MRI, Magnetic resonance imaging; OB, Obstetrics