

R E V I E W  
A R T I C L E

# Prenatal Sonographic Features of Turner Syndrome

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Turner syndrome (TS) was first described by Henry Turner in 1938 and was then known to be secondary to karyotypic variation of 45,X in 1959. Most conceptuses with TS spontaneously abort, and only 1% of these embryos survive to term. Fetuses with a pure and complete monosomy X often have more complicated anomalies than those with mosaicism and structural abnormalities in one X chromosome. Ultrasound has been reported to be a reliable tool in the prenatal diagnosis of TS. This article provides an overview of the common sonographic features of fetuses with TS, including cystic hygromas, increased nuchal translucency, non-immune hydrops fetalis, cardiovascular anomalies, urinary anomalies, short femur length, and other rare structural anomalies. Despite that some sonographic markers are transient and may be resolved later in gestation, detection of these markers in early pregnancy should remind obstetric clinicians of the importance of these predictors in TS. The prognosis for cases with TS detected in fetal life is relatively poor. In addition, several diseases may have phenotypic overlap with fetal TS, including non-TS-related cystic hygromas, non-TS-related non-immune hydrops fetalis and Noonan syndrome. Therefore, prenatal recognition of these sonographic features is of great help in karyotypic confirmation, and in appropriate genetic counseling and obstetric treatment.

**KEY WORDS** — prenatal ultrasound, Turner syndrome

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## Introduction

Turner syndrome (TS), first described by Henry Turner in 1938, is one of the most common monosomies in the fetus [1]. The syndrome is associated with a karyotypic aberration of 45,X, which was observed in 1959 [2,3]. At conception, the incidence of TS is about 3%. However, most conceptuses with TS are spontaneously aborted, and only

1% of these embryos survive to term [4]. TS has been reported to have an incidence of 1/2,500 liveborn females [5]. Children with TS typically manifest with short stature, webbed neck or nuchal skin folds, broad chest with widely spaced nipples, congenital lymphedema, and gonadal dysgenesis. Intellectual development is usually normal. Based on cytogenetic analysis, more than one-half of affected cases have a pure and full monosomy X, whereas

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the remaining cases display mosaicism or structural abnormalities in one sex chromosome [6,7]. Congenital anomalies are detected more frequently in fetuses with complete 45,X than with mosaicism [7,8]. The prognosis for fetuses with TS detected prenatally is relatively worse than the prognosis of those cases observed in postnatal life [9,10]. Advanced maternal age is not considered a major factor in the birth of children with TS, as the maternally derived X chromosome in most cases shows a karyotype of 45,X [11].

Ultrasound has been reported to be a reliable tool in the prenatal diagnosis of TS [7,12,13]. A wide range in the sonographic detection rate of fetuses with TS has been reported, which might be due to different study designs and sample collections. Common sonographic features reported in fetuses with TS are cystic hygromas, increased nuchal translucency (NT) thickness, non-immune fetal hydrops, and renal and cardiac defects [13]. Here, we review the associated prenatal sonographic features in the detection of TS. In addition, differential diagnoses,

including non-TS related cystic hygromas, non-TS related non-immune hydrops fetalis and Noonan syndrome, are discussed.

## Prenatal Sonographic Features

De Vigan et al reported that TS was the most frequent syndrome detected prenatally by sonography [14]. In a large study of unselected European subjects, 67.2% of fetuses with TS and congenital anomalies could be detected by sonography [7]. Clinically prenatal sonographic features suggestive of TS are cystic hygromas, increased NT, non-immune hydrops fetalis, cardiovascular anomalies, urinary anomalies, limb anomalies, and other rare structural anomalies. Despite some of the mentioned sonographic markers being transient, which may also resolve in the later stages of gestation, the detection of these markers in early pregnancy should remind obstetric clinicians of the importance of these predictors in TS [12].

**Table.** Prenatal sonographic features of Turner syndrome and differential diagnosis

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### Prenatal sonographic features

Increased nuchal translucency

Cystic hygroma

Non-immune hydrops fetalis

Cardiovascular anomalies

Coarctation of the aorta, hypoplastic left heart syndrome, atrioventricular septal defects, tricuspid regurgitation, a bicuspid aortic valve, partial anomalous pulmonary venous return, tetralogy of Fallot, dilated right ventricle, and others

Urinary anomalies

Horse-shoe kidney, collecting system malformations, multicystic dysplastic kidney, and others

Limb anomalies

Short femur length

Other rare structural anomalies

Central nervous system anomalies: hydrocephalus, an enlarged cisterna magna, ventriculomegaly

Abdominal wall defects: omphalocele, gastroschisis

Pulmonary defects

### Differential diagnosis

Non-TS related cystic hygroma

Non-TS related non-immune hydrops fetalis

Noonan syndrome

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### **Cystic hygroma**

The typical presentation of webbed neck in girls with TS is probably the end result of fetal cystic hygromas, which are the expression of anomalous lymphatic development. Cystic hygromas are characterized by abnormal fluid accumulation behind the fetal neck after the second trimester or, occasionally, in the first trimester. The cysts often contain thin or coarse septa, which appear in the occiput and posterior aspect of the fetal neck with a diameter larger than the biparietal diameter. Cystic hygromas were the most frequent sonographic signs in 84 fetuses with TS (82.1%) [14]. Most fetuses with cystic hygromas often have a poorer outcome. Cohen et al reported that continuation of pregnancy in 93% of fetuses with cystic hygromas resulted in late fetal or neonatal death [15]. Second-trimester karyotypic evaluation of the cystic fluid in all fetuses with cystic hygromas showed that 86.5% of fetuses were affected by TS, 9.4% had a normal karyotype, 2.7% had trisomy 21, and 1.4% had trisomy 18 [16]. The size of cystic hygromas in fetuses with TS was observed to be much larger than those with other chromosomal abnormalities, such as trisomy 18, trisomy 21, or those with a normal karyotype [17]. Therefore, the presence of fetal cystic hygromas, particularly large hygromas, is usually associated with TS. Transvaginal sonography is helpful in visualizing fetal cystic hygromas in a face-up position [18]. Transvaginal sonographic screening of 13 fetuses with TS and a karyotype of 45,X at 14–16 gestational weeks revealed that all the fetuses had a huge septated cystic hygroma, hydrops, and subcutaneous edema [12]. However, resolution of cystic hygromas in fetuses with TS has been reported during gestation [19–21]. It is important for obstetricians to bear in mind that this sonographic marker suggestive of TS may not be observed in later gestation.

### **Increased NT**

In the first trimester, the term “fetal NT” refers to the sonographic finding of a subcutaneous collection of fluid behind the fetal neck. Increased NT is defined by the vertical thickness equal to or above the 95<sup>th</sup> centile of a reference range at 11–13<sup>+6</sup>

weeks of gestation. Previous studies have provided evidence that increased NT is significantly associated with chromosomal abnormalities [22]. In a study of the relationship between increased NT and chromosomal defects, the distribution of NT was different for each type of chromosomal defect, and the NT was 8.5 mm or more in 69% (145/210) of fetuses with TS [23]. In another study of 53 fetuses with TS, increased NT was observed in 47 fetuses with an average of 9.8 mm, and the mean NT was significantly higher in fetuses with cardiac defects (10.9 mm) than in those without cardiac abnormalities (8.0 mm) [24]. In addition, the NT was higher in fetuses with a pure and complete monosomy X (10.0 mm) than in those with mosaicism in one X chromosome (4.8 mm) [24].

### **Non-immune hydrops fetalis**

Non-immune hydrops fetalis is used to describe a fetus with generalized edema and significant fluid accumulation in body cavities, such as the pericardium, pleura, and peritoneum. It has a wide range of known causes, including hematologic disorders, infections, chromosomal abnormalities, congenital anomalies, and tumors. In a study of 84 fetuses with TS, fetal hydrops (25.0%) was the second most common sonographic sign following cystic hygromas [14]. In a study of 16 fetuses with non-immune hydropic change in association with chromosomal abnormalities, 11 cases were affected by trisomy 21, four cases by TS, and one case by trisomy 18; the authors concluded that it is necessary to carry out a routine karyotypic analysis if the sonography revealed hydrops fetalis in the first trimester [25]. In addition to prenatal ultrasound, second-trimester maternal serum markers, such as low unconjugated estriol levels and elevated human chorionic gonadotropin levels, may be associated with prenatal identification of hydropic fetuses with TS [26,27].

### **Cardiovascular anomalies**

Cardiovascular defects in fetuses with TS include coarctation of the aorta, hypoplastic left heart syndrome, atrioventricular septal defects, tricuspid regurgitation, a bicuspid aortic valve, partial anomalous

pulmonary venous return, tetralogy of Fallot, dilated right ventricle, and others. Fifteen to thirty percent of postnatal cases with TS have structural heart diseases, and the most frequent cardiac abnormalities are a bicuspid aortic valve and coarctation of the aorta [28–30]. In addition, hypoplastic left heart diseases and partial anomalous pulmonary venous return have been reported [31–33]. Fetuses with TS are associated with a higher incidence of various cardiac anomalies detected prenatally when compared with postnatal reports. In prenatal studies, Gembruch et al described a hypoplastic aortic arch and hypoplastic left ventricle as the most common cardiac anomalies in five fetuses with TS [34]. Surerus et al reported the most common cardiac anomalies of 53 fetuses with TS to be coarctation of the aorta in 24 fetuses (45.3%), followed by hypoplastic left heart syndrome in seven fetuses (13.2%), an atrioventricular septal defect in one fetus, and tricuspid regurgitation in one fetus [24]. Papp et al reported nine fetuses with cardiac anomalies in 69 fetuses with TS, of which four fetuses (44.4%) had coarctation of the aorta, two fetuses had ventricular septal defects, two fetuses had tetralogy of Fallot, and one fetus had a dilated right ventricle [8]. Fetuses with a karyotype of 45,X have been reported to be more likely to have a cardiac defect, a more severe form of cardiac disease than mosaicism, and structural abnormalities in one X chromosome [28,35,36].

It has been reported that fetuses with TS with webbed neck or nuchal edema have a higher incidence of coarctation of the aorta than fetuses without webbed or edematous neck [37,38]. However the exact pathophysiologic mechanism between cardiovascular anomalies and webbed neck is not well understood [17].

### **Urinary anomalies**

Renal malformations have been reported in 33–70% of girls with TS, and the frequently associated renal anomalies include horse-shoe kidney, collecting system malformations, multicystic dysplastic kidney, and others. A literature review showed that the frequency of cystic renal diseases in TS was 1.76% [39].

In a study of 82 Turkish patients with TS, 31 had renal malformations (37.8%), of which nine patients (29.0%) had horse-shoe kidney, 17 (54.8%) had various collecting system malformations, and 5 patients (16.2%) had malrotation and other positional abnormalities. The prevalence of renal malformations was significantly higher in patients with TS with a complete monosomy X than in those with mosaicism or structural abnormalities in one X chromosome [40]. In various prenatal studies, urinary anomalies have been detected by sonography in 2.6–11.6% of fetuses with TS [7,8,14].

### **Limb anomalies**

Regarding the characteristic short stature in girls with TS, transvaginal sonographic screening of 13 fetuses with TS and a karyotype of 45,X at 14–16 gestational weeks revealed that 12 fetuses (92%) had an apparent short femur length [12]. Papp et al reported seven fetuses (10.1%) with short femur length (below the 10<sup>th</sup> centile) in 69 fetuses with TS. The authors concluded that the addition of the soft marker of short femur length to the second-trimester sonographic survey may increase the detection rate of TS [8].

### **Other rare structural anomalies**

Central nervous system anomalies are rarely seen in fetuses with TS. The reported anomalies include hydrocephalus in a hydropic fetus with TS [41], an enlarged cisterna magna (10 mm or more) [42], ventriculomegaly (10 mm or more) [8], and others. Abdominal wall defects, such as gastroschisis and omphalocele, accompanied by other TS phenotypes have been reported in fetuses with TS [43–46]. However, gastroschisis in a fetus with TS may have resulted from a ruptured omphalocele [47]. Pulmonary defects have also been documented in fetuses with TS [7,14].

## **Differential Diagnosis**

The definitive diagnosis of a fetus with TS depends on cytogenetic analysis. Differential diagnoses should

include non-TS-related cystic hygroma, non-TS-related non-immune hydrops fetalis, and Noonan syndrome.

### ***Non-TS-related cystic hygroma***

Fetal cystic hygromas are lymph-filled cysts, which may be a result of a failure in the development of communication between the lymphatic system and the jugular vein, an abnormal embryonic sequestration of lymphatic tissue, and then failure to join normal lymphatic channels, or abnormal budding of the lymphatics [46]. Approximately 80% of cases with cystic hygromas are associated with chromosomal abnormalities, of which monosomy X is the most common, and then the abnormal karyotypes trisomies 21, 18 and 13 [48]. In a study of 57 fetuses with cystic hygromas, chromosomal abnormalities were observed in 23 cases (23/57; 40.3%), the most common chromosomal abnormality in non-septated cystic hygromas was trisomy 21 (8/32; 25%) and in septated cystic hygromas was TS (4/22; 21.1%) [49]. Fetuses with cystic hygromas are at high risk of adverse outcome; therefore, prenatal cytogenetic analysis is required for detailed parental counseling.

### ***Non-TS related non-immune hydrops fetalis***

Hydrops fetalis is a morbid condition resulting from a wide variety of causes. Fetuses with hydropic change should be offered antibody screening to exclude immunologic etiologies. Disorders which result in non-immune hydrops fetalis include hematologic disorders, chromosomal abnormalities, cystic hygroma, congenital infections, congenital fetal structural anomalies including cardiovascular, pulmonary and gastrointestinal defects, uncontrolled maternal diabetes mellitus, and others. In Taiwan, the most common cause of non-immune hydrops fetalis is homozygous alpha-thalassemia (25/79; 31.6%) [50]. Fetuses with hydropic change should be offered a detailed prenatal sonographic scan, cytogenetic analysis and laboratory tests to determine the underlying etiology. Determination of the cause is of great help in correcting some of the

underlying pathologies and to allow appropriate genetic counseling and obstetric management.

### ***Noonan syndrome (OMIM 163950)***

Noonan syndrome, first described in 1963 [51], is manifested by short stature, a typical facial appearance with hypertelorism, downward slanting eyes, epicanthic folds, low-set posteriorly rotated ears, webbed neck, and cardiac anomalies (mainly pulmonary stenosis and hypertrophic cardiomyopathy) [52]. It is also called male TS or female pseudo-TS. It is an autosomal dominant disorder caused by mutations in *PTPN11* gene (OMIM 176876) mapped to chromosome 12q24.1, and this gene encodes the non-receptor protein tyrosine phosphatase SHP2, which contains 2 Src homology-2 (SH2) domains [53]. Recently, mutations in the *SOS1* gene (OMIM 182530) have resulted in another distinctive form of Noonan syndrome (OMIM 610733) [54]. Prenatal sonographic features of the fetus with Noonan syndrome are increased NT, cystic hygromas, fetal edema or hydropic change, short femur length, and renal and cardiac anomalies [55]. These features are very similar to the features in fetuses with TS. The major difference is that fetuses with Noonan syndrome have a normal karyotype. Although many cases are sporadic, a positive family history in some affected cases will be of great help in counseling parents about recurrence risks.

## **Conclusion**

This article provides an overview of prenatal sonographic features of TS. Fetuses with cystic hygromas, increased NT, non-immune hydrops fetalis, cardiovascular anomalies, urinary anomalies, short femur length, and other rare structural anomalies may be strongly suggestive of TS, and further fetal karyotyping is warranted. The nature of the karyotype has been strongly associated with the severity of congenital anomalies. Fetuses with a pure and complete monosomy X often have more complicated anomalies than those with mosaicism and structural abnormalities in one X chromosome. Despite that

some sonographic markers are transient and may resolve later in gestation, earlier intrauterine presentation of TS with cystic hygromas, a significantly increased NT, or hydrops might have a poor prognosis for fetal survival. Therefore, prenatal recognition of these sonographic features is of great help in karyotypic confirmation, and in appropriate genetic counseling and obstetric treatment.

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