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ORIGINAL ARTICLE

What are the most common first-trimester ultrasound findings in cases of Turner syndrome?

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Abstract

Objectives: To identify the most common first-trimester ultrasound findings in Turner syndrome (TS). To evaluate which first-trimester findings can be best used to predict the likelihood of TS.
Methods: This was a prospective study, based on singleton pregnancies. The referrals included 6210 patients. Scan protocol covered a review of the early fetal anatomy and markers of aneuploidy.
Results: Study population comprised 5644 pregnancies: 5613 with a normal karyotype and 31 cases of TS. Statistically significant differences ($p < 0.05$) were found between euploidy and TS groups in terms of nuchal translucency (NT; 1.7 mm versus 8.8 mm) and fetal heart rate (FHR; 160 versus 171 beats per minute). None of the TS cases demonstrated absent markers of aneuploidy as opposed to 5133 (91.4%) cases of euploidy. NT and abnormal DV flow (aDV or revDV) were the most common markers found in combination in TS cases ($n = 17$; 54.8%). 27 (0.5%) cases of euploidy and 17 (54.8%) cases of TS revealed congenital heart defects. Fetal hydrops was observed in 14 cases of TS (43.8%) and in 5 of euploidy (0.1%). In backward regression model, NT > 3.5 mm and right dominant heart (RDH) augmented the risk of TS risk by 991 and 314 times, respectively.
Conclusions: First-trimester sonography is a feasible method to identify the most characteristic features of TS fenotype. When the first-trimester pattern of TS is considered, a highly thickened NT, FHR above the 95th percentile, abnormal ductus venosus velocimetry, fetal hydrops, and RDH should be specifically searched for.

Keywords

First trimester, Turner syndrome, monosomy X, nuchal translucency, right dominant heart, ductus venosus

History

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Introduction

The incidence of Turner syndrome (TS) is estimated at 1 in 2500 liveborn girls [1]. It is one of the most common chromosomal aberrations observed after conception with the prevalence of 1–2% [2]. In the screening for TS, the performance of robust Noninvasive Prenatal Testing (NIPT) shows detection rate (DR) at the level of only 88%, not like for trisomy 21 of above 99% [3]. The most common prenatal ultrasound findings that may be found in TS at the time of first-trimester scan include thickening of nuchal translucency (NT) and nonimmune hydrops [4]. However, this ultrasound picture may also be present in other chromosomal aberrations, single gene disorders, and cardiac insufficiency due to non-genetic reasons. Furthermore, short femur, narrow aortic arch, left-sided cardiac defects characterized by the right heart dominance and renal anomalies were described in TS fetuses [5,6]. A beneficial, additional consequence of widely used screening for trisomy 21 was the early detection of other chromosomal anomalies including TS [7,8]. However, there are no data regarding the patterns of ultrasound findings for TS at the time of first-trimester scan basing on logistic regression models. The first aim of the study was to compare sonographic features of TS in contrast with euploidy. Second goal was to evaluate which first-trimester findings can be best used to predict the likelihood of TS.

Methods

This was a prospective study, based on singleton pregnancies examined at 11^{+0} to 13^{+6} weeks at our institution. The referrals constituted of low-risk patients (8317) and a weighty set of high-risk cases (1315) including subjects with maternal age (MA) above 35 years (783), and suspicious ultrasound findings identified at routine antenatal visits performed by obstetricians non-qualified and not trained for first-trimester screening (532). Karyotyping results and postnatal evaluation findings were covered in the database as soon as they were accessible. The patients, who were examined between January 2009 and June 2012, were included in the study. The sonography reports together with digital data were reviewed

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taking into account the following inclusion criteria: singleton pregnancy, crown-rump length (CRL) measurement of 45–84 mm, known pregnancy outcome. The patients' body mass index (BMI) was computed in kg/m^2 on the day of the late first-trimester ultrasound scan. Fetal karyotyping was evaluated from amniotic fluid samples after amniotic cell culture (653 cases). At least 20 metaphases from at least 5 cultures were assessed. Mosaicism was defined if the same chromosomal aberration was identified in more than two cells in two different cultures. The rest of subjects were determined to be euploid, based on normal postnatal evaluation. Aneuploidies, other than TS, were excluded from the exploration. Three examiners qualified for the complete set of sonographic markers by Fetal Medicine Foundation (FMF) were engaged in this study. All scans were performed utilizing the Voluson E6 and Voluson E8 ultrasound scanners (GE Healthcare, Zipf, Austria) from transabdominal approach. In 5.4% transvaginal probe was applied for better definition of fetal anatomy. The scan protocol enclosed a systematic review of the entire early fetal anatomy according to ISUOG guidelines [9], enhanced with fetal cardiac evaluation based on the following parameters: visceral situs, four-chamber view (4CV), outflow tracts, three-vessel and trachea view (3VTV) in B-mode and color mapping. At the level of 4CV, mitral and tricuspid anuli width ratios were measured. Cases presenting these ratio ≤ 0.5 were classified as right dominant heart (RDH). The sonographic signs of chromosomal aberrations (NT, NB, TR, DV) were checked following FMF recommendations. DV was assessed by a qualitative method (reverse a-wave = revDV and absent DV = noDV were considered abnormal) because at the beginning of the study, a quantitative technique by measuring DV pulsatility index for veins (PIV) was not utilized. The sonographic findings among euploidy and TS were investigated. All high-risk subjects had genetic counseling and underwent sonography between 18–19 weeks, according to internationally recognized second-trimester and fetal echocardiography recommendations [10,11]. The outcome data were collected from medical records. The local Ethics Committee approved the study protocol and all subjects gave written consent.

Statistical analysis

The characteristics of the subjects were expressed as frequencies and percentages for categorical variables, mean ± standard deviation or median and range for continuous variables. The χ^2 test was used to demonstrate the differences between categorical variables. The Kolmogorov–Smirnov test was applied to continuous variable distribution. Groups of independent variables were compared using Student's *t*-test. Nonparametric tests were also utilized. SPSS Statistics v(0).17 (IBM Co., New York, USA) software was applied in this study. The figures of $p < 0.05$ were measured as significant. From the most frequent features apparent in our group of fetuses with TS, backward regression parameter model was developed, which was used to calculate odds ratios (ORs) for the commonest ultrasound findings. The number of backward regression parameters applied in the model was calculated by dividing the number of TS cases by 10.

Results

Screening ultrasound was carried out in 9632 singleton pregnancies. 3988 (41.4%) cases were excluded from further analysis because in 380 (3.9%) cases it was impossible to establish the fetal karyotype due to losing them from the follow-up, 43 (0.4%) cases resulted in miscarriages not related to invasive testing and 23 (0.2%) with intrauterine fetal demise without subsequent karyotyping, in 120 (1.2%) cases there was a chromosomal abnormality other than TS. Other chromosomal aberrations demonstrate different ultrasound picture and can potentially interfere with our study observations. Additionally, 3422 (35.5%) euploid fetuses with normal male karyotype were also excluded from the analysis. Therefore, our study population comprised 5644 pregnancies: 5613 with a normal karyotype or delivery of a normal baby (euploid group) and 31 cases of TS including 5 cases (16%) of mosaic 45,X/46,XX. The characteristic of the study population is summarized in Figure 1. The median maternal BMI was 22.4 kg/m^2 (range 17.6–35.2). All women participating in this study were Caucasian.

The mean NT thickness in the subgroup of euploidy was 1.7 mm (range 0.1–4.9) and in the subgroup of TS it was 8.8 mm (range 2.6–15.5) ($p < 0.05$). The mean MA in euploid group was 30.5 years (range 25–42) compared to 28.9 years (range 17–38) in TS ($p = 0.118$). The mean CRL at the time of examination was 63.3 mm in euploid versus 62.9 mm in TS group ($p = 0.872$). Statistically significant differences were found between euploidy and TS groups in terms of NT and FHR (Table 1).

The NT thickness above the 95th percentile was observed in 228 (4.1%) euploid fetuses and in 30 (96.8%) fetuses affected by TS. Delayed nasal ossification was found in 4 (12.9%) cases of TS and in 93 (1.65%) of euploidy, which was statistically significant ($p < 0.05$). By using χ^2 Pearson's test statistical differences were found in the presence of noDV ($p < 0.05$) between the groups of euploidy ($n = 6$; 0.1%) and TS ($n = 10$; 32.3%).

None of the TS cases demonstrated absent markers of aneuploidy as opposed to 5133 cases of euploidy (91.4%). Only 8 cases of TS (25.8%) revealed isolated markers, including 7 cases with increased NT above the 95th percentile and one case with revDV. The most common combinations of aneuploidy markers found in fetuses with TS were NT above the 95th percentile with noDV ($n = 10$; 32.5%) and NT above the 95th percentile with revDV ($n = 7$; 22.5%). The details are presented in Table 2.

Extracardiac malformations (ECMs) were identified in 16 cases of TS (50%) and in 59 cases of euploidy (0.95%). This difference was statistically significant ($p < 0.05$). All TS cases presented isolated ECM. 17 cases of TS (54.8%) and in 26 cases of euploidy (0.5%) revealed congenital heart defects (CHDs). The largest fraction of CHDs in TS were: CoA – 16 cases (94.1%), and one case of hypoplastic left heart syndrome (HLHS) – 5.9%. The details are depicted in Table 3.

Due to the number of TS cases, three most prevalent ultrasound findings in TS cases were computed by backward regression to demonstrate their ORs. In this model the following parameters were included: NT > 3.5 mm; RDH; and noDV (Table 4). The cutoff for NT was selected according to

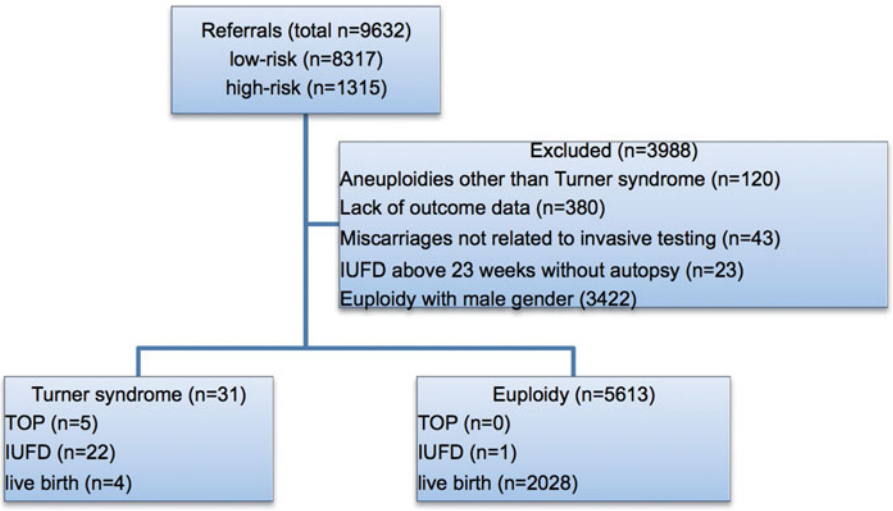

Figure 1. Study population diagram. IUFD: intrauterine fetal demise; TOP: termination of pregnancy.

Table 1. Comparison of fetuses with euploidy and Turner syndrome according to four parameters.

	Euploidy, $n = 5613$			Turner syndrome, $n = 31$			Statistical significance
	Mean	Median	SD	Mean	Median	SD	p
NT (mm)	1.7	1.6	0.5	8.8	8.4	2.7	0.00
CRL (mm)	63.3	62.8	9.1	62.9	64.0	9.7	0.87
FHR (bpm)	160.3	160.0	7.3	171.2	171.0	11.3	0.00
MA (years)	30.5	30.0	4.2	28.9	29.0	5.3	0.12

CRL: crown-rump length; NT: nuchal translucency; FHR: fetal heart rate; bpm: beats per minute; MA: maternal age; SD: standard deviation.

the value of mean −2SD for NT distribution in TS cases, which was equal to 3.4 mm. The regression model demonstrated that, only NT > 3.5 mm and RDH were found as statistically significant parameters (Table 4).

Discussion

Although the prevalence of TS is not as high as that of T21, it remains the most common monosomy in the fetus. The frequency of TS is estimated at 3%, but 99% of affected fetuses are miscarried spontaneously [6].

In our study, an increased NT above 95th percentile was the most common ultrasound feature and it was all but one fetuses with monosomy X. This is similar to the findings of Bronshtein et al. who observed that in TS fetuses examined between 14 and 16 weeks a huge septated cystic hygroma, severe subcutaneous edema or hydrops were typical phenotypic features present in all cases as well [6]. In our report, the mean NT value in TS subjects was 8.8 mm ± 2.7. Comparable findings were presented in the study on 11 315 pregnancies including 163 cases of TS, where the majority of TS fetuses demonstrated NT above 8.5mm [4]. It should be noticed that our observations revealed that 22.6% cases of TS showed isolated increased NT as a set of ultrasound aneuploidy markers. In our report, we avoided the term ''cystic hygroma'' as the septations in the nuchal region can be seen in all fetuses with NT between 2 and 10 mm [12].

Table 2. The configuration and prevalence of isolated and combined markers of aneuploidy in euploid and Turner syndrome fetuses.

	Euploidy ($n = 5613$)		Turner syndrome ($n = 31$)	
	n	%	n	%
No markers	5133	91.44	0	0.0
1 marker	419	7.46	8	25.8
NT	181	3.2	7	22.6
NB(−)	63	1.1	0	0.0
TR	71	1.3	0	0.0
revDV	94	1.7	1	3.2
noDV	4	0.1	0	0.0
SUA	6	0.1	0	0.0
2 markers	50	0.89	18	58.0
NT + NB(−)	7	0.1	3	9.6
NT + TR	10	0.2	1	3.2
NT + revDV	14	0.2	4	12.9
NT + noDV	2	0.1	8	25.8
NB(−) + revDV	7	0.1	0	0.0
NB(−) + TR	6	0.2	0	0.0
TR + revDV	1	0.1	0	0.0
NT + SUA	3	0.1	2	6.5
3 markers	9	0.16	5	16.13
NT + NB(−) + TR	5	0.1	0	0.0
NT + NB(−) + revDV	3	0.1	1	3.2
NT + TR + revDV	1	0.1	2	6.5
NT + TR + noDV	0	0.0	2	6.5
4 markers	2	0.03	0	0.0
NT + NB(−) + TR + revDV	2	0.0	0	0.0

NT: nuchal translucency above the 95th percentile; TR: tricuspid regurgitation; NB(−): absent nasal bone; revDV: reversed a wave in ductus venosus flow; noDV: absent ductus venosus; SUA: single umbilical artery.

Among secondary markers of aneuploidy, abnormal ductus venosus velocimetries are recognized as common findings in aneuploidy [13]. In our study, the abnormal DV flow together with an increased NT was the most common combination of ultrasound markers of aneuploidy in fetuses with TS. Coincidences of severe abnormal DV findings (noDV and revDV) with increased NT constituted 38.7% of our TS cases. In the study of Maiz et al., reversed DV was found in 75% of fetuses with TS and when employed in the combined screening test (CST) it enabled for detection of 100% cases

Table 3. Extracardiac structural malformations (ECM) and congenital heart defects (CHD) summarized in terms of chromosomal status.

Karyotype	*N*	%
Extracardiac anomalies		
Euploidy		
No ECM	5554	98.9
Hydrops	5	0.1
Brain anomalies	12	0.2
Abdominal anomalies	14	0.3
Urinary tract anomalies	8	0.1
Limb anomalies	8	0.1
Facial/neck anomalies	9	0.2
Thoracic anomalies	3	0.1
Turner syndrome		
No ECM	16	50.0
Hydrops	14	43.8
Facial/neck anomalies	2	6.2
Congenital heart defects		
Euploidy		
No CHD	5588	99.6
Septal defects	2	0.0
Conotruncal anomalies	10	0.2
Left heart defects	7	0.1
Right heart defects	5	0.1
Heterotaxy	1	0.0
Aortic arch defects	1	0.0
Turner syndrome		
No CHD	14	45.2
Left heart defects	17	54.8

Table 4. Odds ratios (ORs) for the most common features determined in Turner syndrome fetuses based on backward regression model.

			OR 95% CI	
Backward regression parameters	*p*	OR	Lower limit	Upper limit
NT > 3.5mm	0.000	991.44	107.40	9152.27
RDH	0.001	314.34	11.84	8346.03
noDV	0.064	7.32	0.89	60.15

NT: nuchal translucency; noDV: absent ductus venosus; RDH: right dominant heart.

of TS [13]. Absent nasal bone is not recognized a common finding in fetuses with TS. Kagan et al. did not found absent NB in any of the fetuses with TS [14]. Only 4 of our TS cases (12.9%) revealed delayed nasal ossification, which is consistent with the results of Cicero et al., who showed absent NB in 8.8% of TS series [15]. FHR above the 95th percentile was observed in 52.2% of TS cases according to Liao et al. [16]. It was also in agreement with our study, which showed these values in 48.4%.

As other researchers described, among structural abnormalities, apart from the fetal hydrops (43.8% of our TS cases), the most characteristic for TS are left heart defects, which are often related with RDH (54.8 of our TS cases) [7,17]. These two findings are likely to be found together as the pathogenic relationship exists between the two. The possible explanation derives from the fact that lymphatic sac obstruction and subsequent increase of the pressure at the base of ascending aorta leads to its compression with the development of a spectrum of left heart hypoplasia [18]. In our series, features of CoA were identified in 94.1% followed by 5.9% of HLHS in TS subjects demonstrating CHD. This is in line with the report of Surerus et al. [19], who found that in fetuses with TS the most common associated heart defects detected prenatally are HLHS and CoA.

In a backward regression model, we showed that NT > 3.5 mm and identification of RDH, augment the risk of TS by 991 and 314 times, respectively taking into account the influence of noDV. This information may be especially helpful for examiners who can check for RDH at the time of first-trimester scan and for counseling of the parents prior to an invasive testing.

The advantage of our study is the fact that it comprised a relatively large number of first-trimester TS cases assessed by a detailed ultrasound scan that covered complete package of aneuploidy markers and targeted evaluation of fetal organs. On the other hand extensive ultrasound protocol, which was applied in our study may be difficult for a routine utilization in the screening setting.

Prenatal ultrasound remains the main screening tool for TS despite the fact that recent studies have proposed the introduction of cell-free DNA testing (NIPT) in routine clinical practice [3,20–23]. However, in screening for TS, the performance of the test shows DR at the level of 88% with false positive rate of 0.12% [3]. Compared with male euploid fetuses, the fetal fraction of cfDNA is lower when the fetus has monosomy X [24]. This is why the topic that we raised in our study is still of importance.

To summarize our observations, we confirmed that in the presence of increased NT, the evaluation of the fetal heart at the time of nuchal scan might be helpful in screening for TS as most of the affected fetuses present left heart defects. When the first-trimester pattern of TS is considered, a highly thickened NT, FHR above the 95th percentile, abnormal DV velocimetry (mainly noDV), fetal hydrops, and RDH should be specifically searched for.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References

1. Hsu LYF. Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In: Milunski A, ed. Genetic disorders and the fetus. Baltimore (MD): Johns Hopkins University Press; 1998:179–248.
2. Barr M, Oman-Ganes L. Turner syndrome morphology and morphometrics: cardiac hypoplasia as a cause of midgestation death. Teratology 2002;72:65–72.
3. Gil MM, Akolekar R, Quezada MS, et al. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: meta-analysis. Fetal Diagn Ther 2014;35:156–73.
4. Kagan KO, Avgidou K, Molina FS, et al. Relation between increased fetal nuchal translucency thickness and chromosomal defects. Obstet Gynecol 2006;107:6–10.
5. Papp C, Beke A, Mezei G, et al. Prenatal diagnosis of Turner syndrome: report on 69 cases. J Ultrasound Med 2006;25:711–17.
6. Bronshtein M, Zimmer EZ, Blazer S. A characteristic cluster of fetal sonographic markers that are predictive of fetal Turner syndrome in early pregnancy. Am J Obstet Gynecol 2003;188:1016–20.
7. Nicolaides KH. Screening for fetal aneuploidies at 11 to 13 weeks. Prenat Diagn 2011;31:7–15.
8. Karadzov-Orlic N, Egic A, Milovanovic Z, et al. Improved diagnostic accuracy by using secondary ultrasound markers in the

first-trimester screening for trisomies 21, 18 and 13 and Turner syndrome. Prenat Diagn 2012;32:638–43.
9. Committee CS. ISUOG Practice Guidelines: performance of first-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol 2013; 41:102–13.
10. American Institute of Ultrasound in Medicine. AIUM practice guideline for the performance of obstetric ultrasound examinations. J Ultrasound Med 2010;29:157–66.
11. Fetal Echocardiography Task Force; American Institute of Ultrasound in Medicine Clinical Standards Committee; American College of Obstetricians and Gynecologists; Society for Maternal-Fetal Medicine. AIUM practice guideline for the performance of fetal echocardiography. J Ultrasound Med 2011;30:127–36.
12. Molina FS, Avgidou K, Kagan KO. Translucency at 11–14 Weeks of Gestation. Obstet Gynecol 2006;107:678–83.
13. Maiz N, Valencia C, Kagan KO, et al. Ductus venosus Doppler in screening for trisomies 21, 18 and 13 and Turner syndrome at 11–13 weeks of gestation. Ultrasound Obstet Gynecol 2009;33:512–17.
14. Kagan KO, Cicero S, Staboulidou I, et al. Fetal nasal bone in screening for trisomies 21, 18 and 13 and Turner syndrome at 11-13 weeks of gestation. Ultrasound Obstet Gynecol 2009;33: 259–64.
15. Cicero S, Longo D, Rembouskos G, et al. Absent nasal bone at 11–14 weeks of gestation and chromosomal defects. Ultrasound Obstet Gynecol 2003;22:31–5.
16. Liao W, Snijders R, Geerts L, et al. Fetal heart rate in chromosomally abnormal fetuses. Ultrasound Obstet Gynecol 2000;16:610–13.
17. Bondy CA. Congenital cardiovascular disease in Turner syndrome. Congenit Heart Dis 2008;3:2–15.
18. Clark EB. Neck web and congenital heart defects: a pathogenic association in 45 X-0 Turner syndrome? Teratology 1984;361: 355–61.
19. Surerus E, Huggon IC, Allan LD. Turner's syndrome in fetal life. Ultrasound Obstet Gynecol 2003;22:264–7.
20. Syngelaki A, Pergament E, Homfray T, et al. Replacing the combined test by cell-free DNA testing in screening for trisomies 21, 18 and 13: impact on the diagnosis of other chromosomal abnormalities. Fetal Diagn Ther 2014;35:174–84.
21. Nicolaides KH, Wright D, Poon LC, et al. First-trimester contingent screening for trisomy 21 by biomarkers and maternal blood cell-free DNA testing. Ultrasound Obstet Gynecol 2013;42:41–50.
22. Chiu RW, Akolekar R, Zheng YW, et al. Noninvasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. BMJ 2011;342:c7401.
23. Chen EZ1, Chiu RW, Sun H, et al. Noninvasive prenatal diagnosis of fetal trisomy 18 and trisomy 13 by maternal plasma DNA sequencing. PLoS One 2011;6:e21791.
24. Rava RP, Srinivasan A, Sehnert AJ, Bianchi DW. Circulating fetal cell-free DNA fractions differ in autosomal aneuploidies and monosomy X. Clin Chem 2014;60:243–50.