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Chromosomal Abnormalities in Korean Fetuses with Nuchal Translucency above the 99th Percentile

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Objective: To evaluate the prevalence and distribution of chromosomal defects in Korean fetuses with nuchal translucency (NT) above the 99th percentile and to analyze them according to the degree of NT thickness.

Methods: This study retrospectively reviewed the medical records and ultrasonography images of pregnant women whose fetuses were diagnosed with NT ≥3.5 mm at 11 to 14 weeks of gestation and who underwent karyotyping between 2009 and 2015 at Cheil General Hospital, Seoul, Korea.

Results: Among 514 fetuses that met the inclusion criteria, 198 (38.5%) fetuses were confirmed as having chromosomal defects. 156 (30.4%) fetuses concerned autosomal aneuploidies, 27 (5.3%) sex-chromosome aneuploidies, and 1 (0.2%) triploidy. Besides, 11 fetuses (2.1%) were identified as pathogenic structural unbalanced chromosome aberration. When the study populations were divided based on NT thickness, 19.8% fetuses with a thickness of 3.5-4.4 mm, 33.0% of 4.5-5.4 mm, 50.3% of 5.5-6.4 mm, and 67.2% of 6.5 mm or more had chromosomal defects.

Conclusion: The incidence of chromosomal abnormalities of Korean fetuses with NT thickness above 99th percentile increases with NT thickness, and the prevalence and distribution based on NT thickness were very similar to those of Caucasian fetuses in previous reports.

Key Words: Aneuploidy, Pregnancy trimester, first, Nuchal translucency measurement, Karyotyping

Introduction

Measurement of nuchal translucency (NT) thickness during the first trimester is one of the best available screening methods for aneuploidy.[1-3] A thickened NT was originally described as an NT above the 95th percentile for a given crown–rump length. More recent data have suggested that adverse outcomes are much more common with an NT that exceeds a set threshold of 3.5 mm, a measurement that essentially represents above the 99th percentile throughout the gestational age window for first trimester screening.[4-6]

The prevalence of chromosomal defects actually increases exponentially with NT thickness.[7,8] Thus, we can predict the possibility of chromosomal defects by measurements of NT thickness, and the parents of a fetus with increased NT thickness used to be counseled as reported values in the literatures. However, several authors suggested that the reference ranges of NT thickness differed with regard to ethnicity.[9-12] Therefore, the prevalence and distribution of chromosomal abnormalities according to NT thickness might show ethnic variability. Nevertheless, they have been evaluated only in the Caucasian population to the best of our knowledge.

This study aimed to evaluate the prevalence and distribution of chromosomal defects in Korean fetuses with NT above the 99th percentile and to analyze them according to the degree of NT thickness.

Methods

We conducted a retrospective study by reviewing the medical records and ultrasonography images of pregnant women whose fetuses were aged between 11+0 and 13+6 weeks of gestation. The inclusion criteria were pregnant Korean women whose fetuses were diagnosed with an NT equal to or above 3.5 mm including cystic hygroma and who underwent karyotyping between January 2009 and December 2015 at Cheil General Hospital. Women with multiple pregnancies and pregnant women who did not undergo karyotyping were excluded. This study was approved by the Institutional Review Board of Cheil General Hospital (CGH-IRB-2016-10).

The vast majority of examinations included both transvaginal and transabdominal imaging, and NT measurement and nasal bone status were noted. Well trained obstetric sonographers, who have minimum of 5 years' experience of routine ultrasonography examination at 11-14 weeks of gestation, performed the sonographic evaluations. NT measurement was performed after ensuring that the following criteria were satisfied: the image should be magnified to occupy 75% of the screen and should show only the fetal head, neck, and upper thorax; the fetus must be in the midsagittal plane; the fetal neck must be in a neutral position; three echogenic lines indicating the inner and outer borders of the fetal skin, and the amnion must be displayed; the ultrasonography calipers must be placed with the horizontal cross on the inner borders of the echolucent space and perpendicular to the fetal axis; and the NT must be measured at the widest space. Patients whose fetuses were diagnosed with an NT equal to or more than 3.5 mm were offered the option of an invasive diagnostic test, namely chorionic villus sampling or amniocentesis. Patients who refused karyotyping were reoffered karyotyping when the fetus was diagnosed with abortion or intrauterine fetal death.

We showed the prevalence and distribution of chromosomal defects in fetuses with enlarged NT above 3.5 mm, and analyzed them for each nuchal translucency category: 3.5-4.4 mm, 4.5-5.4 mm, 5.5-6.4 mm, and 6.5 mm or more. In addition, we investigated other ultrasonography findings and pregnancy outcomes of the fetuses who had chromosomal defects other than trisomy 21, trisomy 18, trisomy 13, and monosomy X.

Results

Among 592 singleton pregnant women whose fetus with increased NT equal to or above 3.5 mm, fetal karyotyping was performed in 514 pregnancies. The median maternal age was 33 years (range, 20-48), 316 (61.5%) were nulliparous. The mean gestational age at sonography was 12.8±0.5 weeks, and the mean fetal crown-rump length (CRL) was 64 mm (range, 45-84).

Table 1 shows type of chromosomal defects and their prevalence in Korean patients with enlarged NT above 99th percentile. Overall incidence of chromosomal abnormalities in our study population was 38.5% (198/514). The most common aneuploidy was trisomy 21 (15.8%), and total in 30.4% (156/514) of the cases were confirmed as an autosomal aneuploidy. Besides, sex chromosome aberration including monosomy X was found in 27 (5.3%) fetuses, and a pathologic unbalanced structural chromosome aberration was in 11 (2.1%) fetuses.

Table 2 shows the incidence and distribution of chromosomal abnormalities according to NT thickness. The overall incidence of chromosomal defects increased with NT thickness; approximately 19.8% of fetuses with an NT of 3.5-4.4 mm, 33.0% with an NT of 4.5-5.4 mm, 50.7% with an NT of 5.5-6.4 mm, and 67.2% with an NT of 6.5 mm or more had chromosomal defects. Majority of the fetuses with NT thickness less than 5.5 mm were confirmed with trisomy 21. Whereas, in the fetus with NT thickness 5.5 mm or more, trisomy 18 was most common

Table 1. Type of Chromosomal Abnormality in 514 Fetuses with Enlarged Nuchal Translucency (≥3.5 mm)

Type of chromosomal abnormality	Value
Numerical abnormality	184 (35.7)
Trisomy 21	81 (15.8)
Trisomy 18	65 (12.6)
Trisomy 13	8 (1.6)
Trisomy 16	2 (0.4)
Monosomy X	26 (5.1)
Trisomy X	1 (0.2)
Triploidy	1 (0.2)
Structural abnormality	14 (2.7)
Unbalanced chromosome aberrations	11 (2.1)
Balanced chromosomal aberrations	3 (0.6)

Values are presented as number (%).

Table 2. Incidence of Chromosomal Defects according to Nuchal Translucency Thickness

Nuchal translucency (mm)	Value	Abnormal karyotype	Type of chromosomal defects				
			Trisomy 21	Trisomy 18	Trisomy 13	Monosomy X	Others
3.5-4.4	217 (42.2)	43 (19.8)	31 (72.1)	7 (16.3)	1 (2.3)	0 (0)	4 (9.3)
4.5-5.4	94 (18.3)	30 (33.0)	18 (58.0)	7 (22.6)	2 (6.7)	1 (3.3)	2 (6.7)
5.5-6.4	69 (13.4)	35 (50.7)	13 (37.1)	18 (51.4)	2 (5.7)	1 (2.9)	1 (2.9)
≥6.5	134 (26.1)	90 (67.2)	19 (21.1)	33 (36.7)	3 (3.3)	24 (26.7)	11 (12.2)
Total	514	198 (38.5)	81 (40.9)	65 (32.8)	8 (4.0)	26 (13.1)	18 (9.1)

Values are presented as number (%).

Table 3. Details of Cases with Increased NT and Other Ultrasonography Findings and Chromosomal Defects Other than Common Trisomy

Case	GA at sonography (weeks)	Ultrasonography findings	Karyotype	Inheritance	Pregnancy outcomes
Numerical abnormalities					
1	13+4	NT: 7.1 mm	47,XX,+16	-	Follow up loss
2	12+0	NT: 9.4 mm Megacystis	47,XX,+16	-	IUFD at 13+4 weeks
3	11+4 20+1	NT: 4.7 mm Cleft lip and palate, bilateral club feet, complex CHD, vertebra body abnormality, small for gestational age	46,XXX,der(13;14)(q10;q10)	*De novo*	Follow up loss
4	12+0	NT: 9.2 mm	69,XXX triploidy	NA	Follow up loss
Unbalanced chromosome aberrations					
5	13+6 20+5	NT: 3.6 mm Bilateral angular deformity of fetal feet, echogenic bowel, small for gestational age	46,XY,der(9)t(2;9)(q33;p22)	Paternal	IUFD at 22+5 weeks
6	12+4 20+2	NT: 3.7 mm Intracranial hemorrhage, left ankle deformity, oligohydramnios	46,XY,der(5)t(5;7)(p14;p21)	Paternal	TOP at 22+3 weeks
7	12+3	NT: 5.5 mm	46,XY,der(1)t(1;7)(p36.3;p15)	*De novo*	TOP at 14+5 weeks
8	11+3	NT: 5.6 mm Hypoplastic nasal bone	46,XX,add(17)(p13)	NA	IUFD at 14 weeks
9	13+2	NT: 5.8 mm Cardiomegaly, facial anomaly, echogenic bowel	46,XY,der(22)t(11;22)(p11.1;p11.2)	Paternal	IUFD at 15+4 weeks
10	11+6	NT: 6.5 mm R/O omphalocele	46,XY,der(4)t(3;4)(q23;q35)	Paternal	TOP at 15+2 weeks
11	12+1	NT: 7.2 mm Echogenic bowel	46,XX,del(4)(q32q34)	*De novo*	Follow up loss
12	12+0	NT: 7.3 mm	45,XY,der(13;18)(q10;q10)	NA	TOP at 14+1 weeks
13	13+4	NT: 8.5 mm R/O cardiac anomaly	46,XX,del(5)(p13)	*De novo*	IUFD at 14+0 weeks
14	12+0	NT: 8.7 mm Hypoplastic nasal bone	46,XX,der(18)t(9:18)(p13.1;q22)	Maternal	IUFD at 15+3 weeks
15	12+1	NT: 9.3 mm	46,XX,der(4)t(1;4)(q42;p16), t(6;17)(p21.1;p12)	Maternal/*de novo*	IUFD at 14+4 weeks

Abbreviations: NT, nuchal translucency; GA, gestational age; IUFD, intrauterine fetal demise; CHD, congenital heart disease; NA, not available; TOP, termination of pregnancy; R/O, rule out.

aneuploidy. The percentage of monosomy X was relatively high in the fetus with the NT thickness 6.5 mm or more.

In this study, 18 cases involved chromosomal defects other than trisomy 21, 18, and 13, and monosomy X. Three cases involved balanced chromosomal aberrations with no significant findings until delivery. We describe the details of 15 cases of uncommon aneuploidy, other than balanced chromosomal aberrations, in Table 3.

Discussion

Since NT thickness increases with fetal CRL, compared to fixed cut-offs, the use of CRL-dependent cut-off for NT improves the detection of chromosomal aberrations.[13-15] However, the 99th percentile did not change significantly with CRL, and it was about 3.5 mm.[1]

Souka et al.[7] reported that the prevalence of chromosomal defects increases exponentially with NT thickness. They observed that the prevalence was 21.1% for fetuses with an NT of 3.5-4.4 mm, 33.3% for fetuses with an NT of 4.5-5.4 mm, 50.5% for fetuses with an NT of 5.5-6.4 mm, and 64.5% for fetuses with an NT of 6.5 mm or more. These values are almost the same as those observed in our study. Regarding the distribution of chromosomal abnormalities according to NT thickness, Kagan et al.[8] reported that in the majority of fetuses with trisomy 21, the NT thickness was less than 4.5 mm, whereas in the majority of fetuses with trisomy 13 or 18, it was 4.5-8.4 mm, and in those with Turner syndrome, it was 8.5 mm or more. Our findings were also consistent with the study of them.

Through these studies, we verified that the frequency and type of chromosomal defects in patients with enlarged NT above 99th percentile were similar to those of previous studies in Caucasian fetuses. Furthermore, prevalence and distribution of chromosomal abnormalities according to NT thickness also did not show differences. Therefore, we can assume that ethnic variance does not exist in the prevalence and distribution of chromosomal abnormalities in fetuses with enlarged NT.

In addition to common trisomies and monosomy X, unbalanced translocation is also known to be associated with increased NT.[16,17] Alternatively, the distribution of NT measurements in cases of uncommon aneuploidy, other than unbalanced translocation, was reported to be similar to that of the healthy population.[18] Sonographic findings and pregnancy outcomes of the fetuses that had uncommon aneuploidy is described in this study (Table 3).

The role of ultrasonography in the first trimester has recently changed owing to non-invasive prenatal testing (NIPT) using cell-free DNA. In a study of Beulen et al.,[19] NIPT should not be recommended for the genetic evaluation of the etiology of ultrasonography anomalies, because its negative predictive value is inferior to that of conventional karyotyping and microarray analysis. Srebniak et al.[20] reported that chromosome aberration will be missed by NIPT in 2-10% (depending on the type of analysis) of cases with an enlarged NT (≥3.5 mm) because of the current limitations of NIPT. Because the frequency and distribution of abnormal karyotypes reported in their study were also similar to those in our study population, missing rates of NIPT for chromosomal aberrations may be similar in pregnant Korean women. Clinicians should consider this limitation when they counsel patients who had fetuses with NT above 3.5 mm.

In conclusion, the incidence of chromosomal abnormalities of Korean fetuses with NT thickness above 99th percentile increases with NT thickness, and the prevalence and distribution based on NT thickness were very similar to those of Caucasian fetuses in previous reports. Additionally, we described sonographic findings and pregnancy outcomes of uncommon aneuploidies. We hope that our experiences will be helpful to obstetricians while counseling patients who have fetuses with increased NT thickness.

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