The Value of First Trimester Nuchal Translucency Measurement in Prediction of Cardiac Anomalies in Low Risk Pregnancies

Düşük Riskli Gebelerde Fetal Kardiyak Anormalliklerin Öngörüsünde Birinci Trimesterde Ense Kalınlığı Ölçümünün Değeri

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ABSTRACT Objective: To determine fetal aneuploidy and to assess the value of increased nuchal translucency (NT) to detect congenital cardiac defects (CCD) at 11-14 weeks of gestation. **Material and Methods:** Nine hundred and fifty six women at 11-14 weeks of gestation were enrolled. Screening was performed by calculating the risk from maternal and gestational age, which was adjusted with the NT measurement and maternal serum biochemical markers. An adjusted risk of >1:270 was considered a positive screening test in which case fetal karyotyping was recommended. In cases where the NT was ≥99th percentile for gestational age, echocardiography was performed. All infants underwent examinations for cardiac defects after birth. **Results:** Screening was positive in 21% (203/956) of fetuses. Fetal karyotyping was determined prenatally in 123 (12.9%) cases. Screening test displayed 60% sensitivity, 78.9% specificity, 1.48% positive predictive value (PPV) and 99.7% negative predictive value (NPV) for detecting fetal aneuploidies. For detection of cardiac anomalies, increased nuchal translucency had 28.6% sensitivity, 82.08% specificity, 1.16% PPV and 99.26% NPV. The overall diagnostic value of an increased NT for detection of CCD was 81.7%. **Conclusion:** Screening for fetal aneuploidy by maternal age, nuchal translucency and serum marker measurements can be effective for the detection of fetal abnormalities and during first trimester screening for aneuploidy, fetuses with increased translucencies must be monitored closely with prenatal echocardiography.

Key Words: Nuchal translucency measurement, cardiac abnormalities, screening

ÖZET Amaç: Bu çalışmanın amacı, 11-14. gebelik haftalarında fetal anöploidinin saptanması ve artmış nukal kalınlığın, konjenital kardiyak defektleri tespit etme yeteneğinin araştırılmasıdır. **Gereç ve Yöntemler:** Bu çalışmaya 11-14. gebelik haftasında olan, rastgele seçilmiş 956 gebe katılmıştır. Tarama işlemi, anne ve gebelik yaşına bağlı riskin, ense kalınlık ölçümü ve anne serumundaki biyokimyasal ölçümlerin birlikte değerlendirilmesi sonucunda kestirilmesiyle yapılmıştır. Tahmin edilen riskin 1:270'in üzerinde çıktığı durumlarda tarama testi pozitif olarak kabul edilmiştir. Bu sınırın üzerindeki değerlerde fetal karyotipleme önerilmiştir. Ense kalınlığının, o gestasyon haftası için belirlenmiş olan %99'luk yüzdeliğin üzerinde bulunduğu durumlarda, fetal ekokardiyografi deneyimi olan birisi tarafından, gebeliğin 18. ile 22. haftaları arasında kardiak tarama uygulanmıştır. Doğumdan sonra tüm bebekler kardiyak anomali açısından muayene edilmiştir. **Bulgular:** Tahmin edilen riskin 1:270'in üzerinde bulunduğu durumlarda fetusların %21 (203/956)'inde tarama testi pozitif olarak bulunmuştur. Prenatal olarak 956 olgunun 123 (%12.9)'üne fetal karyotipleme uygulanmıştır. Fetal anöploidilerin saptanmasında tarama testinin duyarlılığının %60, özgüllüğünün %78.9, pozitif kestirici değerinin %1.48 ve negatif kestirici değeri (NKD)'nin %99.7 olduğu bulunmuştur. Kardiyak anomalilerin saptanmasında birinci trimesterde ense kalınlığı değerindeki artışın kardiyak defekti saptamadaki duyarlılığının %28.6, özgüllüğünün %82.8, PKD'nin %1.16 ve NKD'nin %99.26 olduğu belirlenmiştir. Genel olarak gestasyon haftası için belirlenmiş olan %99'luk yüzdeliğin üstündeki bir ense kalınlığı ölçümünün fetal kardiyak defektin saptanmasındaki tanısal değeri %81.7 olarak bulunmuştur. **Sonuç:** Fetal anöploidi taraması için anne yaşı, ense kalınlığı ve serum belirteç ölçümleri fetal anormalliklerin saptanmasında etkindir ve birinci trimester taraması esnasında ense kalınlığı artmış bulunan fetuslar kardiyak defekt açısından artmış riske sahiptirler; bu tür olguların, yakın takip ile özellikle fetal ekokardiyografi ile değerlendirilmeleri uygun bir yaklaşım olacaktır.

Anahtar Kelimeler: Ense kalınlığı ölçümü, kalp anormallikleri, tarama

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Cardiac defects are the most common congenital abnormalities. Recently there has been much interest in the use of sonography in the first trimester. First trimester sonographic screening for fetal cardiac abnormalities by NT thickness measurement in high-risk populations is feasible.[1] Perceived advantages of such first trimester diagnosis may include decreases in surgical and psychological morbidity by allowing the option of an early versus late termination of pregnancy.[2]

Preliminary data on unselected populations have suggested that 41%-65% of fetal structural abnormalities can be detected and that the incidence of such structural anomalies is around 1%.[3] Routine prenatal care of all pregnant women by NT measurement at 10–14 weeks of gestation enabled us to detect fetal aneuploidies, congenital cardiac malformations and other genetic conditions in unselected populations.

Although there is a high prevalence of cardiac defects, the majority of them are still missed because they are usually isolated. Postmortem studies of both chromosomally normal and abnormal fetuses with increased NT have shown an increased incidence of cardiac defects.[4]

The objective of this study was to determine the fetal aneuploidy at 11-14 weeks of gestation and to examine the ability to detect cardiac defects only with increased NT thickness at 11–14 weeks of gestation.

MATERIAL AND METHODS

First trimester scans are offered to all pregnant women who visit our unit. Thus, this study was not approved by the ethical committee, but we obtained informed consents from the parents at the beginning of pregnancy. Only viable singleton pregnancies were included in the study. We studied prospectively 956 viable fetuses at 11-14 weeks visiting our obstetrics department between May 2004 and September 2006. In all cases, there was an unremarkable maternal history including a regular menstrual period and absence of oral contraceptive use or pregnancy during the previous 3 months. Fetuses with extracardiac anomalies, cardiac arrhythmias, history of maternal and paternal congenital heart diseases, diabetes mellitus, polyhydramnios and maternal infection were excluded from the study. The pregnancy was examined for the number of fetuses and measurement of crown-rump length and the NT thickness. Identification of stomach, bladder and extremities were recorded. Cardiac assessment was performed at 18–22 weeks of gestation for fetuses with increased NT.

The screening policy of the hospital was explained in detail and both screening and diagnostic tests for the detection of fetal aneuploidy were discussed. All measurements were performed by one experienced sonographer who was a holder of the Fetal Medicine Foundation Certificate of Competence for first trimester scanning using trans-abdominal ultrasound (Shimadzu SDU 1200 Tokyo, Japan). Maximal anatomical survey was attempted analogous to the criteria used for second trimester anomaly scans.[5] NT was measured in the sagital plane as the maximal sonolucent zone between the inner aspect of the fetal skin and the outer aspect of the cervical spine. The NT was considered to be increased if the measurement was greater than or equal to the 99th percentile for gestational age.[6] Screening was performed by estimating the background risk due to maternal age and this was adjusted for the NT thickness measurement and maternal serum biochemical markers, which were pregnancy-associated plasma protein A and free beta human chorionic gonadotropin.[7] Maternal serum was measured using the Kryptor analyzer (Brahms Diagnostica). The distribution of multiples of median (MoM) of the parameters was defined and normative values were established. The results were adjusted according to gestational age, maternal body weight and smoking. Demographic details and ultrasound findings including crown-rump length and NT thickness were entered into a computer database at the time of scanning. Adjusted risk of more than 1:270 was considered a positive screening test accounting for an estimated 5% false positive rate.[8] Fetal karyotyping was recommended for pregnancies with an adjusted risk over 1:270.

Both the intra and inter-observer variability of the measurements were tested by assessing different components of variability.[9] For each pregnancy at least three measurements were recorded.

In cases where the NT was greater than or equal to the 99th percentile for gestational age, cardiac scans were performed by an expert in fetal echocardiography and included assessment of the position of the heart, four-chamber view, the outflow tracts and venous return combined with color and Doppler flow images at 18-22 weeks gestation.

The abnormal karyotype results of prenatal and postnatal samples were obtained from the local cytogenetics laboratory.

All infants were examined for cardiac defects in their routine examinations after birth by the clinicians from the Department of Pediatrics. The examination findings of the pediatricians (by auscultation, when suspected by echocardiography, etc) were considered the golden standard for cardiac anomaly. The sensitivity, specificity, PPV and NPV of increased NT for detection of cardiac anomaly were calculated with respect to postnatal examination results. Thangoroopan et al. stated that there was incremental diagnostic value in the performance-detailed postnatal cardiac assessment in children of women with congenital heart disease who had already undergone fetal echocardiography.[10]

RESULTS

Each fetus was measured once during the period 11–14 weeks. The mean gestational age at scanning was 12^{+3} weeks (range 11-14). The incidence of anomalous fetuses was 0.5% (5/956). The gestational age at the time of nuchal translucency measurement ranged from 11.2 to 14.1 weeks (mean 12.3). The median maternal age was 34 years (min 18, max 43) and the median crown-rump length was 51 mm (46-79 mm). Table 1 shows the analysis of calculated risks according to gestational age.

Screening was positive in 21% (203/956) of fetuses when the adjusted risk was more than 1:270. Only 112 of those women (55.1%) demanded karyotyping. Additional 11 women desired fetal karyotyping due to their anxiety about anomalous fetuses in low risk patients. Consequently, prenatal fetal karyotyping with amniocentesis was done in 123 out of 956 (12.9%) cases. We did not have any pregnancy loss related to amniocentesis. The fetal karyotype was abnormal in 5 (0.53%) including 2 with trisomy 21 (40%), one with trisomy 13 (20%), one with trisomy 18 (20%) and one with

TABLE 1: Analysis of the frequency of nuchal translucency measurements, adjusted risk and gestational age in relation to an abnormal karyotype.

Gestational Age	No Screened	No of NT $\geq 99^{th}$ percentile	No of Risk >1:270	Total No of Aneuploidies
11^{+0}-11^{+6}	138	34	14	1
12^{+0}-12^{+6}	451	67	105	3
13^{+0}-13^{+6}	367	71	84	1
Total	956	172	203	5

NT: Nuchal translucency.

TABLE 2: Cases of aneuploidies and their relation with gestational age, maternal age and ultrasound findings.

Case	NT (mm)	Gestation	Age	USG	Karyotype
1	3.4	12	31	Cystic Hygroma	47,XY+18
2	2.8	12	28	Increased NT	47,XX+21
3	2.6	13	25	Increased NT	69,XXY
4	1.4	12	29	Cystic Hygroma	47,XX+13
5	1.2	13	38	Increased NT	47,XY+21

NT: Nuchal translucency; USG: Ultrasonography.

TABLE 3: Data obtained from screening for fetal aneuploidies using a cut off level of 1:270.

Risk	Aneuploid	Euploid	Total
>1:270	3	200	203
≤1:270	2	751	753
Total	5	951	956

triploidies (20%) (Table 2). Based on the data shown in Table 3, screening test had 60% (3/5) sensitivity, 78.9% (751/951) specificity, 1.48% (3/203) PPV and 99.7% (751/753) NPV for detecting fetal aneuploidies.

The second trimester anomaly scans were carried out on fetuses with normal karyotype and in the cases of aneuploidy that did not show persistent nuchal edema. Among the chromosomally normal fetuses the following abnormalities occurred: a case of cleft lip, two cases of single umbilical artery, a mild cerebral ventriculomegaly, and four cases of hyperechogenic cardiac ventricular focus in the left ventricle. In the cases of cleft lip and single umbilical artery, the nuchal translucencies were greater than the 99th percentile for gestational age. On the other hand, fetuses with mild ventriculomegaly showed normal NT measurement. The median interval between the first and second measurements was not significantly different in normal and chromosomally abnormal fetuses.

The fetuses with a nuchal translucency of greater than or equal to the 99th percentile for gestational age were examined by two or more examiners but those with normal nuchal translucency by only one examiner. In 42 fetuses four measurements of nuchal translucency thickness were made by two operators with a total of 336 measurements. This displayed that the intra and inter-observer reproducibility in measuring fetal nuchal translucency thickness was less than 0.31 mm and 0.35 mm, respectively (95% confidence interval).

Screening for cardiac malformations was performed prenatally with fetal echocardiography in 98 fetuses with an increased NT and normal karyotype. The remaining 74 patients with an increased NT did not accept or come for the screening. Among the screened 98 patients one case of stenotic pulmonary trunk and one case of ventricular septal defect were found. The remaining 96 fetuses had a normal cardiac scan and no postnatal cardiac defects; in addition, 74 patients who could not be screened prenatally also had no postnatal cardiac defects. In fetuses that had normal NT measurements, postnatal assessment showed major cardiac abnormality in five, one of which was great artery transposition. Those fetuses had no other risk factors related to congenital anomalies. For detection of cardiac anomalies, increased NT had 28.6% sensitivity, 82.08% specificity, 1.16% PPV and 99.26% NPV (Table 4). The overall diagnostic value of a NT greater than or equal to the 99th percentile for gestational age for detection of cardiac heart disease was 81.7%.

DISCUSSION

Certain abnormalities are more easily detectable at 11–14 weeks than others. The value of ultrasound examination on these weeks with the measurement of fetal NT and its implementation as a screening test for fetal aneuploidy is controversial. Increased fetal NT thickness is a common phenotypic expression of trisomy 21 and other chromosomal abnormalities, but it is also associated with fetal death and a wide range of fetal malformations, deformations, dysgenesis, and genetic syndromes.[11] In a study a 40% risk of fetal demise was reported when NT measurement was ≥5 mm.[12] Routine first trimester NT screening was suggested to be an acceptable procedure provided that sonographers were certified and subject to external quality control[9]. Recent studies have attempted to assess the value of NT screening in low risk populations.[13,14]

TABLE 4: Detection of cardiac anomalies with increased nuchal translucency.

	Cardiac Anomaly	No Cardiac Anomaly	Total
NT ≥ 99th percentile	2	170	172
NT < 99th percentile	5	779	784
Total	7	949	956

NT: Nuchal translucency

A number of recent studies have described the use of first trimester maternal serum biochemistry in screening for chromosomal abnormalities.[15] Thus, it would appear that combining maternal age, first trimester maternal serum biochemistry, NT measurement and detection of structural abnormalities could further improve the detection rate of chromosomal abnormalities in the first trimester.

In the first arm of the study, the efficiency of first trimester for detection of aneuploidies was assessed and the screening test was found to have a sensitivity and a specificity of 60% and 78.9%, respectively. The sensitivity of the screening test in our patients is somewhat lower than that reported for other low risk populations.[16] This may be attributed to the lack of standardization of NT, CRL and serum biochemical marker measurements for the Turkish population. Normative values and the distribution parameters of first trimester screening markers in Turkish women should be established.

In the second arm of the study, the value of increased NT in the detection of CCD at 11-14 weeks of gestation was assessed. The frequency of major cardiac defects were reported to be increased in fetuses with an increased NT.[17-19] Although there is considerable variation in reported studies, sensitivities varying from 8 to 56%.[16,18,20-22] A meta-analysis suggested that the use of a NT above the 99th percentile might end up with the detection of approximately 30% of congenital heart defects, which is a similar rate to that in the present study.[23] The prevalence of CCD and the sensitivity of a NT greater than or equal to the 99th percentile for gestational age for the detection of CCD were 7.3/1000 and 29%, respectively in this studied population; however, it should be noted that some of the reported studies used a 2.5 mm or 95 percentile cut-off for the detection of CHD instead of the 99 percentile cut-off used in the present study.

In a retrospective study involving nearly 30.000 pregnancies Hyett et al reported that about 56% of major cardiac defects were found in the sub-group with increased translucency and suggested that this might therefore constitute the most effective method of screening for major abnormalities of the heart and great arteries.[12] Using NT measurements, Wald et al reported that the estimated detection rate of CCD for a 5% false-positive rate was 52% (95% CI: 42-71) and reported that prenatal screening for CCD using NT measurements was likely to be effective; moreover, given that NT measurement was already in use as part of prenatal screening for Down syndrome, they suggested that this was the ideal time to set up demonstration projects to validate these results.[24] Other studies, including this one, have failed to reproduce such a close association and have reported different rates. The overall diagnostic value of a NT greater than or equal to the 99th percentile for gestational age for the detection of CCD was 81.7% in this study. This implies that it would be reasonable to consider fetuses with an increased NT having increased risk for CCD and to monitor them accordingly, especially with a prenatal echocardiography scan. In our view, increased translucency should constitute an indication for fetal echocardiography by a specialist.

Certain anomalies in the first trimester have a uniquely different appearance compared with the second trimester. A notable example is the diagnosis of cardiac defects. A specialist scan starting from 14 weeks can effectively reassure the majority of parents that there is no major cardiac defect. In the cases with a major cardiac defect, the early scan may lead to the correct diagnosis or at least raise suspicions so that follow up scans are carried out. Most previous studies were carried out transvaginally, but in the vast majority of our cases, sufficiently good views were obtained for effective examination using the transabdominal approach. At 14 weeks, the grey scale alone is not sufficient for accurate examination of the heart, and we found it necessary to include color flow also to confirm normal forward flow to both ventricles and identify the outflow tracts.

The benefit of the test has to be evaluated in unselected low risk populations. The detection of cardiac abnormalities in the first trimester in this study was below what one might expect when compared with the second trimester scan. Monni et al stated that in fetuses with enlarged NT and normal karyotype, there were 30 structural defects

(4%), and among those, 15 were heart defects (2%).[25] This may be due to the relatively small size of the fetal heart in the first trimester and even with high resolution transvaginal sonography, small defects will always be very difficult to diagnose. There is a clear need to recognize the normal anatomical structure in the first trimester and it is important to have a good understanding of the embryological basis of when and how defects develop.

In conclusion, there is a need to establish normative values and distribution parameters of first trimester screening markers in Turkish women and during first trimester screening for aneuploidy fetuses with increased translucencies must be considered to have increased risk for congenital heart defects and must be monitored closely with prenatal echocardiography. The question of whether adding a 12-week NT scan to a second trimester fetal anatomy scan would increase the prenatal detection rate of major cardiac malformations can be answered in a randomized controlled trial.

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