Does Down Syndrome Have an Effect on Impaired Myocardial Performance in Fetuses with Increased Nuchal Translucency?

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Abstract

Objective: We aimed to evaluate myocardial performance in fetuses with increased nuchal translucency. Method: Cases with increased NT without any associated structural anomalies were enrolled in this study. The study group consisted of 53 pregnancies complicated with thickened NT $>$ 3.5 mm. Forty-six gestational age-matched pregnant women whose fetuses had normal NT thickness were enrolled in the study as the control group. The TEI index was evaluated before performing CVS in the group with an increase in NT. Karyotype analysis was performed via CVS in all patients with increased NT. In both groups, detailed fetal sonographic examinations, including fetal echocardiograms, were performed between 18 and 24 weeks of gestation. Results: The differences between normal and increased NT groups in terms of isovolumetric relaxation time (IRT), ejection time (ET), and myocardial performance index (MPI) variables were found to be statistically significant (p values of 0.023, 0.004, and $<$ 0.001, respectively). For IRT and MPI variables, the median values of the group with an increase in NT were found to be significantly higher than that of the normal NT group, whereas the median value of the ET variable of the group with increased NT was significantly lower than that of the normal NT group Conclusion: The MPI significantly increased in the group with increased NT, but no difference was observed between those with and without Down syndrome. This suggests that increased NT is caused by cardiac dysfunction, whether or not Down syndrome is present.

Introduction:

The formula proposed by Tei to evaluate myocardial performance in adult humans later was later designated as the TEI index [1]. This index was started to be used in fetuses, nomograms were made according to the weeks of gestation, and it was even started to be used in the first trimester of pregnancy [2–4].

In fetal life, fetal myocardial performance has been investigated in many fetal and maternal diseases (diabetes mellitus, twin-to-twin transfusion syndrome, intrauterine growth restriction, fetal hematological diseases, fetal congenital cardiac and thoracal diseases, and fetal chromosomal abnormalities) that are thought to theoretically affect myocardial performance in the fetuses [4–11].

The aim of this study was to evaluate the effect of increased nuchal translucency (NT) on myocardial performance index in fetuses without cardiac anomaly in the first trimester and to determine whether there is a difference in myocardial performance between those with and without trisomy 21.

Material-method

This study was conducted at the Health Sciences University Kanuni Sultan Suleyman Education and Research Hospital between April 2018 and July 2019. The study protocol was reviewed and approved by the local ethics committee. Informed consent was obtained from all patients prior to involved the study. Cases with increased NT without any associated structural anomalies were enrolled in this study as the **study group** . The study group consisted of 53 pregnancies complicated with thickened NT $>$ 3.5 mm. Forty-six gestational age-matched pregnant women whose fetuses had normal NT thickness were enrolled in the study as the **control group** .

When an increase in NT was detected, those with problems on the first trimester ultrasound scan (fetal heart, bladder, stomach, spine, double umbilical artery, ductus venosus, lower and upper extremities, and cranium) were not included in the study. Patients who did not accept chorionic villus sampling (CVS) were excluded from the study. The other exclusion criteria included several parameters: (1) other chromosomal disorders except Down syndrome, (2) multiple pregnancies, (3) fetal ascites and hydrops, and (4) chronic maternal diseases, such as diabetes mellitus, chronic hypertension, and/or chronic renal disease.

In the study group, detailed fetal sonographic examinations, including fetal echocardiograms, were performed between 18 and 24 weeks of gestation in those with normal karyotype results. Similarly, the control group was also evaluated. Fetuses with significant cardiac anomalies were excluded from the study. However, those with mild tricuspid regurgitation, echogenic cardiac focus, and minimal pericardial effusion were not excluded from the study. Fetal anatomic screening performed during advanced gestational weeks could not be performed for those whose pregnancy termination was performed due to trisomy 21 in the study group.

The TEI index was evaluated before performing CVS in the group with an increase in NT. Karyotype analysis was performed via CVS in all patients with increased NT. Transabdominal ultrasound examinations were performed by a single sonographer using a Voluson E 6 (GE healthcare Ultrasound, Milwaukee, WI, USA) ultrasound machine equipped with a RAB 6D (2–7 MHz) probe.

The sample volume was placed in the left ventricle below the anterior leaflet of the mitral valve, which is closed to outflow of the left ventricle. Isovolumetric contraction time (ICT) was measured from the end of the A wave to the onset of the aortic outflow, ejection time (ET) from the onset to the end of the aortic flow, and isovolumetric relaxation time from the end of the aortic flow to the onset of the E wave (Figure 1).

Statistical analysis

Differences between groups for categorical variables were analyzed using the chi-square or Fisher's exact test where appropriate. The factors that may have correlated with the study and control group were analyzed independently (univariate analysis) by either the Student's t- or Mann–Whitney U test where applicable. Descriptive statistics were presented as percentages or mean $\pm$ standard deviation and median (minimum–maximum). In order to define independent risk factors of variables, we used a multiple logistic regression analysis and adjusted odds ratios. Their confidence intervals were calculated. The correlation between NT and ET was investigated using Spearman's correlation coefficient. The results were analyzed with SPSS for Windows 15.0. and p-values < 0.05 were considered statistically significant.

Results

Of the 53 patients with increased NT in the study group, 20 had Down syndrome, and 33 patients had a normal karyotype. In the control group, 46 patients with normal NT were included in the study.

Accordingly, the differences between normal and increased NT groups in terms of isovolumetric relaxation time (IRT), ejection time (ET), and myocardial performance index (MPI) variables were found to be statistically significant (p values of 0.023, 0.004, and < 0.001, respectively). For IRT and MPI variables, the median values of the group with an increase in NT were found to be significantly higher than that of the normal NT group, whereas the median value of the ET variable of the group with increased NT was significantly lower than that of the normal NT group (Table 1).

In the study group, significant differences were found between the subgroups (normal and abnormal karyotype) in terms of gravidity and NT variables (p values of 0.018 and 0.033, respectively) as shown in Table 2. Accordingly, the trisomy 21 group was significantly higher in terms of gravidity and NT medians. Multiple logistic regression analysis was done for gravida and NT, and the results are summarized in Table 3. In the group with increased NT, there was no statistically significant difference in MPI between those with Down syndrome and normal karyotype ($p = 0.419$).

After examining the variables one by one, the high gravity and NT increase appears to be significantly higher in the trisomy 21 group (p values of 0.018 and 0.033, respectively). Multiple logistic regression analysis was done for gravida and NT and the results are summarized in Table 3.

According to Table 3, the increase one in gravidity, increased the probability of Down syndrome to 1.55-fold, and the increase of 1 mm in NT caused an increase in probability of Down syndrome of 1.34-fold.

Spearman's correlation coefficient was used to examine the variables associated with NT change, and as a result, a significant negative correlation was found between NT and ET in which one was increasing while the other was decreasing ($r = -0.201$; $p = 0.046$). However, a positive and significant correlation was found between NT and MPI variable ($r = 0.261$; $p = 0.009$) as shown in Figure 2.

Discussion

Increased NT thickness in the fetus is a well-defined sonographic marker used in the diagnosis of chromosomal diseases. At the same time, NT increases in congenital heart diseases [11]. Most of the chromosomal anomalies also have congenital heart diseases. In fetuses with chromosomal anomaly without congenital heart disease, an increase in NT was observed; however, this increase was attributed to other causes, such as jugular lymphatic distention (12).

It was found that as the gestational week increases, the MPI value also increases [2,3]. In the literature, the nomograms that were constructed according to the weeks of gestation were different. In some studies, ICT, IRT, and ET times were determined according to the opening or closing of the mitral and aortic valves [2,3,8,13,15], while in others, the mentioned times were determined according to the beginning or end of the E, A waves, and aortic ejection [4,6,14]. The former one is named as modified myocardial performance index (Mod-MPI) [13]. Differences were observed between MPI values even among the studies using the same method [2,3].

We tried both methods before we started this study. Values were monitored similarly. In four chamber images obtained during the first trimester, the cursor was placed close to the interventricular septum on the left just below the mitral valve, and the boundaries of the E and A waves and the ejection of the aorta were sharp and clear (Figure 1). In evaluating myocardial performance with the TEI index in the first trimester, it was easier to use E, A waves, and aortic ejection.

The MPI values that were found in the first trimester fetal cardiac function study conducted by Russell et al. and the values found in the nomogram study performed by Luewan et al. were quite similar to the values in our study [3,15]. In our study, while the beginning and the end of the E, A waves, and aortic ejection borders were used as reference, Mod-MPI was used in these studies. In the Mod-MPI method suggested by Hernandez-Andrade et al., it was suggested that the intra- and inter-observer variation was low [13]. However, differences were observed between MPI values even among the studies using the Mod-MPI method [2,3]. For whichever method is selected, if the same method is applied by a single sonographer in the study and control group, the results found can reveal differences between the two groups.

In a study conducted by Huggon et al., which was similar to our study, myocardial performance in fetuses with increased NT in the first trimester was studied. No significant differences compared to the group with normal NT were found [4]. In addition, those with trisomy 21 had a significantly lower TEI index. Apart from this paper, we could not find any article about the decrease in TEI index in fetuses with trisomy 21. Clur et al. demonstrated that fetuses with trisomy 21, regardless of heart disease, had an increase in MPI [5]. In the study conducted by Mula et al., patients with thick NT had normal heart function, but diastolic dysfunction was observed in those with trisomy 21 [16].

ET decreases in systolic dysfunction. In our study, whether there was a correlation between NT increase and ICT, IRT, ET, and MPI values was investigated, and it was observed that ET decreased and IRT increased as NT increased. Since the formula is $MPI = (ICT + IRT)/ET$, MPI will naturally increase as ET decreases and IRT increases. In our study, fetuses with cardiac anomaly were not included. Systolic dysfunction was observed in the thickened NT group. In this study, different from the literature, there was no difference between those with and without Down syndrome in the NT group with thickened NT. Systolic dysfunction can be observed in fetuses with high NT whether or not Down syndrome is present.

Additional findings except the main subject of the study: When the TEI index was examined in the study group with NT $>$ 3.5 mm, CVS was applied and after the determination of the karyotype result, NT values and gravida in Down syndrome fetuses were significantly higher in the study group compared to the normal ones and those with Down syndrome only (Tables 2 and 3). According to our study, 1 mm increase in NT increases the risk of Down syndrome by 1.34 times, while one increase in gravida led to an increase in the the risk of Down syndrome by 1.55 times.

Limitations of the study: Since the study was performed in the first trimester, whole fetal anatomic examination is limited. In the control group, fetal echocardiograms and detailed fetal sonographic examinations were performed at 18 to 24 weeks of gestation. However, due to early termination for those diagnosed with trisomy 21 in the study group, detailed fetal sonographic examination could not be performed at 20 to 24 weeks of gestation.

In conclusion, the MPI significantly increased in the group with increased NT, but no difference was observed between those with and without Down syndrome. This suggests that increased NT is caused by cardiac dysfunction, whether or not Down syndrome is present.

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