Cardiac defects and ductus venosus flow in fetuses with increased nuchal translucency

ABSTRACT

Objective
The purpose of this study was to evaluate ductus venosus flow velocities and a possible relationship with the type of cardiac defect in fetuses with increased nuchal translucency (NT).

Methods
Seventy-two fetuses with normal NT and 137 fetuses with increased NT (>95th percentile) were evaluated. The ductus venosus pulsatility index for veins (PIV), late diastolic velocity (velocity during atrial contraction (a-V)), and intracardiac velocities were evaluated. In case of pregnancy termination, a post-mortem examination was performed. Cardiac defects were grouped into septal defects, left and right inflow obstruction, left and right outflow obstruction and other defects. Data were evaluated by multilevel analysis.

Results
A cardiac defect was found in 45 fetuses with increased NT. Fetuses with increased NT showed a higher ductus venosus PIV and lower a-V compared to fetuses with a normal NT (P <.05). Within the group of fetuses with increased NT, a higher PIV and lower a-V were found in case of a cardiac defect compared to cases with a normal heart (p<.001). No differences in PIV and a-V were found between the types of cardiac defects. Intracardiac velocities showed no differences between fetuses with normal and increased NT, irrespective of the presence of a cardiac defect.

Conclusion
Ductus venosus flow velocities in fetuses with an increased NT are not related to a certain type of a cardiac defect. This indicates that the altered ductus venosus flow velocities found in fetuses with an increased NT can not be explained by cardiac failure due to a specific altered cardiac anatomy.
INTRODUCTION

Sonographic measurement of nuchal translucency (NT) in human fetuses between 11 and 14 weeks of gestation is a widely used screening method to identify chromosomal abnormalities.1,2 Increased NT is also associated with structural anomalies such as cardiac defects and several genetic syndromes.3 Several mechanisms, such as disturbance in lymphatic development, an altered extracellular matrix, and cardiac failure have been proposed to play a role in the pathophysiology of increased NT.4-9 Cardiac failure has been suggested because of the high proportion of cardiovascular malformations and abnormal ductus venosus Doppler flow velocities in both euploid and aneuploid fetuses with increased NT.4,5,10-13 It was hypothesized that a cardiac defect could result in an impaired cardiac function resulting in a lower velocity of the ductus venosus and subsequently enlargement of the NT.4,12 To our knowledge, however, no study has been performed to assess whether altered ductus venosus flow velocities in fetuses with increased NT are related to a specific type of cardiac defect or anatomy.

The goal of this study was to evaluate whether ductus venosus flow alterations in fetuses with increased NT can be explained by hemodynamic changes due to a certain type of cardiac defect. In addition, the ductus venosus flow velocities in relation to the intracardiac velocities were assessed. The hypothesis that increased NT is caused by cardiac failure due to a certain type of cardiac defect was tested.

MATERIALS AND METHODS

Women referred to our hospital for tertiary care because of increased NT were asked to participate in the study. A total of 135 singleton and 2 bichorial twin pregnancies were examined. Two of these 137 fetuses were part of a bichorial twin of which only the fetuses with increased NT were included. Increased NT was defined as NT above the 95th percentile. A control group of 73 fetuses with normal NT was created from women attending our hospital for first trimester screening. All patients received written information and gave informed consent. The medical ethical committee of the VU University Medical Center approved the study.

Gestational age was calculated on the basis of the reported last menstrual period and adjusted according to crown-rump length if appropriate. After inclusion, ultrasound examinations were performed weekly by 3 experienced sonographers (Y.M.d.M., M.C.H., and M.N.B.) between 11 and 17 weeks’ gestation (Table 1). The number of examinations differed because of different gestational ages at the initial scan and patients’ cooperation.

NT was measured using a transabdominal probe (4-8 MHz; Voluson 730 Expert series, Voluson E8, GE Medical Systems Kretz Ultrasound, Zipf, Austria or 2-4 MHz; ATL HDI 5000; Advanced Technology Laboratories, USA) according to the guidelines of the Fetal Medical Foundation.14
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Flow velocity waveforms of the ductus venosus were obtained from a right ventral mid-sagittal plane of the fetal trunk during fetal quiescence. Color flow was used to visualize the venous circulation. The pulsed Doppler gate (size 0.7 -1.5mm) was placed in the inlet of the ductus venosus where it originates from the umbilical vein. Care was taken to avoid contamination of the flow waveforms of the umbilical vein and inferior vena cava. The interrogation angle was kept as low as possible and always less than 60 degrees. An average of 3 consecutive high-quality waveforms was used to analyze the peak systolic velocity, late diastolic velocity (velocity during atrial contraction (a-V)) and time-average velocity. These variables were used to calculate the pulsatility index for veins (PIV = systolic velocity – a-V / time-averaged velocity). To obtain flow velocity waveforms across the mitral and tricuspid valves, the pulsed Doppler sample gate was placed just distal from the valves in an apical 4-chamber view in the absence of fetal movements. Adjustment was made for the insonation angle which never exceeded 40 degrees. Peak flow velocities in early diastole (E) and late diastole with atrial contraction (A) were measured, and the E/A ratio was calculated. Digital images of each examination were stored.

The cardiac defects were grouped into 6 categories according to the hemodynamic classification adapted from Atzei et al:16 septal defects, left inflow obstruction, right inflow obstruction, left outflow obstruction, right outflow obstruction, and other defects. Where more than 1 of the categories potentially applied, obstruction was given precedence over a septal defect. Karyotyping was performed by chorion villus sampling or amniocentesis. In case of termination of the pregnancy, suction aspiration was performed, or labor was induced. A post mortem morphological examination was carried out if the patient approved. The fetus or aspiration tissue was fixed in formalin 4%. Subsequently, post-mortem evaluation of the whole fetus or the fetal heart (in case of suction aspiration) was carried out using a dissection microscope. An extensive sequential segmental analysis of the heart was performed by an experienced cardiac morphologist (M.M.B.). In ongoing pregnancies, a second-trimester sonographic examination was performed in all cases. After delivery, the parents completed questionnaires concerning their neonate’s health. If necessary, medical records were studied to gain additional information. The ductus venosus indices PIV and a-V and intracardiac velocities of fetuses with normal NT and increased NT, with respect to the presence of a heart defect, were compared. Within the group of fetuses with increased NT, the ductus venosus PIV and a-V and intracardiac velocities of euploid and aneuploid fetuses were compared. Furthermore, within the group of fetuses

<p>| Table 1 Examinations per fetus (n=209) |</p>
<table>
<thead>
<tr>
<th>No. of examinations</th>
<th>Fetuses with normal NT (n= 72)</th>
<th>Fetuses with increased NT (n= 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
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<td>3</td>
<td>49</td>
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<td>4</td>
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<td>5</td>
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NT, nuchal translucency.
with a cardiac defect, the ductus venosus PIV and a-V and intracardiac velocities were assessed for the different types of cardiac defects.

Data were studied using General Estimating Equations analysis (SPSS version 15.0, Chicago, IL). This method takes into account the fact that the same patients are repeatedly measured and allows missing observations and irregularly spaced time intervals.

Variables indicating fetuses with normal NT, fetuses with increased NT without a cardiac defect, and fetuses with increased NT with a cardiac defect were used to create groups. Within the group of fetuses with increased NT and a cardiac defect, variables indicating septal defects, left inflow obstruction, right inflow obstruction, left outflow obstruction, right outflow obstruction, and other defects were used to create groups. We analyzed whether Doppler flow measurements of the compared groups differed significantly in relation to advancing gestational age. If necessary, a log-transformation was used to account for non-normality of the data. General estimating equation analysis was also used to assess a possible relationship between Doppler flow measurements and NT-size (correlation coefficient). The statistical significance level was set on $P = .05$.

RESULTS

In total, 73 fetuses with normal NT and 137 fetuses with increased NT were included in the study. In the group of fetuses with normal NT, 1 patient was excluded from further analysis because of an intrauterine fetal death at 28 weeks’ gestation due to fetal growth restriction. A postmortem examination revealed no abnormalities in this case. Follow-up was complete, and in all 72 cases, healthy infants were born. The characteristics of the included 209 fetuses are listed in table 2.

In case of increased NT, invasive tests were offered, but refused in 3 cases. In these cases, healthy neonates without dysmorphic features were born and were considered euploid. A normal karyotype was found in 83 of the 137 fetuses with increased NT (61%); 54 fetuses were aneuploid (39%). Figure 1 shows the disposition of the fetuses with increased NT included in

| Table 2 Characteristics of the fetuses with normal and increased NT at the first sonographic examination |
|-------------------------------------------------------------|-----------------|-----------------|
| Characteristics                                             | Normal NT (n=72) | Increased NT (n=137) |
| Maternal age, years                                         | 34.4 (3.6)       | 33.5 (4.5)       |
| Gestational age, weeks + days                               | 11^a^ (0^b^)     | 12^a^ (0^c^)     |
| NT, mm                                                      | 1.2 (0.4)        | 4.9 (2.4)        |
| Crown-rump length, mm                                       | 54.0 (5.9)       | 61.7 (10.1)      |
| NT, nuchal translucency.                                    |                 |                 |
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the study. The presence or absence of a cardiac defect of fetuses with increased NT was known by follow-up after birth or postmortem examination in 118 of the 137 fetuses (86%). In 14 of the 137 cases (5%) heart morphology was only assessed by prenatal sonography, and postmortem examination was refused. In 7 of these cases a cardiac defect was suspected. The cardiovascular anomalies (n = 45) included septal defects (n = 20, ventricular and atrioventricular), left inflow obstruction (n = 5, hypoplastic left heart syndrome) left outflow obstruction (n = 8, coarctation of the aorta, aortic valve atresia, and stenosis) right outflow obstruction (n = 5, tetralogy of Fallot, pulmonary valve atresia, and stenosis) and other (n = 7, cardiomyopathy, polyvalvular disease, and an aberrant right subclavian artery).

Ductus venosus flow velocities

The ductus venosus was successfully assessed in 181 of the 221 (82%) examinations of fetuses with normal NT and in 203 of the 251 examinations (81%) of fetuses with increased NT. The ductus venosus PIV was significantly higher in fetuses with increased NT compared to fetuses
with normal NT between 11 and 16 weeks' gestation (P <.05). Within the group of fetuses with increased NT, a significantly higher ductus venosus PIV was found in aneuploid fetuses compared to euploid fetuses and in fetuses with a cardiac defect compared to fetuses with a normal heart (P <.001). No significant differences in ductus venosus PIV were found between the different types of cardiac defects (Figure 2). Greater NT was associated with a higher ductus venosus PIV (r = 0.64, P <.001).

The ductus venosus a-V was significantly lower in fetuses with increased NT compared to fetuses with normal NT (P <.001) (Figure 3). Within the group of fetuses with increased NT, a significantly lower ductus venosus a-V was found in aneuploid fetuses compared euploid fetuses and in fetuses with an abnormal heart compared to fetuses with a normal heart (P <.001). No significant differences in ductus venosus a-V were found between the different types of cardiac defects (Figure 4). Greater NT was associated with a lower ductus venosus a-V (r = -0.61, P <.001).

**Intracardiac flow velocities**

In 187 of the 219 measurements of fetuses with normal NT (85%), intracardiac flow velocity waveforms (tricuspid and mitral valves) could be recorded. In 168 (77%) of the 219 measurements of fetuses with increased NT, intracardiac flow velocity waveforms could be obtained. No significant differences in the intracardiac velocities (E wave, A wave, E/A ratio) between fetuses with normal and increased NT were found (data not shown). Within the group of fetuses with increased NT, no significant differences in intracardiac velocities were found between fetuses with and without a cardiac defect. Within the group of fetuses with increased NT, aneuploid fetuses showed significantly lower E wave and A waves of the mitral and tricuspid valves.
compared to the euploid fetuses ($P < .05$). The E/A ratio of the mitral and tricuspid valves did not show significant differences (data not shown). No relationship between intracardiac flow velocities and NT size was found.
DISCUSSION

This study evaluated whether ductus venosus flow alterations in fetuses with increased NT can be explained by hemodynamic changes due to a certain type of cardiac defect. In the group of fetuses with increased NT, those with a cardiac defect showed a significantly higher PIV and a lower a-V of the ductus venosus. No significant differences were found between the different types of cardiac defects. Previous reports also showed a relationship between altered ductus venosus flow velocities in fetuses with increased NT and cardiac defects. However, to our knowledge, a study assessing increased NT and ductus venosus flow in relation to type of cardiac abnormalities has not been reported previously.

Impaired cardiac function due to cardiac defects has been suggested to play a role in the development of increased NT. Abnormal ductus venosus flow velocities could be the result of an increase in ventricular end-diastolic pressure due to impaired atrial contraction. Left and right heart obstructions, for example, pulmonary valve stenosis, could result in an increase in right ventricular pressure and a reversed flow in the ductus venosus during atrial contraction. Hyett et al. proposed that increased NT could be explained by overperfusion of the head due to preferential blood flow through the head and neck as a result of an obstruction of the aortic arch. However, in our data, no significant differences in ductus venosus PIV between left or right outflow obstructions and for example septal defects, were found. Also, not all fetuses with increased NT and abnormal ductus venosus flow waveforms had a diagnosis of a cardiac abnormality. Within the group of fetuses with increased NT, the aneuploid fetuses showed significantly lower E waves and A waves compared to the euploid fetuses which is in accordance with previous data of our group. However, within this group of fetuses, no significant differences in intracardiac velocities between fetuses with and without a cardiac defect were shown. The left and right ventricle function was not diminished in fetuses with increased NT because no differences were demonstrated in intracardiac velocities between fetuses with normal and increased NT. In addition, no other signs of cardiac failure such as pleural effusion and ascites were found in the fetuses with increased NT. Thus, the results of this study do not support the theory that higher right ventricular pressure is responsible for the alterations in ductus venosus flow velocities. A limitation of the study is the small sample size of the groups with a cardiac defect. The fact that no relation was found between cardiac defects that could influence the hemodynamics and ductus venosus flow velocities indicates that cardiac failure can not explain the altered ductus venosus velocities and pathophysiologic mechanism of increased NT.

Another suggested explanation for increased NT is a disturbance in lymphatic development. First-trimester fetuses with increased NT morphologically show nuchal edema, accompanied by distended jugular lymphatic sacs (JLS). Lymphangiogenesis starts with the development of the JLS, which normally reorganize into lymphatic nodes after 10 weeks’ gestation. Delayed reorganization of the JLS into lymph nodes could explain both transient and regional character of increased NT.
Because this study shows that altered ductus venosus flow velocities are not related to a specific type of cardiac defect such as outflow obstruction, we hypothesize that a mechanism other than cardiac failure is responsible for the alterations found. Interestingly, a recent longitudinal sonographic study by our group, investigating fetuses with increased NT and distended JLS, showed a higher jugular vein and ductus venosus PIV in those fetuses compared to fetuses with normal NT. A disturbance in venous endothelial differentiation was suggested as an explanation for these findings. Previous morphologic studies of both fetuses with increased NT and trisomy 16 mouse embryos, an animal model for trisomy 21, showed abnormal endothelial differentiation of the jugular venous-lymphatic system. Abnormal endothelial differentiation also has been reported to play a role in the development of cardiac defects. Altered endothelial differentiation could explain the finding that altered ductus venosus flow velocities in fetuses with increased NT are independent of a specific type of cardiac defect.

A broad range of abnormalities are associated with increased NT. One single explanation for the origin of increased NT is therefore not likely. A delay or disturbance in endothelial development and differentiation could be the common process related to the lymphatic abnormalities, cardiac defects, and altered ductus venosus and jugular vein flow found in fetuses with increased NT. We hypothesize that a disturbance in endothelial differentiation can vary from a delayed but physiological development to a more disturbed development. Aneuploid fetuses with increased NT probably endure a more severe disturbance in endothelial differentiation. Ductus venosus flow has been suggested as an additional marker in the first-trimester screening for aneuploidy. Our study, however, showed that greater NT was related to a higher ductus PIV and lower a-V of the ductus venosus. A recent study by Maiz et al. showed a similar association between NT-size and the a-V of the ductus venosus. In our opinion, this indicates that ductus venosus flow is not an independent marker in screening for aneuploidy.

In conclusion, we have shown that ductus venosus flow velocities in fetuses with increased NT are not related to a certain type of a cardiac defect. This indicates that the altered ductus venosus flow velocities found in fetuses with increased NT cannot be explained by cardiac failure due to specific altered cardiac anatomy.
REFERENCES


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