The Role of Nuchal Translucency in the Screening of Congenital Heart Defects

Rafael Frederico Bruns, Antonio Fernandes Moron, Carlos Geraldo Viana Murta, Luís Flávio de Andrade Gonçalves, Marina Maccagnano Zamith

OBJECTIVE
Assess the accuracy of the nuchal translucency (NT) measurement between 11 and 13 weeks and 6 days of gestation as a sonographic marker to screen for congenital heart defects (CHD).

METHODS
This is a multi-center retrospective study in which singleton gestations of euploid fetuses were analyzed. NT measurement was performed in the first trimester examination when the fetal crown-rump length (CRL) was 45 to 84 mm, according to the criteria established by the Fetal Medicine Foundation. The cases were followed up to one month postpartum to assess the presence of CHD.

RESULTS
Three thousand six hundred and sixty four gestations were analyzed, of which twenty newborn infants had some congenital heart defect up to the first month of life (prevalence of 0.55%). The median NT in fetuses with CHD was 1.70 mm, and 1.60 mm in fetuses without CHD. However, no statistically significant difference was observed between the two medians (Mann-Whitney test, p > 0.05). The NT sensitivity to detect CHD ranged from 15% to 20%, with a probability of false positive cases of 86.4% to 97.9%, depending on the cut-off point used. Odds ratio for CHD was high when compared to the classical indications for fetal echocardiography, ranging from 4.7 to 33.7, according to the cut-off point used.

CONCLUSION
Despite the low sensitivity of the test, increased NT is an important risk factor for CHD, and should be included in the strategy of prenatal screening for these diseases.

KEY WORDS
Nuchal translucency, congenital heart defects, screening, pregnancy, fetal echocardiography.
Congenital heart defects (CHD) comprise an important part of all major congenital malformations which affect 2% to 3% of newborn infants (NBI). The prevalence of CHD in the general population is estimated at 8:1000 live births. When fetal deaths are studied, the incidence of CHD ranges from 0.5% to 39.5%, according to the gestational age at which the fetal loss occurred. The earliest deaths are mainly associated with the presence of complex CHDs. An average of 35% of child deaths are related to CHD; therefore, CHDs are an important issue in the context of neonatal and child death.

Starting from the principle that the earlier the diagnosis of CHD is made the better the prognosis, some authors have studied the impact of the utilization of fetal echocardiography on the reduction of neonatal morbidity and mortality. Encouraging results are observed especially in the following CHDs: (1) hypoplastic left heart syndrome; (2) transposition of the great arteries; and (3) coarctation of the aorta.

Unfortunately, the detection of CHD in the prenatal period is low because the ultrasound specialist that performs the obstetric examination is not trained for a correct assessment of the anatomy of the heart. Population-based studies on the performance of routine examinations demonstrate disappointing detection rates ranging from 6% to 35%. In addition, the request of a specialized fetal echocardiography examination based on risk factors does not provide the detection of most of the CHDs.

Nuchal translucency (NT) is the hypoechoic space between the skin and the subcutaneous tissue that covers the cervical spine of the fetus. Since the beginning of the 1990’s several studies with small case series and high risk populations have demonstrated the association of increased NT thickness measured between eleven weeks of gestation and thirteen weeks and six days of gestation with the presence of chromosomal anomalies. The pathophysiological mechanisms that explain this transient sonographic marker are not well established yet. Some events that occur in this phase of pregnancy could occasionally explain the transient accumulation of liquid in the fetal nuchal region, which is attributed to alterations in the fetal lymphatic drainage and/or, particularly, to fetal hemodynamic disorders related to heart failure.

It would be very useful to find a marker such as the NT, able to screen which patients among the low risk population should undergo fetal echocardiography. In view of the use of an increased NT as an indication for fetal echocardiography, the objective of this study was to evaluate the accuracy of NT in the screening of CHD.

**Methods**

A multi-center retrospective study for validation of a diagnostic test was conducted. Two study centers were included: the first one in Florianópolis (State of Santa Catarina, Brazil), and the second one in Vitória (State of Espírito Santo, Brazil). The pregnant women included in the study underwent ultrasonographic examination at these centers to measure NT between eleven weeks and thirteen weeks and six days of gestation, as estimated by the crown-rump length (from 45 to 84 mm). The following inclusion criteria were used: (1) singleton gestations; (2) normal fetal karyotype and/or normal phenotype.

Fetal heart assessment was performed with a neonatal clinical examination or, when necessary, with fetal and/or neonatal echocardiography. All cases were followed up until at least one month after delivery. Relevant data were obtained from the database kept by the institutions participating in the study or through contact with the patient’s physician.

The equipment used to perform the examinations were: Acuson™ XP10, Acuson™ Aspen™, Medison™ SONOACE™ 9900, Toshiba™ SSH-140A and GE™ Voluson 730. The examinations were performed by doctors from each center’s medical staff, using the technique recommended by the Fetal Medicine Foundation (FMF): (1) the image should be obtained from a sagittal section of the fetus with a magnification large enough for the cephalic pole to occupy 75% of the image; (2) fetal head should be in a neutral position in relation to the body; (3) care should be taken to distinguish fetal skin and amnion; (4) the widest part of translucency is measured.

After data collection a descriptive univariate analysis of the variables of interest was performed. The Kolmogorov-Smirnov test was used to verify whether NT values distribution was normal.

In the variables with a normal distribution the mean was used to represent the measurement of the central trend of the sample. In the same cases, the standard deviation was calculated to measure the sample dispersion, and the Student’s t parametric test was used to verify the occurrence of statistical significance.

In the variables with a non-normal distribution we chose to use a non-parametric test to evaluate the statistical significance. The Mann-Whitney test was used in such cases. Since in non-normal distributions the mean is under a great influence of the extreme values of the distribution (also known as outliers), we chose the median to represent the central measurement of the sample, and the dispersion was represented as percentiles. P values < 0.05 were considered significant.

The database was then divided into two groups, the first of which was named non-CHD group, and the second was named CHD group. Using the non-CHD group, the 1st, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 99th percentiles of the absolute value of NT were determined in millimeters for the whole sample of normal cases. These percentiles were also determined in relative values expressed as multiples of the median, considering that the median NT value varies according to the CRL. Further, sensitivity, specificity, positive and negative predictive values, and the probability of false positives and false negatives were calculated.
The present study was analyzed and approved by the Research Ethics Committee of the Universidade Federal de São Paulo in July, 2nd, 2004, process number 0665/04.

RESULTS

The final sample of the study comprised 3,664 examinations. The number of examinations performed at each center was relatively similar: 56% (2,061) of them were performed in Vitória and 44% (1,603) in Florianópolis.

Patients’ ages ranged from fourteen to 53 years, with a mean of 32 years. The mean age was higher in the group of patients from Florianópolis than in the group from Vitória, and was 34.5 years and 30.2 years, respectively (Tab. 1).

Twenty cases of congenital heart defect were diagnosed in the sample studied. Of these, fifteen were diagnosed at Florianópolis Center and five at Vitória Center, representing a prevalence of 0.94% and 0.24%, respectively. The cases of heart defects diagnosed are described in Table 2.

The following alterations were observed during the morphologic obstetric examination performed at the Florianópolis Center: one case with sinus bradycardia, two cases with supraventricular tachycardia and three cases of premature atrial contractions. These cases were not included as CHD because they were primarily related to disorders of the heart rhythm.

A progressive increase in the prevalence of CHD according to the NT values obtained in the examination was observed, as shown in Table 3.

NT value distribution in the cases without CHD was not normal, as identified by the Kolmogorov-Smirnov test, in which the p value calculated was lower than 0.05. To demonstrate that the NT value distribution did not follow the normal distribution, the results were evaluated using the Kolmogorov-Smirnov test, with a p value of less than 0.05.

Table 1 - Mean maternal age according to the center where the examination was performed

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florianópolis</td>
<td>1,603</td>
<td>34.5</td>
<td>5.6</td>
<td>17</td>
<td>53</td>
</tr>
<tr>
<td>Vitória</td>
<td>2,061</td>
<td>30.2</td>
<td>5.3</td>
<td>14</td>
<td>49</td>
</tr>
<tr>
<td>Total</td>
<td>3,664</td>
<td>32.0</td>
<td>5.9</td>
<td>14</td>
<td>53</td>
</tr>
</tbody>
</table>

(T test, p < 0.05) SD = Standard deviation.

Table 2 - Cases of congenital heart defects diagnosed in the sample

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Center</th>
<th>GA</th>
<th>CRL</th>
<th>NT</th>
<th>Median NT</th>
<th>MoM</th>
<th>CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>Florianópolis</td>
<td>13</td>
<td>71</td>
<td>1.5</td>
<td>1.77</td>
<td>0.84</td>
<td>Moderate pulmonary stenosis</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>Florianópolis</td>
<td>11</td>
<td>53</td>
<td>1.9</td>
<td>1.41</td>
<td>1.34</td>
<td>Severe pulmonary stenosis</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>Florianópolis</td>
<td>12</td>
<td>62</td>
<td>1.7</td>
<td>1.60</td>
<td>1.06</td>
<td>Pulmonary atresia, RV hypoplasia, VSD</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>Florianópolis</td>
<td>11</td>
<td>57</td>
<td>1.5</td>
<td>1.49</td>
<td>1.00</td>
<td>Pulmonary atresia, Tricuspid regurgitation, RV hypoplasia</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>Florianópolis</td>
<td>12</td>
<td>58</td>
<td>1.3</td>
<td>1.51</td>
<td>0.85</td>
<td>VSD</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>Florianópolis</td>
<td>13</td>
<td>77</td>
<td>2.3</td>
<td>1.87</td>
<td>1.22</td>
<td>Severe tricuspid regurgitation</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>Florianópolis</td>
<td>12</td>
<td>53</td>
<td>1.9</td>
<td>1.41</td>
<td>1.34</td>
<td>Aortopulmonary window</td>
</tr>
<tr>
<td>8</td>
<td>23</td>
<td>Florianópolis</td>
<td>13</td>
<td>80</td>
<td>1.4</td>
<td>1.92</td>
<td>0.72</td>
<td>VSD</td>
</tr>
<tr>
<td>9</td>
<td>31</td>
<td>Florianópolis</td>
<td>13</td>
<td>73</td>
<td>1.7</td>
<td>1.89</td>
<td>0.89</td>
<td>VSD</td>
</tr>
<tr>
<td>10</td>
<td>41</td>
<td>Florianópolis</td>
<td>14</td>
<td>79</td>
<td>2</td>
<td>1.91</td>
<td>1.04</td>
<td>VSD and ASD</td>
</tr>
<tr>
<td>11</td>
<td>33</td>
<td>Florianópolis</td>
<td>13</td>
<td>73</td>
<td>21</td>
<td>1.81</td>
<td>11.59</td>
<td>Cervical cystic hygroma, VSD, pericardial effusion, pleural effusion, ascitis, hydrops</td>
</tr>
<tr>
<td>12</td>
<td>41</td>
<td>Florianópolis</td>
<td>12</td>
<td>61</td>
<td>1.7</td>
<td>1.58</td>
<td>1.07</td>
<td>Ductus arteriosus aneurysm</td>
</tr>
<tr>
<td>13</td>
<td>23</td>
<td>Florianópolis</td>
<td>13</td>
<td>62</td>
<td>1</td>
<td>1.60</td>
<td>0.62</td>
<td>VSD, single umbilical artery, esophageal atresia</td>
</tr>
<tr>
<td>14</td>
<td>28</td>
<td>Florianópolis</td>
<td>11</td>
<td>50</td>
<td>1.1</td>
<td>1.34</td>
<td>0.81</td>
<td>VSD</td>
</tr>
<tr>
<td>15</td>
<td>32</td>
<td>Florianópolis</td>
<td>12</td>
<td>56</td>
<td>0.9</td>
<td>1.47</td>
<td>0.61</td>
<td>Bilateral choroid plexus cyst, VSD</td>
</tr>
<tr>
<td>16</td>
<td>30</td>
<td>Vitória</td>
<td>13</td>
<td>79.2</td>
<td>1.6</td>
<td>1.91</td>
<td>0.83</td>
<td>VSD</td>
</tr>
<tr>
<td>17</td>
<td>25</td>
<td>Vitória</td>
<td>?</td>
<td>65</td>
<td>2</td>
<td>1.66</td>
<td>1.20</td>
<td>Severe pulmonary stenosis</td>
</tr>
<tr>
<td>18</td>
<td>36</td>
<td>Vitória</td>
<td>13</td>
<td>75</td>
<td>4</td>
<td>1.84</td>
<td>2.16</td>
<td>Atrioventricular septal defect Total atrioventricular septal defect</td>
</tr>
<tr>
<td>19</td>
<td>29</td>
<td>Vitória</td>
<td>11</td>
<td>45</td>
<td>5</td>
<td>1.24</td>
<td>4.02</td>
<td>Ostium Primum ASD</td>
</tr>
<tr>
<td>20</td>
<td>23</td>
<td>Vitória</td>
<td>13</td>
<td>73</td>
<td>14</td>
<td>1.81</td>
<td>7.72</td>
<td>Complex cardiac malformation</td>
</tr>
</tbody>
</table>

GA - gestational age estimated by the last menstrual period; CRL - crown-rump length measured on the day of examination; NT - nuchal translucency measurement; Median NT - median nuchal translucency calculated according to the CRL; MoM - nuchal translucency measured in multiples of the median for the respective CRL; ? - last menstrual period is unknown; VSD - ventricular septal defect; ASD - atrial septal defect; RV - right ventricle.
a normal curve, we created the normal quantile-quantile plot of NT values (Figure 1).

Median NT was 1.70 mm for the cases with CHD, and 1.60 for the non-CHD group; however, this difference was not statistically significant, as shown in Table 4.

Among the non-CHD cases, the percentile values found for NT were as follows (Tab. 5):

Different cut-off points were used to evaluate the accuracy of NT in the screening of CHD. These values can be observed in Table 6.

Fig. 2 shows normal and abnormal case distribution in relation to CRL and NT measurement, marking the several cut-off points studied.

The odds ratio of the presence of CHD according to the NT thickness was also determined (Tab. 7).

The number needed to screen (NNS) was calculated to illustrate the efficacy of the method. The NNS is a new statistical method that has gained attention as a form of reporting results of dichotomous tests17. The NNS is defined as the number of patients that need to be screened, in average, to achieve some benefit (in this case, the number of patients undergoing echocardiography to diagnose one CHD) (Tab. 8).

**Table 3 – Prevalence of CHD according to the NT values obtained**

<table>
<thead>
<tr>
<th>NT</th>
<th>total n</th>
<th>n of CHD</th>
<th>Prevalence (per 1,000 fetuses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 2.5 mm</td>
<td>3,506</td>
<td>16</td>
<td>4.5</td>
</tr>
<tr>
<td>2.6 to 3.5 mm</td>
<td>127</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3.6 to 4.5 mm</td>
<td>16</td>
<td>1</td>
<td>62.5</td>
</tr>
<tr>
<td>4.6 to 5.5 mm</td>
<td>6</td>
<td>1</td>
<td>166.7</td>
</tr>
<tr>
<td>Above 5.6 mm</td>
<td>9</td>
<td>2</td>
<td>222.2</td>
</tr>
<tr>
<td>Total</td>
<td>3,664</td>
<td>20</td>
<td>5.6</td>
</tr>
</tbody>
</table>

**Table 4 - Absolute NT values according to the presence of CHD**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Median (mm)</th>
<th>Minimum (mm)</th>
<th>Maximum (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With CC</td>
<td>20</td>
<td>1.70</td>
<td>0.9</td>
<td>21</td>
</tr>
<tr>
<td>Without CC</td>
<td>3,644</td>
<td>1.50</td>
<td>0.5</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>3,664</td>
<td>1.60</td>
<td>0.5</td>
<td>21</td>
</tr>
</tbody>
</table>

(Mann-Whitney test, p > 0.05).
Table 5 – NT percentiles in absolute values (millimeters) and relative values (MoM, multiples of the median)

<table>
<thead>
<tr>
<th>Percentile</th>
<th>NT (mm)</th>
<th>NT (MoM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.74</td>
<td>0.50</td>
</tr>
<tr>
<td>5</td>
<td>0.90</td>
<td>0.63</td>
</tr>
<tr>
<td>10</td>
<td>1.00</td>
<td>0.70</td>
</tr>
<tr>
<td>25</td>
<td>1.30</td>
<td>0.83</td>
</tr>
<tr>
<td>50</td>
<td>1.60</td>
<td>1.00</td>
</tr>
<tr>
<td>75</td>
<td>1.90</td>
<td>1.19</td>
</tr>
<tr>
<td>90</td>
<td>2.30</td>
<td>1.37</td>
</tr>
<tr>
<td>95</td>
<td>2.50</td>
<td>1.51</td>
</tr>
<tr>
<td>99</td>
<td>3.16</td>
<td>2.04</td>
</tr>
</tbody>
</table>

Table 6 – Values found for sensitivity (S), specificity (E), positive predictive value (PPV), negative predictive value (NPV), probability of false positive (PFP), and probability of false negative (PFN)

<table>
<thead>
<tr>
<th>Cut-off point</th>
<th>S</th>
<th>E</th>
<th>PPV</th>
<th>NPV</th>
<th>PFP</th>
<th>PFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mm</td>
<td>20.0 %</td>
<td>95.8 %</td>
<td>2.5 %</td>
<td>99.5 %</td>
<td>97.5 %</td>
<td>0.5 %</td>
</tr>
<tr>
<td>3.5 mm</td>
<td>20.0 %</td>
<td>99.3 %</td>
<td>12.9 %</td>
<td>99.6 %</td>
<td>87.1 %</td>
<td>0.4 %</td>
</tr>
<tr>
<td>4.0 mm</td>
<td>15.0 %</td>
<td>99.5 %</td>
<td>13.6 %</td>
<td>99.5 %</td>
<td>86.4 %</td>
<td>0.5 %</td>
</tr>
<tr>
<td>95th Percentile</td>
<td>20.0 %</td>
<td>95.0 %</td>
<td>2.1 %</td>
<td>99.5 %</td>
<td>97.9 %</td>
<td>0.5 %</td>
</tr>
<tr>
<td>95th Percentile</td>
<td>20.0 %</td>
<td>99.0 %</td>
<td>10.0 %</td>
<td>99.6 %</td>
<td>90.0 %</td>
<td>0.4 %</td>
</tr>
</tbody>
</table>

Fig. 2 – Correlation between the nuchal translucency measurement and CRL in the non-CHD (n = 3644) and CHD (n = 20) groups. The solid black lines depict the 5th, 50th, and 95th percentiles, whereas the red dotted lines depict the 2.5, 3.5, and 4.5-mm cut-off points.

Table 7 – Odds ratio (OR) and 95% confidence interval (95% CI) according to the different cut-off points

<table>
<thead>
<tr>
<th>Cut-off points</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 2.5 mm</td>
<td>5.8</td>
<td>1.4 - 17.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>&gt; 3.5 mm</td>
<td>33.5</td>
<td>7.6 - 112.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>&gt; 4.0 mm</td>
<td>33.7</td>
<td>5.8 - 130.6</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>&gt; 95th percentile</td>
<td>4.7</td>
<td>1.1 - 14.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>&gt; 95th percentile</td>
<td>25.0</td>
<td>5.8 - 82.6</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Table 8 – Number needed to screen (NNS) and 95% confidence interval (95% CI) according to the different cut-off points

<table>
<thead>
<tr>
<th>Cut-off point</th>
<th>NNS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 2.5 mm</td>
<td>48</td>
<td>21 - 200</td>
</tr>
<tr>
<td>&gt; 3.5 mm</td>
<td>8</td>
<td>4 - 21</td>
</tr>
<tr>
<td>&gt; 4.0 mm</td>
<td>8</td>
<td>3 - 23</td>
</tr>
<tr>
<td>&gt; 95th percentile</td>
<td>60</td>
<td>25 - 297</td>
</tr>
<tr>
<td>&gt; 95th percentile</td>
<td>10</td>
<td>5 - 28</td>
</tr>
</tbody>
</table>
DISCUSSION

Much has been discussed recently about the importance of the prenatal diagnosis of congenital malformations. With the improvement in the quality of ultrasound equipment in the past two decades and with the training of professionals capable of performing fetal morphologic analysis, the sensitivity of the examination has reached values close to 83%\(^{18}\). Prenatal diagnosis of fetal diseases enables actions aimed at the maternal and fetal well-being, thus greatly improving the prognosis of the newborn infant.

Despite the advances in the detection of fetal malformations, however, the detection of CHD is far from being optimal. The difficulty to obtain images with the organ in movement and the vast anatomic knowledge required are pointed as the major factors that make CHD a difficult diagnosis\(^{19}\). Therefore, the analysis of the fetal heart depends a great deal on the examiner’s experience, and the sensitivity of the ultrasound examination for the detection of CHD may range from 40% to 90%, even when performed by echocardiography specialists\(^{20}\).

NT is recognized as a marker for risk assessment of chromosome diseases. Although the pathophysiology of the increased NT in fetuses with chromosome diseases is not fully understood, this correlation is well established. Several pathophysiologic mechanisms have been implied in the increased NT, including heart failure.

Heart failure in adults is known to produce edema of the lower extremities, particularly due to the gravitational action, and this edema is more pronounced by the end of the day. Increased NT was associated with the increase in the gene expression of heart failure markers\(^{21}\). However, how fetal heart failure could cause edema restricted to the nuchal region remains unknown.

NT measurement is a simple method to be learned and is easily reproducible. The demonstration of a correlation between increased NT and CHD would be extremely interesting from an epidemiological point of view for the screening of CHD, and this was our major motivation to carry out this study.

In our sample, the use of NT as a screening method for CHD showed a low sensitivity – of 20% when the 95th percentile was used as the cut-off point. However, the specificity of the method was high: 99.4% for the 4.0 mm cut-off point. The negative predictive value was always above 99% at the different cut-off points. The association between any form of CHD (isolated or a group that could induce a similar hemodynamic alteration) and increased NT could not be determined.

The very high specificity and negative predictive values qualify the examination as an important tool to reassure parents, because the likelihood of heart disease in the presence of a normal NT is very low – less than 1%.

CHDs, in turn, are uncommon among the low risk population, with an incidence lower than 1%. Performing a screening test to conclude that the risk after the test (\(a\) posteriori risk) is equal to the risk prior to the test (\(a\) priori risk) does not show any benefit from its use.

Thus, the test would likely have a greater impact for groups at high risk for CHD, such as mothers who already had a child with CHD, whose recurrence risk is of 2%-3% in subsequent gestations\(^{22}\), or for mothers with CHD, whose recurrence risk may reach 5%-10%\(^{23}\). In cases in which the CHD is part of a genetic syndrome, the risk of recurrence is equivalent to that attributed to the risk of recurrence of the genetic disease. In these groups, an \(a\) posteriori risk lower than 1% would be very reassuring. However, it would not exclude the need for a thorough assessment using fetal echocardiography.

Although the 20% sensitivity found in our sample is not as encouraging as the best results already published, it is in agreement with the values available in the literature, that range from 11.1% to 56%. In a meta-analysis published by Makrydimas et al\(^ {24}\), the estimated sensitivity of NT in the screening of CHD was 37%. This large

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consanguineous parents</td>
<td>1.2</td>
<td>1.1 - 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Extracardiac malformation</td>
<td>31.1</td>
<td>15.1 - 60.9</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Chromosome anomaly</td>
<td>34.5</td>
<td>23.3 - 49.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Maternal exposure to teratogenic agents</td>
<td>0.9</td>
<td>0.5 - 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Prior child with congenital heart defect</td>
<td>12.4</td>
<td>10.3 - 14.4</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mother with congenital heart defect</td>
<td>2.3</td>
<td>1.1 - 1.7</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Father with congenital heart defect</td>
<td>1.3</td>
<td>0.5 - 4.3</td>
<td>NS</td>
</tr>
<tr>
<td>NT &gt; 2.5 mm</td>
<td>5.8</td>
<td>1.4 - 17.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>NT &gt; 3.5 mm</td>
<td>33.5</td>
<td>7.6 - 112.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>NT &gt; 4.0 mm</td>
<td>33.7</td>
<td>5.8 - 130.6</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>NT &gt; 95th percentile</td>
<td>4.7</td>
<td>1.1 - 14.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>NT &gt; 99th percentile</td>
<td>25.0</td>
<td>5.8 - 82.6</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Source: Adapted from Roodpeyma et al\(^ {27}\) and Romano-Zelekha et al\(^ {28}\).
variation of sensitivity among different studies is mainly attributable to the following factors:

1. The cut-off point to separate the normal and abnormal NT groups is highly variable – 2.5 mm, 3.5 mm, 4.0 mm, 95th percentile and 99th percentile, depending on the study.

2. The definition of CHD is not very clear in the majority of the studies. Whereas some authors are extremely selective and include only the most severe diseases that require surgical intervention in the first few months of life, others consider even the patent ductus arteriosus (which is very common in premature infants) as a CHD.

3. After the publication of the results obtained by Hyett et al\textsuperscript{20}, demonstrating a 56% sensitivity in a study with approximately thirty thousand examinations, authors with less encouraging results possibly did not publish their studies believing that their results were wrong. This is called a “publication bias”\textsuperscript{26}.

4. The primary studies published usually show flaws in the statistical planning and little care is taken to review the data obtained due to interests and pressures involved in publications. Thus, primary studies published on any subject should be very critically assessed\textsuperscript{26}.

NT value alone should not be used as a single method to select the cases that should undergo a thorough echocardiography examination. The probability of false positives ranged from 86.4% to 97.9%, depending on the cut-off point used. The cut-off point producing the lower number of false positive was 4.0mm. When this cut-off point is used to indicate echocardiography, one out of each eight examinations performed is not normal; however, 85% of the CHDs are not screened.

When increased NT and the presence of CHD are compared with the classical indications of fetal echocardiography, we can observe that an increased NT is responsible for a significant increase in the odds ratio for CHD. The odds ratio is an alternative form of describing the performance of a diagnostic test. It summarizes the same type of information provided by the sensitivity and specificity, and may be used to calculate the odds of a disease after a positive test.

Thus, if maternal exposure to teratogenic agents and a history of a prior child with congenital heart defect are indications for fetal echocardiography (odds ratio for CHD of 0.9 and 12.4, respectively), so should an increased NT be (odds ratios of 4.7 and 25 for the 95th percentile and 99th percentile, respectively)\textsuperscript{27,28}.

A screening test should be applied to an apparently normal population with the purpose of identifying individuals with a high probability of having a certain disease. In the majority of cases, a positive screening test ultimately leads to a diagnostic test. A good screening test should, therefore, have a high sensitivity and a good specificity to reduce the number of false positives that require further investigation. For a screening test to have a clinical significance, once a disease is detected, there should be therapeutic choices able to change the outcome of the case by reducing mortality and morbidity.

Training ultrasound specialists to perform a minimum screening by assessing the four-chamber and the outflow tract views has proven to be an efficient methodology. In a study conducted by Carvalho et al\textsuperscript{29}, the efficacy of adding the outflow tract view to the four chamber view in the routine ultrasound examination performed by obstetricians was evaluated. The rate of detection of CHD in this study was 75%. The authors attributed the successful screening rate of the program to an infrastructure dedicated to the continued education of the ultrasound specialist team by fetal echocardiographers.

Another promising technology to improve fetal cardiac assessment is the STIC (Spatio-temporal image correlation). STIC stores three-dimensional blocks of the fetal heart, thus reducing the need for examiner’s expertise in the assessment of the anatomy of the heart\textsuperscript{30}. The blocks stored are not restricted to two-dimensional images of the region studied, but rather they provide all information on the adjacent anatomy. As a consequence, the examiner may store a block for further study, obtaining different section planes. The blocks may also be sent to other experts in fetal echocardiography.

A study conducted by Gonçalves et al\textsuperscript{31} verified the examiner’s ability to obtain the four chamber plane and the outflow tract view from STIC blocks previously acquired. Twenty blocks were obtained by one investigator. Further, two investigators with notions of fetal echocardiography were trained to handle the blocks and obtain the planes needed to assess the heart anatomy. The images obtained were classified according to their quality. Mean scores ranged from acceptable to good for all planes examined and no significant differences were observed among examiners. Therefore, after larger studies and with the reduction of the cost of this technology, STIC will be able to help implement a more effective and rapid screening method.

We point out the importance of the prenatal detection of CHDs, thus bringing a proven benefit for the newborn infant. Since NT alone does not seem to be a good screening method for CHD, we suggest the implementation of other methods, such as training ultrasound specialists to obtain and analyze the four-chamber and outflow tract views. In the future, technologies such as the STIC should be used to improve CHD screening.

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Potential Conflict of Interest
No potential conflict of interest relevant to this article was reported.
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