Distribution of Normal Nuchal Translucency Thickness: A Multicenter Study in Thailand

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Key Words
Nuchal translucency - Ultrasonography

Abstract
Aims: To establish the normative data distribution of nuchal translucency (NT) thickness in Thai fetuses. Methods: A cross-sectional multicenter study was conducted among 6,455 women with singleton pregnancies and gestational age between 10 and 14 weeks. For each case, the fetal crown-rump length (CRL) and NT were measured by transabdominal ultrasound. Transvaginal ultrasounds were used in poorly visualized cases. The distribution values of the NT thicknesses and their corresponding 10-mm CRL intervals between 45 and 84 mm were examined to obtain the median and 95th percentiles. Quantile regression modeling across the CRLs was performed to obtain the reference values. Results: Transabdominal ultrasound measurements were successfully done on 6,347 fetuses with 39 cases by the transvaginal route. Fetuses with CRL between 45 and 84 mm and normal outcomes made up a total of 4,352 cases. The mean (SD) gestational age, CRL and NT thickness were 12.5 (0.7) weeks, 60.2 (9.7) mm, and 1.15 (0.38) mm, respectively. The mean normal NT increased linearly with CRL. The quantile regression equation to predict the 95th percentile of the NT thickness (mm) was $0.727 + 0.017 \times \text{CRL} \text{(mm)}$. Conclusions: The NT thickness in normal Thai fetuses was found to be thinner than in both Caucasian and other Asian populations.

Introduction
Nuchal translucency (NT) refers to the subcutaneous fluid-filled space between the back of the fetal neck and the overlying skin. This space can be measured by ultrasound in the first trimester. Increased NT is associated with trisomy 21 and other chromosomal abnormalities as well as many fetal malformations and genetic syndromes [1, 2]. NT is the single most effective ultrasonographic marker of Down syndrome (DS) in combination with the serum markers pregnancy-associated plasma protein A (PAPP-A) and free beta human chorionic gonadotrophin (FB-hCG), with a detection rate of 90% and a 5% false-positive rate (FPR) in the first trimester [3, 4]. However, one study found that the sensitivity of NT for screening DS varied from 29 to 100% [5]. This variation could be explained by several factors such as study design, NT cutoff value, gestational age at measurement, selection bias,
Nuchal Translucency in Normal Pregnancy

This study was conducted between June 2002 and April 2007 at 4 tertiary teaching hospitals in Thailand: Songklanagarind (Southern), Maharaj Nakorn Chiang Mai (Northern), Srinagarind (Northeastern) and Phramongkutklao (Central). The research was approved by the Ethics Committees of all centers.

A total of 6,435 women with singleton pregnancies at gestational age between 10 and 14 weeks were recruited into the study. Fetal crown-rump length (CRL) and NT were measured with high resolution sonography (Voluson 730 Expert Diamond and Pro, GE medical system, Zipf, Austria; Aloka 1700, Aloka SSD-2000, Prosound Alpha 10 System, Tokyo, Japan, and HDI 3000, ATL, USA). The measurements were mainly done by transabdominal ultrasound (TAS), with a transvaginal approach (TVA) used only in poorly visualized cases. The NT was defined as the black area between the inner skin outline echo and the outer border of the soft tissue overlying the cervical spine. The calipers were placed on the inner borders of the NT space, perpendicular to the long axis of the fetus when a sagittal section with neutral position of the fetus was obtained. The ultrasound measurements were recorded to the nearest 0.1-mm interval. The scans were performed by various members of our team, all of whom received uniform didactic and practical training in sonographic NT measurements.

To maintain quality, all images of the measurements were taken and continuously audited by the second and third authors. During the first period of the study, in each case the CRL and the NT were measured three times using the technique described by Snijders et al. [10]. In 2004, the NT was measured by the new proposed method and was used for the remainder of the study. In this method only the fetal head and upper thorax were included in the image for measurement and the images were magnified as much as possible [11]. The variability of NT measurements had been evaluated before this study was implemented, with the conclusion that NT measurements were reproducible with only small variation and good agreement [11]. For each fetus, the NT value was expressed in a decimal of a millimeter; the mean value of the three measurements of NT thickness was calculated and recorded. The gestational age was also assessed by the CRL measurement, using the equation by Hadlock et al. [12]. The time taken to perform each measurement was also recorded. Fetal outcomes were evaluated by the neonatologists at birth.

The fetuses with CRL between 45 and 84 mm were analysed and subdivided into four 10-mm ranges of fetal CRL, namely \( \geq 45-<55, \geq 55-<65, \geq 65-<75 \) and \( \geq 75-<85 \) mm, and the distributions of NT thickness within each 10-mm range of CRL were examined. The relationships of the median and 95th percentile of NT thickness with CRL were explored using quantile regression. Data analysis was performed using STATA version 7.0 software (STATA Corporation, College Station, Tex., USA).

Results

The measurements were successfully done on 6,386 fetuses (98.9%), with 6,347 cases (99.4%) by the transabdominal route and 39 cases (0.6%) by the transvaginal route. A known normal fetal outcome was collected from 5,018 cases (78.6%), of which 4,352 cases (68%) had CRLs between 45 and 84 mm. The unknown pregnancy outcomes (1,368 cases) were excluded from the study. The mean (SD) maternal age was 29.5 (5.4) years, gestational age 12.5 (0.7) weeks, CRL 60.2 (9.7) mm, and NT thickness 1.15 (0.38) mm. The mean time of measurement was 8.6 (8.1-12.2) min.

The mean normal fetal NT thickness increased linearly with CRL. The correlation between NT thickness (mm) and CRL (mm) is shown in figure 1 as a scatter plot. The median and 95th percentile values of NT thickness with 10-mm-CRL intervals are shown in table 1. The median values of NT thickness for gestational age 11-14 weeks ranged from 0.93 to 1.33 mm, and the 95th percentile was approximately 0.7 mm greater than the median in each gestational age. The average median NT thickness and 95th percentile values were 1.15 and 1.85 mm, respectively.

The median and 95th percentile of NT thickness were plotted against the median of CRL within each 10-mm range of CRL and the best-fitting straight lines obtained from the 95th quantile and median regression of the NT thickness on CRL are shown in figure 2.

The expected 95th percentile values of NT thickness for a given CRL and corresponding gestational age are shown in table 2. The regression equation relating the 95th percentile of the NT thickness (mm) to the CRL (mm) is:

\[
\text{NT} = 0.727 + 0.017 \times \text{CRL} \text{ (mm)}
\]

There were 120 cases with a normal NT study outcome but abnormal pregnancy outcomes; 96 cases with dead fetuses in utero or abortion, and 24 cases with abnormal chromosomes [trisomy 21 (10 cases), trisomy 18 (4 cases), trisomy 13 (1 case) and other abnormal chromosomes (9 cases)].
Fig. 1. Scatter plot of NT thickness (mm) and CRL (mm) distribution. The 5th, median, and 95th percentile are given as solid lines.

Fig. 2. Correlation between NT thickness and CRL in normal fetuses. Circles represent the median, and squares and triangles the 95th and 5th percentile, respectively, of NT thickness in each 10-mm range of CRL. The lines are the respective quantile regression lines.

Table 1. Median and 95th percentile values of NT thickness in four 10-mm ranges of CRL.

<table>
<thead>
<tr>
<th>CRL</th>
<th>Number of fetuses</th>
<th>%</th>
<th>NT, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>median</td>
</tr>
<tr>
<td>≥45 &lt; 55 mm</td>
<td>1,548</td>
<td>35.6</td>
<td>0.93</td>
</tr>
<tr>
<td>≥55 &lt; 65 mm</td>
<td>1,478</td>
<td>34.0</td>
<td>1.10</td>
</tr>
<tr>
<td>≥65 &lt; 75 mm</td>
<td>907</td>
<td>20.8</td>
<td>1.23</td>
</tr>
<tr>
<td>≥75 &lt; 85 mm</td>
<td>419</td>
<td>9.6</td>
<td>1.33</td>
</tr>
</tbody>
</table>

Table 2. Expected 95th percentile values of NT and CRL and their corresponding GA [12].

<table>
<thead>
<tr>
<th>GA</th>
<th>CRL, mm</th>
<th>Expected 95th percentile, NT thickness, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.3 weeks</td>
<td>45</td>
<td>1.49</td>
</tr>
<tr>
<td>11.7 weeks</td>
<td>50</td>
<td>1.58</td>
</tr>
<tr>
<td>12.1 weeks</td>
<td>55</td>
<td>1.66</td>
</tr>
<tr>
<td>12.5 weeks</td>
<td>60</td>
<td>1.75</td>
</tr>
<tr>
<td>12.8 weeks</td>
<td>65</td>
<td>1.83</td>
</tr>
<tr>
<td>13.2 weeks</td>
<td>70</td>
<td>1.92</td>
</tr>
<tr>
<td>13.6 weeks</td>
<td>75</td>
<td>2.00</td>
</tr>
<tr>
<td>14.0 weeks</td>
<td>80</td>
<td>2.09</td>
</tr>
<tr>
<td>14.4 weeks</td>
<td>85</td>
<td>2.17</td>
</tr>
</tbody>
</table>

The regression equation is: 95th percentile NT thickness = 0.727 + [0.017 × CRL (mm)].

Discussion

This multicenter cross-sectional study included a very large number of pregnant women for analysis and thus offers normative data of the NT thickness in Thai fetuses. The NT distribution increased with increasing CRL and was found to be thinner than in previous reports [13,14]. Pandya et al. [13] reported that NT thickness at the 95th percentile, with a CRL between 45 and 85 mm, varied from 2.3 to 2.8 mm, which was similar to Jou et al. [14] (CRL 35–75 mm, NT 2.18–2.76 mm). Comparing such earlier results with our study, we found median and 95th percentile values to be smaller in every gestational week. The 95th percentile NT thickness at a CRL between 75 and <85 mm (2.10 mm) was thinner than the accepted fixed cut-off point (≥2.5 mm). Several studies have reported significant differences in NT thickness measurements among ethnic groups [6–8]; however, this was clinically insignificant, as only a small proportion of DS fetuses had an NT thickness at 95th percentile values. A reason for the differences between our study and these earlier ones could be that to acquire the NT measurement, we used the average from three measurements instead of the largest measurement. We followed this procedure as there was no standard recommendation before our study started and one study [15] suggested taking several measurements and using the average to reduce the false positive rate. Our study determined the distribution of NT thickness values in normal Thai fetuses and calculated the 95th percentile value as the threshold for an abnormal NT thickness in each gestational age. Using the
95th percentile of our study as a cut-off value for cases at high risk of DS will also result in a higher detection rate for other chromosomal abnormalities or genetic syndromes. However, higher detection rates will necessarily result in a higher false positive rate, increasing the need for prenatal karyotyping and its inherent risks, which should also be considered and appropriate precautions taken when implementing the results of this study in a screening program. We found 24 cases in our study with a chromosome abnormality but normal NT, with 5 cases (21%) having NT thickness at the 95th percentile value. These 5 cases would be considered abnormal if using our cut-off value, resulting in an increased detection rate. Therefore, it is necessary to establish the normative distribution of NT thickness measurements in our population.

Many factors can influence obtaining the correct view for measurement, such as the operator's experience, quality of the ultrasound, method of measurement, gestational age, an inappropriate fetal position, nuchal cord, and maternal obesity. In our study, the measurement of the NT thickness was performed with a high success rate similar to that of another report [16].