First-trimester Down’s Syndrome Screening by Fetal Nuchal Translucency Measurement in Taiwan

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Background: Fetal nuchal translucency (NT) measurement is now widely used in many Western countries as a screening tool for Down’s syndrome during the first trimester. However, at present there is no data on its use in Taiwan. The purpose of the present study was to evaluate the efficacy of NT measurement in first-trimester Down’s syndrome screening in Taiwan.

Methods: We conducted a prospective study from October 1997 to May 1999. Sonographic measurement of fetal NT was performed in 1,249 fetuses at 9–14 weeks of gestation. Transabdominal ultrasound scanning was performed to obtain a sagittal section of the fetus for measuring the crown–rump length (CRL) and the maximum thickness of the subcutaneous translucency between the skin and the soft tissue overlying the cervical spine. Two different cut-off points were used for screening: a fixed cut-off point of at least 2.5 mm and a CRL-related cut-off point. In the latter method, fetuses with an NT measurement in the 95th percentile were considered at high risk for Down’s syndrome.

Results: Three fetuses had Down’s syndrome, with NT measurements of 2.1 mm, 2.7 mm, and 4.0 mm. The false positive rates for the fixed cut-off point and CRL-related cut-off point were 6.3% and 4.6%, respectively. Both methods had a sensitivity of 66.7%. However, the screening program using the CRL-related cut-off point had two advantages: a higher specificity (95.5% vs 93.8%) and a more reasonable distribution pattern for screening.

Conclusion: This study showed that NT measurement is a potential screening tool for Down’s syndrome during the first trimester in Taiwan. Using CRL-related cut-off points for screening is more reasonable than using a fixed cut-off point.

Down’s syndrome is the most common cause of mental retardation, with a prevalence of 1:848 newborns [1]. Definitive antenatal diagnosis of Down’s syndrome requires invasive procedures such as first-trimester chorionic villi sampling (CVS) or second-trimester amniocentesis. Because each test is associated with a risk of unwanted fetal loss, it is usually offered under indications such as advanced maternal age, family history of chromosomal aberrations, or a positive result on noninvasive screening. Second-trimester maternal serum screening is now the most popular screening tool for Down’s syndrome in Taiwan, with a sensitivity of 62.5% and a false positive rate of 6.3% [2]. About half of pregnant women receive the test, which is based on the measurement of serum concentrations of α-fetoprotein and human chorionic gonadotropin [2, 3].

There are several limitations with the second-trimester maternal serum marker test. Major problems include the relatively late gestational age at final cytogenetic diagnosis, often as late as 22 to 24 weeks. Also, more than 100 amniocenteses are required for every case of Down’s syndrome identified [2]. Therefore,
developing a new screening program with higher detection rates at an earlier gestational age is warranted.

In 1992, Nicolaides et al first demonstrated the association between an increased nuchal translucency (NT) measurement during the first trimester of pregnancy and chromosomal aberrations [4]. Fetuses with an NT measurement of 3 to 8 mm at 10 to 14 weeks of gestation had an increased risk of Down’s syndrome. Based on this report and subsequent studies, ultrasound measurement of fetal NT during the first trimester has become a useful marker for antenatal screening of Down’s syndrome and is widely used in many Western countries [5–10].

However, the efficacy and sensitivity of this screening technique have not been reported in Taiwanese or other Asian populations. Here, we report the results of first-trimester Down’s screening using ultrasound measurement of NT based on 1,249 fetuses between 9 and 14 weeks of gestation.

Materials and Methods

A prospective study was conducted from August 1997 to May 1999. Ultrasound measurement of fetal NT was offered between 9 and 14 weeks of gestation to pregnant women who received antenatal care at our institution. The gestational age was determined by the last menstrual period. Recorded data included maternal age, gestational age, fetal crown–rump length (CRL), NT, and fetal anomalies.

We used a curvilinear 5-MHz transabdominal transducer (Acuson 128 XP/10, Acuson, Mountain View, CA, USA). The maximal thickness of the subcutaneous translucency between the skin and the soft tissue of the cervical spine was measured to 0.1 mm on sagittal-section scans of fetuses (Figure). The measurement was performed with the fetus slightly flexed. We carefully distinguished the fetal skin from the overlying amniotic membrane. Sometimes, it was necessary to manipulate the woman’s abdomen to encourage the fetus to change position for adequate measurement. Occasionally, two or three measurements were performed on one fetus, and the largest measurement was used for analysis.

Initially, we used 2.5 mm as the cut-off point for the screening. Fetuses with an NT measurement of at least 2.5 mm were considered at high risk for Down’s syndrome. Genetic consultation was offered, and CVS or amniocentesis was suggested for cytogenetic study. The normal distribution of NT measurements for a chromosomally normal fetus was calculated based on data of the first 879 fetuses [11]. The standard deviation of an NT measurement may be expressed as shown below:

$$S_y = S_x \sqrt{1 + \frac{1}{n} \left(\frac{x - \bar{x}}{\bar{x} - \bar{x}}\right)^2} = 0.19262 \left(1 + \frac{1}{\sqrt{879}} \left(\frac{x - 53.111273}{878^2}\right)^2\right)$$

Then, the 95th percentile value of the NT on a CRL is equal to

$$b = 1.64 \times S_y = 0.953904 + 0.014459x + 1.64 \times 0.19262 \left(1 + \frac{1}{\sqrt{879}} \left(\frac{x - 53.111273}{878^2}\right)^2\right)$$

All measurements were reevaluated with the normal distribution. A fetus with an NT measurement in the 95th percentile was at high risk for Down’s syndrome. The sensitivity and specificity of both methods were calculated using Fisher’s exact test. A $p$ value of less than 0.05 was considered statistically significant. We also compared the two methods.

Results

A total of 1,979 consecutive measurements were performed during the study. Seven hundred and thirty cases were excluded because of loss to follow-up or incomplete data. A total of 1,249 women were enrolled, including 1,231 singleton and nine twin pregnancies.

The mean maternal age was 30.06 ± 3.53 years (range, 19–43 yr). The mean and median of the CRL were 53.92 ± 15.08 mm and 53.75 mm (range, 22.3–98.6 mm), respectively. The distributions of the NT measurement for various gestational ages and CRL groups are summarized in Tables 1 and 2.

Three fetuses with Down’s syndrome had NT measurements of 2.1 mm, 2.7 mm, and 4.0 mm. With a fixed...
cut-off point of 2.5 mm, 79 fetuses had a positive screening result. The false positive rate was 6.3%, sensitivity was 66.7%, and specificity was 93.8%. However, only 58 fetuses had an NT measurement in the 95th percentile. The false positive rate was 4.6%, sensitivity was 66.7%, and specificity was 95.5%. Both methods had similar negative predictive values (99.91% vs 99.92%).

Discussion

Experience with first-trimester Down’s screening using fetal NT measurement is limited in Taiwan, and the efficacy of such a screening program here remains to be determined. Our results showed a detection rate of 66.7%, with a false positive rate of 6.2% using a fixed cut-off point. When a CRL-related cut-off point was used, the detection rate remained the same, but the false positive rate was only 4.6%. These findings show that this screening program is a potentially useful tool for Down’s syndrome screening during the first trimester.

Several reports have described an association between increased fetal NT and aneuploidy. Although NT measurement is feasible and promising, studies of its efficacy have yielded conflicting results with detection rates ranging from 33% to 91% (Table 3). The positive predictive values range from 1.5% to 9.2%. Only 10 to 70 invasive cytogenetic procedures are needed to detect one Down’s syndrome child [7–9, 12–16]. This study required fewer invasive diagnostic procedures to detect one Down’s syndrome child [7–9, 12–16]. This study required fewer invasive diagnostic procedures to detect one case of Down’s syndrome than a previous large population study in Taiwan that used serum screening during the second trimester [2]. The high negative predictive value showed that the risk of Down’s syndrome is less than 0.1% if a fetus does not have a thickened NT.

Table 1. Number of fetuses with increased nuchal translucency (NT) measurement based on gestational age (GA)

<table>
<thead>
<tr>
<th>GA (wk)</th>
<th>Total NT fetuses (n)</th>
<th>NT &gt; 2.5 mm (n (%))</th>
<th>NT &gt; 95th percentile (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>16</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>10</td>
<td>180</td>
<td>2 (1.1%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>11</td>
<td>254</td>
<td>6 (2.4%)</td>
<td>9 (3.5%)</td>
</tr>
<tr>
<td>12</td>
<td>373</td>
<td>18 (4.8%)</td>
<td>21 (5.6%)</td>
</tr>
<tr>
<td>13</td>
<td>323</td>
<td>40 (12.4%)</td>
<td>19 (5.9%)</td>
</tr>
<tr>
<td>14</td>
<td>103</td>
<td>12 (11.7%)</td>
<td>5 (4.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>1,249</td>
<td>79 (6.3%)</td>
<td>58 (4.6%)</td>
</tr>
</tbody>
</table>

Initially, a fixed cut-off point was used for the screening [8, 9, 12, 14]. The basic assumption in using a fixed cut-off point was that the distribution of NT was similar throughout the screening period. However, it has been noted that the NT thickness increases with gestational age [7, 11, 17–21]. In spite of an overall false positive rate of 6.3%, the present study revealed that the false positive rate was not adequate in both tails of the period. Using gestational age- (or CRL-) related cut-off points is more reasonable than using a fixed cut-off point [11]. Studies reported since 1998 have used a gestational age- or CRL-related cut-off point. The present study also showed that the CRL-related cut-off point had a lower false positive rate [7, 16, 17].

The widespread use of Down’s syndrome screening by ultrasound measurement of fetal NT during the first trimester has been questioned in Taiwan, where there are no reported data for this screening test. Also, most obstetricians in Taiwan do not offer CVS because a previous large population survey showed a strong association between CVS and fetal limb reduction anomalies [22]. When a fetus is found to have a thickened NT, the pregnant woman needs to wait about 3 to 4 weeks for amniocentesis and then another 4 weeks for the report. This is too long for a screening program. In most European countries, CVS is used for cytogenetic study in fetuses with a thickened NT measurement. It can be offered immediately after a positive screening result and only 3 to 4 days are needed for the report. Therefore, the association between CVS and fetal limb reduction anomalies should be clarified before this screening program is widely used. One recent report shows that CVS does not significantly increase the incidence of fetal limb reduction when it is offered after 10 weeks of gestation [23].

This study had several limitations. The number of cases in this study was relatively small for a Down’s syndrome screening program, and the prevalence of
Down’s syndrome was high (3/1,249). Also, about one-third of initial cases were excluded. A population bias should be considered. Further data is needed for a definitive conclusion. However, our data provide a first report and reveal that fetal NT measurement by ultrasound during the first trimester is a potentially effective and noninvasive screening tool for Down’s syndrome in Taiwan.

References


Table 3. Published results of Down’s screening by first-trimester nuchal translucency (NT) measurement in the general population

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects (n)</th>
<th>GA (wk)</th>
<th>Cut-off point</th>
<th>FPR</th>
<th>Detection rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bewley et al, 1995 [12]</td>
<td>1,127</td>
<td>8–13</td>
<td>NT 3 mm</td>
<td>6.2%</td>
<td>33% (1/3)</td>
</tr>
<tr>
<td>Whitlow et al, 1999 [17]</td>
<td>6,634</td>
<td>11–14</td>
<td>NT 99th centile</td>
<td>1.0%</td>
<td>57% (13/23)</td>
</tr>
<tr>
<td>Taipale et al, 1997 [14]</td>
<td>10,101</td>
<td>10–15</td>
<td>NT 3 mm</td>
<td>0.8%</td>
<td>54% (7/13)</td>
</tr>
<tr>
<td>Hafner et al, 1998 [9]</td>
<td>4,233</td>
<td>10–13</td>
<td>NT 2.5 mm</td>
<td>1.7%</td>
<td>43% (3/7)</td>
</tr>
<tr>
<td>Pajkrt et al, 1998 [8]</td>
<td>1,473</td>
<td>10–14</td>
<td>NT 3 mm</td>
<td>4.0%</td>
<td>69% (25/36)</td>
</tr>
<tr>
<td>Theodoropoulos et al, 1998 [15]</td>
<td>3,550</td>
<td>10–14</td>
<td>NT &gt; 95th centile</td>
<td>8.3%</td>
<td>82% (168/326)</td>
</tr>
<tr>
<td>Thilaganathan et al, 1999 [16]</td>
<td>11,398</td>
<td>10–14</td>
<td>Risk (NT) 1:200</td>
<td>2.9%</td>
<td>91% (10/11)</td>
</tr>
<tr>
<td>Jou et al (present study)</td>
<td>1,249</td>
<td>9–14</td>
<td>NT 2.5 mm</td>
<td>6.3%</td>
<td>67% (2/3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NT &gt; 95th centile</td>
<td>4.6%</td>
<td>67% (2/3)</td>
</tr>
</tbody>
</table>

GA = gestational age; FPR = false positive rate; MA = maternal age.


