Evaluation of Trisomy 21 Screening by Fetal Nuchal Translucency Thickness, Maternal Age and Biochemical Serum in the South of Vietnam

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Abstract

Aims: This study aimed to evaluate the most effective approach screening of trisomy 21 in the first trimester in Vietnam

Method: A prospective study carried out during 1 year. All pregnancies screened the risk of trisomy 21 by association of the fetal nuchal translucency, maternal age and biochemical serum (free β-hCG and PAPP-A) as a combined test in the first trimester. The amniocentesis was used to diagnose trisomy 21. In each 4 approaches (association of maternal age, the maternal age and fetal NT thickness, maternal age and biochemical, and combined test), the detection rate and false positive rate of trisomy 21 were calculated to find out the most effective screening method.

Results: Followed up 2500 singleton pregnancies, the incidence of trisomy 21 was 0.6% (16/2500) (95%CI 0.4-1.0%). The absence of nasal bone and poly-malformation were the essential ultrasonographic findings of Down’s syndrome. An increased fetal NT (≥ 2.4 mm) related significantly to this aneuploidy (OR=58.6, 95%CI 17.3-251, p < 0.0001). In comparison of 4 approaches screening, the most possibility of Down’s syndrome detection was the combined test (87.5% of sensitivity for 2.6% of false positive rate).

Conclusion: The combined test was effectively screening method for Down syndrome in Vietnamese pregnancies.

Keywords: Absent nasal bone; Combined test; Fetal nuchal translucency thickness; Maternal biochemical serum; Trisomy 21

Introduction

Trisomy 21 screening is an important part of prenatal diagnosis programme. From the last decades, many studies were performed to find out the earliest signs of Down’s syndrome diagnosis. In 1866, the first finding of trisomy 21 was described in the appearance of being too large for the body and flat face with a small nose by Langdon Down. In the 1990s, Nicolaides et al. [1,2] found that the increased nuchal translucency (NT) in the third month of intrauterine life was associated with the prevalence of fetal chromosomal defect, especially trisomy 21. Following, according to Wald et al. [3,4] Down’s syndrome is associated with high values for fetal NT thickness, high maternal serum concentrations of free beta subunit of human chorionic gonadotropin (free β-hCG) and low serum concentrations of pregnancy associated plasma protein A (PAPP-A). They identified that by combining these serum markers with fetal NT measurement, the detection rate of trisomy 21 was 80% for 5% false positive rate [5]. This strategy of Down’s syndrome screening in the first trimester appeared to be potentially more effective than second trimester serum screening (76% of detection rate and 5% of false positive rate) [5]. Enriching to the approaches findings of trisomy 21, Cicero et al. [5] also insisted that screening by a combination with ultrasound markers and maternal serum (free β-hCG and PAPP-A) can identify up to 97% of fetus with trisomy 21 and other major chromosomal abnormalities in the first trimester of pregnancy. In addition, Nicolaides et al. [6] reported that about 75% trisomy 21 fetuses have increased NT thickness, 70% have absent nasal bone and 25% have maxillary hypoplasia.

In the context that the various approaches of trisomy 21 had been determined such as measurement of the fetal NT thickness, or testing of biochemical serum in the first and second trimester, or using of others ultrasonographic markers, the choice of approach of Down’s syndrome screening depends on the strategy of prenatal diagnosis programme in each country. In Vietnam, where the incidence of trisomy 21 was found one case in 700 deliveries [7], it is better to establish a screening programme for detecting Down’s syndrome at the beginning of gestation. The approach of trisomy 21 screening, which was performed the measurement of NT thickness and maternal biochemical serum routinely in the first trimester of gestation, had been established as one part of the prenatal care and diagnostic programme in Vietnam since 2007. However, there is no research done to prove the feasibility of this trisomy 21 screening strategy in Vietnam. In addition, some Vietnam obstetricians, who work in the remote maternal centers prefer to perform and implement an association with the maternal age and fetal NT thickness for reducing the expenses of each examination. It is very necessary to assess the efficacy and feasibility of each trisomy 21 screening strategy in order to develop and build an official and effective prenatal care program in our country. Therefore this study was carried out to evaluate and find out the most efficacy method screening by comparison of four approaches of trisomy 21 detection based on isolated maternal age, or association with maternal age and fetal NT thickness, or association with maternal age and biochemical serum, or combined test (an association with maternal age, fetal NT thickness and serum biochemistry) in the Vietnamese obstetrical population.

Material and Method

Study population

A prospective study carried out in our clinic from January 1st to

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December 31st 2009. 2500 singleton pregnancies were accepted to participate to programme of prenatal screening. They were followed by measuring of the fetal NT thickness and by testing of serum maternal marker routinely (free-β.hCG and PAPP-A) for screening of fetal chromosomal aberration at the 11-14 weeks, then by examination of fetal structural scanning at the 18-22 weeks of gestation. The gestational age was calculated in weeks and days followed measurement of fetal crown-rump length (CRL). The multi-pregnancies and nonviable fetus were excluded.

Clinical test

We used the ultrasound machine SONOACE 8800 and VOLUSON 730Pro with the curvilinear C5-2 transducer for fetal NT measurement in the first trimester and the 3D4-7EK probe for examination of fetal morphology in the second trimester scanning.

The sonographers were trained and certified for measurement of fetal NT by Fetal Medicine Foundation (FMF) and they had experienced at least 5 years for ultrasound scan of fetal morphology. All of pregnancies were scanning by using a transabdominal probe. Fetal NT thickness was measured in according to criteria of FMF guidelines: CRL was in range from 45 to 84 mm; fetus in sagittal position with spine situated posteriorly; fetus in neutral position with no hyperextension or flexion; NT clearly visible for measurement; and at least three measurements were taken then the largest of the these was recorded [1]. A fetal anatomic survey was examined following a standardized protocol at the time of the fetal NT scanning including evaluation of skull and brain, face, spine, heart (4-chamber view and great vessels), stomach, abdominal insertion of umbilical cord, urinary bladder and extremities. We have reviewed together all of the fetal abnormalities (such as an increased fetal NT thickness, fetal structural malformations) for giving a final conclusion.

An increased fetal NT thickness was defined at 3 cut-off points of 2.4 mm, 2.5 mm [8,9] and 95th percentile of CRL measurement [10,11] to evaluate and compare the detection rate of trisomy 21 and its false positive rate.

Laboratory test

Serum maternal biochemistry (free β-hCG and PAPP-A) were taken after performing of fetal NT measurement, analysed and calculated in association with fetal NT thickness and maternal age (as a combined test) by using Immulite DPC 2000 (Diagnostic Products Cooperation) with Prisca software of Germany company. The risk of fetal chromosomal aberration of combined test was presented as a fraction, and threshold of 1 in 250 was defined as a positive test (positive combined test) for prediction of trisomy 21 and trisomy 18 following the recommendation of Wald et al. [3] and Vadiveloo et al. [12] who chose 5% of the false positive rate for Down’s syndrome detection.

Fetal abnormality

Amniocentesis was proposed after having a consultation to couple, offered at 15-24 weeks of gestation and performed to women who had a history of fetal or child chromosomal abnormalities, or a positive combined test or a major structural ultrasonographic anomaly at the second trimester scanning. If the results of amniocentesis showed an aneuploidy, a termination of pregnancy was discussed.

A logistic regression was applied to assess the correlation of trisomy 21 with advanced maternal age, increased fetal NT thickness at 3 cut-off points, and the combined test. P-value <0.01 was chosen a statistical relation significantly. Based on these logistical regressions, the receiver operator characteristic curve (ROC curve) was built to find out the highest value of the various approaches screening for detection of trisomy 21 in Vietnamese pregnancies. Stata software package was used to calculate the detection rate, false positive rate of trisomy 21, to analyse a logistic regression, and to build a ROC curve in present study.

Results

Maternal and fetal characteristics

A total of 2500 singleton pregnancies were participated to the study during one-year period. Women’s mean age was 28.9 ± 4.5 years and distributed in a shape-bell (Figure 1) with 12.1% (302 cases) advanced maternal age (≥ 35 years old). Most of them were multi-paras, and none of studies pregnancies had a history of previously affected pregnancies (fetal or child chromosomal defect) nor resulted from assisted reproduction techniques.

The mean of fetal NT thickness was 1.6 ± 0.5 mm and increased correspondent to CRL (median of CRL was 55 mm, range from 45 to 83 mm). The rate of increased fetal NT thickness was 5.3% (133 cases), 3.7% (92 cases) and 5.0% (126 cases) alternatively at the cut-off point of 2.4 mm, 2.5 mm and 95th percentile.

Fetal abnormality

Amniocentesis was done in 71 pregnancies because of the positive combined test (2.7%, 95% CI 2.1- 3.4%) and presence of major abnormal finding in the second trimester scanning.

0.6% (16/2500, 95% CI 0.4-1.0%) was the incidence of trisomy 21. Of the 16 these cases, 12 cases (75%) had an increased fetal NT thickness (≥ 2.4 mm), 14 cases (87.5%) was positive combined test, and 4 cases (25%) found major structural anomalies findings in the second trimester ultrasound scan, that showed in detail in Table 1.

Relationship between trisomy 21 to the advanced maternal age, the increased of fetal NT thickness and the combined test.

We found that the increased fetal NT thickness had a significant
correlation with trisomy 21 (Fisher’s exact, p <0.0001) at all 3 cut-off points (2.4 mm, 2.5mm and 95th percentile of CRL). The combined test showed the highest relation significantly with trisomy 21 (OR = 285, p <0.0001) and the highest detection rate (87.5%) that illustrated in Table 2.

In comparison of the four approaches for trisomy 21 diagnosis, an increasing of sensitivity, specificity and positive predictive value was showed remarkably by using a combined test, which were illustrated in Table 3 and Figure 2.

**Discussion**

The fetal NT measurement, which combined with maternal age and biochemical serum, was an effective screening method for Down syndrome in the first trimester of gestation in the Vietnamese pregnancies with 87.5% of detection rate for 2.4% of false positive rate.

16 cases of trisomy 21 (prevalence was 1 in 156 pregnancies) were found in present study and similar to result of Wapner et al. [13] (1 in 135 pregnancies), but rather higher than reported by Dhaifalah et al. [15] (1 in 343 pregnancies) in Czech and by Theodoropus et al. [16] (1 in 355 pregnancies) in Greece. This difference was depended on the efficacy of prenatal screening program and the risk of obstetrical study population. In the developed countries, the prenatal screening programme had been built and developed since many decades. The efficacy of this screening program proved in lowering the number of trisomy 21. Therefore, this is the principal reason that their trisomy 21 prevalence was lower than our result.

![Table 1](image)

<table>
<thead>
<tr>
<th>Number</th>
<th>Age (year)</th>
<th>Gestation</th>
<th>Parity</th>
<th>CRL (mm)</th>
<th>NT (mm)</th>
<th>NT MoM</th>
<th>Ultrasound 2</th>
<th>Combined test</th>
<th>Karyotype</th>
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<td>1</td>
<td>1</td>
<td>56</td>
<td>3.3</td>
<td>2.1</td>
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<td>1:50</td>
<td>47XY,+21</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>0</td>
<td>0</td>
<td>51</td>
<td>2.5</td>
<td>1.8</td>
<td>Normal</td>
<td>1:179</td>
<td>47XY,+21</td>
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<tr>
<td>3</td>
<td>37</td>
<td>4</td>
<td>2</td>
<td>65</td>
<td>1.7</td>
<td>1.0</td>
<td>Normal</td>
<td>1:247</td>
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<tr>
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<td>3</td>
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<tr>
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<td>0</td>
<td>0</td>
<td>59</td>
<td>2.6</td>
<td>1.7</td>
<td>Normal</td>
<td>1:54</td>
<td>47XY,+21</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>2</td>
<td>2</td>
<td>59</td>
<td>2.9</td>
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<td>Normal</td>
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<td>47XY,+21</td>
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<tr>
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<td>1</td>
<td>53</td>
<td>2.0</td>
<td>1.4</td>
<td>Normal</td>
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</tr>
<tr>
<td>8</td>
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<td>47XX,+21</td>
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<tr>
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<td>30</td>
<td>0</td>
<td>0</td>
<td>63</td>
<td>2.1</td>
<td>1.2</td>
<td>Absence of NB</td>
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<td>47XY,+21</td>
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<tr>
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<tr>
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<td>1</td>
<td>66</td>
<td>2.6</td>
<td>1.4</td>
<td>Normal</td>
<td>1:21</td>
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</tr>
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<td>1</td>
<td>1</td>
<td>47</td>
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<td>Normal</td>
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<td>47XY,+21</td>
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<td>Absence of NB</td>
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<td>66</td>
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<td>3.3</td>
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<td>47XY,+21</td>
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<tr>
<td>16</td>
<td>33</td>
<td>1</td>
<td>1</td>
<td>61</td>
<td>2.8</td>
<td>1.7</td>
<td>Normal</td>
<td>1:50</td>
<td>47XX,+21</td>
</tr>
</tbody>
</table>

(DW malformation: Dandy-Walker malformation, NB: Nasal bone)

**Table 1**: 16 cases of trisomy 21 in related to the maternal and fetal characters, ultrasound scanning in the second trimester and the combined test.

![Table 2](image)

<table>
<thead>
<tr>
<th>Number</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>DR (%)</th>
<th>FPR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (≥ 35 years)</td>
<td>302</td>
<td>2.45 (0.57-8.13)</td>
<td>0.124</td>
<td>25.0</td>
</tr>
<tr>
<td>Unaffected pregnancies</td>
<td>298</td>
<td>4</td>
<td>65.3 (20.2-243)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>11</td>
<td>45.3 (14.2-168)</td>
<td>&lt;0.0001</td>
<td>68.8</td>
</tr>
<tr>
<td>Increased fetal NT (≥ 2.4mm)</td>
<td>132</td>
<td>25.0</td>
<td>88.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Unaffected pregnancies</td>
<td>115</td>
<td>81.3</td>
<td>88.9</td>
<td>4.5</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>11</td>
<td>87.5</td>
<td>96.8</td>
<td>15.1</td>
</tr>
<tr>
<td>Increased fetal NT (≥ P 95)</td>
<td>92</td>
<td>87.5</td>
<td>97.6</td>
<td>19.2</td>
</tr>
</tbody>
</table>

**Table 2**: Odd ratio (OR), detection rate (DR) and false positive rate (FPR) of maternal age, increased fetal NT in different cut-off point and positive combined test.

![Table 3](image)

**Table 3**: Trisomy 21 diagnosis value in 4 approaches findings screenings.
of sensitivity and a lower false positive for Down’s syndrome detection of trisomy 21 (12 /16 cases) at 2.4mm (Table 1), so we found a higher 1% to 5.4% [6,14,16,17,23,24]. We obtained the most of affected cases detection rate from 75% to 91% and the varied false positive rate from increased fetal NT thickness for screening trisomy 21 with the varied point and 95th percentile depending cut-off were used effectively as an [19,21,22]. Many studies reported: the threshold of fixed 2.5mm cut-off when NT levels increase, the chance that healthy baby will be decrease higher the false positive rate [20].

In literature, the more advanced the maternal age, the higher the prevalence of Down syndrome [17]; and 58% of babies with Down’s syndrome were born to women aged year 35 or more [18]. Nicolaides et al. [1,19] found that when the maternal age was 35 years or more, the detection rate of trisomy 21 was 71.4% for 1.1% false positive rate. However, we didn’t find out a significant correlation with trisomy 21 and the advanced of maternal age (OR = 2.45, p = 0.124) because our study was a low-risk study population (the means of maternal age was 28.9 ± 4.5 years); so it was not eligible to use the maternal age to evaluate the possibility of trisomy 21 in young obstetrical population. Furthermore, according to Nicolaides et al. [1,19] maternal age screening had also a low detection rate (30%) for prediction of trisomy 21 and it also showed no advantage for using maternal age alone in comparison into the combined of fetal NT thickness and biochemical serum [13]. Similarly, Niemimaa et al. [20] believed that trisomy screening by using of maternal age alone has a low detection rate and a high false positive rate. Theodoropoulos et al. [16] reported the coincided result to our study with 2 cases of trisomy 21 in women aged 37 years or more in the low-risk study population in Greece (the median maternal age was 29 years, range 16-48). That’s a necessary reason to develop of prenatal screening routinely in low-risk and intermediate-risk population. In the future, it would be important to find a risk program independent of maternal age, because the greater the proportion of older women, the higher the false positive rate [20].

Choice a fetal NT cut-off point to define an increased fetal NT thickness is very important in the prenatal care program because when NT levels increase, the chance that healthy baby will be decrease [19,21,22]. Many studies reported: the threshold of fixed 2.5mm cut-off point and 95th percentile depending cut-off were used effectively as an increased fetal NT thickness for screening trisomy 21 with the varied detection rate from 75% to 91% and the varied false positive rate from 1% to 5.4% [6,14,16,17,23,24]. We obtained the most of affected cases of trisomy 21 (12 /16 cases) at 2.4mm (Table 1), so we found a higher of sensitivity and a lower false positive for Down’s syndrome detection in the 2.4 mm cut-off point than those in point of 2.5mm and 95th percentile (75.0% and 4.9% versus 65.8% and 3.3%; 68.8% and 4.6%, respectively). Our 75% of detection rate for trisomy 21 at this cut-off point was coincided to reported by Pandya et al. [25] and Nicolaides et al. [26] who used the fetal NT cut-off of point at 2.5 mm, and by Audibert et al. [27] who used the fetal NT above 95th percentile.

An increased fetal NT thickness was an essential ultrasonographic finding of trisomy 21 in the first trimester in our study. This result was different from those of Souka et al. [28] and Weiner et al. [29] who detected half of major structural defects (included cleft-lip, ventricular megaly and abnormal posterior fossa, heart anomaly) by using both of transabdominal and transvaginal scanning in low-risk pregnancies. Because of the cultural reason, or some of misconceptions that transvaginal scanning may cause miscarriage, our pregnant women refused an ultrasonographic examination transvaginally. While Ebrashy et al. [30] determined that ultrasound examination transvaginally was significantly better than transabdominal evaluation in visualizing all the fetal structure. In addition, of 16 cases of trisomy 21 diagnosed, we had 4 cases with normal fetal NT thickness (below 2.4 mm) and without deformities in ultrasound scan at the 18-22 weeks of gestation. We considered that an increased fetal NT thickness screening alone was not enough for trisomy 21 detection in Vietnam, although a significant relation with increased fetal NT thickness at 3 cut-off points and trisomy 21 was obtained (OR=45.3-65.3. p <0.0001).

In literature, the absence of nasal bone was determined as a marker for aneuploidy both in the first and second trimester [31]. Several studies have demonstrated a strong between an absent nasal bone at 11-14 weeks of gestation and trisomy 21 [32-34]. And in the combined data from these studies, the fetal nasal bone was absence in 69% of fetus with trisomy 21 [26]. In present study, the fetal structural defects of Down syndrome were poverty in anatomical ultrasound scanning at the 18-22 weeks of gestation, so an association with many approaches was useful to improve the detection rate of trisomy 21. Because the absence of the nasal bone is not related to fetal NT thickness [31], and the finding screening of maternal age alone showed no advantage for detection of trisomy 21 [13], therefore, they could be combined relatively simply to provide a more effective method of early screening for trisomy 21 [6,33].

Nicolaides [6] found that the most effective method of screening for chromosomal defects is by a combination with maternal age, fetal NT thickness and maternal biochemical serum (free β-hCG and PAPP-A) at 11-14 weeks of gestation (with its detection rate is about 90% for a screen-positive rate of 5%) [6]. Using a positive threshold of 1:250 following the recommendation of Wald et al. [3] and Vadiveloo et al. [12] for a fixed positive rate of 5%, we obtained 87.5% of detection rate (for 2.4% of false positive rate) by combination all of the various finding screening (maternal age, fetal NT thickness, free β-hCG and PAPP-A). The differences in cut-off figures of combined test may explicate the difference in the detection rate of trisomy 21[35] from our result to others studies: Spencer et al. [36] reported an 86% detection rate at cut-off figure of 1:300, Niemimaa et al. [20] obtained an 80% detection rate with a threshold was 1:200, and Wapner et al. [13] found an 85.7% detection rate in using a cut-off of 1:270.

1 case of trisomy 21 was detected in 156 Vietnamese pregnancies, showed a rather high prevalence of trisomy 21 in Vietnam. It required developing an effective strategy of prenatal care and diagnosis for reducing of fetal abnormality (especially trisomy 21). Our studied results were also the initial data, but it proved that the program of trisomy 21 screening by using combined test in the first trimester was accurate and efficient in clinical practice. The advantage of trisomy 21 screening from 11 to 13.6 weeks of gestation was not only giving the screening results earlier, but also allowing more time for counselling
and consideration of the result. Using a combined test for screening of trisomy 21 is really one of the important parts in the prenatal screening strategy in Vietnam.

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