Screening for Down Syndrome Using Nuchal Translucency Thickness and Nasal Bone Examination at Advanced Maternal Age in Jakarta: A Preliminary Report

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Background: Older maternal age leads to increased risk for both the mother and fetus, particularly if the mother is more than 34 years old. We evaluated a non-invasive method to screen for Down syndrome at a maternal age of 35 years or more. We measured nuchal translucency thickness (NT) using a fixed cut-off of 3.0 mm or more with a crown–rump length (CRL) of 50–70 mm and nasal bone (NB) examination at 11–13+6 weeks of gestation.

Materials and Methods: This prospective study was conducted from January 2001 to January 2003. NT was measured at 11–13+6 weeks of gestation. In addition, the NB was examined from January 2002 to January 2003. Cases with an NT of at least 3.0 mm were submitted to TORCH examination (toxoplasma, rubella, cytomegalovirus, and herpes simplex virus I and II). Genetic amniocentesis was performed at 16 weeks of gestation. Both antenatal and postnatal management and observations were carried out.

Results: NT was measured in 175 cases between January 2001 and January 2002. Combined NT measurement and NB examination was performed in 97 cases between January 2002 and January 2003. Maternal ages ranged from 35 to 43 years, with first to fifth gravidity. Of the 175 NT cases, seven had NT of at least 3.0 mm. The detection rate (DR) for Down syndrome was 71.4% (5/7) and the false-positive rate (FPR) was 1.2% (2/170). Of the 97 NT plus NB absence cases, four had an NT of at least 3.0 mm and three had no NB. The combination of maternal age, NT and NB examination gives a DR for Down syndrome of 87.5% (3/4 paralleled to 3/3) and an FPR of 1% (1/94).

Conclusion: Screening for Down syndrome can be performed in the clinical setting by measuring NT (using a fixed cut-off of ≥ 3.0 mm and CRL of 50–70 mm) and NB examination at 11–13+6 weeks of gestation. Abnormal NT with normal karyotype requires strict antenatal and postnatal observation.

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KEY WORDS: • Down syndrome • nuchal translucency • nasal bone • ultrasonography
INTRODUCTION

Over the last few decades, substantial changes in living and marital patterns have occurred in Indonesia, particularly in urban areas. For reasons associated with career and occupation, women in Indonesia generally marry and become pregnant at a more advanced age than ever before. The increase in maternal age results in increased risk for both the mother and fetus. If maternal age is 35 years or more, the pregnancy is considered high risk [1].

Many authors indicate that the incidence of pregnancy and labor complications, such as pre-eclampsia/eclampsia and postpartum hemorrhage, is higher in women aged 35 years or more. Similarly, the more advanced the maternal age, the higher the risk for congenital anomalies, chromosomal anomalies, and fetal growth abnormalities [2–4].

The incidence of chromosomal anomalies, such as trisomy 21 (Down syndrome), tends to increase with advancing maternal age. It is estimated that at a maternal age of 30 years, one case of Down syndrome is found in 900 deliveries; at a maternal age of 35 years, one case is found in 360 deliveries; at a maternal age of 38 years, one case is found in 170 deliveries; and at a maternal age of 42 years, one case is found in 55 deliveries [5].

A number of methods are recognized in diagnosing Down syndrome in pregnancy, such as biochemical examination, biophysical examination (invasive and non-invasive), and combined biochemical and biophysical examination.

Genetic chorionic villi sampling, which is performed at 11 weeks of gestation or more, and genetic amniocentesis at 15–16 weeks of gestation are used in the diagnosis of Down syndrome in pregnant women aged 35 years or more. However, these methods are invasive and have some serious shortcomings, i.e. complications that may threaten fetal life [6,7].

Non-invasive biophysical examinations used to screen for Down syndrome include ultrasonographic measurement of nuchal translucency thickness (NT) and identification of the presence or absence of the nasal bone (NB).

At issue was whether the determination of NT cut-off point, which was established by the Fetal Medicine Foundation (FMF) for diagnosis of Down syndrome, could be applied in an Asian population or Asian ethnic groups [8–10]. Jou et al suggest that it might be best to use an NT cut-off based on MoM (Multiple of Median) of the crown–rump length (CRL) for Asian populations [9]. For this reason, it is necessary to conduct studies to obtain relevant NT values [9]. With no database of Asian populations, Jou et al proposed that a fixed NT cut-off of 2.5 or 3.0 mm could be used with a CRL of 50–69 mm [9]. To facilitate its application in the clinical setting, a fixed NT cut-off of 3.0 mm was chosen with a CRL of 50–70 mm.

Similarly, in identification of the presence or absence of the NB to screen for Down syndrome, other factors such as CRL and ethnicity should be taken into account [11,12].

The objective of this study was to find a non-invasive method (without complications) to screen for Down syndrome. We measured NT and looked for the NB using ultrasonography at 11–13+6 weeks of gestation using a CRL of 50–70 mm, which was considered feasible in the clinical setting.

MATERIALS AND METHODS

This preliminary, prospective study was performed at Budhi Jaya Maternity and Children Hospital, Bunda Women Hospital, Tebet General Hospital, and Christian University General Hospital in Jakarta between January 2001 and January 2003. Budhi Jaya Maternity and Children Hospital and Bunda Women Hospital are the main centers for infertility and perinatal health care in Jakarta. The criteria for pregnant women to be included in this preliminary study were: age 35 years or more, healthy, single pregnancy, 11–13+6 weeks of gestation, and CRL of 50–70 mm (based on ultrasonographic examination).

Pregnant women who met these criteria underwent NT measurement (between January 2001 and January 2002) or the combination of NT measurement and NB examination (from January 2002 to January 2003). One operator with 20 years of experience performed the ultrasonographic examinations; most examinations were carried out using a transabdominal probe, while a small number of cases underwent examination using a transvaginal probe. The machines used were Apoge 800-ATL (Advance Technology Laboratories Inc, Bothel, WA, USA), SSD 680-Aloka (Aloka Co Ltd, Tokyo, Japan), Logic α 200 GE (GE Medical Systems, Milwaukee, WI, USA), and Veluson 730 Pro GE (GE Medical Systems Kretztechnik GmBH & Co OHG, Zipf, Austria).
NT was measured in accordance with a number of requirements established by the FMF: fetus in sagittal position with spine situated posteriorly; fetus in neutral position with no hyperextension or flexion; and NT clearly visible for measurement [13]. To facilitate NT measurement, a fixed cut-off of at least 3.0 mm and a CRL of 50–70 mm were used.

In NB examination, the fetus should preferably be facing toward the transducer, the image should be magnified so that only the head and the upper thorax are visible on the screen, and the mid-sagittal view of the fetal profile must be obtained. The angle between the ultrasound transducer and an imaginary line passing through the fetal profile should be about 45° and the probe should be gently tilted from one side of the fetal nose to the other to demonstrate three distinct lines. The top line represents the skin and the bottom one, usually thicker and more echogenic than the overlying skin, represents the NB, whereas a third line, almost in continuity with the skin but at a higher level, represents the tip of the nose. When the NB appears as a thin line, less echogenic than the overlying skin, it suggests that the NB is not yet ossified, and it is, therefore, classified as being absent.

When the NT was at least 3.0 mm and the NB was invisible, a serum TORCH (toxoplasma, rubella, cytomegalovirus, and herpes simplex virus I and II) examination was performed. Genetic amniocentesis was carried out in mothers at 16 weeks of gestation. All cases with an NT of at least 3.0 mm and no visible NB had strict antenatal observation follow-up until delivery.

The detection rate (DR) and false-positive rate (FPR) were calculated to evaluate the results of screening. The DR was the percentage of persons with a positive test who had trisomy 21, while the FPR was the percentage of persons without trisomy 21 who had a positive test. The combined test was expected to enhance the DR and FPR. The estimated risk for Down syndrome is indicated in relation to NT and NT plus NB absence.

**RESULTS**

From January 2001 to January 2002, 175 pregnant mothers who met the requirements for the study underwent NT measurement. Maternal age ranged from 35 to 43 years (mean, 37.8 years) and mean gravidity was 3.9. NT showed seven cases with NT of at least 3.0 mm, of which five turned out to have trisomy 21 (Fig., Table 1). TORCH examination in seven of these cases was normal and karyotype was normal in two cases. Thus, in women aged 35 years or more, NT measurement had a DR for Down syndrome of 71.4% (5/7) and an FPR of 1.1% (2/170).

From January 2002 to January 2003, 97 pregnant mothers who met the requirements for this study underwent NB examination as well as NT measurement. Maternal age ranged from 35 to 43 years (mean, 37.6 years) and mean gravidity was 3.7. NT showed four cases with NT of at least 3.0 mm, although only three cases had no NB. TORCH examination in four cases was normal. Genetic analysis from four cases with NT of at least 3.0 mm (three cases had no NB) showed three cases with Down syndrome (Table 1). In women aged at least 35 years, NT plus NB examination had a DR of 87.5% (3/4 paralleled to 3/3) and an FPR of 1% (1/94).

In the three cases with an NT of at least 3.0 mm and normal karyotype (two cases with 46,XY and one with 46,XX; between January 2001 and January 2003), pregnancy lasted to term. At 16 weeks of gestation, fetal echocardiography was normal. Follow-up fetal echocardiography at 20 weeks of gestation was also normal. Three babies from three cases with an NT of at least 3.0 mm and normal karyotype were delivered normally.
DISCUSSION

Babies with Down syndrome typically have a small oval-shaped head, low-set ears, small ear lobes, an oriental appearance with eyes pointing upward and outward, absence of or a poorly developed nose bridge, and a Brushfield spot at the epicanthal folds. In the past, the life expectancy of Down syndrome patients was low, approximately 8 years. Children died from infection and cardiac anomalies and were at risk for leukemia. With the introduction of antibiotics and the rapid advances in cardiac surgery, Down syndrome patients now have a longer life expectancy [13].

The more advanced the maternal age, the higher the prevalence of Down syndrome. This may be because most Down syndrome karyotypes are caused by non-disjunction of the autosome chromosome in meiosis during ovum formation.

In the 1990s, screening for Down syndrome was introduced with a combination of maternal age and NT measurement at 11–14 weeks of gestation. Most studies have been conducted in unselected cases, i.e., women of reproductive age. Studies of Down syndrome have been performed at research centers [14,15]. A multicenter study has also been performed in 43 countries in conjunction with the Multicenter Project of the FMF [13]. This preliminary study, conducted in selected cases where the maternal age was 35 years or more, showed a DR for trisomy 21 of 71.4% (5/7) and an FPR of 1.1% (2/170) using NT measurement. These results are not very different from those of previous studies (Table 2) [13–15].

In this preliminary study (2001–2003), three cases had NT above the threshold but normal karyotype. In the first case, the mother was 37 years old and the NT was 3.6 mm; in the second case, the mother was 39 years old and the NT was 3.4 mm; while in the third case, the mother was 36 years old and the NT was 3.5 mm (and NB +). In all cases, there was strict antenatal observation and the babies were delivered normally. In contrast, in Souka et al’s study, only 5.56% of 1,080 live births had fetal defects, genetic syndromes that required surgical intervention, or mental abnormality [16]. They conducted the study in 1,320 singleton pregnancies at 10–14 weeks of gestation using an NT threshold of at least 3.5 mm and normal karyotype. Only 81.82% (1,080 pregnancies) resulted in live births; 5.15% (68 pregnancies) ended in spontaneous abortion or intrauterine fetal death, 1.36% (18 pregnancies) ended in fetal/neonatal death, and 11.67% (154 pregnancies) were terminated.

The FMF Multicenter Project found congenital anomalies (fetal defect and genetic syndrome) in 3.9% of singleton pregnancies using increased NT thickness and normal karyotype [13]. The prevalence of fetal anomalies increased with increasing NT. Thus, it is recommended that strict antenatal and postnatal observations be carried out in cases with NT above the threshold and normal karyotype.

There are a number of ways to enhance the DR for Down syndrome at 11–14 weeks of gestation, e.g., combined NT measurement and NB examination. The NB can be visualized using two-dimensional ultrasonography at 11–14 weeks of gestation [11]. In 60–70% of trisomy 21 cases, no NB is found. In addition, NB is not visualized in less than 1% of fetuses with normal karyotype. Absence of NB or NB hypoplasia is affected by race/ethnic factors.
In the present study, a combination of maternal age of at least 35 years, NT measurement, and NB examination gave a DR of 87.5% (3/4 paralleled to 3/3) and an FPR of 1% (1/94). This was not significantly different from rates obtained by Nicolaides, who found a DR of 90% and an FPR of 5% [12].

It remains to be determined whether NB examination for Down syndrome screening can be applied in Asian populations or Asian ethnic groups. In his study, Prefumo did not find NB in 3.4% of the Asian ethnic group, 1.9% of the Afro-Caribbean ethnic group, and 1.7% of the Caucasian ethnic group [17]. For this reason, it is necessary to conduct further studies on NB that involve Asian populations.

CONCLUSIONS

Screening for Down syndrome can be performed in a clinical setting by measuring NT (with a fixed cut-off NT*3.0 mm and CRL at 50–70 mm) and NB examination at 11–13+6 weeks of gestation. Cases with NT above the threshold and normal karyotype require strict antenatal and postnatal observation.

REFERENCES


Table 2. Studies examining the implementation of fetal nuchal translucency thickness (NT) screening

<table>
<thead>
<tr>
<th>Author</th>
<th>Gestation (wk)</th>
<th>NT cut-off (mm)</th>
<th>DR (trisomy 21, %)</th>
<th>FPR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zimmerman et al(^1^)</td>
<td>10–13</td>
<td>≥ 3.0</td>
<td>67.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Pajkrt et al(^2^)</td>
<td>10–14</td>
<td>≥ 3.0</td>
<td>67.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Multicenter Project, FMF(^3^)</td>
<td>11–13</td>
<td>95(^{th}) centile</td>
<td>71.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Current study</td>
<td>11–13</td>
<td>≥ 3.0</td>
<td>71.4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

DR = detection rate; FPR = false-positive rate.

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[11,12].
17. Prefumo F. First-trimester absence of nasal bone: effect of ethnicity. 11th World Congress on Ultrasound in Obstetrics and Gynecology, 2–7 November 2002, New York, USA.