Artikel Asli

Down Syndrome Screening Using Nuchal Translucency Thickness and Nasal Bone Examination of Fetus at Maternal Age ≥ 3d 35 Years. A Preliminary Report

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Abstract

The aim of this study is to evaluate a non-invasive method to screen for Down syndrome. We measured nuchal translucency thickness (NT) using a fixed cut-off of ≥'3d 3.0 mm with a crown-rumph length (CRL) of 50-70 mm and nasal bone (NB) examination at 11-13 $^{+6}$ weeks of gestation. The study was conducted from January 2001 to January 2004. NT was measured at 11-13^{+6} weeks of gestation and NB was examined from January 2002 to January 2004. Case with NT of at least 3.0 mm were submitted for toxoplasma, rubella, cytomegalovirus, and herpes simplex virus I and II (TORCH) examinations. Genetic amniocentesis was performed at 16 weeks of gestation. Both antenatal and postnatal management were carried out. NT was measured in 175 cases between January 2001 and January 2002. Combined NT measurement and NB examination were performed in 215 cases between January 2002 and January 2004. Maternal age ranged from 35 - 43 years, with first to fifth gravidity. Seven out of 175 NT cases, had NT of at least 3.0 mm. The detection rate (DR) was 71.4% (5/7) and the false-positive rate (FPR) was 1.2% (2/170). Of the 215 NT plus NB absence cases, eight had an NT of at least 3.0 mm and seven had no NB. The combination of maternal age, NT and NB examination gives a DR of 87.5% % (7/8 paralleled to 7/7) and FPR of 0.48 % (1/208). Screning can be performed in the clinical setting by measuring NT and NB examination at 11-13^{+6} weeks of gestation.

Key Words: Down syndrome, nuchal translucency, nasal bone, ultrasonography

Abstrak

Penelitian ini bertujuan untuk menilai penggunaan metode non invasif untuk penapisan sindrom down. Diukur *nuchal translucency thickness* (NT) dengan *cut-off* of ≥'3d 3.0 mm, *crown-rumph length* (CRL) 50-70 mm dan pemeriksaan tulang hidung (*nasal bone*-NB) pada umur kehamilan 11-13 $^{+6}$ minggu. Penelitian dilakukan sejak January 2001 sampai dengan January 2004. NT diperiksa pada umur kehamilan 11-13^{+6} minggu dan NB diperiksa pada January 2002 sampai January 2004. Pada kasus dengan NT 3,0 mm atau lebih dilakukan pemeriksaan TORCH. Amniosentesis untuk pemeriksaan genetik dilakukan pada minggu ke-16 kehamilan. Selain itu, juga dilaksanakan pemeriksaan dan penanganan antenatal dan postnatal. NT dinilai pada 175 kasus antara January 2001 dan January 2002. Kombinasi pengukuran NT dan NB dilakukan pada 215 kasus antara January 2002 dan January 2004. Umur ibu hamil berkisar antara 35 - 43 tahun, dengan variasi kehamilan pertama sampai kelima. Tujuh dari 175 kasus NT, mempunyai ukuran 3,0 mm.atau lebih. Angka deteksi pemeriksaan (DR) tersebut adalah 71,4% (5/7) dan angka positif palsu (FPR) 1,2% (2/170). Pada 215 kasus NT dan NB, delapan mempunyai ukuran NT 3,0 mm atau lebih dan tujuh tanpa NB. Kombinasi umur ibu, dan pemeriksaan NT dan NB memberikan angka DR 87,5% % (7/8 paralel terhadap 7/7) dan FPR 0,48 % (1/208). Penapisan dapat dilakukan di klinik dengan mengukur NT dan NB pada minggu 11-13^{+6} kehamilan.

Kata kunci: Sindroma Down, translusensi nukhal, tulang nasalis, ultrasonografi

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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 result 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 studies indicate that the incidence of pregnancy and labor complications, such as preeclampsia/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 maternal age of 38 years, one case is found in 170 deliveries; and at meternal age of 42 years, one case is found in 55 deliveries .[5]

A number of methods are used 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 (CVS), which is performed at 11 weeks gestation or more, and genetic amniocentesis at 15-16 weeks of gestation are used in the diagnosis of Down's 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 examination used to screen for Down syndrome include ultrasonographic measurement of nuchal translucency (NT) thicknes 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; can this be applied in an Asian population or Asian ethnic group? [8-10] Jou *et al* [9] suggest that it might be best to use an NT cut-off based on Multiple of Median (MoM) of the crown-rumph length (CRL) for Asian populations. For this reason, it is necessary to conduct studies to obtain relevant NT values . With no database of Asian population, Jou *et al*[9] proposed that a fixed NT cut-off of 2.5 or 3.0 mm could be used with CRL of 50-69 mm. To facilitate its application in the clinical setting, a fixed NT cut-off 3.0 mm was chosen with a CRL of 50-70 mm.

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

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

Materials and Methods

This 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 2004*. Budhi Jaya Maternity and Chldren 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 study were: age 35 years or more, healthy, single pregnancy, $11\text{-}13^{+6}$ 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 2004). One operator with 20 years of experience performed the ultrasonographic examinations; most examination were carried out using a transabdominal probe while small number of cases underwent examination using a transvaginal probe. The ultrasonographic examination (transabdominal sonographic and transvaginalsoographic examination) used machines from Apoge 800-ATL (Advance Technology Laboratories Inc, Bothel, WA 98021, USA), SSD 680-Aloka (Aloka Co.Ltd,Tokyo,Japan), Logic α 200 GE (GE Medical Systems, Milwaukee, Wisconsin 53201, USA); and Veluson 730 Pro GE (GE Medical Systems Kretztechnik GmBH & Co OHG,Tiefenbach 15, A-4871 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-sagital view of 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 bottom one, usually thicker and more echogenic than overlying skin, represents the nasal bone, whereas a third line, almost in continuity with the skin but at a higher level, represents the tip of the nose. When the nasal bone appears as a thin line, less echogenic than then overlying skin, it the suggests that the nasal bone 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 siplex virus I and II) examination was performed. Genetic amniocentesis was carried out in mother 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 percentage of persons with a positive test who had trisomy 21, while the FPR was percentage of persons without trysomy 21 who had a positive test. The combined test was expected to enchance the DR and FPR. The estimated risk for Down's syndrome is indicated in relation to NT and NT plus NB absence.

Results

From January 2001 to January 2002, 175 pregnant mothers enrolled to the sutudy and 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.1, 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 measrument had a DR for Down syndrome of 71.4% (5/7) and an FPR of 1.1% (2/170).

Table 1. Number of case with Down syndrome (DS)

Case	Maternal age	NT only	NT+NB	Estimated DS risk (1/number given)	Karyotype
1	39 years	3.7 mm	-	35 (n= 175)	47,XX,+21
2	43 years	5.7 mm	-		47,XY,+21
3	37 years	3.8 mm	-		47,XX,+21
4	40 years	4.3 mm	-		47,XX,+21
5	42 years	4.5 mm	-		47,XY,+21
6	36 years	-	4.7 mm/-	36 (n= 215)	47,XY,+21
7	37 years	-	4.1 mm/-		47,XX,+21
8	41 years		5.5 mm/-		47,XY,+21
9	38 years		4.0 mm/-		47,XX,+21
10	42 years		4.4 mm/-		47,XY,+21
11	39 years		3.5 mm/-		47,XY,+21
12	40 years		4.4 mm/-		47,XX,+21

NT, nuchal translucency; NB, Nasal bone; DS, Down syndrome

From *January 2002 to January 2004*, 215 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 37.5 years) and mean gravidity was 3.5. NT showed eight cases with NT of least 3.0 mm, although only seven cases had no NB. TORCH examination in eight cases was normal. Genetic analysis from 8 cases with NT of least 3.0 mm (seven cases had no NB), showed seven cases with Down syndrome (Table 1). In women aged least 35 years, NT plus NB examination had a DR of 87.5% (7/8 paralled to 7/7) and FPR of 0.48%. (1/208).

In the three cases with an NT of at least 3.0 mm and normal karyotype (2 cases with 46,XY and 1 with 46,XX) (between January 2001 and January 2004), pregnancy lasted to term. At 16 weeks of gestation, fetal echocardiography was normal Folow-up fetal echocardiography at 20 week 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.

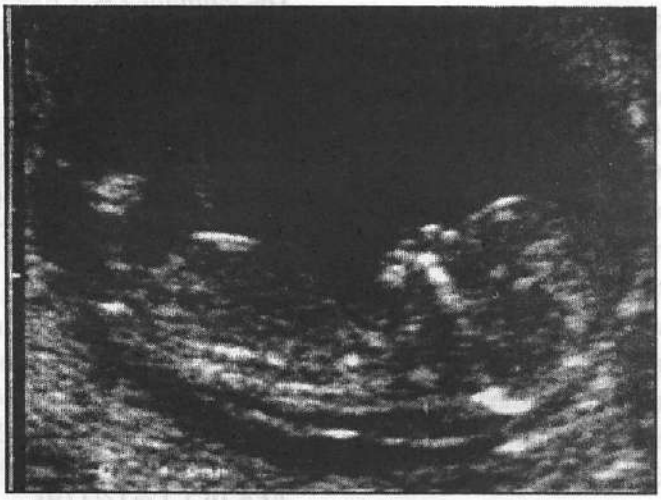

Figure 1. Fetal Down syndrome with measurement of nuchal translucency thickness (3,7 mm) at 12 weeks of gestation.

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 have 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 caused by non-disjunction of the autosome chromosome in myosis during ovum formation.

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

Author	Gestation (weeks)	NT cut-off (mm)	DR (trisomy 21)	FPR
Zimmerman et.al.[14]	10 -13	≥'3d 3.0	67.0 %	1.9 %
Pajkrt et.al.[15]	10 -14	≥'3d 3.0	67.0 %	2.2 %
Multi Project FMF[13]	11 -13	≥'3d 95th centile	71.8 %	4.4 %
Marsis (2004)	11 -13	≥'3d 3.0	71.4 %	1.1 %

DR, Detection rate; FPR, False Positive rate

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 FMF.[13] That 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 FPR of 1.1% (2/170) using NT measurement. These result are not different from those of previous studies (Table 2).[13-15] In this study (2001-2004) 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 both cases, there was strict antenatal obseravation and the babies were delivered normally. In contrast, in Souka et al's study, only 5.56% of 1,080 live birth had fetal defect, 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 anomaly (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 number of ways to enhance the DR for Down syndrome at 11-14 weeks of gestation, e.g. combined the NT measurement and the NB examination. The NB can be visualized using two dimension (2D) at 11-14 weeks of gestatio 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.[11,12]

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% (7/8 paralled 7/7) and a FPR of less than 1% (1/208). This was not significantly different from rates obtained by Nicolaides[12], who found a DR of 90% and FPR of 5%. It remains to be determinated whether NB examination for screening for Down syndrome can be apllied in Asian populations or Asian ethnic group.In their study, Prefumo[17] did not find NB in 3.4% of the Asian ethnic group, 1.9% of the Afro-Caribean ethnic, and 1.7% of the Caucasian ethnic group. For this reason, it is necessary to conduct further study 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 ≥'3d 3.0 mm and CRL at 50-70 mm) and NB examination at $11\text{-}13^{+6}$ weeks of gestation. Cases with NT above the threshold and normal karyotype require strict antenatal and postnatal observation.

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