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CLINICAL ARTICLE

Fetal facial sonographic markers for second trimester Down syndrome screening in a Thai population

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ABSTRACT

Objective: To assess the efficacy of using facial sonographic markers for screening fetuses in the second trimester for Down syndrome (DS) in a high-risk Thai population. *Method:* Frontomaxillary facial angle (FMF) and nasal bone length (NBL) were measured prospectively in pregnant women at high-risk for DS who were undergoing genetic amniocentesis from November 2008 to October 2009. The receiver operator characteristic (ROC) curves were constructed to assess the screening efficacy of FMF angle and NBL. *Result:* A total of 460 pregnant women were recruited, and a mid-sagittal facial profile was obtained for 403 fetuses. There were 386 fetuses with normal chromosomes, 10 fetuses with DS, 1 fetus with trisomy 13, and 1 fetus with trisomy 18. The remaining 5 fetuses had balanced translocation (n = 2), deletion (n = 1), and mosaic Turner (n = 2). Two different combinations of FMF angle and biparietal diameter to nasal bone length (BPD:NBL) ratio for DS screening in the second trimester achieved 50% and 90% detection rates and 4.4% and 14.0% false positive rates, respectively. *Conclusion:* The combination of FMF angle and BPD:NBL ratio has a high sensitivity and specificity for screening for DS in the second trimester in a high-risk Thai population.

1. Introduction

John Langdon Down first described common phenotypes of Down syndrome (DS) such as flat face, prominent forehead, hypertelorism, and hypoplasia of maxilla in 1866 [1]. Mental disability is nearly always present. The anatomic features of DS can be identified in the fetus by sonographic markers. Each marker has a different sensitivity and specificity. No single sonographic sign enables identification of all fetuses with DS and the combination of structural findings usually yields a higher sensitivity and specificity. A scoring system and modified scoring system have been developed to detect DS [2,3].

Fetal facial profile can be evaluated using high resolution ultrasound machines. Sonek et al. [4] first demonstrated the method of quantifying the flat face of fetuses with DS by measuring the frontomaxillary facial (FMF) angle. The FMF angle in fetuses with DS is higher than that of euploid fetuses [4–6]. Most studies that have evaluated the FMF angle for DS have been conducted in white populations [7]. Ethnic differences in facial structure between white and Thai populations have been reported: the nasal bone length (NBL) of Thai fetuses was found to be shorter compared with that of white and African American fetuses [8]. Therefore, the study using a white population may not be applicable to the Thai population.

A previous study from Thailand demonstrated that nasal bone hypoplasia was a potential marker for prenatal detection of DS in a Thai population [9]. NBL can be measured at the same time as FMF angle. The aim of the present study was to assess the screening efficacy of the combination of FMF angle and NBL measurement for detection of DS in the second trimester.

2. Materials and methods

A prospective descriptive study was carried out in pregnant Thai women at high-risk for DS undergoing genetic amniocentesis at 16–20 weeks of pregnancy between November 1, 2008 and October 31, 2009 at the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. The study was approved by the Institutional Review Board and written informed consent was obtained from all patients.

Maternal demographic characteristics, duration of pregnancy, indication for karyotyping, and ultrasonographic measurements including fetal abnormalities and markers for aneuploidy were recorded. The duration of pregnancy was calculated from the last menstrual period and confirmed by ultrasound in the first or early second trimester.

In each case, transabdominal ultrasound examination using a Voluson 730 Expert or a Voluson E8 machine (GE Medical Systems, Waukesha, WI, USA) with a 2–7 MHz curvilinear transducer was performed to assess fetal morphology and biometry. The FMF angle and NBL measurements were then made by one sonographer (RS), who was blinded to the fetal biometry, structural, and other ultrasonographic

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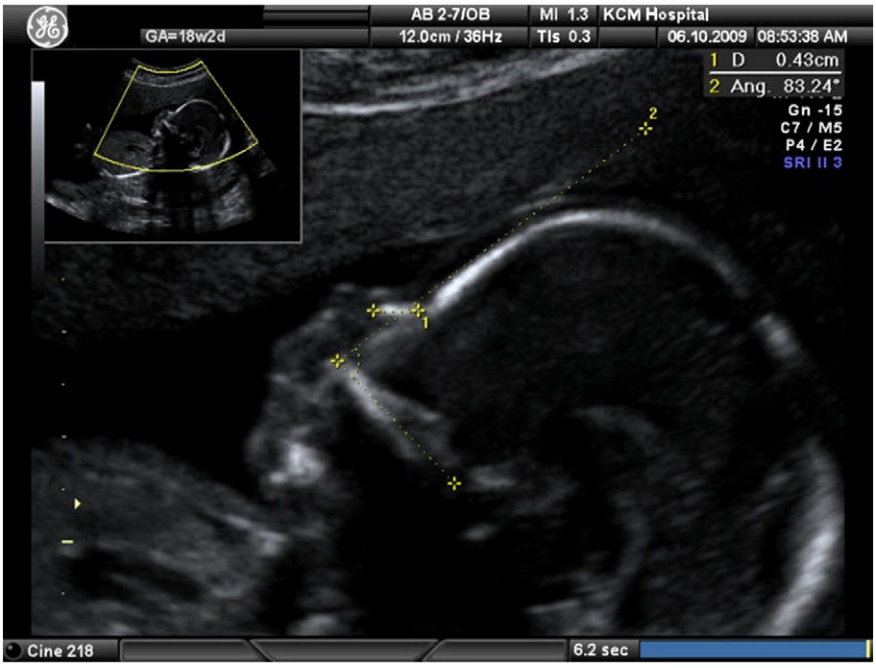

Fig. 1. A sagittal fetal facial profile showing measurement of: (1) nasal bone length; and (2) frontomaxillary facial angle.

markers. All measurements were taken before amniocentesis for fetal karyotype.

The nasal bone was measured in the mid-sagittal plane of the facial profile view and was identified as an echogenic structure that projected anteriorly [10]. The FMF angle is the angle between the upper border of the hard palate and the external surface of the frontal bone [5]. It was measured using a technique described previously [6], using the generic angle 3-points technique. The first line was drawn from the anterior nasal spine of the maxilla to the anterior point of the palatine bone (upper border of the hard palate), and the second line was drawn from the anterior nasal spine to the external surface of the frontal bone (Fig. 1). Participants were excluded from the analysis if the FMF angle measurement could not be obtained in the appropriate facial position.

Maternal demographic data, duration of pregnancy, indication for amniocentesis, estimation of fetal weight, and other parameters were expressed as percentage, mean ± SD, and median and range as appropriate. The distribution of the FMF angle was tested by the Kolmogorov-Smirnov test. The mean FMF angle between the groups was compared with a *t* test, and the correlation between gestational age and the FMF angle in normal fetuses was determined by bivariate analysis. The optimal threshold for association between FMF angle and the biparietal diameter (BPD):NBL ratio and DS was determined using a receiver operator characteristic (ROC) curve. $P<0.05$ was considered statistically significant. The intraclass correlation coefficient (ICC) was used to compare the measurement agreement and bias for each examiner.

3. Results

A total of 460 women with singleton pregnancies who met the inclusion criteria were recruited between November 2008 and October 2009. FMF angle and NBL could not be assessed in 57 fetuses (12.4%) because of inappropriate position of the fetal face; these fetuses were excluded from the analysis. There were 2 fetuses (3.5%) with DS in this excluded group. Of the 403 fetuses analyzed, there were 386 euploid fetuses (46, XX chromosomes in 192 fetuses; 46, XY chromosomes in 194 fetuses), 10 fetuses with DS, 1 fetus with trisomy 13, and 1 fetus with trisomy 18. The remaining 5 fetuses had balanced translocation (n = 2), deletion (n = 1), and mosaic Turner (n = 2).

All of the mothers were of Thai ethnicity. The demographic characteristics of the euploid and DS groups were similar (Table 1). A major indication for amniocentesis was advanced maternal age. The

Table 1
Demographic characteristics of the euploid and Down syndrome groups (n = 396).[a]

Characteristics	Euploid group (n = 386)	Down syndrome group (n = 10)	*P* value
Maternal age, y	37.1 ± 2.2	38.9 ± 3.3	>0.05
Gravidity	2 (1–9)	2 (1–3)	>0.05
Parity	1 (0–4)	1 (0–2)	>0.05
No. of abortions	0 (0–6)	0 (0–1)	>0.05
Duration of pregnancy, wk	18.0 ± 0.8	17.9 ± 1.1	>0.05
Indication for karyotype			>0.05
Advanced maternal age	384 (99.5)	10 (100)	
Previous child trisomy 18	1 (0.3)	–	
Thick nuchal fold	1 (0.3)	–	
Estimation of fetal weight, g	221.9 ± 38.0	194 ± 26.7	>0.05

[a] Values are given as mean ± SD, median (range), or number (percentage) unless otherwise indicated.

Table 2
Ultrasound findings in euploid and Down syndrome fetuses during the anatomical survey (n = 396).[a]

Ultrasound findings	Euploid group (n = 386)	Down syndrome group (n = 10)	*P* value
Choroid plexus cyst	13 (3.4)	1 (10)	>0.05
Nuchal fold thickness, mm	3.4 ± 0.8	5.5 ± 2.0	<0.05
Nasal bone length, mm	4.8 ± 0.7	3.8 ± 0.8	<0.01
BPD:NBL ratio	8.6 ± 1.2	10.8 ± 2.6	<0.01
Frontomaxillary facial angle, °	83.5 ± 4.5	88.5 ± 2.0	<0.05
Atrioventricular septal defect	0	2 (20)	<0.01
Ventricular septal defect	1 (0.3)	5 (50)	<0.01
Overriding aorta	1 (0.3)	3 (30)	<0.01
Echogenic intracardiac foci	15 (3.9)	3 (30)	<0.05
Hyperechoic bowel	1 (0.3)	0	>0.05
Renal pyelectasis	2 (0.5)	3 (30)	<0.01
Clinodactyly	0	3 (30)	<0.01
Rocker bottom feet	1 (0.3)	0	>0.05
Single umbilical artery	2 (0.5)	0	>0.05

Abbreviation: BPD, biparietal diameter; NBL, nasal bone length.
[a] Values are given as mean ± standard deviation or number (percentage).

Table 3
Screening efficacy of FMF angle and BPD:NBL ratio.

Feature	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR+, OR (95% CI)	LR–, OR (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
FMF angle ≥ 89°	50.0 (24.2–75.7)	92.5 (91.8–93.2)	6.66 (2.96–11.05)	0.54 (0.26–0.83)	14.7 (7.1–22.3)	98.6 (97.9–99.3)
FMF angle ≥ 90°	30.0 (11.1–57.9)	96.1 (95.6–96.7)	7.72 (2.54–18.29)	0.73 (0.44–0.93)	16.7 (6.2–32.1)	98.1 (97.6–98.9)
BPD:NBL ratio ≥ 10.5	60.0 (32.1–82.8)	92.2 (91.5–92.8)	7.72 (3.78–11.53)	0.43 (0.19–0.74)	16.7 (8.9–23.0)	98.9 (98.1–99.5)
BPD:NBL ratio ≥ 12.1	30.0 (12.1–43.8)	99.5 (99.0–99.8)	57.9 (12.4–272.3)	0.70 (0.56–0.89)	60.0 (24.3–87.6)	98.2 (97.8–98.6)
FMF angle ≥ 89° and/or BPD:NBL ratio ≥ 10.5	90.0 (60.4–98.2)	86.0 (85.2–86.2)	6.43 (4.09–7.13)	0.12 (0.02–0.46)	14.3 (9.6–15.6)	99.7 (98.8–99.9)
FMF angle ≥ 90° and/or BPD:NBL ratio ≥ 12.1	50.0 (24.6–75.2)	95.6 (94.9–96.2)	11.35 (4.85–20.03)	0.52 (0.26–0.80)	22.7 (11.2–34.2)	99.7 (98.8–99.9)

Abbreviations: LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; FMF, frontomaxillary facial angle; BPD, biparietal diameter; NBL, nasal bone length.

ultrasound findings (structural anomalies and sonographic markers) were recorded after evaluation of fetal anatomy (Table 2). The structural anomalies of atrioventricular septal defect (AVSD), ventricular septal defect (VSD), overriding aorta, and clinodactyly were more prevalent in the fetuses with DS. There were significant differences in renal pyelectasis, echogenic intracardiac foci (EIF), nuchal fold thickness, NBL, and BPD:NBL ratio between the groups. Our data confirmed that the FMF angle is significantly wider in fetuses with DS.

In euploid fetuses, there was no correlation between FMF angle and duration of pregnancy ($r = -0.07$). The mean of the FMF angle was $83.5° \pm 4.5°$. The optimal thresholds of FMF angle for detecting DS were 89° and 90°, which yielded 50% and 30% detection rates, respectively (Table 3). Using the cut-off FMF angle of 89° or greater yielded a sensitivity of 50.0%, a specificity of 92.5%, a likelihood ratio for a positive test of 6.66, a positive predictive value (PPV) of 14.7%, and a negative predictive value (NPV) of 98.6% for detecting fetuses with DS (Table 3).

Nasal bone hypoplasia was also useful for detecting DS; a BPD:NBL ratio of 10.5 or greater was defined as an optimal cut-off, which yielded a 60% sensitivity and 92.2% specificity.

From the ROC curve diagnostics, the cut-off BPD:NBL ratios of 10.5 and 12.1 or greater were used for detecting DS. These cut-off values could detect 60% and 30% of fetuses with DS, respectively (Table 3). The FMF angle and BPD:NBL ratio were found to be independent from each other ($r = 0.08$; Fig. 2). The combination of FMF angle greater than 89° and BPD:NBL ratio greater than 10.5 identified 9 of the fetuses (90%) with DS with a 14.0% false-positive rate. The combination of FMF angle greater than 90° and BPD:NBL ratio greater than 12.1 identified 50% of the fetuses with DS and had a substantially lower false-positive rate of 4.4%. Fetuses with DS were screened with high sensitivity and specificity using the combination of wide FMF angle and/or high BPD:NBL ratio (Table 3).

The mean difference in FMF angle with 95% limit of agreement between paired measurements by the same sonographer was –0.10° (1.3°) and –0.52° to 0.32°, respectively. The intraobserver ICC was 0.94.

4. Discussion

The present study of a Thai population demonstrated that FMF angle does not vary with gestational age, which is in agreement with

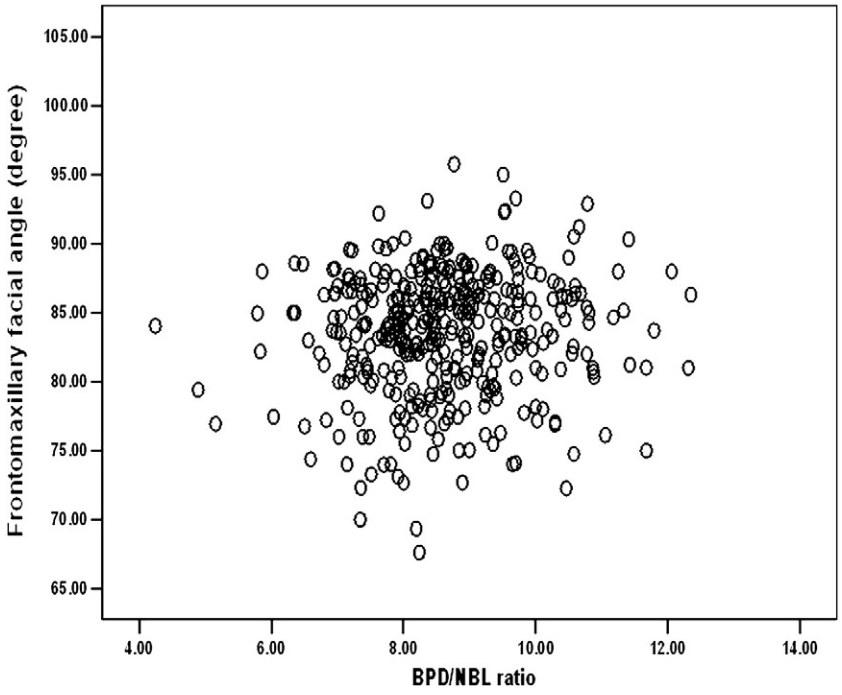

Fig. 2. Scattergram of frontomaxillary facial angle and biparietal diameter to nasal bone length (BPD:NBL) ratio.

the study by Molina et al. [5]; however, some studies have given conflicting results [6,11].

In clinical practice, FMF angle and NBL can both be assessed in the mid-sagittal plane of the facial profile at the same time. If a low false-positive rate is considered a priority, a cut-off (FMF angle greater than 90° and/or BPD:NBL ratio greater than 12.1) gives a moderate sensitivity while maintaining a low false-positive rate. However, fetuses with an FMF angle of less than 89° and a BPD:NBL ratio of less than 10.5 have a significantly lower risk of DS. Some pregnant women with this substantially lower risk may choose not to undergo an invasive procedure.

Odibo et al. [11] found that the combination of FMF angle and nasal bone hypoplasia did not increase the detection rate, but the present study demonstrated a significant increase in detection rate. Ethnic differences may play a significant role, and the different cut-offs for abnormal FMF angle and nasal bone hypoplasia used in the present study might also contribute to the different finding. A further study with a larger sample size is necessary to clarify the issue.

In conclusion, the combination of FMF angle and BPD:NBL ratio has a high sensitivity and specificity for screening fetuses with DS in the second trimester in a high-risk Thai population.

Conflict of interest

The authors declare that they have no conflicts of interest.

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