Modified Sonographic Scoring Index Using a Combination of Sonographic Markers for Detection of Down Syndrome

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Abstract

Objective: To determine the diagnostic performance of modified sonographic scoring index for detection of Down syndrome in high risk population for fetus with chromosomal abnormality.

Methods: Singleton high-risk pregnant women at 16-24 weeks of gestation (elderly mothers, abnormal biochemical screening, or a history of fetal abnormal chromosome in prior pregnancy) who were going to have amniocentesis for chromosomal analysis in King Chulalongkorn Memorial Hospital between October 2008 and November 2009 were included in the study. Detailed sonographic study was performed before an amniocentesis in each woman. Twelve sonographic markers of interest included major structural defects, choroid plexus cyst, mild ventriculomegaly, nuchal fold thickening, nasal bone hypoplasia, echogenic intracardiac foci, echogenic bowel, clinodactyly, renal pyelectasis, single umbilical artery, short humerus and short femur. A modified sonographic scoring index was obtained from the likelihood ratio (LR) of the 9 sonographic markers which were identified in Down syndrome. Score of 3 was assigned for markers with LR ≥ 10 (clinodactyly, major structural abnormalities, nuchal fold thickening, echogenic bowel), score of 2 for markers with LR 5-9 (echogenic intracardiac foci, short humerus length, nasal bone hypoplasia, and score of 1 for markers with LR < 5 (short femur length, choroid plexus cyst). The diagnostic performance of sonographic scoring index for detection of Down syndrome was determined.

Results: A total of 693 pregnancies were recruited. Of these, 668 fetuses (96.4%) had normal karyotype, 13 (1.9%) were Down syndrome (trisomy 21), and 12 (1.7%) had other abnormal karyotypes. Among the 9 sonographic parameters, nasal bone hypoplasia was the most sensitive marker to detect Down syndrome (sensitivity = 72.7%). Modified sonographic index scores of ≥ 3 was the optimal cutoff level to detect Down syndrome, yielding 76.9% sensitivity, 89.4% specificity, and 0.790 area under the curve.

Conclusions: Our modified sonographic scoring index yielded good diagnostic performance for second trimester detection of fetal Down syndrome.

Keywords: chromosomal abnormality, Down syndrome, sonographic marker, sonographic scoring index

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บทคัดย่อ

ดัชนีการให้คะแนนทางคลื่นเสียงความถี่สูงแบบประยุกต์ ในการทำนายทารกกลุ่มอาการดาวน์

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วัตถุประสงค์: เพื่อประเมินความสามารถของดัชนีการให้คะแนนทางคลื่นเสียงความถี่สูงแบบประยุกต์ (modified sonographic scoring index) ในการทำนายทารกกลุ่มอาการดาวน์ในหญิงตั้งครรภ์ที่มีความเสี่ยงสูงที่จะมีทารกที่มีโครโมโซมผิดปกติ

วิธีดำเนินการวิจัย: หญิงตั้งครรภ์เดี่ยวที่มีความเสี่ยง (อายุมาก ผลการครวจคัดกรองสารไบโอเคมีผิดปกติ หรือมีประวัติทารกในครรภ์มีความผิดปกติทางโครโมโซม) และมีอายุครรภ์ในช่วงไตรมาสที่สอง คือ 16-24 สัปดาห์ที่มารับการเจาะน้ำคร่ำที่โรงพยาบาล-จุฬาลงกรณ์ ระหว่างเดือนตุลาคม พ.ศ. 2551 ถึง เดือน พฤศจิกายน พ.ศ. 2552 จะได้รับการตรวจคลื่นเสียงความถี่สูงก่อนการเจาะน้ำคร่ำ เพื่อหาลักษณะผิดปกติ 12 ประการ ได้แก่ ความผิดปกติที่สำคัญของโครงสร้าง ถุงน้ำที่คอรอยด์เพลกซัส โพรงน้ำในสมองโตกว่าปกติ การหนาตัวผิดปกติของผิวหนังต้นคอทารก กระดูกจมูกสั้น จุดหินปูนที่หัวใจทารก ลำไส้มีความเข้มเสียงมากกว่าปกติ ไม่พบกระดูกข้อกลางของนิ้วก้อย กรวยไตโตผิดปกติ หลอดเลือดสายสะดือไม่ครบ กระดูกแขน หรือขาสั้น และจากนั้นหาค่าความไว ความจำเพาะ และความน่าจะเป็น (likelihood ratio; LR) ของแต่ละลักษณะ ในการทำนายทารกกลุ่มอาการดาวน์ นำค่า LR ของ 9 ลักษณะ ที่พบในทารกกลุ่มอาการดาวน์มาใส่ในดัชนีการให้คะแนนทางคลื่นเสียงความถี่สูงแบบประยุกต์ โดยความผิดปกติที่มี LR > 10 ได้แก่ ไม่พบกระดูกข้อกลางของนิ้วก้อย ความผิดปกติที่สำคัญของโครงสร้าง การหนาตัวผิดปกติของผิวหนังต้นคอทารก ลำไส้มีความเข้มเสียงมากกว่าปกติ จะให้ 3 คะแนน ความผิดปกติที่มี LR 5-9 ได้แก่ จุดหินปูนที่หัวใจทารก กระดูกแขนสั้น กระดูกจมูกสั้น จะให้ 2 คะแนน ความผิดปกติที่มี LR < 5 ได้แก่ กระดูกขาสั้น และถุงน้ำที่คอรอยด์เพลกซัส จะให้ 1 คะแนน และคำนวณหาความสามารถของดัชนีการให้คะแนนทางคลื่นเสียงความถี่สูงแบบประยุกต์ ในการทำนายกลุ่มอาการดาวน์

ผลการวิจัย: จากหญิงตั้งครรภ์ 693 ราย มีทารกโครโมโซมปกติ 668 ราย (ร้อยละ 96.4) ทารกกลุ่มอาการดาวน์ (trisomy 21) จำนวน 13 ราย (ร้อยละ 1.9) และ โครโมโซมผิดปกติแบบอื่น ๆ 12 ราย (ร้อยละ 1.7) ภาวะกระดูกจมูกสั้นเป็นลักษณะที่ไวที่สุดใน 9 ลักษณะ ที่ตรวจพบในทารกกลุ่มอาการดาวน์ (ค่าความไว ร้อยละ 72.7) ส่วนคะแนนของดัชนีการให้คะแนนทางคลื่นเสียงความถี่สูงแบบประยุกต์ ที่มากกว่าหรือเท่ากับ 3 มีความไว ร้อยละ 76.9 ความจำเพาะ ร้อยละ 89.4 และค่า area under the curve 0.790 ในการทำนายทารกกลุ่มอาการดาวน์

สรุป: รูปแบบการให้คะแนนโดยใช้ดัชนีการให้คะแนนทางคลื่นเสียงความถี่สูงแบบประยุกต์สามารถทำนายทารกกลุ่มอาการดาวน์ ในช่วงไตรมาสที่สองของการตั้งครรภ์ได้ดี

Introduction

Down syndrome is the most common chromosomal abnormality of the fetuses and live-born neonates.[1,2] This chromosomal abnormality is associated with fetal loss, many structural abnormalities, delayed growth development and mental retardation.[3,4] The risk of Down syndrome in a fetus is positively correlated with maternal age. A definite prenatal diagnosis requires invasive tests such as chorionic villus sampling, amniocentesis, or cordocentesis. However, these procedures are associated with a 0.5-2% risk of miscarriage.[1,5,6]

Other than invasive prenatal diagnosis, several studies have shown that ultrasonography is a non-invasive screening procedure which can detect fetal structural abnormalities associated with fetal aneuploidy including Down syndrome.[3,7,8] These sonographic features include both major and minor fetal structural abnormalities. In order to increase the diagnostic function of each sonographic parameter, many studies have also evaluated these markers in combination.[9-12] Benacerraf et al[9] were among the first few pioneer groups who established a sonographic scoring index to screen Down syndrome in 1992. This scoring index was later modified by the authors themselves in 1994 and 1997.[10,11] The most recent version consisted of 7 abnormal sonographic features (major structural abnormalities, nuchal fold thickening, short femur, short humerus, renal pyelectasis, hyperechoic bowel, and echogenic intracardiac foci) in combination with maternal age. Using the cutoff score of ≥ 2, their scoring index yielded a sensitivity of 86.8% with a specificity of 72.9%. Later in 1998, Nyberg et al[12] proposed an age-adjusted ultrasound risk assessment (AAURA) as an alternative method for Down syndrome screening. This method calculated the risk by multiplying 'a priori risk' based on maternal age (i.e. a priori risk for Down syndrome was 1:690 at age 30) by the likelihood ratio (LR) of each sonographic marker (i.e. the LR of short femur was 2.2). Using the cutoff risk of > 1:200, its sensitivity and specificity were 74% and 85.3%, respectively.

Despite a potential utility of these 2 scoring indices, which were nonspecific and can be found in normal karyotypic fetuses.[13,14] Besides, both scoring indices were established using database of Western populations and their application in Asian women has not been validated. With the continuing search for more scientific data to improve health care, various new sonographic markers have recently been described to be highly and consistently associated with Down syndrome. These include hypoplastic or absent nasal bone, clinodactyly, frontomaxillary facial angle, and widening of iliac angle.[2,5,6,15] Therefore, incorporating these novel markers into the previously adopted scoring index should be useful.

The aim of this study was to integrate both previously known and some of these new sonographic markers into a modified sonographic scoring index, and to determine its diagnostic performance for detection of Down syndrome in Thai pregnant women at risk.

Methods

This prospective study was conducted at the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Inclusion criteria were singleton, high-risk pregnant women (elderly mothers, abnormal biochemical screening, or a history of fetal abnormal chromosome in prior pregnancy) at 16-24 weeks of gestation who underwent genetic amniocentesis between October 2008 and November 2009. Exclusion criteria were women who declined to participate or those with amniotic fluid cell culture failure. Written informed consent was obtained from each participant. The study was approved by the institutional review board.

Before amniocentesis, the fetal anatomic survey was performed and 12 sonographic markers[2,6,9,10,14,16-18]

were carefully sought out. These markers included choroid plexus cyst (well-defined anechoic area in choroid plexus), mild ventriculomegaly (transverse diameter of atrium of lateral ventricles ≥ 10 mm. and < 15 mm.), nuchal fold thickening (outer aspect of occipital bone to skin edge ≥ 6 mm. in occipito-bregmatic plane), nasal bone hypoplasia (biparietal diameter/nasal bone length ratio ≥ 10, or absent nasal bone), echogenic intracardiac foci (bright hyperechogenicity seen within either ventricular chamber), echogenic bowel (subjectively as bright as or brighter than surrounding bone), clinodactyly (hypoplasia of middle phalanx of fifth digit), renal pyelectasis (anteroposterior diameter of renal pelvis > 4 mm.), single umbilical artery (2 vessels umbilical cord seen, confirmed by color doppler), short humerus (ratio of observed/expected humerus length ≤ 0.91) and short femur (ratio of observed/expected femur length ≤ 0.91) and major structural defects (heart defect, gastrointestinal defect, central nervous system defect, diaphragmatic hernia, facial cleft, limb anomaly or hydrops fetalis). These markers were evaluated for incorporation into a modified sonographic scoring index. Ultrasound machines used were a GE Voluson 730, GE Voluson 730 Expert, and GE E8 (GE Medical systems, Milwaukee, Wisc, USA) with a 2-7 MHZ curved array transducer. All measurements were performed by the first author (N.C.) who was a fellow in-training of maternal-fetal medicine supervised by an experienced attending staff (S.M.). Fetal karyotypes were examined by the cytogenetic laboratory of King Chulalongkorn Memorial hospital. The result was approved by laboratory staff before a final report.

Data collection included age of pregnant women, gestational age when amniocentesis and sonographic procedure was performed, presence or absence of sonographic markers, and fetal karyotypes. The diagnostic function including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio (LR) for Down syndrome of each sonographic marker were calculated. The LR of each marker was transformed into score which was subsequently entered into a modified sonographic scoring index. In any event when a fetus had multiple abnormal sonographic markers, the score of each was summed up to obtain a total score. Diagnostic performances of a modified sonographic scoring index were then calculated at different cutoff scores.

Statistical data were analysed using SPSS statistical software version 11.5 and CIA 2.0. A receiver-operating characteristic (ROC) curve was constructed and the area under the curve (AUC) was calculated to determine the optimal cutoff score.

Results

A total of 693 pregnant women were recruited during the study period. Their mean age was 37.0 ± 2.5 years and mean gestational age when ultrasonography and amniocentesis was performed was 17.6 ± 0.8 weeks. The indications for genetic amniocentesis were: advanced maternal age (686 cases; 99.0%), abnormal biochemical screening (2 cases; 0.3%), and previous child with chromosomal abnormality (5 cases; 0.7%).

Abnormal sonographic marker of any kind was found in 238 fetuses (34.3%) while 455 (65.7%) had no abnormal findings. Single sonographic marker abnormality was found in 158 fetuses (22.8%) while 80 fetuses (11.5%) had multiple sonographic marker abnormalities. The sonographic markers of humerus and nasal bone lengths were not performed in 21 cases (3.0%) and 196 cases (28.3%), respectively. The most common abnormal feature identified was nasal bone hypoplasia (80 out of 497 cases or 16.1%) followed by short femur length (93 out of 693 cases or 13.4%) and short humerus length (82 out of 672 cases or 12.2%), respectively. Table 1 shows the incidence of each abnormal sonographic marker.

Table 1 Association of sonographic markers and chromosomal analysis in fetus with normal and abnormal chromosome (n=693)

Sonographic markers, number (%)	Normal chromosome (n=668) number (%[d])	Abnormal chromosome		
		Total (n=25) number (%[d])	Down syndrome (n=13) number (%[e])	Others (n=12) number (%[e])
No abnormal marker, n=455 (65.7%)	447 (66.9%)	8 (32.0%)	2 (15.4%)	6 (50.0%)
Abnormal markers[a]				
Short femur length, n=93 (13.4%)	85 (12.7%)	8 (32.0%)	6 (46.2%)	2 (16.7%)
Short humerus length[b], n=82 (12.2%)	73 (11.3%)	9 (37.5%)	7 (58.3%)	2 (16.7%)
Nasal bone hypoplasia[c], n=80 (16.1%)	67 (14.1%)	13 (61.9%)	8 (72.7%)	5 (50.0%)
Echogenic intracardiac foci, n=43 (6.2%)	38 (5.7%)	5 (20.0%)	4 (30.8%)	1 (8.3%)
Choroid plexus cyst, n=33 (4.8%)	30 (4.5%)	3 (12.0%)	1 (7.7%)	2 (16.7%)
Echogenic bowel, n=6 (0.9%)	5 (0.7%)	1 (4.0%)	1 (7.7%)	0
Nuchal thickening, n=5 (0.7%)	4 (0.6%)	1 (4.0%)	1 (7.7%)	0
Clinodactyly, n=2 (0.3%)	1 (0.1%)	1 (4.0%)	1 (7.7%)	0
Single umbilical vein, n=2 (0.3%)	1 (0.1%)	1 (4.0%)	0	1 (8.3%)
Renal pyelectasis, n=5 (0.7%)	5 (0.7%)	0	0	0
Mild ventriculomegaly, n=0 (0%)	0	0	0	0
Major structural abnormalities[f], n=13 (1.9%)	8 (1.2%)	5 (20.0%)	3 (23.1)	2 (16.7%)

[a] One fetus may have more than 1 abnormal sonographic marker

[b] Humerus length was not performed in 21 cases (number performed in normal chromosome = 648 cases, in Down syndrome = 12 cases, in other abnormal chromosome = 12 cases; all number performed = 672 cases)

[c] Nasal bone length was not performed in 196 cases (number performed in normal chromosome = 476 cases, in Down syndrome = 11 cases, in other abnormal chromosome = 10 cases; all number performed = 497 cases)

[d] Percentages of abnormal sonographic marker according to the results of normal or abnormal chromosomal analysis

[e] Percentages of abnormal sonographic marker among each type of chromosomal abnormalities

[f]Major structural abnormalities in normal chromosome were cardiac defect (4 cases), limb anomaly (2 cases), central nervous system anomaly (1 case) central nervous system anomaly together with cardiac defect (1 case); in Down syndrome were cardiac defect (1 case) and gastrointestinal defect (1 case), hydrops fetalis with cardiac defect (1 case); and in other chromosome abnormalities were central nervous system anomaly (1 case) and limb anomaly (1 case)

Subsequent cytogenetic results revealed chromosomal abnormalities in 25 fetuses (3.6%). Thirteen fetuses had trisomy 21 (Down syndrome), 3 fetuses with trisomy 18, and 9 fetuses had other phenotypically normal karyotypes (1 mosaic 46, XY/47, XXY, and 8 had balanced translocation, deletions, or inversions). The other 668 fetuses had euploid chromosomes: 340 with 46, XX and 328 with 46, XY.

We studied sonographic findings in association with chromosomal analysis. Among 13 fetuses with Down syndrome, we found that nasal bone hypoplasia was the most common sonographic marker identified (8 out of 11 cases or 72.7%) followed by short humerus length (7 cases out of 12 cases or 58.3%) and short femoral length (6 cases out of 13 cases or 46.2%). Eight of fetuses with Down syndrome had multiple abnormal sonographic findings, and only 2 cases (15.4%) had no abnormal sonographic marker. Of note, among 12 fetuses who had other abnormal chromosome, half of them had no abnormal sonographic markers demonstrated (6 cases) while the abnormal sonographic markers identified in order of frequency were: nasal bone hypoplasia (5 out of 10 cases or 50.0%); short femoral length, short humerus length, choroid plexus cyst, major structural abnormalities (2 out of 12 cases or 16.7%, each); and echogenic intracardiac foci (1 case or 8.3%). Among 12 sonographic markers studied, 3 features of ventriculomegaly, renal pylectasis, and single umbilical artery were not found in any fetuses with Down syndrome (Table 1), hence we included only 9 markers found in the fetuses with Down syndrome in our modified sonographic scoring index.

The sensitivity, specificity, PPV, NPV, and LR of 9 sonographic markers for detection of Down syndrome are shown in Table 2. We found that nasal bone hypoplasia yielded the best sensitivity (72.7%) and clinodactyly yielded the highest specificity (99.9%) and LR (51.4) to detect Down syndrome. Base on the LR of these markers, the score of each was obtained. Score of 3 was assigned for LR ≥ 10 (clinodactyly, major structural abnormalities, nuchal fold thickening, echogenic bowel), score of 2 for LR 5-9 (echogenic intracardiac foci, short humerus length, nasal bone hypoplasia, and score of 1 for LR < 5 (short femur length, choroid plexus cyst). After summing up the score from 2 fetuses

Table 2 Diagnostic performance of each marker for detection of Down syndrome (n=693)

Sonographic markers	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Likelihood ratio (95% CI)
Short femal length	46.2 (23.2-70.9)	87.3 (84.5-89.5)	6.5 (3-13.4)	98.8 (97.6-99.4)	3.6 (1.9-67)
Short humerus length	58.3 (32-80.7)	88.7 (86-90.8)	8.5 (4.2-16.6)	99.2 (98-99.6)	5.2 (3-8.7)
Nasal bone hypoplasia	72.7 (43.4-90.3)	85.9 (81.8-88.1)	10.0 (5.2-18.5)	99.3 (97.9-99.8)	5.2 (3.2-7.5)
Echogenic intracardiac foci	30.8 (12.7-57.6)	94.3 (92.3-95.8)	9.3 (3.7-21.6)	98.6 (97.4-99.3)	5.4 (2.2-12.8)
Choroid plexus cyst	7.7 (1.4-96.6)	95.5 (93.4-96.6)	3.0 (0.5-15.3)	98.2 (96.8-99)	1.7 (0.2-11.1)
Echogenic bowel	7.7 (1.4-33.3)	99.3 (98.3-99.7)	16.7 (3-56.4)	98.3 (97-99)	10.3 (1.3-83.4)
Nuchal fold thickening	7.7 (1.4-33.3)	99.4 (98.5-99.8)	20.0 (3.6-62.4)	98.3 (97-99)	12.8 (1.6-109)
Clinodactyly	7.7 (1.4-33.3)	99.9 (99.2-100)	50.0 (9.5-90.5)	98.3 (97-99)	51.4 (3.5-791)
Structural abnormalities	23.1 (8.2-50.3)	98.8 (97.3-99.2)	23.1 (8.2-50.3)	98.5 (97.3-99.2)	19.3 (4.9-50.4)

NNV = negative predictive value; PPV = positive predictive value; CI = confidence interval

Table 3 Diagnostic performances of a modified sonographic scoring index at various cutoff scores for detection of Down syndrome (n=693)

Sonographic score	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	AUC (95% CI)
≥ 1	92.3 (66.7-98.6)	66.8 (63.1-70.2)	5.1 (3-8.7)	99.8 (98.7-100)	0.753 (0.634-0.872)
≥ 2	84.6 (57.8-95.7)	74.7 (71.3-77.8)	6.1 (3.4-10.6)	99.6 (98.6-99.9)	0.754 (0.621-0.888)
≥ 3	76.9 (49.7-91.8)	89.4 (86.8-91.5)	12.3 (6.8-71.3)	99.5 (98.5-99.8)	0.790 (0.641-0.939)
≥ 4	69.2 (42.4-87.3)	95.5 (93.7-96.8)	23.1 (12.6-38.3)	99.4 (98.4-99.8)	0.783 (0.621-0.945)
≥ 5	53.8 (29.1-76.8)	97.5 (96-98.4)	29.2 (14.9-49.2)	99.1 (98-99.6)	0.716 (0.540-0.893)
≥ 6	23.1 (8.2-50.3)	99.4 (97.7-99.4)	27.3 (9.7-56.8)	98.5 (97.3-99.2)	0.570 (0.396-0.744)

NNV = negative predictive value; PPV = positive predictive value; AUC = area under curve; CI = confidence interval

with no marker identified, 3 fetuses with single abnormality, and 8 with multiple abnormalities, the total score of fetus with Down syndrome by our modified sonographic scoring index ranged from 0-12.

The sonographic scoring indices were then evaluated for their diagnostic performances to detect Down syndrome (Table 3). Score ≥ 3 yielded the optimal function with 76.9% sensitivity, 89.4% specificity, 12.3% PPV, 99.5% NPV, and AUC of 0.790 for detection of Down syndrome.

Discussion

Over the past decades, various sonographic markers identified during second trimester of pregnancy e.g. nuchal fold thickening, short femur, echogenic intracardiac foci, etc. have been studied in association with Down syndrome. For example, nuchal fold thickening > 6 mm. was reported to have high sensitivity of 36-43% for prenatal detection of Down syndrome in Caucasian population.[9-11] Other studies in Asian population did not have corroborated findings.[19,20] Previous studies by Tannirandorn et al[19] in Thai and Liu et al[20] in Chinese pregnant women, using nuchal fold thickening of > 6 mm., found only 10.5% and 12.5% sensitivity to detect Down syndrome, respectively. Our study had similar finding as the two studies in Asia that we found only 7.7% sensitivity of nuchal fold thickening in detection of Down syndrome. Ethnic factor may influence the sonographic features of the fetus as well as diagnostic functions for chromosomal abnormality.

Aside from nuchal fold thickening, nasal bone hypoplasia has been proposed as the new sonographic marker for Down syndrome. One observation is that this feature may not be influenced by the ethnicity despite a difference of Asian nasal structure from that of Caucasian adults. Cicero et al[21] reported 61.8% sensitivity of nasal bone hypoplasia to detect Down syndrome in 1,046 British women. Naraphut et al[18] showed 80% sensitivity using nasal bone hypoplasia for detection of Down syndrome in Thai pregnant women. We also found nasal bone hypoplasia as the most sensitive sonographic parameter for Down syndrome detection in our Thai women, with the sensitivity of 72.7%.

Because there is no single marker which is highly specific for Down syndrome detection,[9-11] a combination of multiple markers has later been proposed to en-

hance the sensitivity and specificity for detection of abnormal chromosomes especially Down syndrome.[22-25] Among several sonographic scoring indices, the most commonly used was the one developed by Benacerraf et al[11] which found high sensitivity (87%) and specificity (73%) in detection of Down syndrome. However, their index included only 7 known sonographic features together with maternal age. With the new sonographic feature of nasal bone hypoplasia, we speculated that including this nasal bone hypoplasia might improve the diagnostic function of their index. Moreover, we included choroid plexus cyst and clinodactyly in our scoring index. We excluded maternal age from our scoring index because almost all of our study population was elderly mother (99%). We also excluded renal pyelectasis from our scoring index because none of our Down syndrome patients had renal pyelectasis.

Our modified sonographic scoring index with 9 sonographic markers using a cutoff score of ≥ 3 yielded better diagnostic function than any single sonographic markers particularly nasal bone hypoplasia which was the best marker among other features we evaluated as previously mentioned. Although our scoring index had high sensitivity (76.9%) and specificity (89.4%), they appeared to be slightly inferior to those of Benacerraf's sonographic index.[11] This might be due to the different proportion of pregnant women at risk in each study e.g. maternal age. When we applied Benacerraf scoring index for our dataset, we actually found lower sensitivity of 61.5% and AUC of 0.762 with slightly improved specificity of 91.0% (data not shown). These results were similar to the findings of Winter et al[26] who studied their data using Benacerraf's sonographic index and found only 45% sensitivity and 95% specificity. When Nyberg' age-adjusted ultrasound risk assessment was used, Winter et al[26] also found only 43% sensitivity. Unfortunately, we were unable to explore the diagnostic performance of Nyberg scoring system because their model was complicated and our data were insufficient to fit into their model.

Thus, it seemed that our modified sonographic scoring index was superior to that scoring system in the detection of Down syndrome in Thai fetuses. Few limitations of our study were to be noted. First, the first researcher was the only one who evaluated the sonographic features of the fetuses in the study. However, the variation or pitfall in assessment was minimized by special training courses attendance of the researcher prior to the study. Besides, the second researcher who was an expert in this area was ready to provide second opinion or confirmation when there was any uncertainty. Second, a small number of fetuses with Down syndrome might affect the strength of our results. A larger study with more number of fetuses with Down syndrome to demonstrate the same results is required. Lastly, because all pregnant women in our study were Thai, so a generalization of this modified sonographic scoring index in other ethnic populations should be validated.

In conclusion, our modified sonographic scoring index comprising of 9 sonographic markers yielded good diagnostic performance for prenatal Down syndrome detection in Thai pregnant women. Further prospective trial is needed to verify the efficacy.

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