Nasal Bone Hypoplasia in Trisomy 21 at 15 to 24 Weeks' Gestation in A High Risk Thai Population

Bongkoch Naraphut MD*,
Boonchai Uerpairojkit MD*, Surasith Chaithongwatthana MD*,
Yuen Tannirandorn MD*, Somchai Tanawattanacharoen MD*,
Saknan Manotaya MD*, Dhiraphongs Charoenvidhya MD*

** Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University*

Objective: *To assess the utility of nasal bone hypoplasia in the detection of fetuses with trisomy 21 in the second trimester in a high risk Thai population.*
Material and Method: *A prospective study involving pregnant women undergoing amniocentesis due to increased risk of aneuploidy from January 2005 to December 2005. Fetal biometry and nasal bone measurements were obtained at the time of amniocentesis. Linear regression model and diagnostic tests were analyzed using the SPSS computer program.*
Results: *A total of 407 fetuses were evaluated. In euploid fetuses, the Nasal Bone Length (NBL) increased linearly with advancing gestational age. Fetuses with Down syndrome had a significantly higher proportion of NBL below the 5th centile when compared with normal fetuses ($p < 0.05$). The optimal nasal bone threshold associated with trisomy 21 is a BiParietal Diameter/Nasal Bone Length (BPD/NBL) ratio of 10 or greater, yielded a sensitivity of 80%, specificity of 86% for detection of trisomy 21.*
Conclusion: *Nasal bone hypoplasia is associated with an increased risk of Down syndrome in the presented population.*

Keywords: *Nasal bone, Nasal bone hypoplasia, Biparietal diameter/nasal bone length ratio, Trisomy 21, Down syndrome*

J Med Assoc Thai 2006; 89 (7): 911-7
Full text. e-Journal: *http://www.medassocthai.org/journal*

Down syndrome is the most common chromosomal abnormality in newborns[1]. Women aged 35 years or more in current prenatal care are considered to be at risk for a Down syndrome pregnancy and are therefore, routinely offered invasive tests to detect chromosomal abnormalities. Some of these patients prefer to have a screening test for Down syndrome to avoid the risk of fetal loss associated with invasive diagnostic procedures. The screening methods, either by maternal serum biochemistry or sonographic markers have been introduced in clinical practice. Several sonographic features have been studied and used for a screening for Down syndrome pregnancy with a variety of sensitivity and specificity[2-4].

Recently, many reports have suggested that an absent fetal Nasal Bone (NB) or nasal bone hypoplasia is a powerful marker for aneuploidy but almost all studies were in Caucasian populations[5-11]. Several reports have demonstrated the effect of ethnicity on the absence of nasal bone in normal first trimester fetuses. A trend for a higher prevalence of nasal bone absence in the 1st trimester was observed in fetuses of Asian mothers[5]. To the authors' knowledge; no data has been published on the use of Nasal Bone Length (NBL) of fetuses to assess trisomy 21 during the 2nd trimester in an Asian population. Therefore, the authors conducted a study to determine the usefulness of NBL as a predictor of trisomy 21, and the reproducibility

Correspondence to : Naraphut B, Department of Obstetrics and Gynaecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. Phone: 0-2256-4824, Fax: 0-2256-4825, E-mail: bongkochz@yahoo.com

of measurement of the NBL of fetuses in the mid-trimester in a high risk Thai population.

Material and Method

A prospective study was performed on Thai pregnant women undergoing amniocentesis for fetal karyotyping at 15-24 weeks' gestation in the Division of Maternal Fetal Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand from January 2005 to December 2005. The institutional ethical committee approved the research protocol. The subjects were all Thai ethnics. The gestational age was established by a history of certain last menstrual period and confirmed by ultrasound assessment of the first trimester crown-rump length or second trimester biometry. Only fetuses having sonographic examinations dating within 7 days of the established due date were included. Exclusion criteria were uncertain date, suboptimal fetal position (fetal back up) and multiple pregnancies. Transabdominal ultrasound examination was routinely performed to assess fetal morphology and biometry before amniocentesis.

Facial nasal bone was assessed as previously described by Sonek JD and Nicolaides KH[7]. The facial profile was obtained in the precisely midsagittal view, identifying the nasal bone, lips, maxilla, and mandible with an angle between the insonation beam and the nasal axis of close to 45°. Images were then enlarged to fill at least 70% of the screen (Fig. 1, 2). The maximum length of the nasal bone was measured in millimeters to one decimal place. Two measurements were obtained and averaged by one observer who was trained in the visualization and measurement of the facial Nasal Bone on 120 cases preceding the study period and approved by an experienced perinatologist (Boonchai Uerpairojkit). The predicted fetal NBL was established from a normal fetus and the ratio of BPD/NBL was also calculated. Fetal karyotype was obtained from amniocentesis. The ultrasound equipments used were ALOKA model Prosound SSD-5000 and ALOKA model SSD-2000 (ALOKA Co., Ltd., Tokyo, Japan). The system was interfaced with either 3 or 5 MHz abdominal transducer.

Statistical analysis

Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA). Data were described as percent or mean and standard deviation where appropriate. The linear regression model was used to determine the relationship between NBL and gestational age and to define the 5th centile of NBL on each gestational age. Categorical variables were compared using x^2 tests or Fisher's exact tests. The accuracy of the various BPD/NBL for the detection of trisomy 21 was analyzed by plotting Receiver Operating Characteristic (ROC) curves for the detection of trisomy

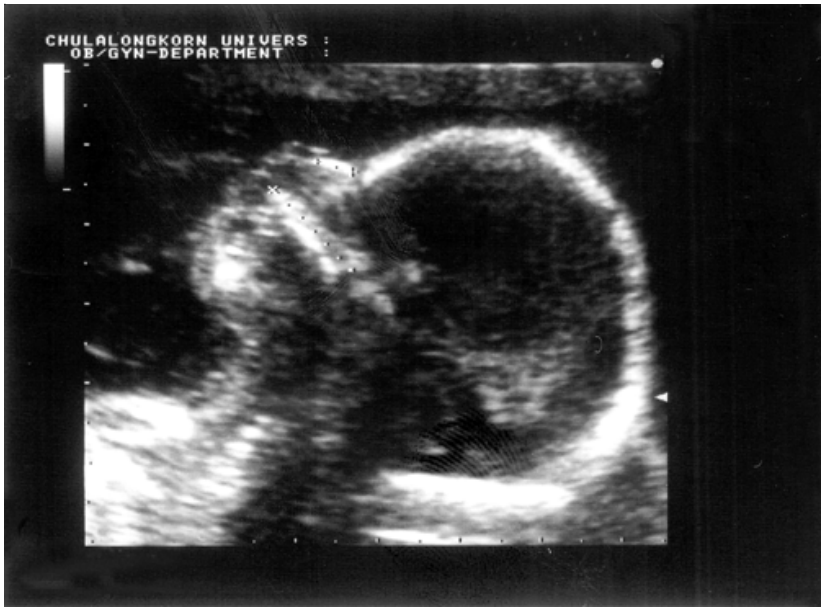

Fig. 1 Nasal bone of chromosomally normal fetus

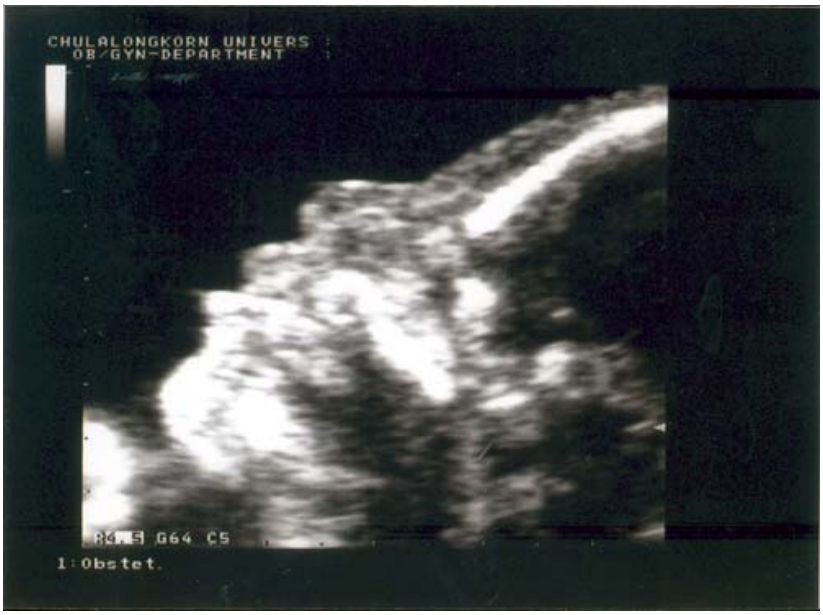

Fig. 2 Absent fetal nasal bone

21 and aneuploidy. From the ROC curves, the diagnostic performance (sensitivity, specificity, likelihood ratio (LR) for positive and negative tests, PPV and NPV) of the various BPD/NBL at different cut-off points for the detection of trisomy 21 was derived. All statistical significance testing was two sided, and $p < 0.05$ was considered to be statistically significant.

Results

Four-hundred-and-seven fetuses were included in this study from January 2005 to December 2005. There were nine aneuploid fetuses; trisomy 21 in five cases, mosaic trisomy 21 in one case, and trisomy 18 in three cases. The mean maternal age was 36.5 ± 2.4 (SD) years, and the mean gestational age was 18.2 ± 1.2 (SD) weeks. The indications for amniocentesis were advanced maternal age in 403 cases, previous chromosomally abnormal pregnancy in two cases and abnormal ultrasound findings in five cases (one case each of cystic hygroma, diaphragmatic hernia, hypoplastic left heart, bilateral pyelectasis, and tetralogy of Fallot) (some patients had more than 1 indication). Intraobserver variability was assessed in 400-paired observations. The mean difference of the two measurements was 0.03. Correlation analysis showed a high association between the two measurements ($R = 0.97$). Nasal bone absence was seen in 1 of 6 of trisomy 21 fetuses (Fig. 2) and none in all euploid and trisomy 18 fetuses. This yielded a sensitivity of 17%, specificity of 100%. In euploid fetuses, NBL increased linearly with advancing gestational age (Fig. 3). The fetuses with Down syndrome had a significantly higher proportion of fetuses with NBL below the 5th centile compared to normal fetuses ($p < 0.05$). The fetuses that had NBL below the 5th centile were found in two of five cases (40%) of trisomy 21 (not including one trisomy 21 fetus with absent NB), and in 11 of 398 cases (3%) of normal fetuses. This yielded a sensitivity of 40% and specificity of 97% for detection of trisomy 21. Predicted fetal NBL from 14 to 24 weeks' gestation is shown in Table 1. The present study demonstrated that the BPD/NBL ratio remained constant at any gestational age. The authors then examined the sensitivities and specificities for various BPD/NBL ratio cutoffs. As the ratio increased, the sensitivity declined markedly while the specificity conversely improved. The BPD/NBL ratio of 9 or greater yielded the highest sensitivity (100%) for detecting trisomy 21, with a specificity of 50% (Table 2). The ROC curve using various BPD/NBL ratios to detect trisomy 21 showed that the optimal nasal bone threshold associated with trisomy 21 was a BPD/NBL ratio of 10 or greater (Fig. 4). This yielded a sensitivity of 80%, specificity of 86%, LR for positive test of 5.7, LR for negative test of 0.23, PPV of 6.7%, and NPV of 99.7% for detection of trisomy 21. The area under the ROC curve was 0.85. Regarding ROC for detection of all

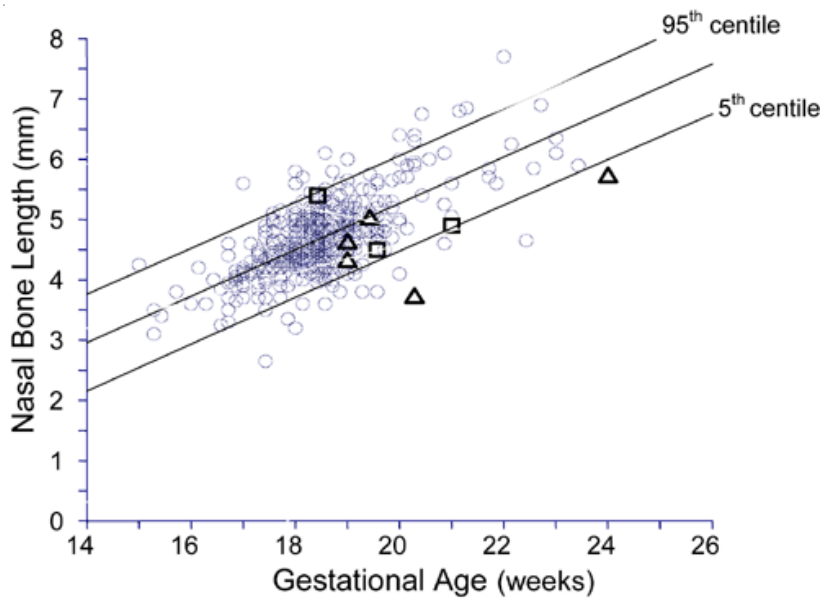

Fig. 3 Reference ranges of nasal bone length from 15 to 24 weeks' gestation. 95% confidence interval is given and 5th centile line is indicated. **O** : normal cases, : trisomy 21 cases, □ : trisomy 18 cases

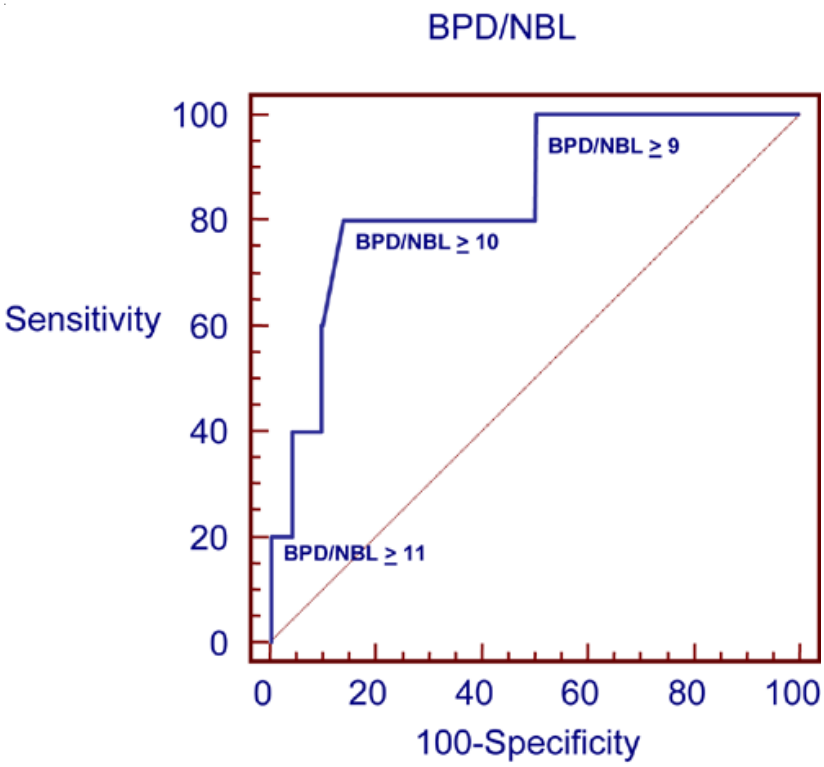

Fig. 4 The receiver operating characteristic curve using various BPD/NBL ratios to detect trisomy 21

Table 1. Predicted fetal NBL from 14 to 24 weeks' gestation

GA (weeks)	5 centile (mm)	Predicted NBL (mm)	95 centile (mm)
14	2.20	2.96	3.71
15	2.59	3.34	4.10
16	2.97	3.73	4.49
17	3.36	4.11	4.87
18	3.74	4.50	5.26
19	4.13	4.88	5.64
20	4.51	5.27	6.03
21	4.90	5.65	6.41
22	5.28	6.04	6.80
23	5.67	6.42	7.18
24	6.05	6.81	7.57

Table 2. The sensitivities and specificities for various BPD/NBL ratio cutoffs for detection of trisomy 21

BPD/NBL ratio	Sensitivity (%)	Specificity (%)	PPV(%)	NPV(%)	LR+
>9	100	50	2.4	100	2
>10	80	86	6.7	99.7	5.7
>11	20	97.5	9.1	99	8
>12	20	99	16.7	99	15.9

Likelihood ratio for positive test

aneuploidy, the optimal threshold is a BPD/NBL ratio of 10 or greater. This yielded the sensitivity of 75%, specificity 86%, LR for positive test of 5.3, LR for negative test of 0.29, PPV of 9.7%, and NPV of 99.4%.

Discussion

Women aged 35 years or more in current prenatal care are considered high risk for Down syndrome pregnancy and are therefore routinely offered invasive tests in order to exclude chromosomal abnormalities. Alternatively some of these patients are reluctant to take the risk of the invasive diagnostic procedures and therefore prefer to have either serum biochemistry or ultrasound screening for Down syndrome. The authors studied the power of NBL for screening Down syndrome in the second trimester because most of the patients in the presented setting are usually recommended screening ultrasound at this period to look for congenital anomalies as well as assessment of gestational age.

The fetal nasal bone first becomes histologically apparent at a crown-rump length of 42 mm, which corresponds to 11 weeks' gestation[12]. The present study has shown an increase in NBL with advancing gestational age. This is consistent with the study of Guis F, et al[13]. The data from the present study demonstrated that absent nasal bone, found in one of six cases of trisomy 21 fetuses had a low sensitivity but high specificity. There was no chromosomally normal fetus that demonstrated absent nasal bone in the present study, which was consistent with other studies in Caucasian populations[6,14,15]. This seemed to be a powerful marker for Down syndrome. However, the number of cases of absent nasal bone in the present study was too small to draw any conclusion. The absence of fetal nasal bone might be the consequence of hypoplasia or delayed ossification of the fetal NB[16,17]. Both post mortem radiologic and histopathologic evidence exist to support this association between absent nasal bone and trisomy 21[17,18]. In one fetus with mosaic Down syndrome, the NBL was in normal range compared with chromosomally normal fetuses. These genotypic differences may reflect phenotypic differences in the Down syndrome group.

When fetal nasal bone was present, BPD/NBL ratio was evaluated. The authors demonstrated that a BPD/NBL ratio of 10 or greater was the optimal threshold definition of nasal bone hypoplasia associated with trisomy 21 fetuses. This has a sensitivity of 80%, specificity of 86%, LR for positive test of 5.7, and false positive rate of 14%. In screening for trisomy 21 by

maternal age alone or maternal age and second-trimester maternal serum biochemistry, the detection rates, for a fixed false-positive rate of 5%, are 30% and 65%, respectively[6]. The present study demonstrated that sensitivities at various BPD/NBL ratio cutoffs are similar to those reported by Lante T, et al[19] and Bromley B, et al[11]. Lante T, et al reported that BPD/NBL ratio of 10 or greater yielded a sensitivity of 80.7%. Bromley, et al reported that the best cutoff of the BPD/NBL ratio for optimizing sensitivity and specificity is 10 or greater, which allows identification of 81% of fetuses with Down syndrome with a false positive rate of 11%. In the present study, the optimal cutoff of the BPD/NBL ratio of 10 yielded a lower PPV. This is probably due to a lower prevalence of trisomy 21 in the presented population (1.2% versus 7%). The BPD/NBL ratio may be applicable in patients with uncertain date since this ratio remained constant throughout gestation[11]. It is important to consider the possibility of variability when ultrasound examination of the NBL is used in clinical practice. The present data showed that intra-observer difference were clinically acceptable. Correlation analysis showed a high association between the two measurements (R = 0.97).

Limitations of the present study exist as small numbers of aneuploid fetuses were enrolled. Moreover, the present study was confined to only a high-risk population; the result could not be extrapolated to apply in a general low risk population.

In conclusion, nasal bone hypoplasia is associated with an increased risk of Down syndrome in the presented population. A large sample size as well as a prospective study in a general population is needed for a more applicable result.

References

1. Bunduki V, Ruano R, Miguelez J, Yoshizaki CT, Kahhale S, Zugaib M. Fetal nasal bone length: reference range and clinical application in ultrasound screening for trisomy 21. Ultrasound Obstet Gynecol 2003; 21: 156-60.
2. Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. Lancet 1998; 352: 343-6.
3. Bindra R, Heath V, Liao A, Spencer K, Nicolaides KH. One-stop clinic for assessment of risk for trisomy 21 at 11-14 weeks: a prospective study of 15,030 pregnancies. Ultrasound Obstet Gynecol 2002; 20: 219-25.
4. Benacerraf BR, Nadel A, Bromley B. Identification of second-trimester fetuses with autosomal trisomy by use of a sonographic scoring index. Radiology 1994; 193: 135-40.
5. Cicero S, Bindra R, Rembouskos G, Tripsanas C, Nicolaides KH. Fetal nasal bone length in chromosomally normal and abnormal fetuses at 11-14 weeks of gestation. J Matern Fetal Neonatal Med 2002; 11: 400-2.
6. Cicero S, Sonek JD, McKenna DS, Croom CS, Johnson L, Nicolaides KH. Nasal bone hypoplasia in trisomy 21 at 15-22 weeks' gestation. Ultrasound Obstet Gynecol 2003; 21: 15-8.
7. Sonek JD, Nicolaides KH. Prenatal ultrasonographic diagnosis of nasal bone abnormalities in three fetuses with Down syndrome. Am J Obstet Gynecol 2002; 186: 139-41.
8. Prefumo F, Sairam S, Bhide A, Penna L, Hollis B, Thilaganathan B. Maternal ethnic origin and fetal nasal bones at 11-14 weeks of gestation. BJOG 2004; 111: 109-12.
9. Cicero S, Longo D, Rembouskos G, Sacchini C, Nicolaides KH. Absent nasal bone at 11-14 weeks of gestation and chromosomal defects. Ultrasound Obstet Gynecol 2003; 22: 31-5.
10. Chen M, Lee CP, Leung KY, Hui PW, Tang MH. Pilot study on the midsecond trimester examination of fetal nasal bone in the Chinese population. Prenat Diagn 2004; 24: 87-91.
11. Bromley B, Lieberman E, Shipp TD, Benacerraf BR. Fetal nose bone length: a marker for Down syndrome in the second trimester. J Ultrasound Med 2002; 21: 1387-94.
12. Sandikcioglu M, Molsted K, Kjaer I. The prenatal development of the human nasal and vomeral bones. J Craniofac Genet Dev Biol 1994; 14: 124-34.
13. Guis F, Ville Y, Vincent Y, Doumerc S, Pons JC, Frydman R. Ultrasound evaluation of the length of the fetal nasal bones throughout gestation. Ultrasound Obstet Gynecol 1995; 5: 304-7.
14. Cusick W, Provenzano J, Sullivan CA, Gallousis FM, Rodis JF. Fetal nasal bone length in euploid and aneuploid fetuses between 11 and 20 weeks' gestation: a prospective study. J Ultrasound Med 2004; 23: 1327-33.
15. Viora E, Errante G, Sciarrone A, Bastonero S, Masturzo B, Martiny G, et al. Fetal nasal bone and trisomy 21 in the second trimester. Prenat Diagn 2005; 25: 511-5.
16. Keeling JW, Hansen BF, Kjaer I. Pattern of malfor-

mations in the axial skeleton in human trisomy 21 fetuses. Am J Med Genet 1997; 68: 466-71.
17. Stempfle N, Huten Y, Fredouille C, Brisse H, Nessmann C. Skeletal abnormalities in fetuses with Down's syndrome: a radiographic post-mortem study. Pediatr Radiol 1999; 29: 682-8.
18. Minderer S, Gloning KP, Henrich W, Stoger H. The nasal bone in fetuses with trisomy 21: sonographic versus pathomorphological findings. Ultrasound Obstet Gynecol 2003; 22: 16-21.
19. Tran LT, Carr DB, Mitsumori LM, Uhrich SB, Shields LE. Second-trimester biparietal diameter/nasal bone length ratio is an independent predictor of trisomy 21. J Ultrasound Med 2005; 24: 805-10.

ภาวะกระดูกจมูกสั้นในทารกดาวน์ที่อายุครรภ์ 15-24 สัปดาห์ในหญิงตั้งไทยครรภ์ ที่มีความเสี่ยงสูงต่อการเกิดทารกดาวน์

บงกช นราพุฒิ, บุญชัย เอื้อไพโรจน์กิจ, สุรสิทธิ์ ชัยทองวงศ์วัฒนะ, เยื้อน ตันนิรันดร, สมชาย ธนวัฒนาเจริญ, ศักนัน มะโนทัย, ธีระพงศ์ เจริญวิทย์

วัตถุประสงค์*: เพื่อศึกษาถึงการนำภาวะกระดูกจมูกสั้นของทารกในครรภ์ไตรมาสที่ 2 มาใช้ทำนายโอกาสเกิดทารกดาวน์*

วัสดุและวิธีการ*: วัดความยาวของกระดูกจมูกของทารกในครรภ์จำนวน 407 ราย โดยใช้เครื่องอัลตราซาวด์ก่อนการเจาะน้ำคร่ำเพื่อตรวจโครโมโซมในระหว่างเดือนมกราคม พ.ศ. 2548 ถึง เดือนธันวาคม พ.ศ.2548 ใช้สถิติวิเคราะห์หาความสัมพันธ์ระหว่างความยาวของกระดูกจมูกกับอายุครรภ์ในทารกที่มีโครโมโซมปกติ และหาค่าความไวและความจำเพาะของภาวะกระดูกจมูกสั้นในการทำนายโอกาสเกิดทารกดาวน์*

ผลการศึกษา*: ในทารกที่มีโครโมโซมปกติพบว่าความยาวของกระดูกจมูกเพิ่มขึ้นตามอายุครรภ์ ในทารกดาวน์พบภาวะกระดูกจมูกสั้นกว่า 5 เปอร์เซ็นไตล์ในสัดส่วนมากกว่าทารกที่มีโครโมโซมปกติ ($p < 0.05$) ค่าที่เหมาะสมของการใช้อัตราส่วนระหว่างส่วนกว้างที่สุดของศีรษะกับความยาวของกระดูกจมูกของทารก (fetal BPD/NBL ratio) ในการทำนายโอกาสเกิดทารกดาวน์คือ 10*

สรุป*: ภาวะกระดูกจมูกสั้นของทารกในครรภ์ไตรมาสที่ 2 สัมพันธ์กับโอกาสเกิดทารกดาวน์ในหญิงไทยตั้งครรภ์ที่มีความเสี่ยงสูงต่อการเกิดทารกดาวน์*