

Original Article

Three-dimensional ultrasonography measurement of fetal nasal bone length during the midtrimester in Taiwanese women

Pei-Yin Yang, Joung-Liang Wu, Guang-Perng Yeh, Charles Tsung-Che Hsieh*

Department of Obstetrics and Gynecology, Changhua Christian Hospital, Changhua, Taiwan

Accepted 14 June 2012

Abstract

Objective: To evaluate the normal range of the fetal nasal bone length (NBL) in Taiwanese women using three-dimensional (3D) ultrasound, and compare the NBL of normal fetuses with Down syndrome to determine its significance in screening for trisomy 21.

Materials and Methods: A total of 102 consecutive fetuses and another 7 fetuses with trisomy 21, determined by karyotyping at 15–22 weeks' gestation, were evaluated with 3D ultrasound before amniocentesis at Changhua Christian Hospital between November 2003 and April 2004.

Results: The normal range for NBL in the second trimester in the Taiwanese population was investigated, and a linear relationship with gestational age was noted. The NBL increased with advancing gestational age (NBL in cm = $0.0264 \times$ gestational age in weeks -0.042 ($R^2 = 0.2416$)). The median of the biparietal diameter/nasal bone length ratio had a stable value which tended to change minimally between 15 and 22 weeks of gestation. Chromosomally normal fetuses had statistically longer nasal bones than fetuses with Down syndrome ($p = 0.014$).

Conclusion: We present a reference range for 3D ultrasound measurement of the fetal NBL. A short nasal bone at 15 to 22 weeks is associated with a high risk of trisomy 21.

Copyright © 2012, Taiwan Association of Obstetrics & Gynecology. Published by Elsevier Taiwan LLC. All rights reserved.

Keywords: fetal nasal bone length; ultrasonography

Introduction

Facial abnormalities, including a flat facial profile and a small nose, are often noted in newborns with Down syndrome. The association between the sonographic absence or hypoplasia of the fetal nasal bone and Down syndrome in the first and mid-second trimesters has been reported [1–6]. Sonographic findings of fetal nasal bone hypoplasia in the second trimester have a sensitivity of 77.7% with a false-positive rate of 0.9% in screening for trisomy 21 [7]. Examination of the fetal nose and its measurement serves as an objective method of prenatal detection of Down syndrome. Normal values for fetal nasal bone measurements have been established in Caucasian, African American, and South Asian

populations [4,8,9]. Cicero et al [4] reported that within the chromosomally normal group in the second trimester, hypoplastic nasal bones were found in 0.5% of Caucasians and 8.8% of Afro-Caribbean people. Chen et al [9] and Hung et al [10] analyzed the fetal nasal bone length (NBL) of normal fetuses in the second trimester in a Chinese population in a pilot study with two-dimensional (2D) ultrasonography. They concluded that the fetal NBL in the Chinese population appeared shorter than that in white and black people.

We conducted a preliminary study with 3D ultrasound to compare the NBL and biparietal diameter (BPD)/NBL ratio between fetuses of Taiwanese women, and compared this result with fetuses with trisomy 21.

Materials and methods

Between November 2003 and April 2004, a total of 102 Taiwanese gravidas undergoing prenatal ultrasound examination at Changhua Christian Hospital at 15 to 22 weeks of

* Corresponding author. Department of Obstetrics and Gynecology, Changhua Christian Hospital, Number 135 Nan-Hsiao Street, Changhua 500, Taiwan.

E-mail address: 40129@cch.org.tw (C. Tsung-Che Hsieh).

gestation were recruited before amniocentesis because of a high risk of aneuploidy. Patients who met one or more of the following criteria were included: maternal age >35 years, risk of trisomy 21 >1:270 based on combined maternal serum test results (including β -human chorionic gonadotropin, α -fetoprotein, unconjugated estriol, and inhibin-A), prior pregnancy carrying a fetus with trisomy 21, or an enlarged nuchal translucency >3 mm. The exclusion criteria were fetal death, maternal complications, and fetal anomalies diagnosed by ultrasound. Seven fetuses with trisomy 21 confirmed by karyotype also received fetal nasal bone measurements as described below.

Examination of the fetal nasal bone and measurement of the fetal NBL were performed by two skilled ultrasonographers (C.T.C. H.; J.L. Wu). Using an abdominal probe (Voluson 730 Expert; General Electric, Milwaukee, WI, USA) an, following the method described by Rembouskos et al [11], 3D volume datasets were acquired by longitudinal screening of the fetal face using notarized curved array transducers (2–5 and 4–8 MHz). Three-dimensional reconstruction of the nasal bones in the anterior–posterior and profile projection views was performed with a maximum intensity projection algorithm. The maximum intensity mode is a rendering algorithm applied to 3D demonstrations of bone structure. All fetuses were successfully recorded three times. A midline sagittal view of the facial profile was chosen during post-scan analysis. Biometry and measurement of the NBL were obtained (Fig. 1). A permanent record of the image was retained on a hard disk and VCD-ROM.

Statistical analysis

Statistical analysis was performed with SPSS for Windows I O software (SPSS, Inc., Chicago, IL, USA). A p value <0.05 was considered statistically significant.

Results

A total of 102 fetuses with normal karyotype were enrolled in the present study. The median gestational age was 17.9 weeks. All fetuses were considered suitable for analysis. Examination of the facial profile was successful in all cases.

Table 1 shows the median, maximal, and minimal data of the NBL at different gestational ages.

Regression analysis demonstrated a significant positive correlation between the fetal NBL and gestational age ($p < 0.05$), as follows: NBL (cm) = $0.0264 \times$ gestational age in weeks $- 0.042$ ($R^2 = 0.2416$). The resulting reference ranges are graphically illustrated in Fig. 2. The relation between NBL and BPD within 15–22 weeks of gestation is also shown in Fig. 2 (NBL cm = $0.122 \times$ BPD $- 0.609$; $R^2 = 0.3829$, $R < 0.001$). Fetuses with trisomy 21 had a shorter NBL than euploid fetuses, despite having a similar BPD and gestational age, as shown in Table 2 ($p = 0.014$).

In our results, the expected values of the BPD/NBL ratio were significantly different between the euploid fetuses and the trisomy 21 fetuses from 15 to 22 weeks. In the euploid fetuses, the mean of the BPD/NBL ratio was 9.573, the SD was 1.625, and the regression equation was BPD/NBL = $11.421 - 0.0999 \times$ gestational age in weeks; in the trisomy 21 group, the mean of the BPD/NBL ratio was 14.261, the SD was 3.964, and the regression equation reported BPD/NBL = $47.841 - 1.7467 \times$ gestational age in weeks (Table 2, Fig. 3).

Table 2 also shows a comparison of the BPD/NBL ratio in the two groups (Down syndrome and normal fetus group). The p value was <0.001. The BPD/NBL ratio in fetuses with Down syndrome was statistically higher than that in fetuses that were chromosomally normal.

Table 3 shows the results of multiple linear regression of the BPD/NBL ratio; if the predictor was gestational age (GA

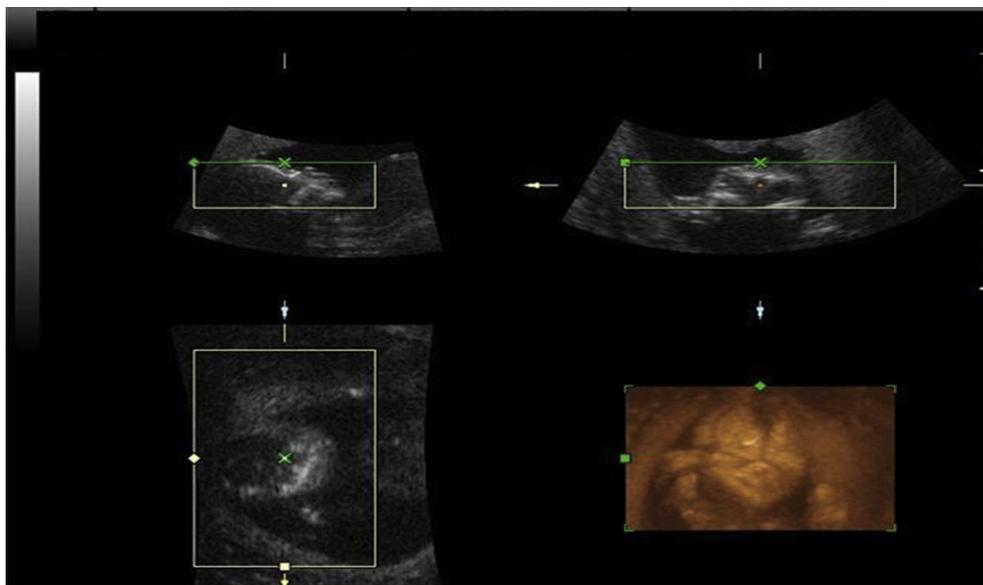


Fig. 1. The fetal nasal bone is measured by three-dimensional ultrasound using both the surface and max modes. A rendering box over a normal surface is viewed from the ventral direction. The bottom-right panel reveals both nasal bones.

Table 1
Length of the nasal bone (cm) in the mid-second trimester in Taiwanese fetuses.

GA week	N	Nasal bone				
		Mean	SD	Median	Min	Max
16	14	0.399	0.069	0.399	0.289	0.542
17	37	0.425	0.087	0.441	0.258	0.572
18	14	0.432	0.058	0.451	0.330	0.505
19	16	0.448	0.072	0.473	0.309	0.553
20	10	0.539	0.062	0.537	0.446	0.678
21	7	0.533	0.072	0.525	0.448	0.684
22	4	0.513	0.109	0.506	0.413	0.626

GA = gestational age.

week), the *p* value was 0.178, which was not significant. If the predictor was groups (Down syndrome or normal fetuses group), the *p* value was <0.001. We proposed that the BPD/NBL ratio of the fetuses in the Taiwanese population from 15 to 22 weeks gestational age had a stable value and changed minimally, and is not related to gestational age but related to Down syndrome fetuses.

Discussion

The aim of this study was to establish the reference range of the NBL with 3D ultrasound throughout the gestation period of 15 to 22 weeks based on chromosomally normal Taiwanese fetuses, as 3D ultrasound is presumed to be helpful in identifying the exact sagittal plane for an accurate NBL measurement.

The nasal bones develop from paired independent ossification tissues located in a membrane within the cone-septal cartilage of the nasal capsule. Several studies have proposed that delayed maturation of the nasal bones may be a possible explanation for the increasing prevalence of absent or hypoplastic nasal bones in fetuses with Down syndrome [12,13]. Some histological sections or radiologic studies have revealed asymmetric distribution or unilateral absence of nasal bone tissue in fetuses with Down syndrome.

Hypoplastic nasal bones are more easily identified and missed less often on 3D-rendered anterior–posterior

projection views [14,15]. Previous studies reported the absence of the nasal bone as the single most sensitive and specific second trimester marker for trisomy 21 in all populations. On 2D or 3D prenatal ultrasonography, absent or hypoplastic nasal bones occur in 40–70% of first and second trimester fetuses with Down syndrome, but also in approximately 1% of the normal population [1,5,14]. In the study conducted by Benoit and Chaoui [14], the detection rate was 45% in the 3D-rendered mode. They suggested that maximal mode rendering in 3D and 4D should be used for suspicious findings of absence or hypoplasia of the nasal bone.

Goncalves et al [15] reported that 9 of 10 fetuses with absent nasal bones had Down syndrome, 42.3% (11 of 26) of fetuses with Down syndrome showed hypoplastic nasal bones, and a unilateral bone was found in only one case. Furthermore, hypoplastic nasal bone was also observed in 22.2% (6 of 27) cases of the fetuses without abnormalities in their study group, including 27 normal fetuses and 26 Down syndrome fetuses confirmed by karyotype. The risk of Down syndrome in fetuses with hypoplastic nasal bones is lower than in those with complete absence of the nasal bones. In their conclusions, they noted that the hypoplastic nasal bone might be not identified on 2D ultrasound.

The measurement of the nasal bone by 2D ultrasound was significantly influenced by fetal position and the angle between the ultrasound beam and the axis of the nasal bone. Through 3D ultrasound, we can improve the accuracy of nasal bone measurements. We can also measure hypoplastic nasal bones by 3D ultrasound, although the efficiency seems lacking [14].

Increasing NBL with gestation and with BPD was again demonstrated in our study population. In the study by Hung et al [10], the reference value at a gestational age of 18 weeks was 5.29 ± 0.05 mm. In our data, the value reported was 4.32 ± 0.058 mm. Jung et al [16] proposed an NBL value of 4.0 ± 0.66 mm at 18 weeks of gestation in a South Korean population. Our data have established reference ranges of the NBL at different gestational ages in normal singleton Taiwanese fetuses with 3D ultrasound measurement of the NBL.

Some researchers have attempted to use the BPD/NBL ratio for further scanning purposes, because the size of the nasal bone in unaffected pregnancies is gestational age-dependent [3]. In Bromley et al’s study [3], the BPD/NBL ratio in euploid fetuses was 8.1 ± 1.4 compared with 11.3 ± 2.0 in fetuses with trisomy 21. In another study conducted on a healthy Japanese population, the BPD/NBL ratio was 9.01 ± 1.20 [17]. In our study, the ratio was 9.573 ± 1.625 . We speculate that the ratio is stable and changed minimally unrelated to the gestational age of fetuses in Taiwanese women at 15 to 22 weeks of gestation, as shown in Table 3. This result was also noted in a previous study. In one study, the optimal cutoff of the BPD/NBL ratio for optimizing sensitivity and specificity was ≥ 10 , which allowed identification of 81% of fetuses with trisomy 21 with a false-positive rate of 11% [3]. Tran et al [18] reported an 81% detection rate, but a false-positive rate of 44% under the same criteria. Odibo et al [19] reported that the use of $BPD/NBL > 11$ provided

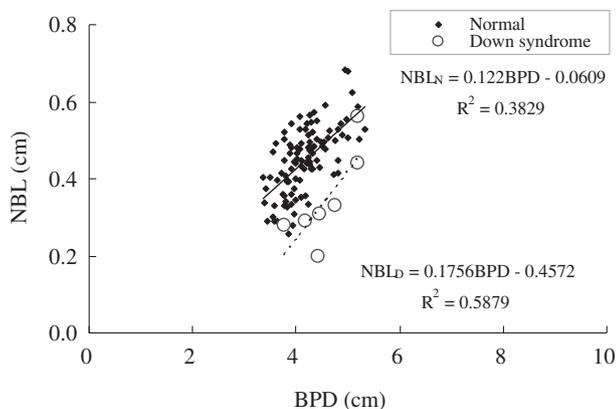


Fig. 2. Distribution of nasal bone length (mm) in the study population. ◆ = normal karyotype; ○ = Down syndrome; BPD = biparietal diameter; NBL = nasal bone length.

Table 2
Comparison of NBL and BPD/NBL ratio in fetuses with a normal karyotype and those with Down syndrome.

	Group										p
	Normal (n = 102)					Down syndrome (n = 7)					
	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	
GA week	18.508	1.622	17.929	16.143	22.857	19.229	1.340	18.600	18.000	21.400	0.108
BPD (cm)	4.172	0.441	4.110	3.360	5.320	4.564	0.520	4.460	3.760	5.180	0.053
Nasal bone length (cm)	0.448	0.087	0.451	0.258	0.684	0.344	0.119	0.310	0.200	0.560	0.014
BPD/NBL	9.573	1.625	9.192	7.200	14.865	14.261	3.964	14.387	9.250	22.150	<0.001

p value by Mann–Whitney U-test. BPD = biparietal diameter; GA = gestational age; NBL = nasal bone length.

a sensitivity of 59%, with a false-positive rate of 15% and a specificity of 85% (95% confidence interval, 84–86%) for detecting Down syndrome. Our BPD/NBL ratio in normal Taiwanese fetuses seems slightly higher. One possible reason is the shorter NBL in the Taiwan population. Odibo et al and Tran et al did not adjust for race in their studies of NBL [3,19].

Maymon et al [20] combined prenatal thickness with NBL for detecting Down syndrome, and their results achieved a 70% detection rate with a 5% false-positive rate, in which data were expressed as multiples of the normal gestation-specific median (MoM). Gianferrari et al [21] proposed using $NBL < 0.8$ MoM as a cutoff for detecting Down syndrome fetuses; the sensitivity achieved 95.2%, and the false-positive rate was 7.4%. If the cutoff was lowered to 0.75 MoM, it resulted in a sensitivity of 85.7% and a 2.9% false-positive rate. They also emphasized that using cutoffs only derived from a Caucasian population to calculate MoM for the

entire population might result in increased false-positive rates. The multiplicative correction factor for the Asian race was 0.948 for NBL. They also concluded that detecting fetuses with Down’s syndrome using the BPD/NBL ratio is a useful method. In their study population, the correction factor was listed as 1.0500 for Asian women [21]. However, the study included fewer than 100 Asian women. In another study by Odibo et al [22], in which 218 Asian women were enrolled, a factor of 0.96 was used for correcting normal medians of nasal bones [22]. These correction factors were calculated for the authors’ study population by comparing the median values of the Caucasian population to other races. It seems to need more data on Asian pregnant women population for calculating a more specific ethnicity-adjusted correction factor.

Our data echoed the results of ethnicity-adjusted BPD/NBL ratios reported in other studies [8,11,21]. Shorter nasal bones were noted in our study compared with the study by Hung et al [9]. This may be attributed to the estimated accuracy of using 2D or 3D ultrasound or the limited number of fetuses. We agree with the conclusions in other studies that shortened nasal bones are a useful ultrasound marker for detecting Down syndrome in second trimester fetuses. So far, the most sensitive and effective method for screening fetuses with Down syndrome is undeniably a combination test of maternal age, fetal nuchal translucency, and maternal serum free β -human chorionic gonadotropin and pregnancy-associated plasma protein-A at 11 to 14 weeks of gestation. Measurement of NBL in the second trimester might be an alternative to serum-based second trimester Down syndrome screening in pregnant women who were not screened in the first trimester of pregnancy.

Although we set the reference range of nasal-bone length of the normal Taiwanese population in the early second trimester using 3D ultrasound, a large, fully prospective study is required to confirm our observations.

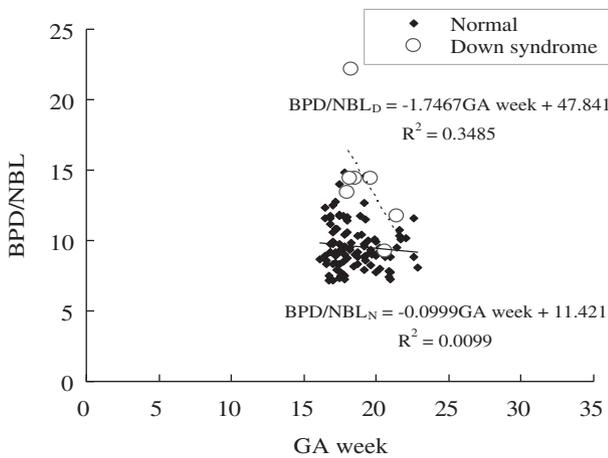


Fig. 3. BPD/NBL ratio versus gestational age (GA) in the study population. \blacklozenge = normal karyotype; \circ = Down syndrome; BPD = biparietal diameter; NBL = nasal bone length.

Table 3
Multiple linear regression results of BPD/NBL.

Predictors	β	SE	Std β	95% CI for β	p	R^2
(Constant)	12.236	1.970		8.330 to 16.142	<0.001	0.297
GA Week	-0.147	0.109	-0.111	-0.362 to 0.068	0.178	
Group (Down vs. Normal)	4.803	0.720	0.547	3.376 to 6.230	<0.001	

BPD = biparietal diameter; GA = gestational age; NBL = nasal bone length.

References

- [1] Cicero S, Curcio P, Papageorgiou A, Sonek J, Nicolaides K. Absence of nasal bone in fetuses with trisomy 21 at 11–14 weeks’ gestation: an observational study. *Lancet* 2000;1(358):1665–7.
- [2] Sonek JD, Nicolaides KH. Prenatal ultrasonographic diagnosis of basal bone abnormalities in three fetuses with Down syndrome. *Am J Obstet Gynecol* 2002;186:139–41.
- [3] 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.

- [4] 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.
- [5] Cicero S, Rembouskos G, Vandecruys H, Hogg M, Nicolaides KH. Likelihood ratio for trisomy 21 in fetuses with absent nasal bone at the 11–14 week scan. *Ultrasound Obstet Gynecol* 2004;23:218–23.
- [6] Vintzileos A, Walters C, Yeo L. Absent nasal bone in the prenatal detection of fetuses with trisomy 21 in a high-risk population. *Obstet Gynecol* 2003;101:905–8.
- [7] Viora E, Errante G, Sciarone 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.
- [8] Sonek JD, McKenna D, Webb D, Croom C, Nicolaides K. Nasal bone length throughout gestation: normal ranges based on 3537 fetal ultrasound measurements. *Ultrasound Obstet Gynecol* 2003;21:152–5.
- [9] 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.
- [10] Hung JH, Fu CY, Chen CY, Chao KC, Hung J. Fetal nasal bone length and Down syndrome during the second trimester in a Chinese population. *J Obstet Gynaecol Res* 2008;34:518–23.
- [11] Rembouskos G, Ciceros S, Longo D, Vandecruys H, Nicolaides KH. Assessment of the fetal nasal bone at 11–14 weeks of gestation by three-dimensional ultrasound. *Ultrasound Obstet Gynecol* 2004;23:232–6.
- [12] Keeling JW, Hansen BF, Kjaer I. Pattern of malformations in the axial skeleton in human trisomy 21 fetuses. *Am J Med Genet* 1997;68:466–71.
- [13] Stempfle N, Hutten 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.
- [14] Benoit B, Chaoui R. Three-dimensional ultrasound with maximal mode rendering :a novel technique for the diagnosis of bilateral or unilateral absence or hypoplasia of nasal bones in second-trimester screening for Down syndrome. *Ultrasound Obstet Gynecol* 2005;25:19–24.
- [15] Goncalves LF, Espinoza J, Lee W, Schoen ML, Devers P, Mazor M, et al. Phenotypic characteristics of absent and hypoplastic nasal bones in fetuses with Down syndrome; description by 3-dimensional ultrasonography and clinical significance. *J Ultrasound Med* 2004;23:1619–27.
- [16] Jung E, Won HS, Lee PR, Kim A. Ultrasonographic measurement of fetal nasal bone length in the second trimester in Korean population. *Prenat Diagn* 2007;27:154–7.
- [17] Kanagawa T, Fukuda H, Kinugasa Y, Son M, Shimoya K, Murata Y, et al. Mid-second trimester measurement of fetal nasal bone length in the Japanese population. *J Obstet Gynaecol Res* 2006;32:403–7.
- [18] 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.
- [19] Odibo AO, Sehdev HM, Sproat L, Parra C, Odibo L, Dunn L, et al. Evaluating the efficiency of using second-trimester nasal bone hypoplasia as a single or a combined marker for fetal aneuploidy. *J Ultrasound Med* 2006;25:437–41.
- [20] Maymon R, Levinsohn-Tavor O, Cuckle H, Tovbin Y, Dreazen E, Wiener Y, et al. Second trimester ultrasound prenatal thickness combined with nasal bone length: a new method of Down syndrome screening. *Prenat Diagn* 2005;25:906–11.
- [21] Gianferrari EA, Benn PA, Dries L, Brault K, Egan JF, Zelop CM. Absent or shortened nasal bone length and the detection of Down syndrome in second trimester fetuses. *Obstet Gynecol* 2007;109:371–5.
- [22] Odibo AO, Sehdev HM, Stamilio DM, Cahill A, Dunn L, Macones GA. Defining nasal bone hypoplasia in second-trimester Down syndrome screening: does the use of multiples of the median improve screening efficacy? *Am J Obstet Gynecol* 2007;197: 361.e1–361.e4.