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Evaluating the Efficiency of Using Second-Trimester Nasal Bone Hypoplasia as a Single or a Combined Marker for Fetal Aneuploidy

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Objective. Although second-trimester nasal bone (NB) hypoplasia has been associated with fetal aneuploidy, its role as a single marker is still uncertain. Our objective was to evaluate the efficiency of NB hypoplasia as an independent marker for fetal aneuploidy. **Methods.** This was a prospective cohort study of women undergoing an anatomic survey between 16 and 22 weeks' gestation. The fetal NB and other markers of fetal aneuploidy, including nuchal fold, femur and humeral lengths, choroid plexus cysts, major fetal anomalies, echogenic bowel, pyelectasis, and hypoplastic fifth digits, were evaluated. Nasal bone hypoplasia was defined either as an absent NB or by a ratio of the biparietal diameter to NB. Fetuses or infants with fetal aneuploidy were compared with those without for the presence of NB hypoplasia either as a single marker or in the presence of other markers for aneuploidy. **Results.** Of 2885 women evaluated, NB measurements were obtained in 2465 (85%). There were 35 (1.4%) cases with fetal aneuploidy. The sensitivity and specificity of a single NB in detecting Down syndrome varied from 23% to 64% and 57% to 99%, respectively, depending on the definition of NB hypoplasia used. There was an improvement in the efficiency of using the NB when combined with other markers, with sensitivity and specificity increasing from 59% to 82% and 74% to 87%, respectively. **Conclusions.** Nasal bone hypoplasia is a marker for fetal aneuploidy. The combination of the NB with other markers was associated with an improvement in detection of fetal aneuploidy. **Key words:** aneuploidy; Down syndrome; hypoplasia; nasal bone.

Abbreviations

BPD, biparietal diameter; CI, confidence interval; NB, nasal bone; ROC, receiver operating characteristic

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Several studies have suggested that an absent fetal nasal bone (NB) or NB hypoplasia is a marker for aneuploidy in the first and second trimesters of pregnancy.¹⁻¹¹ These studies have used several definitions of NB hypoplasia making generalizability problematic. In a recent study limited to women having prenatal diagnosis, we reported that a ratio of the biparietal diameter (BPD) to NB of greater than 11.0 was the best definition of NB hypoplasia associated with aneuploidy.¹²

It is, however, still uncertain how the NB performs as a single marker for fetal aneuploidy compared with when combined with other proven markers of aneuploidy. This current study aimed to evaluate the efficiency of using NB hypoplasia as a single marker for fetal aneuploidy.

Materials and Methods

This was a prospective cohort study of women undergoing an anatomic survey between 16 and 22 weeks' gestation over 18 months. The study patients were identified consecutively. The fetal NB and other markers of fetal aneuploidy, including nuchal fold, femur and humeral lengths, choroid plexus cysts, major fetal anomalies, echogenic bowel, pyelectasis, and hypoplastic fifth digits, were evaluated. Approval from the institutional review boards of all study centers was obtained.

The fetal NB was assessed as previously described by Sonek and Nicolaides.² The facial profile of the fetus was obtained in the midsagittal plane and by rocking the transducer sideways. The angle of insonation was maintained at 45° or 135°. The NB is seen as a triangular echogenic structure in this view. All sonographic evaluations were performed by experienced American Registry for Diagnostic Medical Sonography–certified sonographers, with training in first-trimester screening ultrasound. Several definitions of NB hypoplasia, including an absent NB and BPD/NB ratios of greater than 9, 10, 11, and 12, were evaluated. Short femur and humeral lengths were defined as measurements of less than 0.91 and 0.89 compared with the expected measurements for the gestational age, respectively.¹³ Fetuses or infants with fetal aneuploidy were compared with those without for the presence of NB hypoplasia either as a single marker or in the presence of other markers. Fetal karyotypes were confirmed either by chromosomal analysis when available or by neonatal examination.

Statistical analysis was performed with the χ^2 test for categorical variables and the Student *t* test for continuous variables. The primary outcome was the association between NB and fetal aneuploidy. All analyses were performed with Stata version 8.0 (StataCorp, College Station, TX).

Results

During the study period, 2885 women were evaluated, and NB measurements were obtained in 2465 (85%). The demographic characteristics for our study population are shown in Table 1. The mean maternal age \pm SD was 30.2 \pm 6.7 years, and 50% of the study population were white. There

Table 1. Demographics of Subjects Evaluated for NB (n = 2885)

Characteristic	Value
Mean age \pm SD, y	30.2 \pm 6.7
Race, n (%)	
White	1442 (50)
Black	1154 (40)
Asian	173 (6)
Other	116 (4)

were 35 (1.4%) cases with fetal aneuploidy, with most having trisomy 21 (Table 2).

The efficiency of using NB hypoplasia to screen for trisomy 21 as a single maker is shown in Table 3. Although a BPD/NB ratio of greater than 9 had the best sensitivity, an absent NB had the best specificity of 99%. The information in Table 3 was used to construct a receiver operating characteristic (ROC) curve, which reveals the optimal tradeoff between sensitivity and specificity to be the point correlating with the use of a BPD/NB ratio of greater than 11.0 (Figure 1). The specificity of using a BPD/NB ratio of greater than 11 to screen for Down syndrome is 85% (95% confidence interval [CI], 84%–86%) compared with using a BPD/NB ratio of greater than 12, with specificity of 93% (95% CI, 92%–94%). The nonoverlapping CIs indicate a statistically significant difference in specificity with these two NB criteria. Conversely, the sensitivity of a ratio of greater than 11 was 59% (95% CI, 36%–79%), and a ratio of greater than 12 had sensitivity of 41% (95% CI, 27%–64%), the overlapping CIs indicating statistical nonsignificance. An absent NB was associated with the highest positive predictive value and positive likelihood ratio.

The efficiency of the NB when combined with other markers (as part of a genetic sonogram) is depicted in Table 4. The sensitivity and specificity

Table 2. Types of Chromosomal Anomalies Detected in the Study Population (n = 2885)

Abnormality	n (%)
Abnormal karyotypes	35 (1.2)
Trisomy 21	22 (63)
Trisomy 18	7 (20)
Triploidy	1 (3)
45 XO	2 (6)
Others	3 (8)

Table 3. Relationship Between NB and Down Syndrome According to Various Definitions of NB Hypoplasia

Parameter	Absent NB	BPD/NB >9	BPD/NB >10	BPD/NB >11	BPD/NB >12
Sensitivity, n (%)	5/22 (23)	14/22 (64)	13/22 (59)	13/22 (59)	9/22 (41)
Specificity, n (%)	2433/2446 (99)	1382/2423 (57)	1783/2423 (74)	2061/2423 (85)	2262/2423 (93)
PPV, n (%)	5/18 (28)	14/1055 (1)	13/653 (2)	13/375 (3)	9/170 (5)
NPV, n (%)	2433/2450 (99)	1382/1390 (99)	1783/1792 (99)	2061/2070 (99)	2262/2275 (99)
LR+	23	1.5	2.3	3.9	5.9
LR-	0.8	0.6	0.6	0.5	0.6

LR+ and LR- indicate positive and negative likelihood ratios; NPV, negative predictive value; and PPV, positive predictive value.

ty for trisomy 21 with the use of other markers without adding the NB were 45% (95% CI, 24%–68%) and 87% (95% CI, 86%–88%), respectively. When the NB (using a BPD/NB ratio of >11 to define NB hypoplasia) was combined with other markers, the sensitivity and specificity for detection of trisomy 21 were 82% (95% CI, 60%–95%) and 74% (95% CI, 72%–76%), respectively. The use of an absent NB and other markers was associated with a modest increase in sensitivity but maintained the same specificity. The likelihood ratios for positive or negative NB hypoplasia in predicting trisomy 21 as a single finding or combined with other markers are also shown in Table 4. Figure 2 is an ROC curve depicting the efficiency of combining NB with other markers. The optimal threshold point for this curve corresponds to the use of a BPD/NB ratio of greater than 11 combined with other markers.

Table 5 shows the screening performance of using NB as a single marker or in combination with other markers to screen for all aneuploidy. The sensitivity and specificity were lower compared with screening for Down syndrome only. An absent NB was seen in a case of Edward syndrome and when a BPD/NB ratio of greater than 11 was used as the definition of NB hypoplasia; 1 additional case of Edward syndrome was detected. There was only 1 case of Turner syndrome with a BPD/NB ratio of greater than 11.

Discussion

Our findings confirm the association between NB hypoplasia and aneuploidy. This association was stronger with trisomy 21 compared with other types of aneuploidy. In addition, our results suggest the NB to have modest efficiency as a single maker for trisomy 21. The finding of an absent NB when single was highly specific for

detecting Down syndrome, and the likelihood ratio of 23 suggests that this is one of the most powerful markers in the second trimester. However, to improve second-trimester detection of Down syndrome, the goal will be to maximize the sensitivity of a combination of markers while maintaining reasonable specificity. Our findings using the ROC curve (Figure 2) suggest that the use of a BPD/NB ratio of greater than 11 could achieve this goal. The lower specificity, however, indicates the need for a stricter definition of NB hypoplasia, such as a BPD/NB ratio of greater than 12.

The specificity of a BPD/NB ratio of greater than 11 in this study is lower compared with that given in previous reports on the association between NB hypoplasia and Down syndrome.^{9,11,12} One possible reason for our lower specificity could be the higher percentage of black patients in our study population compared with those in previous reports.¹⁴ The small study population was, however, insufficient to perform a stratified analysis by race or ethnicity. The specificity of an

Figure 1. Receiver operating characteristic curve of model using different definitions of NB hypoplasia only for detection of Down syndrome.

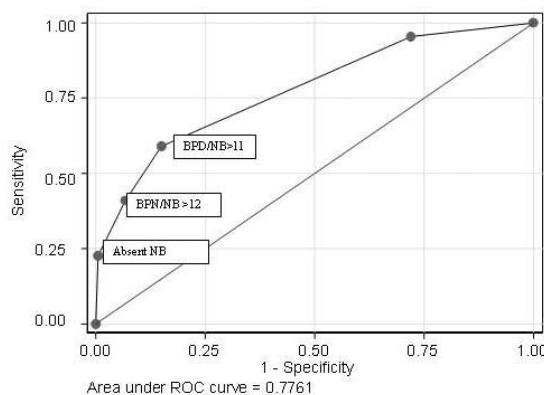


Table 4. Efficiency of Including NB Hypoplasia With Other Second-Trimester Markers for Down Syndrome

Parameter	Other Markers Only	Absent NB + Other Markers	BPD/NB >11 + Other Markers	BPD/NB >12 + Other Markers
Sensitivity, n (%)	10/22 (45)	13/22 (59)	18/22 (82)	15/22 (68)
Specificity, n (%)	2109/2423 (87)	2116/2423 (87)	1798/2423 (74)	1968/2423 (81)
PPV, n (%)	10/324 (3)	13/343(3)	18/643 (3)	15/470 (3)
NPV, n (%)	2109/2121 (99)	2116/2125 (99)	1798/1802 (99)	1968/1975 (99)
LR+	3.5	3.9	3.2	3.6
LR-	0.6	0.5	0.2	0.4

LR+ and LR- indicate positive and negative likelihood ratios; NPV, negative predictive value; and PPV, positive predictive value.

absent NB is, however, similar to those previously reported. In addition, the sensitivity values of other genetic markers for predicting Down syndrome reported in this study are lower than those previously reported from most centers evaluating second-trimester genetic sonograms.¹⁵ Previous studies have reported sensitivity ranging from 67% to 93%, compared with 45% in this study population.¹⁵ Possible explanations for this observation include differences in study populations, methods, sample sizes, and gestational ages at screening. The wide CI around the sensitivity for other markers seen in this study (24%–68%) would suggest that the small number of fetuses with Down syndrome may be responsible for the variation. Because many studies do not report the CI around their point estimate for the accuracy of these markers, it is difficult to compare these reports with ours. Consequently, in centers that have had higher accuracy with the use of the genetic sonogram, the addition of the NB could result in a greater improvement in the

prediction of Down syndrome than what we have reported in this study.

These findings are important in counseling patients for whom NB hypoplasia is the only finding on sonography regarding the utility of a diagnostic test such as amniocentesis. The importance of these findings will, however, be influenced by the a priori risk of the patient. In women with an a priori risk of less than 1 per 1500, the positive likelihood ratio of 3.9 for NB hypoplasia as a single marker (using a BPD/NB ratio of >11) and risk of Down syndrome may not appreciably affect their posttest (sonography) risk. Conversely, for a patient with an a priori risk of greater than 1 per 1500, the presence of NB hypoplasia as a single marker could lead to an appreciable change in her a priori risk, resulting in acceptance of a diagnostic test. The finding of an absent NB as the only finding is, however, significant, and our results would suggest that recommending an invasive test for this indication is reasonable. When combined with other markers for fetal aneuploidy, the performance of NB hypoplasia in detecting aneuploidy improved. This was more significant for trisomy 21 compared with all types of aneuploidy.

This study has some limitations, including a small sample size and the associated difficulty with performing a stratified analysis based on the gestational age at screening. For example, it was not possible to stratify our groups into those seen before 18 weeks and those after 18 weeks. Our study population also included a considerable number of high-risk women, accounting for the high prevalence of aneuploidy within this small cohort. This may be a reflection that most of our patients are high-risk women being evaluated in maternal-fetal medicine units. The results are not affected by any selection bias because all patients were identified consecutive-

Figure 2. Receiver operating characteristic curve of model using combinations of different definitions of NB hypoplasia and other markers for detection of Down syndrome.

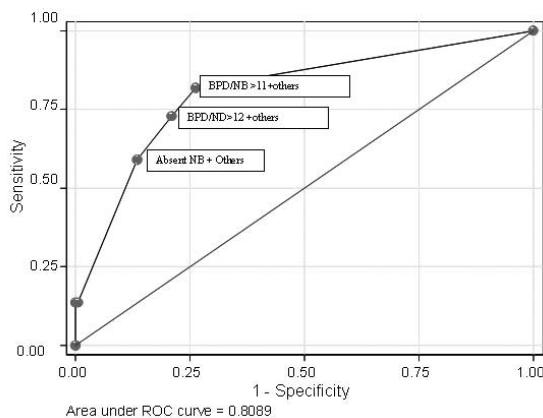


Table 5. Relationship Between NB as a Single Marker, Combinations With Other Markers, and All Aneuploidy

Characteristic	Sens, n (%)	Spec, n (%)	PPV, n (%)	NPV, n (%)	LR+	LR-
Absent NB	6/35 (17)	2421/2433 (99)	6/18 (33)	2450/2468 (99)	17	0.83
BPD/NB >11	16/35 (46)	2051/2410 (85)	16/375 (4)	2051/2070 (99)	3.1	0.63
BPD/NB >12	10/35 (29)	2250/2410 (93)	10/170 (6)	2250/2275 (99)	4.1	0.76
Other markers only	16/35 (46)	2102/2410 (87)	16/324 (5)	2102/2121 (99)	3.5	0.62
Absent NB + other markers	19/35 (54)	2109/2433 (87)	19/343 (6)	2109/2125 (99)	4.2	0.53
BPD/NB >11 + other markers	25/35 (71)	1792/2410 (74)	25/643 (4)	1792/1802 (99)	2.7	0.39
BPD/NB>12 + other markers	21/35 (60)	1961/2410 (81)	21/470 (4)	1961/1975 (99)	3.2	0.49

LR+ and LR- indicate positive and negative likelihood ratios; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; and Spec, specificity.

ly. Consequently, our findings may not be generalizable to a low-risk population. Finally, we were unable to obtain adequate facial profiles in 15% of our study population because of fetal position. It is impossible to determine how this could have affected our results. If the NB is to be used as a marker for aneuploidy, then greater efforts at obtaining optimal facial profiles cannot be overemphasized.

This study corroborates the findings of previous reports associating NB hypoplasia and fetal aneuploidy and suggests that such an association could be important when this finding is a single marker. Future larger studies addressing this issue and evaluating the best definition of NB hypoplasia are urgently needed.

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