

Fetal Nose Bone Length

A Marker for Down Syndrome in the Second Trimester

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Objective. To evaluate the significance of nasal bone length in relation to the detection of Down syndrome in the second trimester. **Methods.** We evaluated consecutive fetuses referred to our facility between 15 and 20 weeks' gestation for sonography and amniocentesis because of an increased risk of aneuploidy. A detailed structural survey, biometric measurements, and measurement of the nasal bone were obtained at the time of amniocentesis and subsequently compared with karyotype. The characteristics of the fetuses with Down syndrome were compared with those of the euploid fetuses. **Results.** A total of 239 fetuses were evaluated. Sixteen fetuses (7%) had Down syndrome, and 223 were euploid. In fetuses with Down syndrome, 6 (37%) of 16 did not have detectable nose bones, compared with 1 (0.5%) of 223 control fetuses, yielding a likelihood ratio of 83. Detectable nasal bones were seen in 10 fetuses with Down syndrome and 222 euploid fetuses. A receiver operating characteristic curve for the biparietal diameter–nasal bone length ratio showed that a value of 9 or greater detected 100% of fetuses with Down syndrome and 22% of euploid fetuses. If the ratio were 10 or greater, then 81% fetuses with Down syndrome and 11% of euploid fetuses would have been identified. If the ratio were 11 or greater, 69% of fetuses with Down syndrome would be identified, compared with 5% of euploid fetuses. **Conclusions.** The absence of a nasal bone is a powerful marker for Down syndrome. A short nasal bone is associated with an increased likelihood for fetal Down syndrome in a high-risk population. **Key words:** aneuploidy, second trimester; fetal nose bone length; marker, fetal Down syndrome; midsagittal profile; sonography.

Abbreviations

BPD, biparietal diameter; DS, Down syndrome; NBL, nasal bone length; ROC, receiver operating characteristic

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Down syndrome (DS) is the most common chromosomal aneuploidy to result in a live birth. Prenatal sonography has been helpful in the detection of affected fetuses by relying on a variety of sonographic features. Within the 11- to 14-week gestational age window, prominent nuchal translucency has been the hallmark for identifying fetuses with DS.¹ Recently, the nasal bone has been shown to be absent in 73% of fetuses with DS in the first trimester, compared with 8.3% of control fetuses, suggesting this as a promising new sonographic marker.²

Very little systematic study has been done of the nasal bone in the second trimester as a marker for DS.³ Between 15 and 20 weeks, identification of affected fetuses is dependent on sonographic markers such as a thickened nuchal skin fold, long-bone length, pyelectasis,

echogenic intracardiac foci, and hyperechoic bowel. The sonographic identification of these features has allowed the detection of 60% to 80% of fetuses with DS, with false-positive rates of 5% to 15%.^{4,5}

In this study, we sought to evaluate the significance of the nasal bone length (NBL) in relation to the detection of trisomy 21 in the second trimester.

Materials and Methods

The study group comprised consecutive fetuses referred to our facility for sonography and amniocentesis because of an increased risk of aneuploidy and who were subsequently found to have DS by karyotype. The control group was composed of euploid fetuses by karyotype, referred for the same evaluation on the basis of the same indications. The study was conducted over a 6-month period between November 2001 and April 2002.

Each fetus in this study had a sonographic examination between 15 and 20 weeks' gestation followed by amniocentesis for fetal karyotype. The findings of the sonography were prospectively recorded in the medical record before the knowledge of karyotype.

Each sonographic examination included a structural fetal survey, which was as detailed as possible given the limitations of gestational age. Biometric measurements included biparietal diameter (BPD) and femoral and humeral lengths. Criteria for a short femur and humerus have been published previously.^{6,7} Each fetus was prospectively evaluated for the presence of a nuchal fold of 5 mm or larger, an echogenic intracardiac focus, hyperechoic bowel, pyelectasis, and major congenital defects.⁵ In addition, an image of the fetal profile was taken in the midsagittal plane, and the nasal bone was identified as a discrete thin echogenic line. The NBL was measured with electronic calipers from the base of the nose closest to the frontal bones to the farthest extent of ossification on the nose (Figs. 1–3). A ratio between BPD and NBL was calculated to ascertain NBL while taking gestational age into account. This measure was chosen to avoid confusion with uncertain dating parameters.

Fetuses were excluded if a midsagittal profile was not obtainable and an accurate measurement of the nose bone was not possible. Fetuses

referred to our laboratory for sonograms specifically for the presence of suspected abnormalities or markers detected by outside scans or with known karyotypes were excluded from the study.

The characteristics of the DS cases and controls were compared. Mean maternal age and mean gestational age were compared by *t* tests. We then evaluated 2 aspects of nose bone length. We considered first whether the absence of a fetal nose predicted the presence of DS and then, among those with detectable fetal nose bones, whether a shorter nose was associated with DS. For fetuses with detectable noses, we compared the mean NBL and BPD/NBL ratio. $P < .05$ was considered statistically significant for all comparisons.

Linear regression analyses were used to examine the change in NBL and the BPD/NBL ratio according to gestational age among those with detectable nose bones. We then constructed a receiver operating characteristic (ROC) curve, plotting 1 – specificity on the x-axis and the sensitivity on the y-axis, to evaluate how well the BPD/NBL ratio predicted the presence of DS and the false-positive rate in fetuses without abnormalities using a variety of cutoffs. To include the fetuses with undetectable noses in the ROC curve, a BPD/NBL ratio was estimated for these fetuses by using 0.5 mm as the NBL in the denominator. The 0.5 value was chosen because it is the minimal reasonably measurable value.

To assess intraobserver and interobserver variability, a group of consecutive fetuses between 15 and 20 weeks' gestation had NBLs measured twice by 1 individual. If possible, later, during the same scan, the nasal bone was measured by a second observer. The second observer had no knowledge of the measurement obtained by the first observer. The measurements were performed by sonographers with 1 to 20 years of experience and by 1 of 3 physicians (B.R.B., B.B., and T.D.S.). The mean difference between measurements was determined. The correlation between the 2 readings (either by the same individual or between 2 individuals) was compared with the use of a Pearson correlation coefficient.

Results

A total of 239 fetuses were included in the study. There were 16 fetuses with DS by karyotype and 223 euploid fetuses. The prevalence of DS in this population was slightly greater than 7%. The mean maternal age \pm SD for the fetuses with DS

was 37.3 ± 4.0 years, and the age for the euploid control fetuses was 37.1 ± 3.2 years ($P = .09$). The mean gestational age for the fetuses with DS was 17.2 ± 1.4 weeks, and the age for the control fetuses was 16.6 ± 1.3 weeks ($P = .8$). The indications for referral for amniocentesis included advanced maternal age ($n = 193$), abnormal serum screen results ($n = 41$), and a family history of DS ($n = 5$). The distribution of NBLs versus BPD is shown in Figure 3.

Intraobserver variability was assessed in 24 paired observations. The mean difference in measurement between observers was 0.28 ± 0.21 mm. Differences ranged from 0 to 0.8 mm ($r = 0.94$). Interobserver variability was obtained on 23 paired observations with a mean difference of 0.55 ± 0.35 mm. The differences ranged from 0 to 1.3 mm ($r = 0.69$).

We first evaluated the likelihood ratio for the absence of a nose bone. Among the 16 fetuses with DS, 6 (37%) had absent nose bones, whereas only 1 (0.5%) of the 223 euploid fetuses had no detectable nasal bone. The likelihood ratio for DS with the absence of a nasal bone was 83.

We then evaluated the significance of nose bone length among the fetuses with detectable nasal bones. Detectable nasal bones were seen in 10 fetuses with DS and 222 euploid fetuses. The mean NBL for fetuses with DS was 3.5 ± 0.47 mm compared with 4.6 ± 0.89 mm for euploid fetuses ($P < .001$). Figure 4 shows the distribution of nose bone length versus BPD in fetuses with

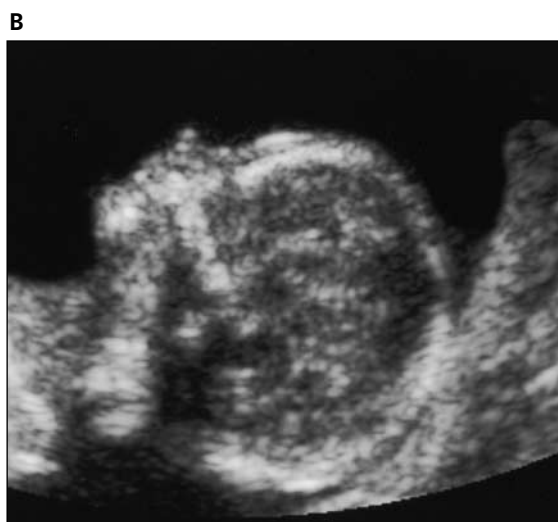


Figure 1. Sagittal profile of a 20-week euploid fetus with a normal nasal bone.

and without DS. The regression analysis indicates an increase in NBL of 0.13 mm for every 1-mm increase in estimated BPD in euploid fetuses. In contrast, there was no significant increase in NBL associated with increasing BPD in fetuses with DS.

We then evaluated the BPD/NBL ratio in fetuses with detectable nose bones. The mean BPD/NBL ratio among fetuses with DS was 11.3 ± 2.0 compared with 8.1 ± 1.4 in euploid fetuses, indicating a shorter nose length in infants with DS ($P < .001$). Although mathematically this

Figure 2. **A**, Sagittal profile of a 19-week fetus with Down syndrome showing a small nasal bone (arrow). **B**, Sagittal profile of a 16-week fetus with an absent nasal bone.



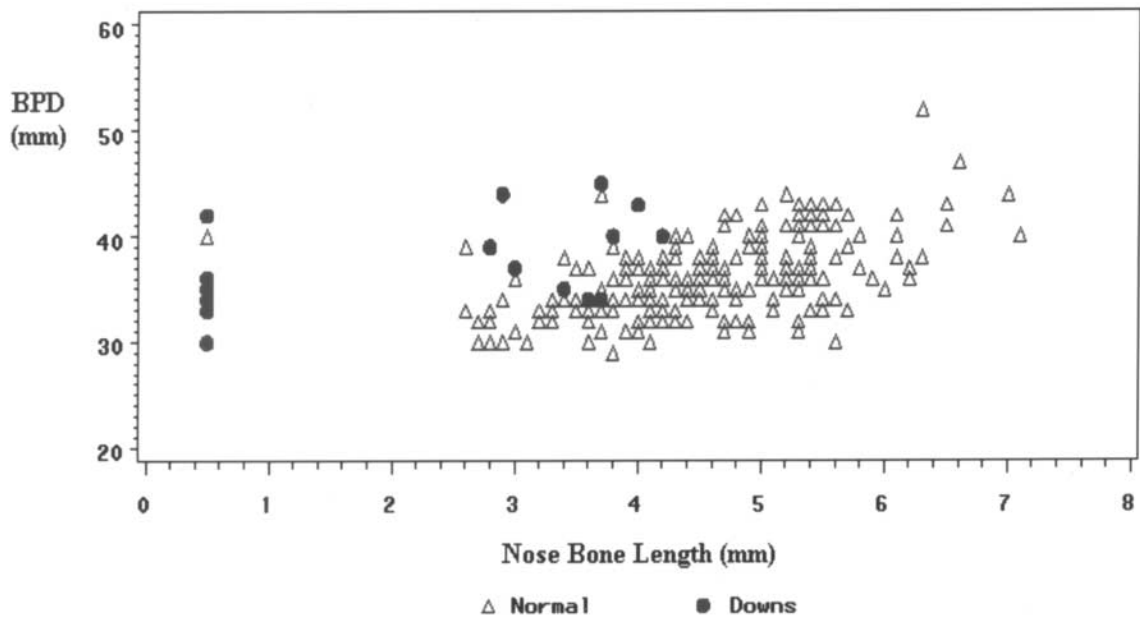


Figure 3. Distribution of NBLs in the study population.

could result from a larger head, most fetuses with DS are not known to have a BPD larger than expected for gestational age compared with euploid fetuses.⁸

The regression examining the BPD/NBL ratio versus gestational age for euploid fetuses (Fig. 5) indicates that the ratio did not change with gestational age throughout the gestational age window studied. This suggests that a single cutoff can be used to define abnormality regardless of gestational age. The BPD/NBL ratio for DS is also shown in Figure 5. Although the regression suggests that there may be an increase in the BPD/NBL ratio with advancing gestational age for fetuses with DS, the change was not statistically significant ($P = .1$)

Figure 6 shows an ROC curve for prediction of fetuses with DS by using the BPD/NBL ratio. The ROC curve includes all fetuses in the study. If a BPD/NBL ratio cutoff of 9 or greater were used, 100% of fetuses with DS would be identified, as well as 22% of euploid fetuses, yielding a likelihood ratio of 4.5. If the cutoff were raised to 10 or greater, then 81% of fetuses with DS and 11% of euploid fetuses would be identified. This would yield a likelihood ratio of 7.5 for DS. If the cutoff were raised further to 11 or greater, then 69% of fetuses with DS would be identified compared with 5% of euploid fetuses, yielding a likelihood

ratio of 11.6. If a BPD/NBL ratio of 12 or greater were used, the likelihood ratio for DS would be 34.8, with a false-positive rate of 2%.

In the fetuses with DS, 13 of 16 had other sonographic markers to suggest aneuploidy. Four fetuses had short long bones (both humeri and femurs); 3 had pyelectasis; 9 had nuchal folds measuring greater than 5 mm; 2 had hyperechoic bowel; 5 had echogenic intracardiac foci; and 7 had cardiac abnormalities, 1 of whom also had ventriculomegaly. Of the 3 fetuses with DS and no other sonographic markers, 2 had absent nasal bones, and 1 had a BPD/NBL ratio of 9.1.

There were 12 euploid fetuses with a BPD/NBL ratio of 11 or greater. One euploid fetus had an absent nasal bone and had other sonographic features, including a nuchal fold and short long bones, suggesting that although the karyotype was normal, a syndromic situation could not be excluded. At the time of submission of this article, the fetus had not been delivered. Of the 11 other euploid fetuses with a BPD/NBL ratio of greater than 11, 4 had short femurs, and 2 of the 4 with short femurs also had short humeri. One fetus with short long bones had an echogenic intracardiac focus and pyelectasis. This reflects the fact that the sonographic identification of affected fetuses continues to rely on features that are not distinct structural abnormalities but,

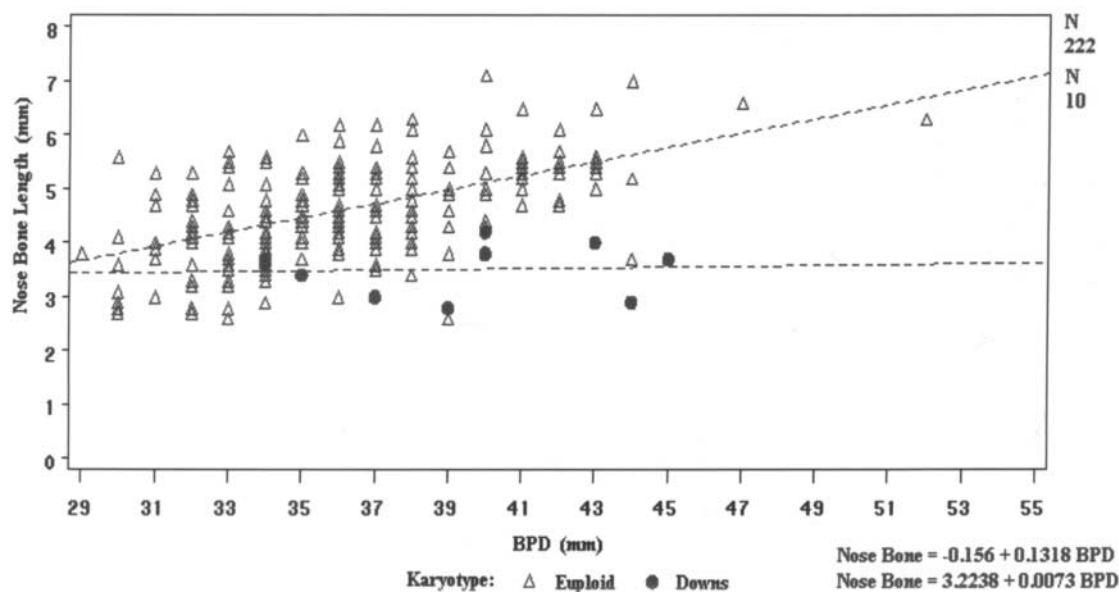


Figure 4. Nasal bone length versus BPD in fetuses with detectable nasal bones.

rather, “markers” that are more prevalent in the aneuploid population but also occur in euploid fetuses without clinical relevance (other than the association with aneuploidy).

Discussion

The fetal nasal bone first becomes histologically apparent at a crown-rump length of 42 mm, which corresponds to 11 weeks' gestation.⁹ Guis et al¹⁰ established a nasal bone growth curve in a series of 376 fetuses with no abnormalities between 14 and 35 weeks' gestation. These authors showed an increase in NBL with advancing gestational age, which is similar to our experience as well as others in the literature.⁹⁻¹¹ Stempfle et al¹¹ studied the ossification of the nasal bone in fetuses with and without DS. These investigators reported that in postmortem radiographs, ossification of the nasal bone is present from 15 weeks' gestation in fetuses without abnormalities. By contrast, 14 (23%) of 60 trisomic fetuses in their series had no nasal bone ossification at any time in gestation. These authors showed a statistically significant relationship between the absence of nasal bone ossification and trisomy 21. In addition, fetuses with DS in whom the nasal bone was ossified tended to have shorter nasal bones than did

euploid fetuses.¹¹ This is similar to our experience, and in fact, we have shown that nasal bone growth does not appear to increase with advancing gestational age in fetuses with DS.

Keeling et al¹² investigated axial radiographs in fetuses between 12 and 24 weeks' gestation and reported agenesis of the nasal bone in 6% of fetuses with DS. Malformations of the nasal bone such as a short nose were seen in another 11 of 31 fetuses. Overall, 19 (61%) of 31 fetuses with DS had either absent or short nasal bones.¹²

The second trimester provides an opportunity to identify fetuses affected with DS on the basis of a variety of sonographic markers. In this study, the high prevalence of DS is a reflection of our use of the genetic sonogram in women at increased risk of aneuploidy on the basis of age and maternal serum screening to further refine risks based on sonographic markers. The nasal bone was not used to include patients in the study and was not used in counseling patients. The second trimester remains an important gestational age window, because patients may have their first sonographic assessment at this time. With the fetus in a favorable position, a sagittal scan of the fetal face provides an easy assessment of nose bone length. Our data show that during the second trimester, fetuses with DS tend to have absent or shorter nasal bones than

Fetal Nose Bone Length: A Marker for Down Syndrome

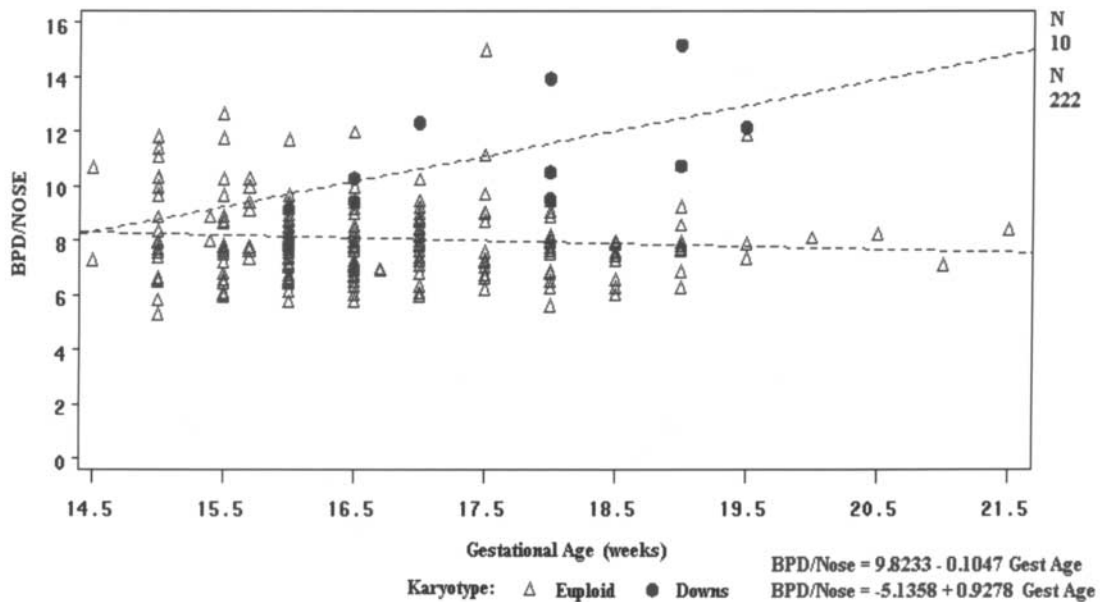


Figure 5. Biparietal diameter–nose bone length ratio versus gestational age in fetuses with detectable nasal bones.

euploid fetuses. To obtain 100% sensitivity in the detection of affected fetuses, a BPD/NBL ratio of 9 or greater would be required; however, this results in an unacceptably high false-positive rate of 22%. In our opinion, 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 DS with a false-positive rate of 11%. This is reasonably similar to the 73% detection rate of DS reported by Cicero et al² in the 11- to 14-week gestational age window with a false-positive rate of 8.3%, using the absence of the nasal bone as a criterion.

The complete absence of nasal bone ossification was seen in 6 of (37%) 16 fetuses with DS compared with 0.5% of euploid fetuses in the second trimester. This is less than the 73% of affected fetuses with absent nasal bone ossification seen in the 11- to 14-week gestational age window, suggesting that there may be delayed ossification or hypoplasia of the nasal bones. Our data also show that the NBL in fetuses with DS does not increase linearly with enlarging BPD (advancing gestational age). In addition, the absence of the fetal nasal bone in the second trimester occurred only in a single euploid fetus with other disturbing sonographic findings, suggesting that the complete absence of the nasal bone in the second trimester is a very worrisome

observation, as reflected in the likelihood ratio of 83 for DS.

The presence and size of the nasal bone constitute an important new marker in the detection of fetuses with DS in the second trimester as well as the first trimester. The population studied in this report included fetuses at high risk for aneuploidy, as reflected in a prevalence of DS of approximately 7%. This reflects the changing environment in which patients are choosing amniocentesis based not only on age-based risk and serum screening results but also on the results of genetic sonograms, which use sonographic markers to identify fetuses at a particularly high risk for aneuploidy. The positive predictive value of a sonographic marker is based on the prevalence of the disease in the study population. In this high-risk population, a small or absent nasal bone was clearly associated with a high likelihood ratio for DS. These results may not have the same significance in a low-risk population, and the significance of the NBL as an isolated finding in the low-risk population remains to be established.

Although many affected fetuses in this study had other sonographic features to suggest aneuploidy, 3 had the absence of the nasal bone as the only sonographic feature to suggest aneuploidy. Despite the relatively small number of fetuses

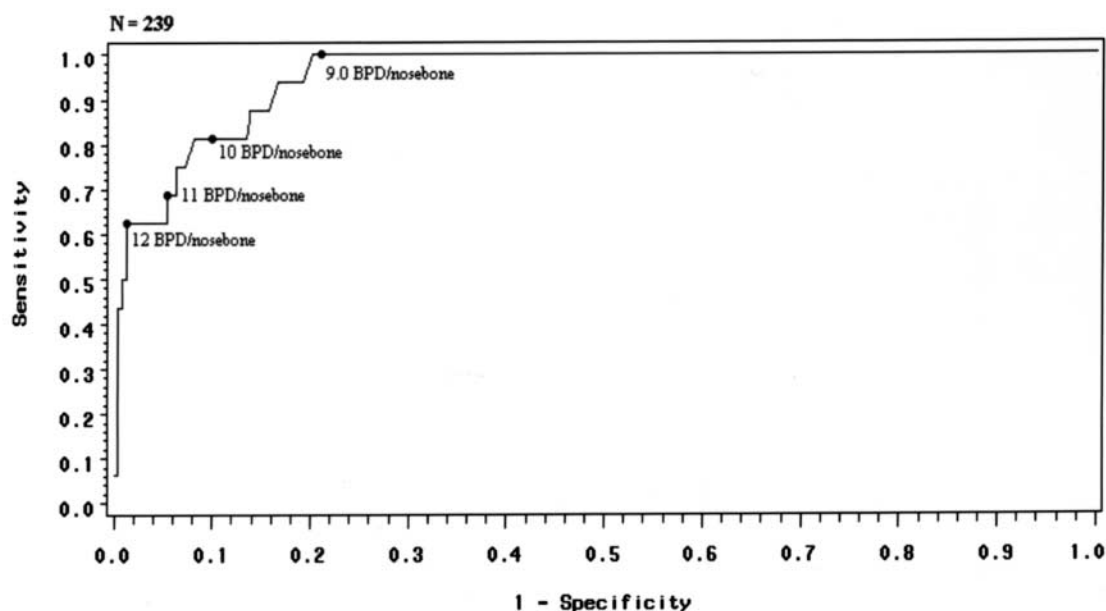


Figure 6. Receiver operating characteristic curve showing sensitivity and 1 – specificity for different BPD/NBL ratios in the study group.

with DS in this study, we agree with the statement by Stempfle et al¹¹ that the absence of the nasal bone, even as an isolated finding, should serve as a warning for the clinician to suspect DS, and we recommend that amniocentesis for karyotype should be offered to a patient if prenatal diagnosis is desired.¹⁰ Our study is limited in that most patients in our population were white, precluding any comment on possible ethnic variation in NBL.

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Fetal Nose Bone Length: A Marker for Down Syndrome

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