First-Trimester Ultrasound Assessment of the Nasal Bone to Screen for Aneuploidy

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Increasingly, women are choosing first-trimester risk assessment for Down syndrome and other aneuploid conditions. Recent studies have suggested that adding ultrasound assessment of the nasal bone to nuchal translucency thickness and maternal serum analytes in the first trimester will improve performance. This report assesses the current literature and discusses practical issues that must be addressed before widespread implementation of nasal bone screening in the United States. (Obstet Gynecol 2007;110:399–404)

Investigators have suggested that assessment of the fetal nasal bone can be used to predict trisomy 21 and other aneuploidies. One of the missions of the Maternal–Fetal Medicine Foundation is to evaluate emerging technologies in obstetrics and to provide guidance in incorporating these technologies into clinical practice. In response to questions from practicing obstetricians and maternal–fetal medicine specialists, this report summarizes the opinions of the Maternal–Fetal Medicine Foundation’s Nuchal Translucency Oversight Committee on evaluation of the nasal bone to assess Down syndrome risk.

Risk assessment for Down syndrome and other aneuploid conditions in the first trimester of pregnancy is gaining increased acceptance in the United States, with more than half of obstetricians offering this option to their patients. A recent meta-analysis of combined first-trimester risk assessment with nuchal translucency and serum biochemistry included more than 200,000 women and found that approximately 85% of cases of Down syndrome can be detected at a false-positive rate of 5%, a performance superior to second-trimester quad (alpha-fetoprotein, unconjugated estriol, human chorionic gonadotropin, inhibin-A) testing.

Recently, it has been suggested that first-trimester performance can be further improved with the addition of nasal bone evaluation. Cicero and colleagues published the first large prospective trial of nasal bone assessment in a high-risk population undergoing chorionic villus sampling (CVS) to assess for aneuploidy. They determined that absence of the nasal bone during first-trimester sonography was associated with trisomy 21 (Fig. 1). In a high-risk population undergoing CVS, the nasal bone was absent in 43 of 59 (73%) trisomy 21 fetuses and in only 3 of 603 (0.5%) euploid fetuses. Because of the high likelihood ratio for trisomy 21 with an absent nasal bone and a similarly low negative likelihood ratio when the nasal bone was present, the authors predicted that nasal bone evaluation would make Down syndrome risk assessment more accurate. They estimated that if nasal bone assessment were combined with maternal age and nuchal translucency measurement, 93% of Down syndrome cases would be detected at a 5% false-positive rate and that 85% of cases would still be detected if the false-negative rate was 0.5%.

These data suggest that in high-risk pregnancies, nasal bone assessment is a sensitive and highly specific marker...
positive rate were set at 1%. In subsequent studies, the same investigators found that an absent nasal bone was also associated with trisomy 18, trisomy 13, and monosomy X. These data suggest that in high-risk pregnancies, nasal bone assessment is a sensitive and highly specific marker and could be a useful adjunct to nuchal translucency and serum biochemistry.

A summary of ultrasound scanning techniques suggested for assessing nasal bone are listed in the box, “Required Components for Nasal Bone Imaging.”

**BASIS FOR ASSESSING THE NASAL BONE**

A small nose and mid-face hypoplasia are well-known components of the Down syndrome phenotype. This has led investigators to study whether abnormalities of the nasal bone can be detected in the Down syndrome fetus. Several histopathological and radiographic studies have identified differences in the nasal bones of Down syndrome fetuses compared with euploid fetuses. Stempfle and colleagues studied 60 Down syndrome abortuses at gestational ages ranging from 15 to 40 weeks and compared them to 82 euploid controls. They found that nasal bone ossification was absent in one quarter of Down syndrome fetuses and present in all of the controls. Tuxen and colleagues evaluated Down syndrome fetuses between 14 and 25 weeks gestational age by radiograph and histopathologic study and found that the nasal bone was absent in one third of specimens. These data and others give biologic plausibility to the idea that assessment of the nasal bone by ultrasonography may be a useful tool for prenatally diagnosing Down syndrome.

**REVIEW OF LITERATURE OF FIRST-TRIMESTER NASAL BONE ASSESSMENT**

Published studies of first-trimester nasal bone assessment for aneuploidy were identified through a MEDLINE search, and a summary of the included trials is provided in Table 1. Ten studies were included for review of nasal bone performance. Five screened for the presence or absence of the nasal bone in women from a general population. In three studies, subjects scheduled for CVS because they were high risk for aneuploidy were prospectively evaluated. The study by Cicero and colleagues included data from previously published reports. The 2005 report from Monni and colleagues included patients from a 2003 study, and only the former was included. One study assessed film loops retrospectively.

In all, 35,312 women had first-trimester nasal bone assessment for aneuploidy.

**Table 1. Performance of Nasal Bone Screening for Trisomy 21 in the First Trimester**

<table>
<thead>
<tr>
<th>Author</th>
<th>Successful Examination</th>
<th>Euploid</th>
<th>T21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otano 2002</td>
<td>183/194 (94.3)</td>
<td>1/175 (0.6)</td>
<td>3/5 (60.0)</td>
</tr>
<tr>
<td>Viora 2003</td>
<td>1,752/1,906 (91.9)</td>
<td>24/1,733 (1.4)</td>
<td>8/10 (80.0)</td>
</tr>
<tr>
<td>Senat 2003</td>
<td>956/1,040 (91.9)</td>
<td>4/944 (0.4)</td>
<td>3/4 (75)</td>
</tr>
<tr>
<td>Wong 2003</td>
<td>119/143 (83.2)</td>
<td>1/114 (0.9)</td>
<td>2/3 (66.7)</td>
</tr>
<tr>
<td>Cicero 2004</td>
<td>5,851/5,818 (98.9)</td>
<td>129/5,223 (2.5)</td>
<td>229/333 (68.8)</td>
</tr>
<tr>
<td>Kelekci 2004</td>
<td>600/642 (93.5)</td>
<td>9/394 (1.5)</td>
<td>1/2 (50)</td>
</tr>
<tr>
<td>Orlandi 2005</td>
<td>2,411/2,411 (100)</td>
<td>9/2,396 (0.4)</td>
<td>8/15 (53.3)</td>
</tr>
<tr>
<td>Monni 2005</td>
<td>16,641/16,654 (99.9)</td>
<td>76/16,558 (0.5)</td>
<td>56/96 (58.3)</td>
</tr>
<tr>
<td>Malone 2004</td>
<td>4,801/6,324 (76)</td>
<td>21/6,311 (0.3)</td>
<td>0/11 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>33,314/35,132 (94.3)</td>
<td>274/34,048 (0.8)</td>
<td>310/479 (65)</td>
</tr>
</tbody>
</table>

Data are expressed as n/N (%).

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Fig. 1. Ultrasound images of first-trimester fetuses demonstrating presence of the nasal bone in a euploid fetus (A) and an absent nasal bone in a fetus with a cystic hygroma affected by trisomy 21 (B). The cartilage at the tip of the nasal bone and echogenic skin can be seen in both fetuses (down arrows). The nasal bone (up arrow) is visible only in the euploid fetus. 

Required Components for Nasal Bone Imaging

1. Clear fetal margins
   a. Clear ultrasound image
   b. Fetal facial profile well defined
2. Fetus occupies majority of image
   a. Image predominantly filled by fetal head, neck, and upper thorax
   b. Fetus should occupy more than 50% of image
   c. A second fetus of the same magnitude should not fit in the surrounding space
   d. The image should be magnified so that each movement of the calipers causes a 0.1-mm incremental change
3. A mid-sagittal view of the fetal profile is obtained
   a. Tip of nose is seen in fetal profile
   b. Third and fourth ventricle is seen in fetal central nervous system
4. The angle between the ultrasound transducer and a line passing from the fetal forehead to the chin should be 45 degrees
5. When the nasal bone is present, three echogenic lines should be visible (Fig. 1). The nasal bone and overlying skin appear similar to an equal sign. In the same view, the skin over the nasal tip should be visible. If both the nasal tip and skin are present, and the nasal bone echo cannot be visualized or is not more echogenic than the skin, the nasal bone is considered absent.

trimester ultrasound assessment for nasal bone. In 33,314 cases (94.3%) the nasal bone was successfully imaged. A total of 479 cases of trisomy 21 were identified in these populations, for a prevalence of 13.6 in 1,000 (95% confidence interval [CI] 12.4–14.9). This is approximately 10 times the first-trimester incidence of Down Syndrome in the United States, reflecting the high-risk nature of the patients seen in such referral centers. Sensitivity of absent nasal bone alone for detecting trisomy 21 was 65% (95% CI 62–70%), with a false-positive rate of 0.8% (95% CI 0.7–0.9%). If the nasal bone were absent, the likelihood that a fetus had trisomy 21 was increased 87-fold (95% CI 77–97). The negative likelihood ratio with a visualized nasal bone was 0.35 (95% CI 0.32–0.39). As with many analyses performed in the early stages of technology development, high disease prevalence in studied populations may lead to an overestimation of subsequent test performance when used in the general population.

Of the trials included, the majority followed the Fetal Medicine Foundation’s protocol for evaluating the nasal bone. However, few studies adequately described quality control methods in detail. In the Senat et al trial, four film loops were assessed by three independent operators to determine interobserver reproducibility. A kappa statistic was determined for each pair of operators. Kappa values ranged from 0.26 to 0.44, which suggested poor-to-fair agreement between the observers.

Malone and colleagues from the First- and Second-Trimester Evaluation of Risk (FASTER) trial provided detailed descriptions of techniques for assessing the nasal bone and the quality control methods used in their study. In that series, all studies were assessed by an independent reviewer to determine if an acceptable image had been obtained. Of the 6,324 patients, 157 were studied before 11 weeks (crown-rump length [CRL] less than 45 mm), which is a time when previous studies suggested that the nasal bone has not yet ossified. In contrast to the findings in other reports, the nasal bone was present in nine of 11 Down syndrome cases and was not satisfactorily imaged in the remaining two. The authors concluded that nasal bone evaluation in the first trimester did not improve aneuploidy detection in an unselected population.

FACTORS INFLUENCING NASAL BONE DEVELOPMENT

The initial report by Cicero and colleagues found no relationship between the presence or absence of the nasal bone and crown-rump length or nuchal translucency size. However, as experience with nasal bone has increased, relationships between absent nasal bone, fetal crown-rump length, and nuchal translucency have been established. In addition, a relationship between ethnicity and nasal bone development has been uncovered.

Investigators have explored these relationships in recent publications. The current data demonstrate that, in aneuploid pregnancies, nasal bone absence occurs more frequently with increasing nuchal translucency. In this series of 5,851 high-risk patients including 333 trisomy 21 fetuses, absence of the nasal bone had a likelihood ratio of 37.1 for trisomy 21 when the nuchal translucency was at the 95th percentile or less, and this was reduced to 13.4 when the nuchal translucency was between 3.5 and 4.4 mm. When the nuchal translucency was 5.5 mm or more, the likelihood ratio for trisomy 21 with an absent nasal bone was only 5.3. Conversely, with an nuchal translucency at the 95th percentile or less, the presence of the nasal bone had a likelihood ratio of 0.40, and improved to 0.28 for an nuchal translucency between 3.5 and 4.4

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mm. These data suggest that nasal bone assessment has the greatest potential to increase Down syndrome detection rates when the nuchal translucency suggests low risk and to reduce false-positive rates when the nuchal translucency predicts a high Down syndrome risk.

The same study showed that the nasal bone was more likely to be absent at earlier gestational ages. For example, in euploid fetuses with a CRL between 45 and 54 mm, the nasal bone was absent in 4.7% of cases. At a CRL between 75 and 84 mm, the nasal bone was absent in only 1.0% of cases. Although false-positive rates decreased as gestational age advanced, aneuploidy detection rates also decreased with advancing gestational age.

Prefumo and colleagues\(^\text{16}\) found that nasal bone hypoplasia was more common in the euploid fetuses of women of African descent when compared with either Asian or Caucasian populations (odds ratio 2.3). Cicero and colleagues\(^\text{4}\) also found an increased incidence of absent fetal nasal bone in the first trimester in women of Afro-Caribbean and Southern Asian descent. The nasal bone was absent in 2.5%, 9.0%, and 5.0% of Caucasian, Afro-Caribbean, and Southern Asian populations, respectively. Likelihood ratios for trisomy 21 with absent nasal bone were 31.3, 8.8, and 14.2, respectively, in these three populations.

**NUCAL TRANSLUCENCY, NASAL BONE, AND SERUM BIOCHEMISTRY COMBINED**

Initial data suggest that nasal bone status is independent of serum biochemistry. Although absent nasal bone is associated with increased nuchal translucency thickness, these ultrasound findings can be combined as long as the calculation of trisomy 21 risk takes this association into account. Therefore, adding nasal bone assessment to measurements of nuchal translucency and maternal serum markers has the potential to improve accuracy of risk assessment, and the inclusion of nasal bone likelihood ratios to risk estimates is statistically valid. In a prospective study of a high-risk population with a median maternal age of 35 years assessed by nuchal translucency, nasal bone, and biochemistry,\(^\text{17}\) it was estimated that 93.6% of Down syndrome cases would be detected at a false-positive rate of 5%. For a false-positive rate of 2.5%, the detection rate would be 90.0%. Although these data are promising, they reflect the experience of highly specialized and high-risk centers and are not generalizable to less experienced centers.

Further information is also required to determine how to integrate nasal bone imaging into practice. It needs to be determined whether race-specific, gestational age-specific, and nuchal translucency–correlated likelihood ratios are needed. Cicero et al\(^\text{17}\) have published formulas that take these multiple variables into account.

**CURRENT STATUS OF NASAL BONE ASSESSMENT IN THE FIRST TRIMESTER**

Studies from multiple centers have demonstrated that in experienced centers addition of the nasal bone to first-trimester risk assessment improves performance. However, a number of important questions remain before introduction into general practice can be recommended.

**What Is the Role of Fetal Nasal Bone in a Low-Risk Population?**

Many of the studies to date have assessed performance in high-risk populations, including women who have screened positive after nuchal translucency and serum biochemistry, making Down syndrome detection rates higher and overestimating performance of the test. The average age of women screened by Cicero et al\(^\text{17}\) was 35 years, compared with the average age of women giving birth in the United States of 25.2 years in 2003. In addition, Prefumo and colleagues\(^\text{18}\) assessed adding nasal bone assessment in both high-risk and unscreened populations and found that routine nasal bone evaluation was of value in high-risk populations but performed poorly in an unscreened population.

**What Is the Performance of Nasal Bone in Nonspecialized Centers?**

Reported experience with the nasal bone technique has been predominantly from a few specialized centers. There is no information on how well nasal bone will perform in other settings. Effects of different manufacturer’s equipment and ultrasound technologies on performance of nasal bone imaging have not been assessed.

Appropriate imaging of the nasal bone appears to be more difficult to master than measurement of the nuchal translucency. Cicero and colleagues\(^\text{19}\) reported that an average of 80 studies (range 40–120) were required for experienced sonographers to become proficient. The difficulty in obtaining proper images was highlighted by participants in the First- and Second-Trimester Evaluation of Risk trial, which prospectively assessed nasal bone sonography in 6,324 patients.\(^\text{8}\) Imaging was performed by sonographers experienced in first-trimester ultrasonography but new to nasal bone evaluation. Acceptable images were obtained in only 76% percent of cases.
What Educational and Quality Control Techniques Are Required to Maximize the Potential of Fetal Nasal Bone?

Cicero and colleagues have documented the difficulty in mastering sonography for assessment of nasal bone. Their experience suggests that both education and hands-on experience are required to routinely obtain adequate images. Both the Nuchal Translucency Quality Review Program in the United States and Fetal Medicine Foundation in the United Kingdom suggest that obtaining the basic skill will require approximately 40 scans. After this, a minimum of five images should be submitted for external review. Only when these are confirmed to be accurate should clinical acquisition begin.

Although the Nuchal Translucency Quality Review and the Fetal Medicine Foundation provide ongoing epidemiologic audit of nuchal translucency, results may not apply to nasal bone imaging. Whether periodic external reappraisal is necessary or whether only initial documentation of competence is sufficient to maintain precise nasal bone results is unclear. Presently, we suggest that ongoing monitoring of nasal bone imaging be performed locally by a supervising physician who is skilled and credentialed in nasal bone imaging. To assure accurate clinical management, backup reading by a second trained individual may be considered, especially when results of the study will significantly alter clinical management.

Can Nasal Bone Be Used in Multiple Gestations?

There are only limited data available on the use of nasal bone evaluation for Down syndrome risk assessment in multiple gestations. Of the studies reviewed here, only one explicitly stated that nasal bone performance was assessed in multiple gestations. However, because each fetus is viewed individually by ultrasonography, it is expected that this technique is valid in twins and higher-order multiple gestations.

Is Nasal Bone a Primary or Secondary Marker?

Because nasal bone assessment is technically difficult to perform, availability of the test by skilled operators may be limited. For this reason we recommend that nasal bone be used as a secondary or contingency marker. Nicolaides and colleagues have proposed a two-stage process, only performing nasal bone assessment on a subgroup of patients in which initial evaluation by combined screening reveals a borderline risk assessment. In this model, patients evaluated by nuchal translucency and serum markers with a risk of 1 in 100 or greater would be referred to CVS, and those with a risk of less than 1 in 1,000 would be deemed to have such a low risk that no further testing is offered. Those with a risk between 1 in 101 and 1 in 1,000 would have nasal bone evaluation. In initial studies, performance of this two-stage approach was similar to using nasal bone assessment as part of the initial screen, but only approximately 15% of pregnancies required nasal bone evaluation, and the false positive rate declined from 5.0% to 2.1%. This limited number of secondary tests could be referred to centers that have developed special expertise in this technique. Although this approach may not be feasible or practical in some areas of the United States, it may be a useful adjunct to screening in others.

SUMMARY

Initial experience with assessment of first-trimester nasal bone for detection of trisomy 21 has shown it to be a valuable technique. The relationship between nonvisualization of the nasal bone on first-trimester sonography and trisomy 21 is certain. Further evaluation of nasal bone assessment performance in a low-risk population must be determined, sufficient adequately trained centers must be available, and appropriate educational and credentialing procedures must be established. With education, hands-on experience, and ongoing monitoring of nasal bone images, the addition of nasal bone assessment to first-trimester screening has the potential to lower false-positive rates and improve the detection rate for Down syndrome.

REFERENCES


APPENDIX

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