Nuchal Translucency and Nasal Bone for Trisomy 21 Screening: Single Center Experience

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Aim
To evaluate the feasibility and diagnostic accuracy of fetal nuchal translucency and nasal bone assessment at 11-14 weeks for screening of trisomy 21 at a single center.

Methods
Nuchal translucency measurement and nasal bone evaluation in relation to the fetal karyotype for singleton fetuses were retrospectively assessed at the Ospedale Microcitemico, Cagliari, Italy, in a three-year period (2001-2004). Nuchal translucency was considered enlarged if greater than or equal to the 95th centile for crown-rump length (CRL) of the reference ranges, and nasal bone was described as present or absent during the evaluation of the fetal facial profile. Sensitivity and specificity for trisomy 21 were assessed for nuchal translucency and absent nasal bone.

Results
Among 32,000 cases recorded in the database including fetuses from 11 to 14 weeks, 16,654 fetuses were included in the study with both nuchal translucency measurement and nasal bone evaluation. Median maternal age was 32 years (range, 14-49). In 854 fetuses (5.1%), nuchal translucency was greater than the 95th centile, and 744 (87.1%) of them had a normal karyotype. Among 141 (0.8%) diagnosed cases of chromosomopathies, there were 96 cases of trisomy 21. Nuchal translucency was enlarged in 110 chromosomopathies and in 72 trisomies 21. Sensitivity was 75.0% (95% confidence interval [CI], 65.5-82.6), and specificity 95.5% (95% CI, 95.2-95.8). In fetuses with enlarged nuchal translucency and normal karyotype, there were 30 structural defects (4%), and among these, 15 heart defects (2%). Measurement of nuchal translucency was possible in all cases where it was attempted. In 13 cases (0.1%), it was not possible to determine the visibility of the nasal bone. In 16,486 cases, the nasal bone was defined as visible and in 155 cases (0.9%) the nasal bone was described as absent. The nasal bone was absent in 56 trisomies 21 and in 23 other chromosomopathies, as well as in 76 normal karyotype fetuses. The sensitivity was 58.3% (95% CI, 48.3-67.7) and specificity 99.5% (95% CI, 99.4-99.6). The sensitivity of enlarged nuchal translucency and absent nasal bone was 80.2% (95% CI, 71.1-86.9).

Conclusions
Enlarged nuchal translucency and absent nasal bone are useful markers of trisomy 21 in the first trimester ultrasound screening, increasing the sensitivity of detection of affected fetuses.

The thickness of nuchal translucency is an anechoic space behind the fetal neck (1), visible and measurable in all fetuses from 10 to 14 weeks (Fig. 1). Enlarged nuchal translucency has been shown to identify fetuses at higher risk for aneuploidies (2,3) and its measurement has been used as a prenatal ultrasound screening test for trisomy 21 (Fig. 2). An enlarged nuchal translucency at 11-14 weeks of gestation has been found in about 80% of fetuses with trisomy 21 and in 8% of normal karyotype fetuses (4-6).

Prenatal ultrasound studies in 11-14 weeks fetuses at high risk for aneuploidies have shown that the nasal bone is not visible in about
60-70% of cases of trisomy 21 and in 0.5-1% of the normal karyotype fetuses (7-8). The ultrasound sign of absent nasal bone seems to be a promising marker of trisomy 21 in the first trimester ultrasound screening (9-10), either alone or in association with the nuchal translucency test (Figs. 3 and 4).

A validated system of quality certification has been carried out for nuchal translucency measurement in the last 10 years, and there is a large body of evidence supporting the reliability of nuchal translucency test for screening for chromosomopathies, if the quality of measurements is assured (5,11,12).

There are currently some reservations about the applicability of the nasal bone evaluation for screening, because of problems have been reported with reproducibility among different operators and relations with enlarged nuchal translucency (13).

In this study, we report the experience at a single center for fetal nuchal translucency and nasal bone evaluation at 11-14 weeks gestation for trisomy 21 screening, focusing on the feasibility of the assessment of both markers and on the diagnostic accuracy of these signs either separately or together.

Methods

Sample and Procedure

The First Trimester Database of the Ospedale Microcitemico, Cagliari, Italy, has been in use since 1996 for nuchal translucency screening for Down syndrome. First trimester screening for trisomy 21 has been offered to pregnant women if they ask for it, according to the current Italian National Health Ministry Guidelines for prevention of congenital abnormalities. The software of the Fetal Medicine Foundation (FMF) has been used since 1996 to calculate the individual risk for Down syndrome on the basis of maternal age, previous history, and nuchal translucency.
measurement (4). Nuchal translucency measurement was performed according to the guidelines of the FMF, by 7 certified operators throughout the period, and the center’s results have been audited on the annual basis.

Since 2001, data have been collected on the presence and absence of the nasal bone. The fetal nasal bone was visualized by transabdominal ultrasound in an adequately magnified midsagittal view of the fetal profile, as previously described (14). When nasal bone was visualized, it was recorded in a database as “present,” and when it was not visualized, as “absent.”

Prenatal invasive procedures for fetal karyotype analysis were offered in the hospital, providing the case was within the categories eligible under the Italian law (Italian Health Ministry Decree 1998, www.ministerosalute.it). Prenatal karyotype, pregnancy outcome, and neonatal outcomes (neonatal assessment or necropsy), provided by outcome sheets or telephone interviews, were entered in the database.

For this study, we analyzed the data on fetuses from singleton pregnancies with no chromosomal abnormalities as assessed prenatally or postnatally, or presumed by clinical examination after delivery, and Down syndrome fetuses, diagnosed prenatally or postnatally or other chromosomal abnormalities. The data available in the database in December 2004 were analyzed in this study. Normal variants, common inversions, balanced translocations, and pseudomosaicism were classified as normal for this study. Fetuses with unknown outcomes and multiple pregnancies were excluded.

For the purpose of this study, fetal nuchal translucency was retrospectively considered “enlarged,” if greater than or equal to 95th centile of reference range values of the FMF software (4), and “normal” if lesser than the cut-off. Nasal bone was recorded as either present or absent.

Statistical Analysis

Data on maternal age, crown-rump length (CRL), and nuchal translucency measurement were presented as medians and ranges (min and max). Sensitivity and specificity (95% confidence interval [CI]) for trisomy 21 were evaluated for nuchal translucency greater than or equal to 95th centile of reference range values of the FMF software and for absent nasal bone sign.

Microsoft Excel 2000 software was used for data storage and calculations.

Results

Among 32,000 cases in the database, including fetuses from 11 to 14 weeks for nuchal translucency screening, 16,654 fetuses underwent both nuchal translucency measurement and nasal bone evaluation and met the inclusion criteria, whereas 15,346 cases were excluded.

The median maternal age was 32 years (range, 14-49), median CRL length 53.4 mm (range, 45.0-82.0), and median nuchal translucency 1.4 mm (range, 0.5-11.0). In 854 cases (5.1%), nuchal translucency was greater than the 95th centile, and 744 of them (87.1%) had a normal karyotype.

Among 141 diagnosed cases of chromosomal abnormalities (0.8%), there were 96 cases of trisomy 21. Nuchal translucency was enlarged in 110 chromosomalopathies (78.0%), 72 of which were trisomies 21 (75.0%). The sensitivity of the measurement was 75.0% (95% CI, 65.5-82.6), specificity 95.5% (95% CI, 95.2-95.8). The flow diagram of nuchal translucency is shown in Figure 5.

Among fetuses with enlarged nuchal translucency and normal karyotype, there were 30 structural defects, including 15 heart defects (2%). Nuchal translucency was measured in all cases in which it was attempted and performed by transabdominal ultrasound.

In 13 cases (0.1%), it was not possible to ascertain if the nasal bone was visible or not. In 16,486 cases, the nasal bone was defined as visible and in 155 cases (0.9%) as absent. The nasal bone was absent in 56 (58.3%) cases of trisomy 21 and in 23 (51.1%) cases of other chromosomal abnormalities. The data available in the database in December 2004 were analyzed in this study. Normal variants, common inversions, balanced translocations, and pseudomosaicism were classified as normal for this study. Fetuses with unknown outcomes and multiple pregnancies were excluded.

Nuchal translucency was enlarged in 145 cases (93.5%) with absent nasal bone and in 51 out of 56 cases with trisomy 21 with absent nasal bone. It was also enlarged in 71 out of 76 normal karyotype fetuses with absent nasal bone. No abnormalities of the face development at birth have been reported in these cases. Flow diagram of nasal bone results is shown in Figure 6.
The sensitivity for trisomy 21 of enlarged nuchal translucency and absent nasal bone was 80.2% (95% CI, 71.1-86.9), because 77 out of 96 trisomy 21 fetuses showed either enlarged nuchal translucency or absent nasal bone. Among 744 normal fetuses with enlarged nuchal translucency, 673 showed present nasal bone (90.5%).

**Discussion**

This study confirmed that enlarged nuchal translucency and absent nasal bone were more frequent in trisomy 21 fetuses than in normal karyotype fetuses (75% sensitivity for nuchal translucency and 58% for nasal bone, with a screen positive rate of 0.9% for absent nasal bone and 5% for enlarged nuchal translucency). Another evident finding was that nasal bone assessment was more difficult than that of nuchal translucency. In this series from a single center with experience in the first trimester pregnancy screening, and in a setting where seven operators are involved in the screening, the measurement of nuchal translucency by transabdominal ultrasound was successful in all cases, whereas in 0.1% of the fetal profile assessments it was not possible to define the presence or absence of the nasal bone.

Therefore, it seems easier to perform nuchal translucency, than nasal bone measurement, which is not so specific as it can be defined as “present,” “visible,” or “absent.” Similar criticism has been presented by other studies on the nasal bone sign (13). A tested system of certification of training in the nuchal translucency measurement used in our center with a periodical audit of the results for the last 10 years showed the quality of this measurement for trisomy 21 screening (5). An equivalent system has not yet been introduced for the nasal bone, and some of the problems with this assessment may reflect the need of standardization and training.

In our series, fetuses with absent nasal bone frequently had enlarged nuchal translucency, either with trisomy or with normal karyotype. In trisomy 21, alteration in the ossification of the nasal bone can depend on the failure in the migration of the neural crest cells, because of the abnormal composition of the connective tissue (15). In these fetuses, the same cause involved in the pathogenesis of the enlarged nuchal translucency could be involved in the absence of the nasal bone, and therefore the two signs may be inter-dependent.

On the other hand, in 5 out of 56 cases of trisomy 21 with absent nasal bone, the finding of absent nasal bone was the only ultrasound marker for trisomy 21 because the finding of nuchal translucency was normal. Therefore, the importance of absent nasal bone as the first level marker should not be ignored. Whereas the performance of nasal bone evaluation alone was modest (58.3% sensitivity in this series), absent nasal bone improved the sensitivity of the nuchal translucency screening for trisomy 21, which can mean a decrease in the rate of normal
fetuses considered at high risk because of enlarged nuchal translucency.

A possible explanation for enlarged nuchal translucency and absent nasal bone in normal karyotype fetuses is an evaluation bias by the operator, who was not necessarily blinded to the results.

Enlarged nuchal translucency can identify fetuses at risk for chromosomopathies other than trisomy 21 and the fact that some cases with chromosomopathies other than trisomy 21 showed an absent nasal bone confirms both the results from our center and from multicenter studies (4,12).

Enlarged nuchal translucency can identify fetuses at risk for structural defects (16). In our series, heart defects were more frequent in fetuses with nuchal translucency greater than or equal to 95th centile (about 2% of normal karyotype fetuses) than expected in general population, as reported by others (17,18).

Absent nasal bone was found in chromosomal abnormalities other than trisomy 21. This confirms previous reports (10,19). As far as enlarged nuchal translucency is concerned, it is suspected that it has different background in different chromosomopathies. Therefore, further studies are needed to resolve this issue.

In conclusion, our experience with a large number of fetal screening tests and comprehensive database shows that nuchal translucency and nasal bone evaluation are useful markers on first trimester ultrasound screening for trisomy 21, increasing the sensitivity of detection. Further studies to explain the relationship between absent nasal bone and enlarged nuchal translucency should be addressed in order to promote the use of both markers.

References


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