IMAGING

Frontomaxillary facial angle in fetuses with trisomy 21 at 11-13^6 weeks

Jiri Sonek, MD; Marisa Borenstein, MD; Themistoklis Dagklis, MD; Nicola Persico, MD; Kypros H. Nicolaides, MD

OBJECTIVE: The objective of the study was to investigate the location of the front of the maxilla in relation to the forehead in fetuses with trisomy 21 at 11-13 weeks of gestation.

STUDY DESIGN: A three-dimensional volume of the fetal head was obtained before karyotyping in 100 fetuses with trisomy 21 and 300 euploid fetuses. The frontomaxillary facial (FMF) angle, defined as the angle between the upper surface of the upper palate and the frontal bone in a midsagittal view of the fetal face, was measured.

RESULTS: The FMF angle was significantly larger in the trisomy 21 than in the euploid fetuses (mean 88.7°, range 75.4-104° vs mean 78.1°, range 66.6-89.5°, $P < .001$). The FMF angle was more than 85° in 69% of the trisomy 21 fetuses and in 5% of the euploid fetuses. There was no significant association between the FMF angle and nuchal translucency thickness.

CONCLUSION: Measurement of FMF angle is likely to be a useful adjunct in screening for trisomy 21.

Key words: frontomaxillary facial angle, maxilla, 3D ultrasonography first-trimester screening, trisomy 21

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Trisomy 21 is associated with a specific phenotype, which includes a flat profile. This observation is part of Langdon Down's original description of what later became known as Down syndrome.[1] Several radiological studies reported underdevelopment of the upper jaw, delayed dental growth, reduction in the number and size of teeth, and absence or hypoplasia of the nasal bone in individuals with trisomy 21.[2–7] Furthermore, prenatal sonographic studies have reported that a significant proportion of fetuses with trisomy 21 have shortening of the maxillary length and maxillary depth.[8–10] However, the reported differences between maxillary measurements in between trisomy 21 and euploid fetuses have not been shown to be large enough to be clinically useful.[8–10] It is possible that the clinically evident flat nature of the profile in trisomy 21 individuals is in part due to not only the size but also the location of the maxilla.

The aim of this study was to determine whether the maxilla is dorsally displaced with respect to the forehead in fetuses with trisomy 21 at 11-13^6 weeks of gestation. This was accomplished using a novel technique of measuring the angle between the upper palate and the frontal bone on images generated by three-dimensional (3D) ultrasonography.

Materials and Methods

This study utilized 3D volumes of the fetal face, which had been acquired before fetal karyotyping by chorionic villus sampling at 11-13^6 weeks of gestation. The fetuses were at risk of trisomy 21 based on the combination of maternal age and nuchal translucency measurement.[11] Singleton pregnancies only were used. In each fetus the crown-rump length and nuchal translucency thickness were measured in a standard fashion.[11] A midsagittal image of the fetal face was examined for the presence or absence of the nasal bone.[9,12]

We searched our database and identified 100 consecutive cases of fetal trisomy 21 and 300 consecutive euploid fetuses in which a 3D volume of the fetal face had been obtained. This was done with the fetus in the midsagittal plane with the transducer being parallel to the long axis of the nose. All 3D examinations were carried out transabdominally (RAB 4-8L probe, Voluson 730 Expert, GE Medical Systems, Milwaukee, WI), by sonographers with extensive experience in first-trimester scanning and 3D ultrasound.

Analysis of the 3D volumes was carried out by sonographers who were not aware of the fetal karyotype. The 3D volumes were displayed in the 3 orthogonal planes that compose the multiplanar mode of the 3D image. In this mode, an optimal sagittal view was produced to show the fetal profile. As this plane was scrolled, a series of corresponding trans-

From the Department of Obstetrics and Gynecology, Wright State University, and the Fetal Medicine Foundation/USA, Dayton, OH (Dr Sonek), and the Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, London, UK (Drs Borenstein, Dagklis, Persico, and Nicolaides).

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Reprints: Professor K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, Denmark Hill, London SE5 8RX, United Kingdom.

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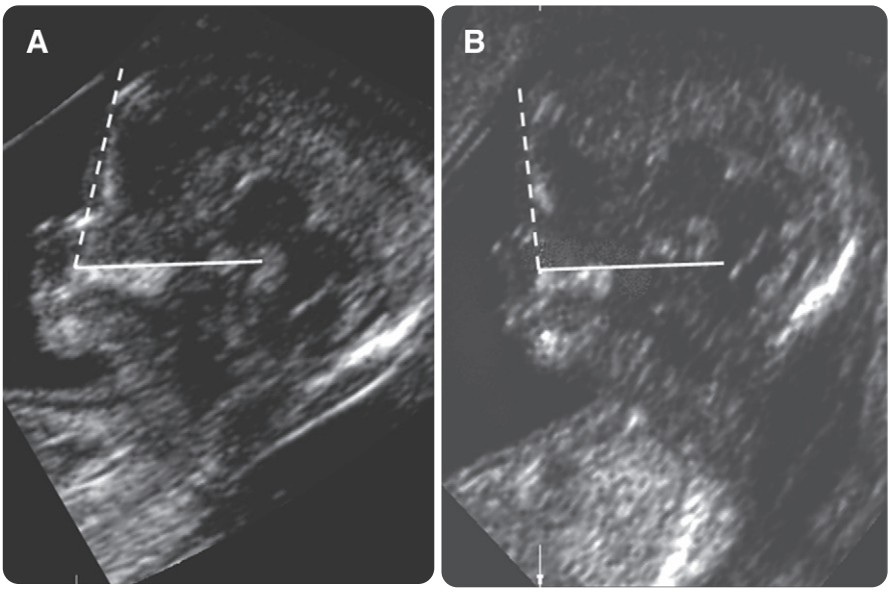
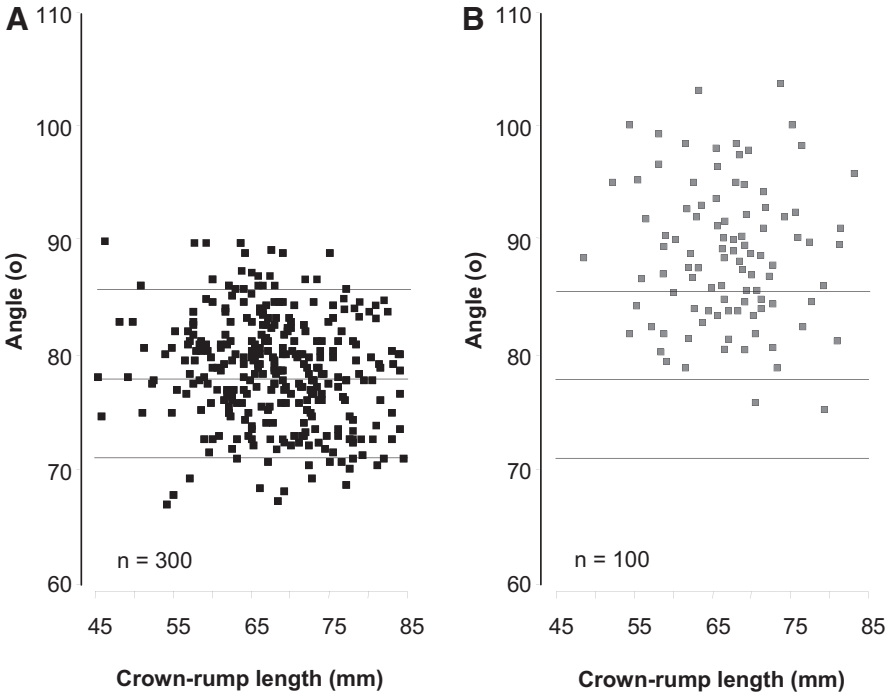
FIGURE 1
Fetal profiles and facial angles (euploid and trisomy 21 fetuses)



Ultrasound images of facial angle in **A**, a euploid fetus and **B**, 1 with trisomy 21.

FIGURE 2
Graphs of facial angle measurements (euploid and trisomy 21 fetuses)



Graphs of facial angle measurements in **A**, euploid fetuses and **B**, trisomy 21 fetuses with their corresponding crown-rump lengths are plotted on the reference range (mean and 95th and 5th percentiles) with crown-rump length of the euploid fetuses. Normal ranges (mean and 5th and 95th percentiles) are shown.

verse and coronal images of the fetal face were simultaneously demonstrated. A midsagittal view of the fetal face showing the maxilla was thus obtained. The frontomaxillary facial (FMF) angle was measured. We defined this angle as the angle between a line along the upper surface of the upper palate and a line that traverses the upper corner of the anterior aspect of the maxilla extending to the external surface of the frontal bone at the point of its greatest anterior excursion (Figure 1).

The 3D volumes of the trisomy 21 and euploid fetuses were used for previous studies, but this is the first study describing the measurement of the FMF angle.

Statistical analysis

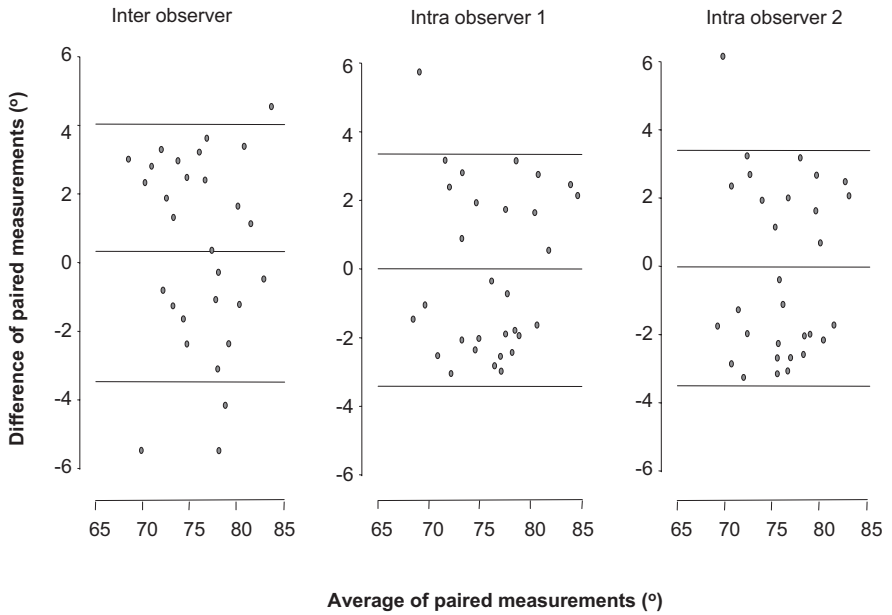
The potential association between the FMF angle and the crown-rump length and nuchal translucency thickness was examined using linear regression analysis. The Student *t* test was used to examine whether there was a significant difference in the mean FMF angle between fetuses with present and those with absent nasal bone. The Student *t* test for independent samples was used for the comparison of the FMF angle between euploid and trisomy 21 fetuses. The intra- and interobserver agreement for the measurement of the FMF angle were tested in sets of 30 cases each, as described by Bland and Altman.[13] The data were analyzed using the statistical software SPSS 13.0 (Chicago, IL) and Excel for Windows 2000 (Microsoft Corp, Redmond, WA). A *P* value of less than .05 was considered statistically significant.

Results

The median maternal age was 36 years of age (range 17 to 47) in both the trisomy 21 and the chromosomally normal groups. The median fetal crown-rump length was 68 (45-84) mm and the median gestation was 12 (11-13^{6}) weeks in both groups. An absent nasal bone was found in 6 (2%) of the 300 euploid fetuses and in 58% of the 100 trisomy 21 fetuses.

The FMF angle was successfully measured in all 400 patients. In the euploid group, the mean FMF angle was 78.1°

FIGURE 3
Bland-Altman graphs of paired facial angle measurements



Intra- and interobserver agreement (Bland-Altman) is expressed as difference against the average of paired measurements for the facial angle.

(range 66.6° to 89.5°). No significant association was found between the FMF angle and crown-rump length (r = 0.058, P = .318; Figure 2) or nuchal translucency thickness (r = 0.017, P = .774). The median FMF angle was not significantly different between those euploid fetuses in which the nasal bone was present or absent (mean difference 1.35°, 95% confidence interval [CI] = –2.31° to 5.01°, P = .469).

In the fetuses with trisomy 21, the mean FMF angle was 88.7° (range 75.4° to 104°). This was significantly larger than in the euploid group (mean difference 10.6°, 95% CI = 9.5° to 11.7°, P < .001). In 69% of the trisomy 21 fetuses, the FMF angle was larger than the 95th percentile (85°) of the euploid population. In 40% of the trisomy 21 fetuses, the FMF angle was above the upper limit of the range of angles (90°) of the euploid population. There was no significant association between the FMF angle and crown-rump length (r = 0.02, P = .686; Figure 2) or nuchal translucency thickness (r = 0.12, P = .286). The median angle was not significantly different between those trisomy 21 fetuses with an absent or present nasal bone (mean difference 0.53°, 95% CI = −1.86° to 2.94°, P = .658).

Mean difference and the 95% limits of agreement between paired measurements of the FMF angle by the same sonographer in 30 cases and between paired measurements by different observers in 30 cases are shown in Figure 3 and the Table.

TABLE
Table Mean difference in degrees and the 95% limits of agreement between 30 paired measurements by the same sonographer and between 30 paired measurements by two sonographers

Paired measurements	Mean difference (°) and SD	95% Confidence interval
Observer 1	−0.004% (2.354)	−4.600 to 4.592
Observer 2	−0.008% (2.532)	−5.105 to 5.089
Interobserver	0.147 (2.673)	−5.021 to 5.315

Comment

We previously published a two-dimensional (2D) sonographic study at 11-13[6] weeks, which showed that trisomy 21 fetuses had a significantly shorter maxillary length as compared with normal. It was below the 5th percentile of the normal range in 24% of affected fetuses.[8] However, the degree of deviation from normal was too small (mean of 0.7 mm) for this measurement to be useful in screening for trisomy 21. Similarly, a 3D sonographic study at 11-13[6] weeks reported that in trisomy 21 fetuses the maxillary depth was shorter than normal by a mean of only 0.3 mm, and it was below the 5th percentile of the normal range in only 10% of affected fetuses.[9] Therefore, we suspect that additional factors leading to the clinically evident flat profile in trisomy 21 exist.

The increased FMF angle in trisomy 21 fetuses noted in our study may be due to a dorsal displacement of the apex of the angle (front of the maxilla) with respect to the forehead. This effect can also be produced by a certain degree of frontal bossing. However, frontal bossing is not recognized as a feature of trisomy 21. Lastly, the difference in the FMF angles could result from differences in the direction of the longitudinal axis of the upper palate: a deviation of this axis toward the base of the skull would lead to an increase in the FMF angle. However, this hypothesis does not lend itself easily to an objective evaluation.

This study has demonstrated the feasibility of measuring the FMF angle at 11-13[6] weeks of gestation. The use of 3D ultrasonography allowed us to obtain a perfect midsagittal view of the fetal face and to rotate the image to the optimal plane for measurement of the FMF angle. The maxilla was successfully visualized and the FMF angle was measured in all fetuses and in 95% of cases the difference between two consecutive measurements was less than 5°.

Determination of the FMF angle may become useful in screening for trisomy 21 between 11 and 13[6] weeks of gestation. The potential utility in trisomy 21 detection is underscored by the fact that in 69% of trisomy 21 fetuses the FMF

angle was above the 95th percentile of the normal range, and in 40% of trisomy 21 fetuses, the angle was above the upper limit of the normal range. Measurement of the FMF angle may also be useful in reducing the false-positive rate: only 2% of the affected fetuses had angle sizes that were below the 50th percentile. Because the FMF angle is a continuous variable, likelihood ratios can be constructed for each measurement. The fact that there is no significant association among the FMF angle, nuchal translucency thickness, and the presence or absence of the nasal bone will allow its inclusion in the combined first-trimester ultrasound-based assessment of risk for trisomy 21.[11,12] Whether these results can be duplicated using 2D ultrasonography needs to be evaluated in a prospective fashion.

Before the FMF angle is incorporated into routine screening, it is imperative that the results are confirmed in prospective studies and that sonographers undertaking risk assessment receive appropriate training and certification of their competence in measuring the FMF angle. ■

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