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Frontomaxillary facial angle in trisomy 21 fetuses at 16–24 weeks of gestation

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KEYWORDS: frontomaxillary facial angle; maxilla; second-trimester screening; three-dimensional ultrasound; trisomy 21

ABSTRACT

Objectives *To establish a normal range for the frontomaxillary facial (FMF) angle by three-dimensional (3D) ultrasound imaging and to examine the FMF angle in trisomy 21 fetuses at 16–24 weeks of gestation.*

Methods *We measured the FMF angle using 3D volumes of the fetal profile obtained with the transducer parallel to the long axis of the nose and at 45° to the palate, which had been acquired from 150 normal fetuses and 23 fetuses with trisomy 21.*

Results *In the normal group there was no significant association between the FMF angle and gestational age; the mean FMF angle was 83.9° (range, 76.9–90.2°) and the 95th centile was 88.5°. In 15 (65.2%) of the fetuses with trisomy 21 the FMF angle was greater than 88.5°. Repeatability studies demonstrated that in 95% of cases the difference between two measurements of FMF angle by the same operator and different operators was less than 5°.*

Conclusions *In the majority of second-trimester fetuses with trisomy 21 the FMF angle is increased. Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

A common phenotypic feature of individuals with trisomy 21 is a flat face[1]. We have recently reported a method for quantifying the flat face of fetuses with trisomy 21 and demonstrated an increase in the frontomaxillary facial (FMF) angle, which is the angle between the upper surface of the palate and the leading edge of the forehead[2,3]. A three-dimensional (3D) ultrasound study of fetuses at 11 + 0 to 13 + 6 weeks of gestation reported that the FMF angle was above the 95th centile of the normal range in more than 60% of fetuses with trisomy 21[2]. Similarly, a study of stored images of fetal profiles taken by two-dimensional (2D) ultrasound examination before amniocentesis at 14–24 weeks reported that the FMF angle was above the 95th centile of the normal range in 79% of 34 fetuses with trisomy 21[3].

In our continuing 3D ultrasound studies of the FMF angle we found that the palate is visible as a single homogeneously hyperechogenic rectangular structure in the mid-sagittal view of the fetal face at 11 to 13 + 6 weeks[4]. In the second and third trimesters we noticed that there are at least two echogenic structures, the inferior one representing the palate and the superior ones the vomer (Figure 1). The vomer is a thin bone that forms the posterior and inferior portion of the nasal septum. It extends from the midline to the sphenoid, ethmoid, left and right palatine bones, and left and right maxillary bones.

The aim of this prospective 3D ultrasound study was to present a reference range of the FMF angle and to evaluate the angle in fetuses with trisomy 21 at between 16 and 24 weeks of gestation.

METHODS

We measured the FMF angle using 3D volumes of the fetal face, which had been successfully acquired in the mid-sagittal plane of the face from two groups of patients. The first group comprised 150 singleton pregnancies with appropriately growing fetuses and no sonographic evidence of fetal abnormality. These patients were attending our fetal medicine centers for routine ultrasound examination at 16–25 weeks and for this study we prospectively recruited 15 consecutive cases per gestational week. The

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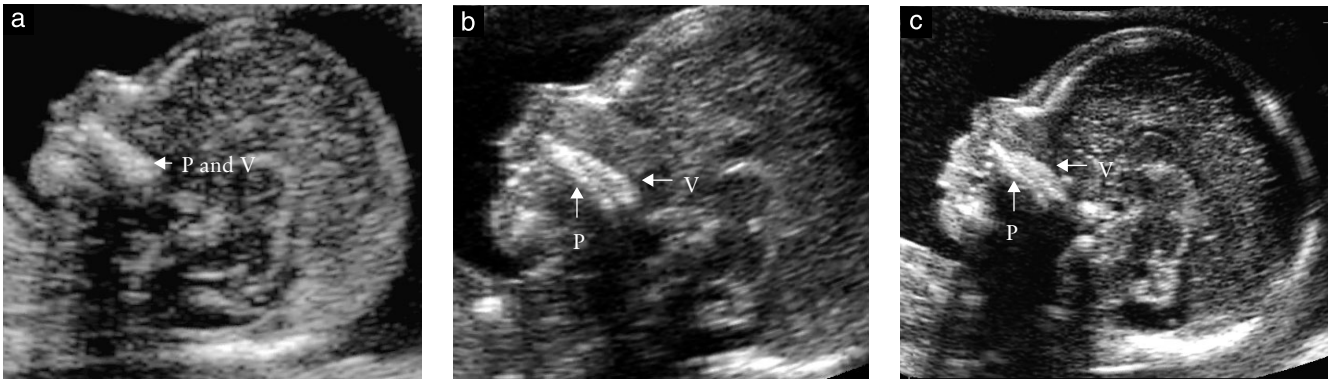

Figure 1 Ultrasound images of a normal fetal profile at 12 weeks (a), 16 weeks (b) and 20 weeks (c) of gestation. At 12 weeks the palate (P) and vomer (V) appear as a single hyperechogenic rectangular structure, but in the second trimester there are two echogenic structures. The inferior one, which is directed towards the basilar portion of the occipital bone posteriorly, represents the palate. The vomer is the superior one, with an irregular convex shape on the top, and is directed towards the sphenoid bone posteriorly.

second group comprised 23 fetuses with trisomy 21 confirmed by chorionic villus sampling or amniocentesis carried out because of a high risk of a chromosomal defect. In 13 (56.5%) cases the maternal age was 35 years or more, and in all but one case there was at least one fetal abnormality or sonographic marker of a chromosomal defect, including mild ventriculomegaly ($n = 5$), nuchal edema ($n = 8$), absent nasal bone ($n = 6$), cardiac defect ($n = 8$), intracardiac echogenic focus ($n = 4$), hyperechogenic bowel ($n = 2$), collapsed stomach ($n = 2$), duodenal atresia ($n = 1$), mild hydronephrosis ($n = 3$), short femur ($n = 4$), talipes ($n = 1$) and clinodactyly ($n = 1$).

In each case transabdominal ultrasound examination (RAB 4-8L probe, Voluson 730 Expert, GE Medical Systems, Milwaukee, WI, USA) was carried out by sonographers with extensive experience in 3D ultrasound imaging. A 3D volume of the fetal head had been acquired in the mid-sagittal plane of the face with the transducer parallel to or within 30° of the long axis of the nose and 45° to the palate. In this plane, the palate is visualized as an echogenic line, with a downwards diagonal direction from the maxillary bone anteriorly towards the basilar portion of the occipital bone posteriorly (Figure 2). Care was taken to distinguish between the palate and the overlying vomeral bone, which is less echogenic and has an irregular convex shape on the top. The vomeral bone courses diagonally from the maxilla anteriorly towards the sphenoid bone posteriorly. The 3D volumes were examined offline using the multiplanar mode to verify the exact mid-sagittal plane and to make minor corrections from the original acquisition plane when necessary. For measurement of the FMF angle the first ray was drawn along the superior edge of the palate and the second ray from the upper anterior corner of the maxilla extending to the external surface of the frontal bone. This technique differs from that used at 11 to 13 + 6 weeks and the one used in our previous second-trimester retrospective study[2,3]. At 11 to 13 + 6 weeks the vomer and palate are indistinguishable, and so the first ray of the FMF angle is drawn in the upper part of the palate–vomer complex. As far as the second trimester is concerned, the vomer and palate can be seen separately and in our previous study we drew the first ray of the angle in the upper part of the vomer[3]. In the present study we selected the palate rather than the vomer because the upper surface of the former is straight whereas that in the vomer is usually convex.

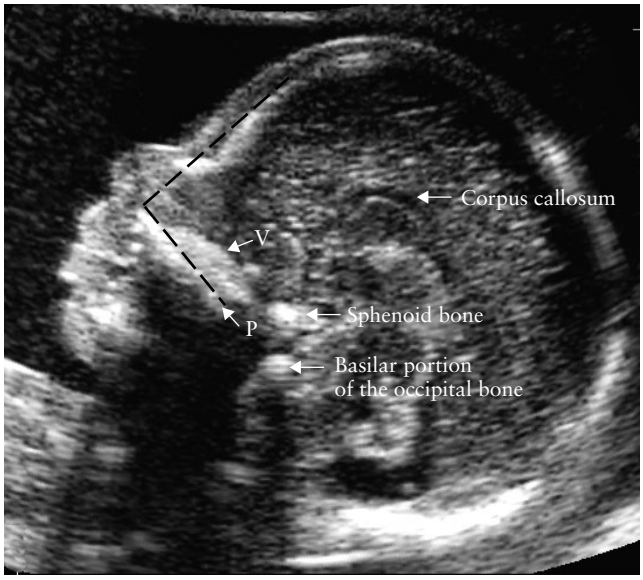

Figure 2 Ultrasound image of a normal fetal profile at 20 weeks demonstrating the measurement of the frontomaxillary facial angle.

The FMF angle measurements were made independently by two sonographers who were not aware of the fetal karyotype. Intraobserver variability in measurements was assessed based on FMF angle measurements by two observers in 100 cases. Intraobserver variability was assessed by one sonographer measuring 50 randomly selected cases on two occasions.

Statistical analysis

Regression analysis was used to determine the significance of the association between the FMF angle and gestational age. Mann–Whitney *U*-test was used to compare the FMF angle between the normal group and the trisomy

21 fetuses, and between those with and without common defects (ventriculomegaly, nuchal edema, absent nasal bone, cardiac defect) within the trisomy 21 group.

Bland–Altman analysis was used to examine the measurement agreement and bias for a single examiner and between two examiners[5]. The data were analyzed using the statistical software SPSS 12.0 (Chicago, IL, USA) and Excel for Windows 2000 (Microsoft Corp., Redmond, WA, USA). $P < 0.05$ was considered statistically significant.

RESULTS

In the group of 150 normal fetuses the median maternal age was 32 (range, 16–44) years and the median gestational age was 21 (range, 16–25) weeks. The maternal ethnicity was Caucasian in 97 (64.7%), Afro–Caribbean in 39 (26.0%), Indian or Pakistani in eight (5.3%), and Chinese or Japanese in six (4.0%). There was no significant association between the FMF angle and gestational age ($r = 0.002$, $P = 0.981$) (Figure 3). The mean FMF angle was 83.9° (range, 76.9–90.2°). The Kolmogorov–Smirnov test confirmed the normality of the distribution, and the 5th and 95th centiles were 79.3° and 88.5°, respectively.

In the 23 fetuses with trisomy 21 the median maternal age was 35 (range, 20–44) years and the median gestational age was 20 (range, 16–24) weeks. There was no significant association between the FMF angle and gestational age ($r = 0.189$, $P = 0.387$). The mean FMF angle was 89.4° (range, 83.1–95.6°) and was significantly larger than that in the normal fetuses ($P < 0.001$). The measurement was above the 95th centile of the normal range in 15 (65.2%) of the trisomy 21 fetuses (Figure 3). There was no significant difference in mean FMF angle between those with and without ventriculomegaly (90.9° vs. 89.1°, $P = 0.491$), with and without nuchal edema (90.1° vs. 88.4°, $P = 0.294$), or with and without cardiac defect (89.4° vs. 89.3°, $P = 0.946$). The mean FMF angle was significantly higher in those with an absent rather than present nasal bone (92.0° vs. 88.6°, $P = 0.036$) and it was above the 95th centile in all six cases with an absent nasal bone.

The mean difference and 95% limits of agreement (with their 95% CI) between paired measurements by the same observer were −0.06° (−2.57° (−2.88 to −2.25) to 2.45° (2.13–2.57)) and the respective values in paired measurements by the two different observers were −0.321° (−2.70° (−2.96 to −2.52) to 2.10° (1.88–2.31)).

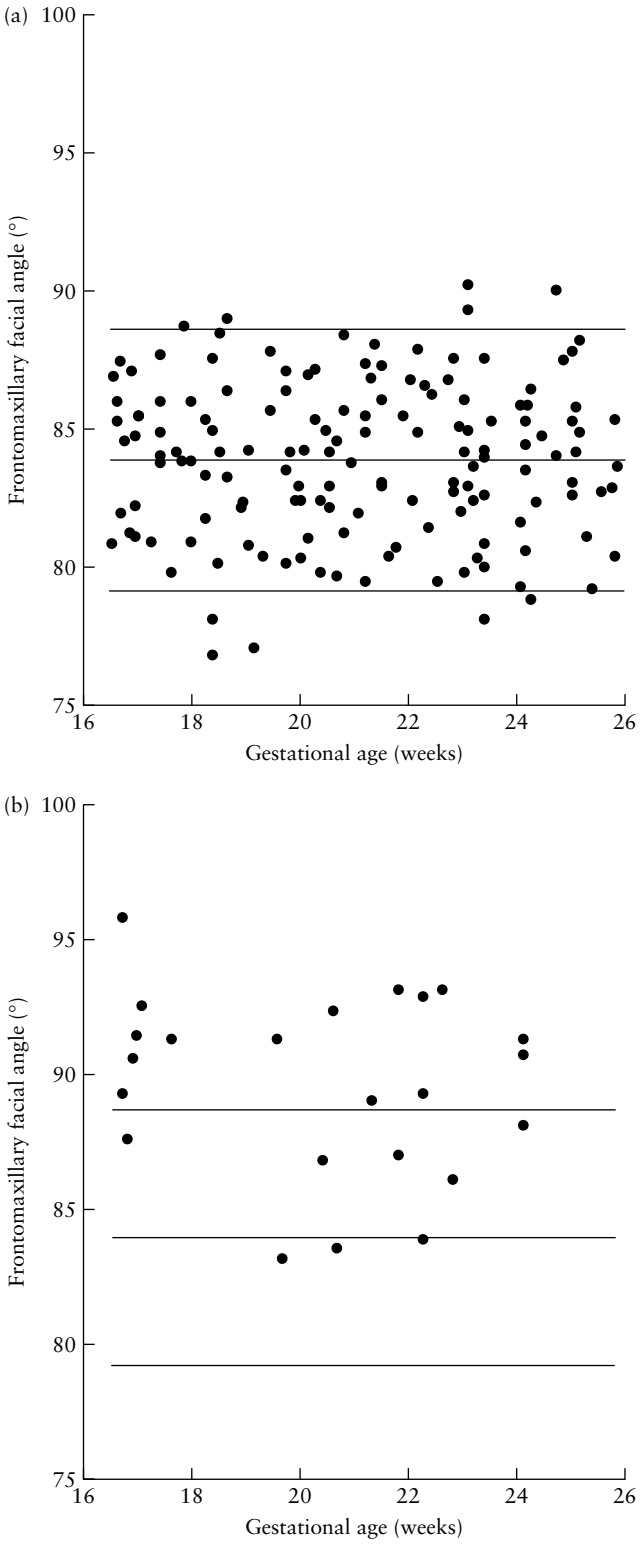

Figure 3 Frontomaxillary facial angle in 150 normal fetuses (a) and 23 fetuses with trisomy 21 (b), plotted on the reference range (mean, 95th and 5th percentiles) for normal fetuses with gestation.

DISCUSSION

The data in this prospective 3D ultrasound study confirm our observations from a previous retrospective 2D ultrasound study that the FMF angle during the second trimester in fetuses with trisomy 21 is substantially bigger than that in normal fetuses. We established that the FMF angle does not change between 16 and 25 weeks of gestation in normal fetuses, and that the 95th centile is 88.5°. However, in about 65% of fetuses with trisomy 21 the FMF angle is above this value. The measurement of the FMF angle in the second and third trimesters is reproducible, and in 95% of the cases the difference between two measurements by the same operator and different operators is less than 5°.

When measuring the FMF angle it is important to appreciate that the palate and vomer appear as a single rectangular structure in the scan performed at 11 to 13 + 6 weeks, whereas in the second and third trimesters the two structures are joined anteriorly at the maxilla but diverge posteriorly to produce two separate echogenic lines. In a previous second-trimester study we drew the first ray of the FMF angle in the upper part of the vomer and reported that the FMF angle decreases with gestation[3]. In the present study we used the palate rather than the vomer because the upper surface of the former is straight whereas that of the vomer is usually convex.

The wide FMF angle in fetuses with trisomy 21 could explain the flat face, which is a common phenotypic expression characteristic of this chromosomal defect[1]. Farkas *et al.* examined 120 patients with trisomy 21 at 7 months to 36 years of age, and reported an abnormally short distance between the nostril and ear in 62% of the cases[6]. Allanson *et al.* examined 199 patients with trisomy 21 at 6 months to 61 years of age and reported that maxillary growth was reduced in comparison to mandibular growth[7]. Shapiro *et al.* examined 153 patients with trisomy 21 at 7–66 years of age and reported that the length of the palate was below the 2.5th centile of the normal range in 95%[8]. Lauridsen *et al.* examined 31 aborted fetuses with trisomy 21 at 16–25 weeks of gestation, and reported that both components of the hard palate, the maxilla and the palatine bones were shorter than in chromosomally normal fetuses[9].

In this study all cases of trisomy 21 had been identified by previous screening through maternal age, second-trimester serum biochemistry or routine ultrasound examination, and in 22/23 cases there was a fetal abnormality or sonographic marker of a chromosomal defect. However, there was no significant association between the FMF angle and any of the commonly detected defects. It is therefore reasonable to assume that our findings concerning the FMF angle are representative of all fetuses with trisomy 21.

In the first trimester of pregnancy effective screening for trisomy 21 is provided by a combination of fetal nuchal translucency thickness and maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A levels, with a detection rate of 90% for a false-positive rate of 5%[10]. The incorporation of additional sonographic markers, such as nasal bone, FMF angle, and tricuspid and ductus venosus flow, could increase the detection rate to more than 95% with a simultaneous reduction in false-positive rate to less than 3%[10].

In the second trimester, screening for trisomy 21 by maternal age or maternal serum biochemistry have detection rates of 30% and 65%, respectively, for a false-positive rate of 5%[11]. Although many reports have highlighted the association between trisomy 21 and several defects or sonographic markers, such as cardiac abnormalities, increased nuchal fold thickness, short femur, echogenic intracardiac focus, hyperechogenic bowel, or hydronephrosis, each one of these features is observed in a minority of affected fetuses[12]. In contrast, sonographic assessment of the fetal profile for the FMF angle is likely to prove a sensitive method of second-trimester screening for trisomy 21. The fetal profile is examined routinely during the second-trimester scan and so the skill necessary to obtain this view is widely available. When the profile is obtained with the transducer parallel to the long axis of the nose and at 45° to the palate, it is possible to examine in the same view the FMF angle as well as the nasal bones and prenasal skin thickness, the other two promising second-trimester markers[13,14].

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