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Frontomaxillary facial angle in fetuses with trisomy 13 at 11 + 0 to 13 + 6 weeks

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KEYWORDS: first-trimester screening; frontomaxillary facial angle; maxilla; three-dimensional ultrasound; trisomy 13

ABSTRACT

Objective *To investigate the frontomaxillary facial (FMF) angle in fetuses with trisomy 13 at 11 + 0 to 13 + 6 weeks of gestation.*

Methods *A three-dimensional (3D) volume of the fetal head was obtained before karyotyping at 11 + 0 to 13 + 6 weeks of gestation in 23 fetuses with trisomy 13. The FMF angle, defined as the angle between the upper surface of the maxilla and the frontal bone in a midsagittal view of the fetal face, was measured and compared to the angle in 500 chromosomally normal fetuses.*

Results *In 10 of 12 (83.3%) fetuses with trisomy 13 and holoprosencephaly, the FMF angle was above the 95th centile of the normal range. In the 11 fetuses with no holoprosencephaly, the FMF angle was not significantly different from normal. There was no significant difference in the FMF angle between the trisomy 13 fetuses with and without facial cleft.*

Conclusions *In fetuses with trisomy 13, the FMF angle at 11 + 0 to 13 + 6 weeks of gestation is increased only in cases with associated holoprosencephaly. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Trisomy 13 is the third most common chromosomal abnormality, with a birth prevalence of about 1 in 5000. The condition is lethal, with death occurring usually *in utero* or within the first few days of postnatal life[1].

Measuring the frontomaxillary facial (FMF) angle is a recently described sonographic method of defining the relative position of the maxilla to the forehead. In a study of fetuses with trisomy 21, which is known to be associated with midfacial hypoplasia, the FMF angle at 11 + 0 to 13 + 6 weeks of gestation is significantly larger than that in chromosomally normal fetuses[2].

The aim of this study was to investigate the FMF angle in fetuses with trisomy 13, because in this condition both of the landmarks for the measurement of the angle, the palate and forehead, are often abnormal. Trisomy 13 is commonly associated with cleft palate and holoprosencephaly, in which there is accelerated development of the frontal bones and premature closure of the metopic suture[3].

METHODS

This study utilized three-dimensional (3D) volumes of the fetal face which had been acquired before fetal karyotyping by chorionic villus sampling (CVS) in singleton pregnancies at 11 + 0 to 13 + 6 weeks of gestation. The women chose to have risk assessment by a combination of maternal age and fetal nuchal translucency (NT) thickness[4]. In each fetus the crown–rump length and NT thickness were measured and the presence or absence of facial or other abnormalities was recorded.

We searched our database and identified 23 consecutive cases of fetuses with trisomy 13 in which a 3D volume of the fetal face had been obtained with the fetus in the midsagittal plane and 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, USA) by sonographers with extensive experience in first-trimester scanning and 3D ultrasound.

The 3D volumes were reconstructed to obtain the fetal profile for measurement of the FMF angle. In this image the direction of the nose is parallel to the transducer (0°), the palate has a rectangular shape and the forehead is clearly visible (Figure 1). The upper anterior corner of the maxilla constituted the apex of the FMF angle. The first

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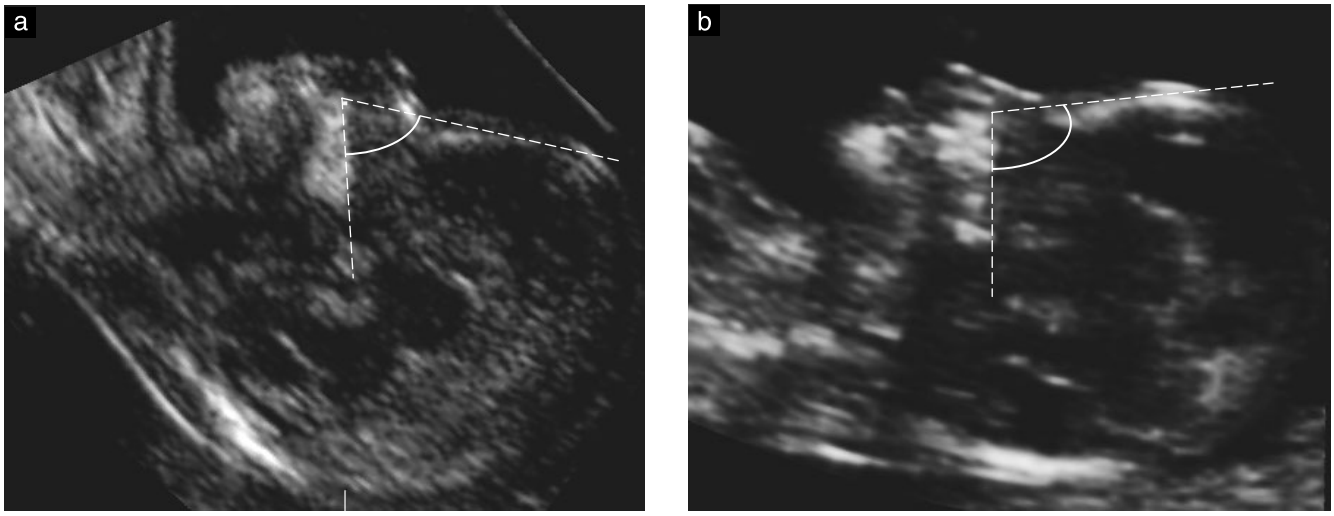

Figure 1 Ultrasound images demonstrating the measurement of the frontomaxillary facial angle in a chromosomally normal fetus (a) and in one with trisomy 13 and holoprosencephaly (b).

arm of the angle was drawn along the upper surface of the palate. Then the external table of the frontal bone or echogenic line under the skin was identified and the second arm was defined as the line joining the apex with the frontal bone[2] (Figure 1). The transverse plane of the fetal head at the level of the biparietal diameter was examined to determine the presence or absence of holoprosencephaly (Figure 2) and the transverse plane at the level of the maxilla was examined to determine the presence or absence of facial cleft (Figure 3). A coronal view of the forehead was used to determine whether the metopic suture was closed or open[3,5] (Figure 2).

Statistical analysis

Each measurement in the trisomy 13 fetuses was expressed as a difference in standard deviation from the expected appropriate normal mean for CRL (*z*-score)[6]. The Kolmogorov–Smirnov test confirmed that the *z*-scores were Normally distributed. Mann–Whitney *U*-test was used to compare the *z*-scores in the trisomy 13 fetuses with our previously reported 500 chromosomally normal fetuses[6], and within the trisomy 13 group those with and those without holoprosencephaly or facial cleft.

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 trisomy 13 fetuses, the median maternal age was 37 (range 30–45) years, the median crown–rump length was 61 (range 51–82) mm and the median gestational age was 12 (range 11 + 0 to 13 + 6) weeks. In 12 (52.2%) cases there was holoprosencephaly and in nine (39.1%) there was bilateral cleft of the palate (Figures 2 and 3). Premature closure of the metopic suture[3] was observed in all cases with holoprosencephaly and in none without holoprosencephaly.

In the 500 chromosomally normal fetuses, the mean FMF angle decreased with CRL from 84.3° at CRL 45 mm to 76.5° at CRL 84 mm (FMF angle = $93.34 - 0.200 \times$ CRL, $r = 0.374$, $P < 0.0001$; SD 4.283; Figure 4)[6]. In the trisomy 13 fetuses with holoprosencephaly, the mean *z*-score was 2.74 (95% CI 1.55–3.93), which was significantly higher than that in chromosomally normal fetuses (mean *z*-score 0, 95% CI −0.08 to 0.08, $P < 0.001$). In contrast, in the trisomy 13 fetuses without holoprosencephaly, the mean *z*-score was −0.61 (95% CI −1.85 to 0.62), which was not significantly different from normal ($P = 0.285$) (Figure 4). The FMF angle in fetuses with facial cleft, within each subgroup with and without holoprosencephaly, tended to be lower than that in fetuses without a cleft. However, the number of cases was too small for statistical assessment. In the total group of nine fetuses with facial cleft, the mean delta FMF angle was not significantly different from that in the 14 fetuses without facial cleft (mean 0.77, 95% CI −0.99 to 2.54, vs. mean 1.36, 95% CI −0.17 to 2.91; $P = 0.557$).

DISCUSSION

The findings of this study confirm the association between trisomy 13 and a high incidence of holoprosencephaly and facial cleft. In a previous study of 54 trisomy 13 fetuses in the second and third trimesters of pregnancy, 39% had holoprosencephaly and facial cleft[7]. The data demonstrate that in fetuses with holoprosencephaly, with or without a facial cleft, the FMF angle is substantially increased. In contrast, in trisomy 13 fetuses with no holoprosencephaly, the FMF angle is normal. Within each subgroup, with and without holoprosencephaly, the angle in those with a cleft tended to be lower than in those without.

The FMF angle provides an objective measurement of the position of the anterior end of the upper palate to the forehead. The increased FMF angle in fetuses with

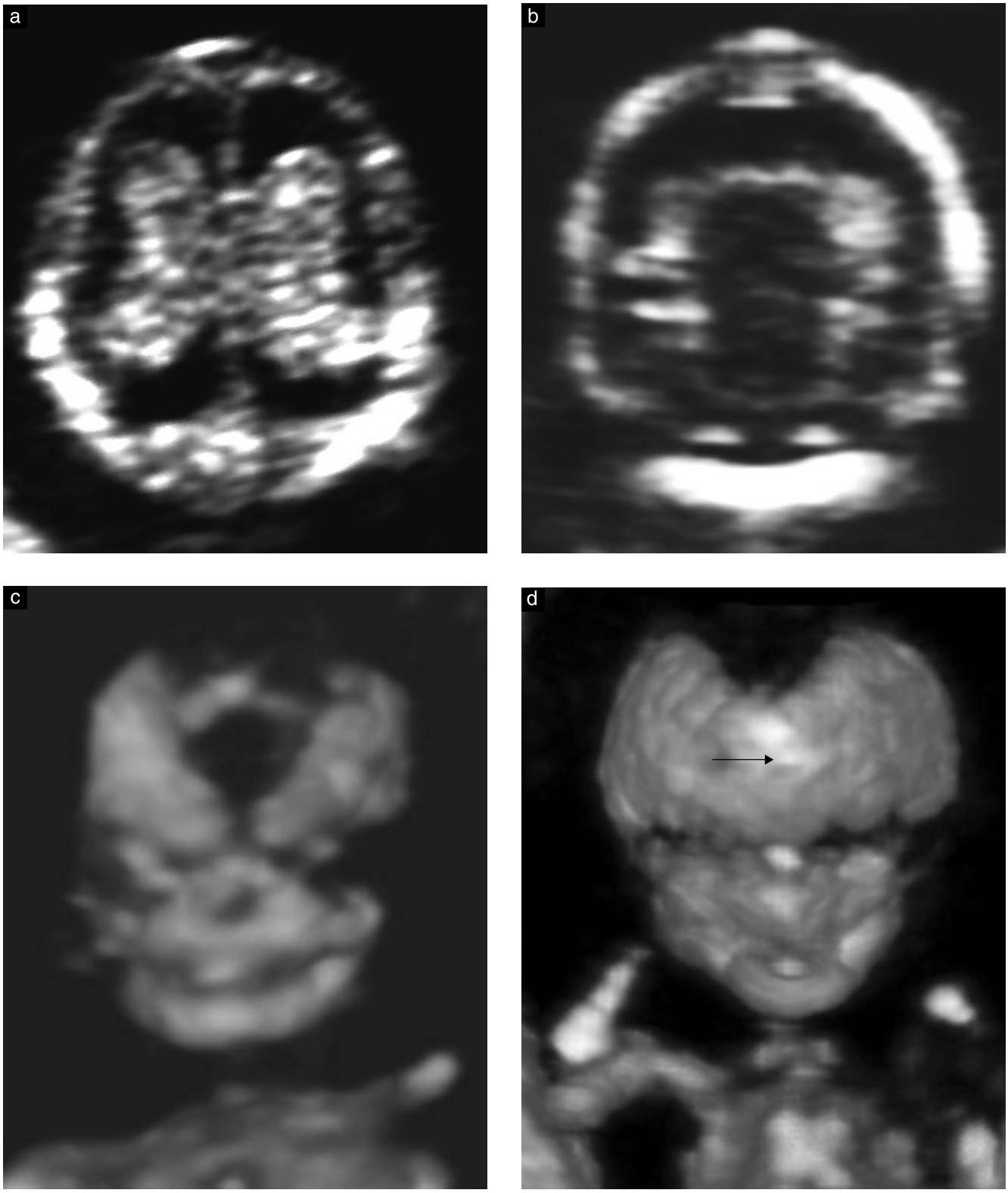

Figure 2 Transverse view of the brain in a normal fetus (a) and in one with holoprosencephaly (b) and coronal view of the frontal bones, demonstrating the open metopic suture in a normal fetus (c) and the premature closure of the metopic suture (arrow) in a fetus with holoprosencephaly (d) at 12 weeks of gestation.

holoprosencephaly is the consequence of either forward displacement of the forehead and/or dorsal displacement of the palate. In normal fetuses and in those with trisomy 13 but no holoprosencephaly, there is a complete gap between the frontal bones at 11 + 0 to 13 + 6 weeks[3,5]. Therefore, one ray of the FMF angle is between the upper anterior corner of the maxilla and the dura between the frontal bones. In holoprosencephaly there is no evidence of frontal bossing, but the FMF angle would increase because there is an accelerated development of the frontal

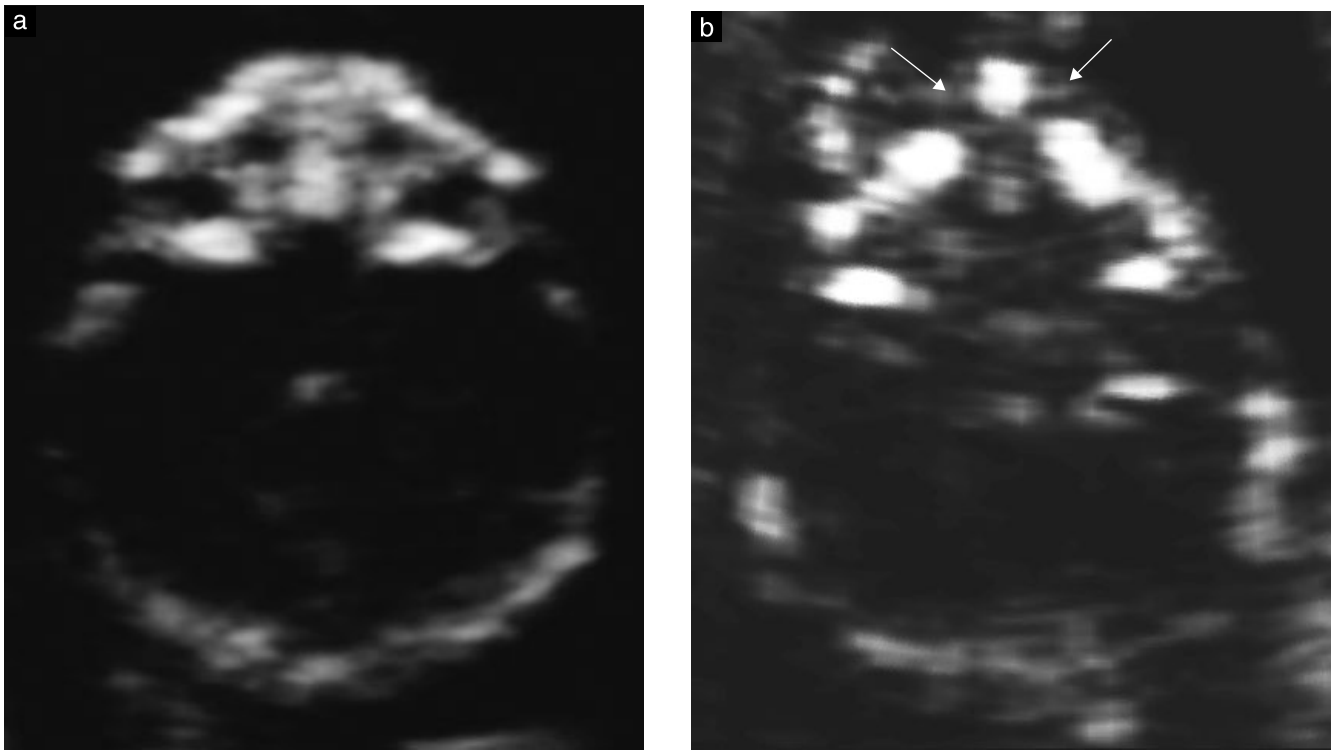

Figure 3 Transverse views of the fetal face, demonstrating a normal maxilla with no facial cleft (a) and a maxilla with bilateral facial cleft (b, arrows) in a fetus with trisomy 13 at 12 weeks of gestation.

bones and premature closure of the metopic suture[3]. In addition, it is likely that there is dorsal displacement of the palate, presumably due to the midfacial maldevelopment that accompanies holoprosencephaly, which is apparently unrelated to the presence or absence of facial cleft.

Effective first-trimester screening for trisomy 13 is provided by a combination of maternal age, fetal NT thickness and maternal serum free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A)[4,8]. In addition, the diagnosis can be suspected by the presence of fetal tachycardia, holoprosencephaly, megacystis or exomphalos[9]. Since the FMF angle is abnormal only in the fetuses with holoprosencephaly, which should in any case be detectable at the $11+0$ to $13+6$ weeks scan, it is unlikely that measurement of the FMF angle will improve early identification of trisomy 13. Nevertheless, measurement of the FMF angle is likely to be incorporated into routine first-trimester screening for trisomy 21, because preliminary results suggest that this sonographic marker is associated with a detection rate of more than 60% for a false positive rate of 5% and is independent of NT thickness[2]. If in such screening the FMF angle is increased, the sonographer should be alerted to the possibility of an associated holoprosencephaly and undertake a more careful examination of the fetal anatomy. The extent to which the FMF angle is increased in chromosomally normal fetuses with holoprosencephaly remains to be determined.

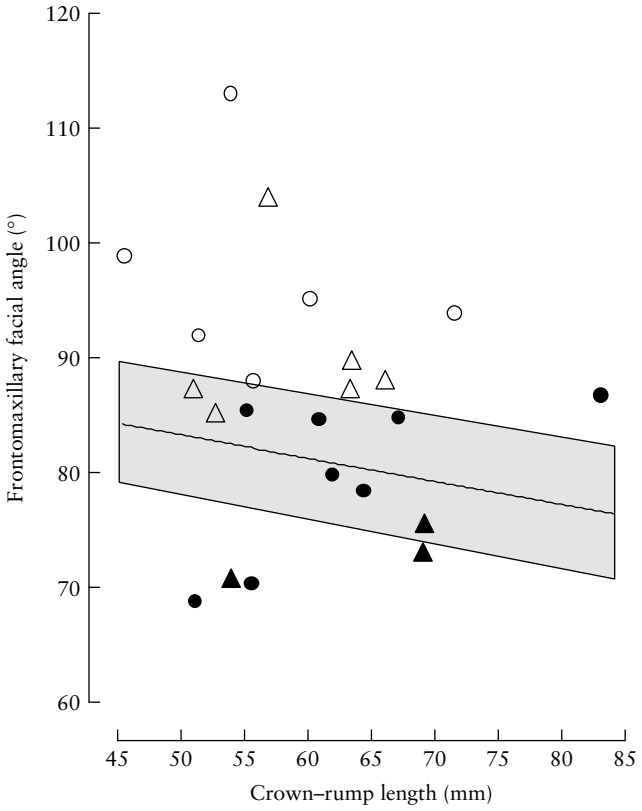

Figure 4 Frontomaxillary facial angle in trisomy 13 fetuses plotted on the reference range (mean, 95th and 5th percentiles) of chromosomally normal fetuses[6]. The open symbols represent fetuses with holoprosencephaly and the closed ones represent those with no holoprosencephaly. The triangles represent fetuses with facial cleft and the circles represent those with no cleft.

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