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Frontomaxillary and mandibulomaxillary facial angles at 11 + 0 to 13 + 6 weeks in fetuses with trisomy 18

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KEYWORDS: 3D ultrasound; first-trimester screening; frontomaxillary facial angle; mandible; maxilla; trisomy 18

ABSTRACT

Objective *To define the relative position of the maxilla and mandible in fetuses with trisomy 18 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 36 fetuses subsequently found to have trisomy 18, and 200 chromosomally normal fetuses. The frontomaxillary facial (FMF) angle and the mandibulomaxillary facial (MMF) angle were measured in a mid-sagittal view of the fetal face.*

Results *In the chromosomally normal group both the FMF and MMF angles decreased significantly with crown–rump length (CRL). In the trisomy 18 fetuses the FMF angle was significantly greater and the angle was above the 95th centile of the normal range in 21 (58.3%) cases. In contrast, in trisomy 18 fetuses the MMF angle was significantly smaller than that in normal fetuses and the angle was below the 5th centile of the normal range in 12 (33.3%) cases.*

Conclusions *Trisomy 18 at 11 + 0 to 13 + 6 weeks of gestation is associated with both mid-facial hypoplasia and micrognathia or retrognathia that can be documented by measurement of the FMF angle and MMF angle, respectively. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Trisomy 18, which is the second most common chromosomal abnormality after trisomy 21, is associated with early-onset growth restriction and multisystem defects that can be detected by prenatal sonography. A common facial feature is micrognathia[1]. On prenatal ultrasound, the diagnosis of micrognathia is subjective and is made by noting the presence of a receding or small chin with a prominent upper lip.

Attempts at providing an objective basis for the prenatal diagnosis of micrognathia by two-dimensional (2D) ultrasound have essentially focused on the measurement of the anteroposterior diameter of the mandible and the distance between the two rami (Figure 1)[2–6]. However, these measurements have not been incorporated into routine scanning and would not be expected to help in diagnosing retrognathia. The advent of three-dimensional (3D) ultrasound has made it possible to define the relative position of the mandible compared to other facial bones, making it possible to diagnose retrognathia. Rotten *et al.*[7] reported that in retrognathia there is a decrease in the inferior facial angle (Figure 1). The angle was defined in the mid-sagittal view of the profile by the crossing of a line joining the tip of the chin with the anterior border of the upper lip and a line drawn at 90° to the forehead at the junction between the forehead and nasal bone (nasion). Roelfsema *et al.*[8] obtained a mid-sagittal view of the face and drew a reference line between the nasion anteriorly and the sella turcica posteriorly (Figure 1). They then drew lines between the nasion superiorly and either the anterior part of the maxilla or the mandible inferiorly. In retrognathia there is an increase in the difference in the angle between the reference line and the nasion to maxilla and in the angle between the reference line and the nasion to mandible.

In a previous 3D ultrasound study we demonstrated that the mid-facial hypoplasia in fetuses with trisomy 21 can be evaluated by measurement of the frontomaxillary facial (FMF) angle, which was significantly greater in fetuses with trisomy 21 than in chromosomally normal fetuses[9].

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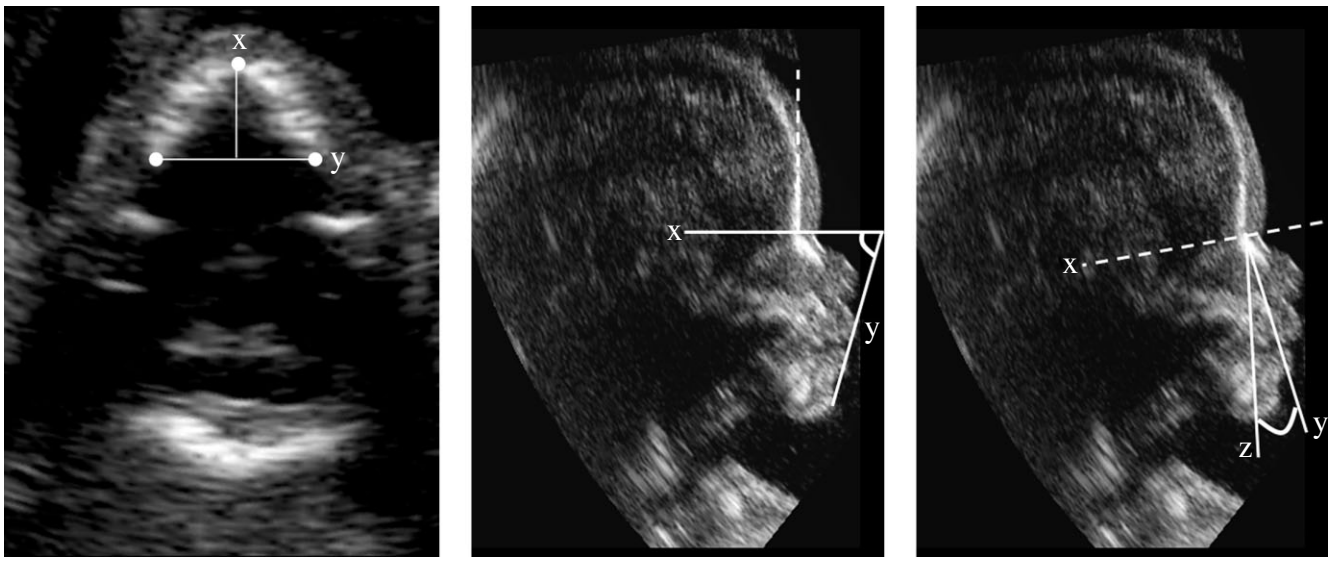

Figure 1 Assessment of the mandible in previous studies. (a) Transverse view of the fetal mandible showing measurement of the anteroposterior diameter of the mandible (x) and the distance between the two rami (y)[2–6]. (b) Mid-sagittal view of the fetal face showing the measurement of the inferior facial angle, between a line at 90° to the forehead at the junction between the forehead and nasal bone (x) and the line joining the tip of the chin with the anterior border of the upper lip (y)[7]. (c) Mid-sagittal view of the fetal face showing the angle between a line from the nasion anteriorly to the sella turcica posteriorly (x) and the lines between the nasion superiorly and either the anterior part of the maxilla (y) or the mandible (z)[8].

The aims of this study were firstly, to investigate whether trisomy 18 at 11 + 0 to 13 + 6 weeks of gestation is also associated with mid-facial hypoplasia by comparing the FMF angle with that of chromosomally normal fetuses and secondly, to define the relative position of the mandible to the maxilla by introducing a new measurement, the mandibulomaxillary facial (MMF) angle. The methodologies described by Rotten *et al.*[7] and Roelfsema *et al.*[8] are not applicable to the investigation of first-trimester fetuses with chromosomal defects; in many chromosomally abnormal fetuses the nasal bone is either hypoplastic or absent at this gestation and therefore, accurate and consistent identification of the nasion is not possible.

METHODS

This study utilized 3D volumes of the fetal face that 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 CVS after risk assessment by a combination of maternal age and measurement of fetal nuchal translucency (NT) thickness[10].

We searched our database and identified 36 cases of fetuses with trisomy 18 and 500 chromosomally normal fetuses in which a 3D volume of the fetal face had been obtained with the fetus in the mid-sagittal 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 ultrasonography, who were not aware of the fetal karyotype.

The 3D volumes from all 36 fetuses with trisomy 18 and 200 selected by computerized randomization from the 500 chromosomally normal fetuses were used for this study. The 500 cases were previously used to establish a normal range of FMF angle with crown–rump length (CRL)[11]. The 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 and nuchal membrane are clearly visible (Figure 2)[12]. The upper-anterior corner of the maxilla constituted the apex of the FMF angle. The first arm of the angle was drawn along the upper surface of the palate. The second arm was drawn upwards from the anterior aspect of the maxilla at a point where the first line intercepts it. The inner aspect of this second line was positioned in such a way that it was flush with either the outer aspect of the frontal bone or the outer aspect of an echogenic line located underneath the skin representing the unfused metopic suture (Figure 2)[9]. The MMF angle was generated by using the same first arm and the same apex as for the FMF angle. The second arm, however, was drawn downwards and positioned so that the inner aspect of the line was flush with the upper anterior corner of the mandible (Figure 2).

Statistical analysis

In the chromosomally normal fetuses regression analysis was used to determine the significance of the association between the FMF angle and the MMF angle and the ratio of the FMF angle to the MMF angle with CRL. Each measurement in both the chromosomally normal and the trisomy 18 fetuses was then expressed as a difference in SDs from the appropriate normal mean for CRL (Z-score). The Kolmogorov–Smirnov test confirmed that

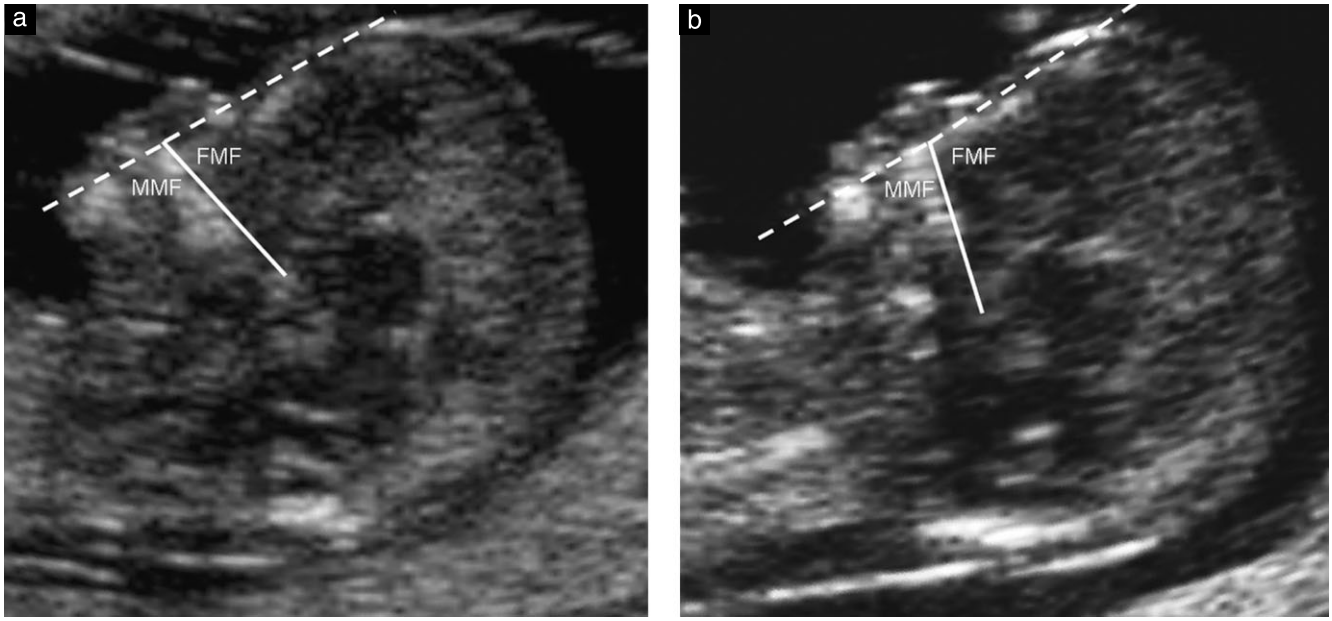

Figure 2 Mid-sagittal view of the fetal face demonstrating the measurement of the frontomaxillary facial (FMF) angle and the mandibulomaxillary facial (MMF) angle in a chromosomally normal fetus (a) and a fetus with trisomy 18 (b).

the Z-scores in both groups were normally distributed. Independent-samples *t*-test was used to determine the significance of difference in the Z-scores between the chromosomally normal and trisomy 18 fetuses. The inter-observer agreement for the measurement of the MMF angle was tested in sets of 35 cases each, as described by Bland and Altman[13]. The data were analyzed using the statistical software SPSS 12.0 (Chicago, IL, USA) and Excel for Windows 2000 (Microsoft Corp., Redmond, WA, USA). A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

In the 200 chromosomally normal fetuses the median maternal age was 35 (range, 20–45) years, the median fetal CRL was 68.5 (range, 49.3–84.0) mm and the median gestational age was 12 (range, 11 + 0 to 13 + 6) weeks. The FMF angle was not significantly different from that in the 500 previously reported chromosomally normal fetuses (mean difference in Z-scores −0.004, 95% CI −0.17 to 0.16). The mean FMF angle in the 500 cases decreased with CRL from 84.3° at a CRL of 45 mm to 76.5° at a CRL of 84 mm (FMF angle = 93.34 − 0.200 × CRL, $r = 0.374$, $P < 0.0001$, SD = 4.283; Figure 3). In the 200 chromosomally normal fetuses the mean MMF angle decreased with CRL from 114.5° at a CRL of 45 mm to 103.1° at a CRL of 84 mm (MMF angle = 128.1 − 0.303 × CRL, $r = 0.346$, $P < 0.001$, SD = 8.040; Figure 3).

In the trisomy 18 fetuses, the median maternal age was 37 (range, 25–43) years, the median CRL was 59.6 (range, 47.5–71.2) mm and the median gestational age was 12 (range, 11 + 0 to 13 + 6) weeks. The FMF angle was significantly greater than that in the 500 previously reported chromosomally normal fetuses (mean difference in Z-scores 1.51, 95% CI 1.13 to 1.90, $P < 0.0001$; Figure 4). The FMF angle was above the normal mean for CRL in 33 (91.7%) cases and above the 95th centile in 21 (58.3%) cases. The MMF angle was significantly smaller than in the 200 chromosomally normal fetuses (mean difference in Z-scores −0.90, 95% CI −1.30 to −0.41, $P < 0.0001$; Figure 4). The MMF angle was below the normal mean for CRL in 28 (77.8%) cases and below the 5th centile in 12 (33.3%) cases.

In the chromosomally normal fetuses the mean ratio of the FMF angle to the MMF angle was 0.74, and it did not change significantly with CRL (FMF to MMF angle ratio = 0.758 + 0.001 × CRL, $r = 0.170$, $P = 0.812$, SD = 0.070; Figure 5). In the trisomy 18 fetuses the mean FMF angle to MMF angle ratio was 0.86, which was significantly greater than that in the normal group (mean difference −0.11, 95% CI −0.15 to −0.07, $P < 0.001$; Figure 5). The mean difference and the 95% limits of agreement in paired measurements of the MMF angle by different observers in 35 cases are shown in Figure 6.

DISCUSSION

Facial dysmorphism is an important part of the phenotype of many syndromes, including trisomy 18. Measurement of the FMF angle provides an objective way of evaluating the position of the maxilla with respect to the fetal forehead. The new angle, MMF, provides an objective method for evaluating the location of the mandible with respect to the maxilla and could be used for early diagnosis of micrognathia and/or retrognathia.

This study has demonstrated that in chromosomally normal fetuses both the FMF and MMF angles decrease with CRL, but the ratio between the two angles remains

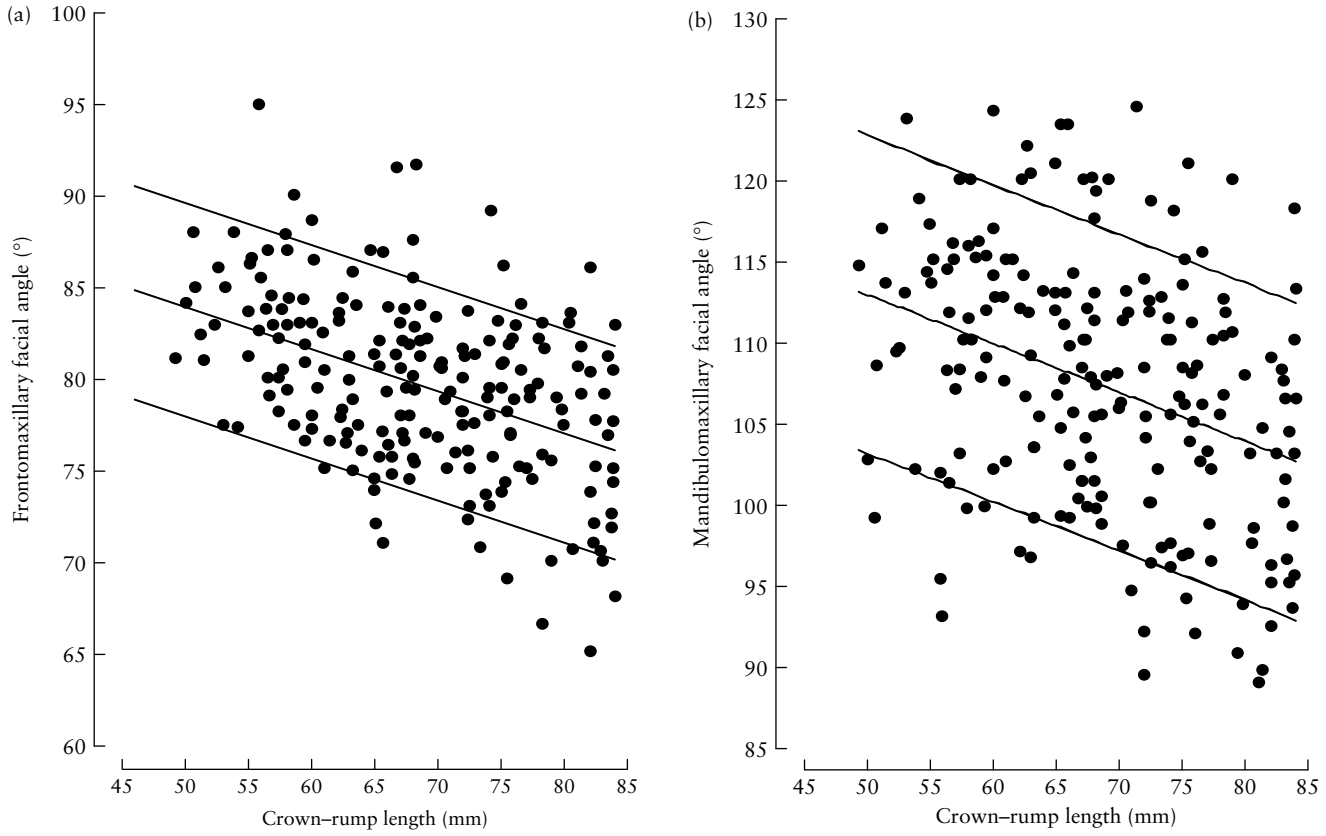

Figure 3 Reference range (mean, 5th and 95th centiles) of the frontomaxillary facial angle (a) and the mandibulomaxillary facial angle (b) in chromosomally normal fetuses.

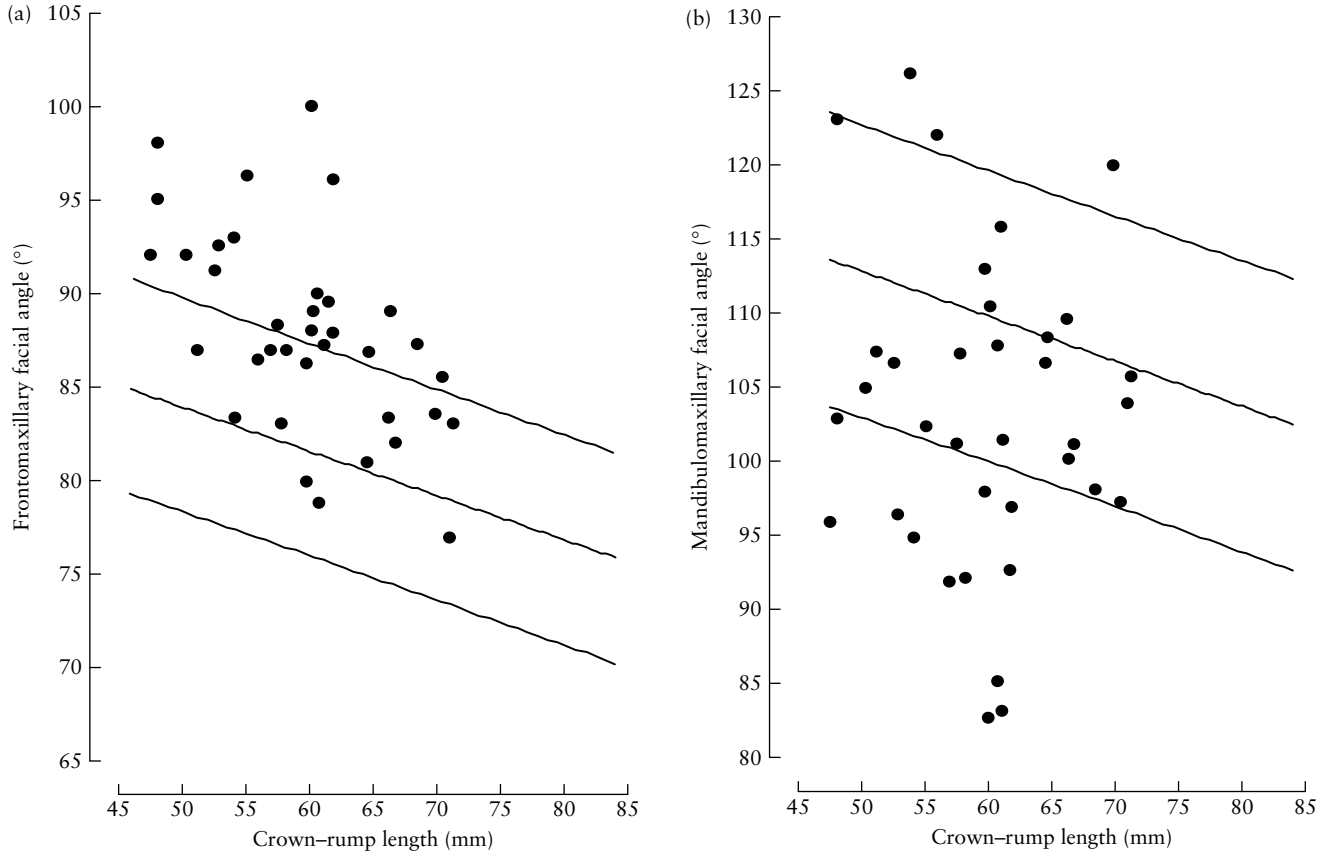

Figure 4 Frontomaxillary facial angle (a) and mandibulomaxillary facial angle (b) in trisomy 18 fetuses plotted on the appropriate reference range (mean, 5th and 95th centiles) for chromosomally normal fetuses.

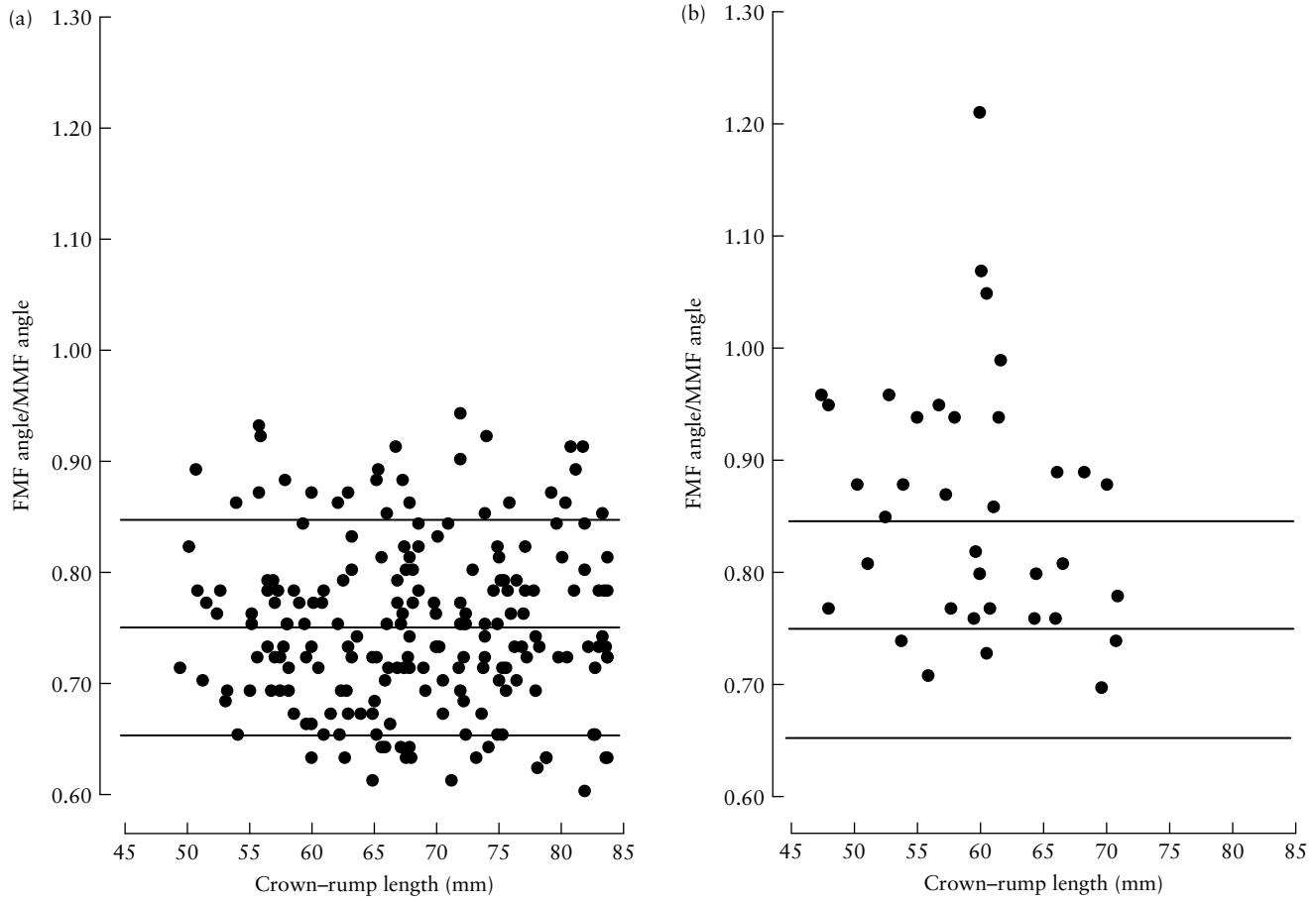

Figure 5 Ratio of frontomaxillary facial (FMF) angle to mandibulomaxillary facial (MMF) angle in chromosomally normal fetuses (a) and trisomy 18 fetuses (b) plotted on the reference range (mean, 5th and 95th centiles) for chromosomally normal fetuses.

constant. This finding suggests that within the gestational range of 11 + 0 to 13 + 6 weeks there is a progressive forward displacement of the upper palate with respect to both the forehead and the mandible. In the trisomy 18 fetuses the FMF angle was greater than normal, suggesting that in this chromosomal abnormality, as in trisomy 21, the maxilla is dorsally displaced with respect to the forehead. The additional findings of a smaller MMF angle and increased FMF to MMF ratio demonstrate that the well-described association between trisomy 18 and micrognathia/retrognathia is evident from the first trimester of pregnancy.

Effective first-trimester screening for both trisomy 21 and trisomy 18 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)[10,14,15]. The mid-sagittal view needed for measurement of the FMF angle is the same as that needed for measurement of NT and assessment of the nasal bone[12]. 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 that it is independent of NT thickness[8]. If in such screening the FMF angle is increased

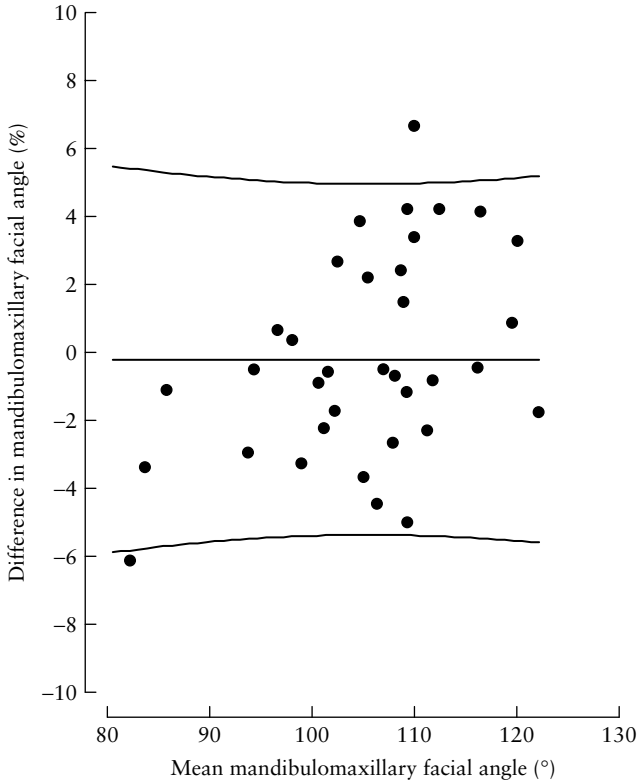

Figure 6 Interobserver agreement (Bland–Altman) expressed as percentage difference against the average of paired measurements for the mandibulomaxillary facial angle.

the sonographer should be alerted to the possibility that the fetus may be affected by trisomy 18 and should search for such first-trimester sonographic markers as reduced MMF angle, clenched hands and early-onset growth restriction, in addition to the more obvious exomphalos and megacystis[16]. In addition, at 11 + 0 to 13 + 6 weeks' gestation both trisomy 21 and trisomy18 are associated with increased NT thickness and low maternal serum PAPP-A, but in trisomy 21 serum free β-hCG tends to be high whereas in trisomy 18 free β-hCG is low[14,15].

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