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# Three-dimensional evaluation of mid-facial hypoplasia in fetuses with trisomy 21 at 11 + 0 to 13 + 6 weeks of gestation

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**KEYWORDS:** 3D ultrasound; first-trimester screening; maxilla; nasal bone; trisomy 21

## ABSTRACT

***Objective*** *To investigate the mid-facial hypoplasia of fetuses with trisomy 21 at 11 + 0 to 13 + 6 weeks of gestation, by three-dimensional (3D) evaluation of the maxilla and the nasal bones.*

***Methods*** *A 3D volume of the fetal head was obtained before fetal karyotyping at 11 + 0 to 13 + 6 (median 12) weeks of gestation in 80 fetuses that were subsequently found to have trisomy 21 and in 862 fetuses subsequently found to be chromosomally normal. The multiplanar mode was used to obtain a sequence of transverse views of the fetal face and to demonstrate the maxilla, the adjacent rami of the mandible and the nasal bones. The maxillary depth, defined as the distance between the alveolus of the maxilla in the midline anteriorly and the midpoint of the line joining the rami posteriorly, was measured. Ossification of the nasal bones was considered to be normal if both bones were more echogenic than the overlying skin.*

***Results*** *In the chromosomally normal group the maxillary depth increased linearly with crown–rump length (CRL) from 3.1 mm at a CRL of 45 mm to 4.8 mm at a CRL of 84 mm, and in the trisomy 21 fetuses the depth was significantly smaller than normal (mean difference = −0.3 mm,* $P < 0.001$*). There was no significant association between the delta maxillary depth and delta nuchal translucency thickness in either the trisomy 21 or the chromosomally normal fetuses. Impaired ossification of the nasal bones was observed in 3.1% of the chromosomally normal fetuses and in 60.0% of those with trisomy 21. The mean maxillary depth was significantly smaller in fetuses demonstrating impaired ossification than in those with normal ossification of the nasal bones (mean difference = −0.2 mm; 95% CI, −0.3 to −0.1,* $P = 0.001$*).*

***Conclusions*** *In a high proportion of fetuses with trisomy 21 there is sonographic evidence of mid-facial hypoplasia at 11 + 0 to 13 + 6 weeks of gestation. Copyright © 2006 ISUOG. Published by John Wiley & Sons, Ltd.*

## INTRODUCTION

Trisomy 21 is associated with mid-facial hypoplasia, which led to the original observation by Langdon Down that, in individuals with this condition, the face is flat[1]. Several radiological studies reported that in patients with trisomy 21 there is underdevelopment of the upper jaw, delayed dental growth, reduction in the number and size of teeth and absence or hypoplasia of the nasal bone[2–7]. Furthermore, prenatal sonographic studies have reported that at 11 + 0 to 13 + 6 weeks' gestation, a high proportion of fetuses with trisomy 21 have non-visible or hypoplastic nasal bones and shortening of the maxillary length[8–10].

The aim of this study was to investigate further the mid-facial hypoplasia in fetuses with trisomy 21 at 11 + 0 to 13 + 6 weeks by three-dimensional (3D) evaluation of the nasal bones and measurement of the maxilla.

## METHODS

A 3D volume of the fetal face was acquired before fetal karyotyping by chorionic villus sampling (CVS), at 11 + 0 to 13 + 6 weeks of gestation, in singleton pregnancies that had been evaluated for the risk of trisomy 21 by a combination of maternal age and fetal nuchal translucency (NT) thickness[11]. In 970 cases the 3D volume was obtained with the fetus in the mid-sagittal plane with the transducer parallel to the nose. All 3D examinations were carried out transabdominally (RAB 4-8L probe,

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Voluson 730 Expert, GE Medical Systems, Milwaukee, WI, USA), by sonographers with extensive experience in 3D ultrasonography. In addition, the fetal crown–rump length (CRL) and NT thickness were measured[11].

For the analysis of the maxilla and the nasal bones, the volume was displayed in the three orthogonal planes that compose the multiplanar mode of the 3D image. The sagittal view showing the fetal profile in this mode was then selected, and, as this plane was scrolled, the series of corresponding transverse and coronal images of the fetal face were simultaneously demonstrated. A transverse view showing the whole maxilla and adjacent rami of the mandible was obtained and the contrast was increased to highlight two echogenic 'circles' posteriorly, representing the rami, and a sonolucent circle anteriorly, representing the alveolus of the maxilla in the midline anteriorly (Figure 1). Two measurements were performed: the distance between the rami, and the maxillary depth, defined as the distance between the alveolus of the maxilla in the midline anteriorly and the midpoint of the line joining the rami posteriorly. In each case both nasal bones were examined and considered to be normal if both were more echogenic than the overlying skin, or hypoplastic if one or both were either absent or their echogenicity was the same or less than that of the skin (Figure 2).

### Statistical analysis

In the chromosomally normal group, regression analysis was used to determine the significance of the association between the CRL and the distance between the rami and the maxillary depth. Each measurement in both the chromosomally normal and the trisomy 21 fetuses was then expressed as a difference from the expected normal

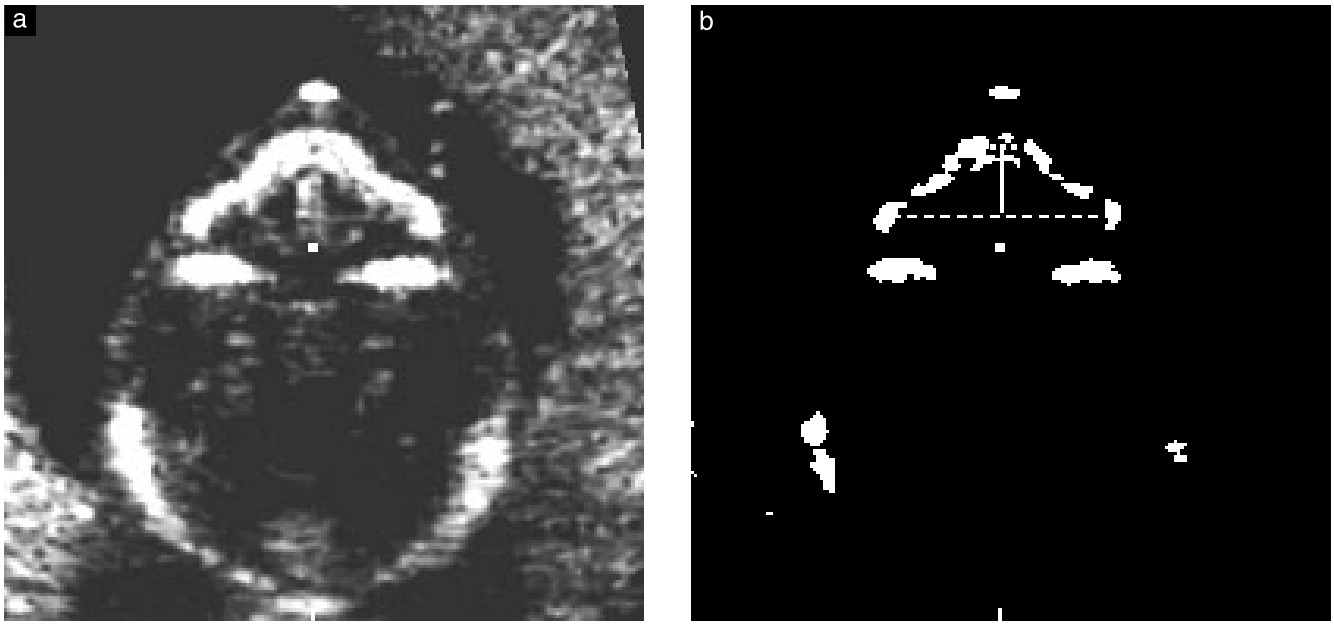


**Figure 1** (a) Transverse view through the maxilla in a fetus of 12 weeks' gestation. (b) The contrast was increased to highlight two echogenic 'circles' posteriorly, representing the rami of the mandible, and a sonolucent circle anteriorly, representing the alveolus in the midline of the maxilla. The horizontal dashed line is the distance between the rami, and the vertical solid line is the maxillary depth.

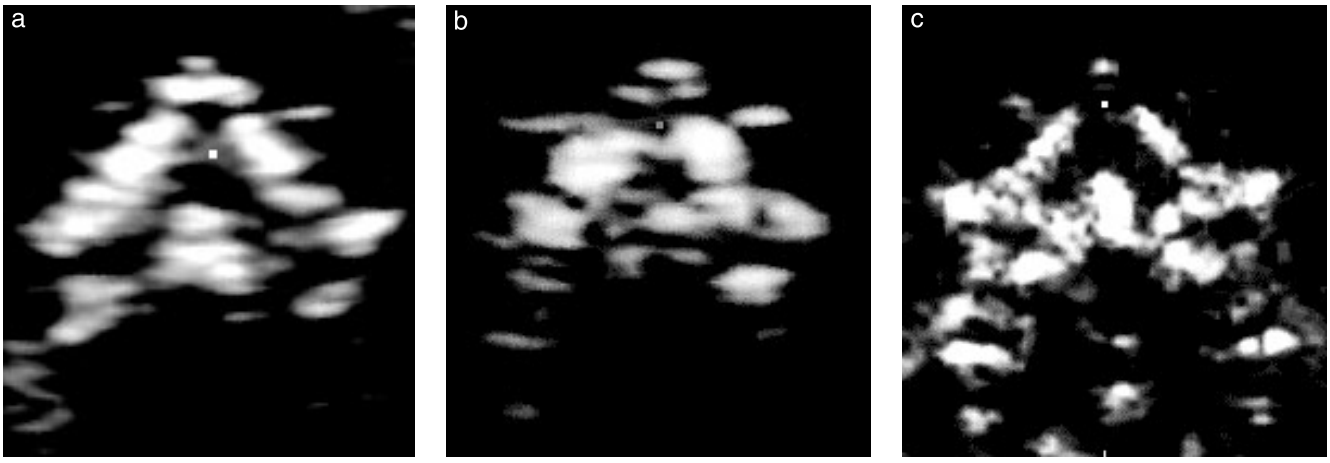


**Figure 2** Transverse views of the fetal nasal bones. In (a) the nasal bones are more echogenic than the overlying skin, in (b) the nasal bones are less echogenic than the skin, and in (c) there is absence of both nasal bones.

 

mean for CRL (delta value). The Kolmogorov–Smirnov test confirmed that the delta values in both groups were normally distributed. Independent-samples *t*-test was used to determine the significance of differences in the delta values between the chromosomally normal and trisomy 21 fetuses and between fetuses with normal and hypoplastic nasal bones. Regression analysis was used to determine the significance of the association between delta maxillary depth and delta NT thickness both in the chromosomally normal and trisomy 21 fetuses.

In 30 cases, the Bland–Altman analysis was used to compare the measurement agreement and bias for a single examiner and between different examiners[12]. The data were analyzed using the statistical software SPSS 13.0 (Chicago, Illinois, USA) and Excel for Windows 2000 (Microsoft Corp., Redmond, WA, USA). $P < 0.05$ was considered statistically significant.

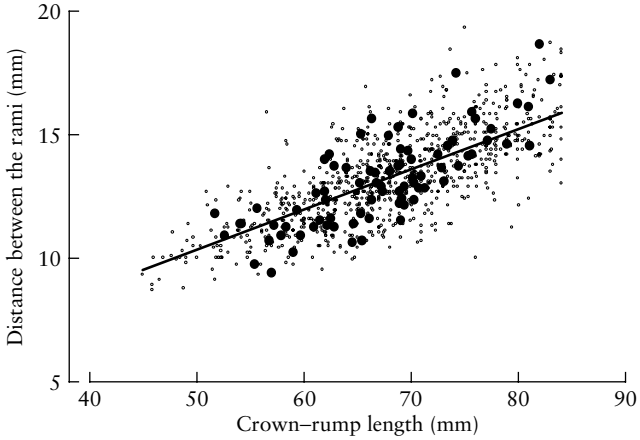


**Figure 3** Distance between the rami in relation to crown–rump length in chromosomally normal (open dots) and trisomy 21 (filled circles) fetuses. The diagonal line is the regression line for the chromosomally normal fetuses.

## RESULTS

The median maternal age was 36 (range, 17–47) years, the median fetal CRL was 68 (range, 45–84) mm and the median gestation was 12 (range, 11 + 0 to 13 + 6) weeks. The fetal maxilla and nasal bones were successfully examined in all cases. The fetal karyotype was normal in 862 cases and abnormal in 108, including trisomy 21 ($n = 80$), trisomy 18 ($n = 18$), trisomy 13 ($n = 2$), sex chromosome aneuploidy ($n = 7$) and deletion 4q ($n = 1$).

In the chromosomally normal group the distance between the rami and the maxillary depth increased linearly with CRL, from 9.5 mm and 3.1 mm, respectively, at a CRL of 45 mm to 15.9 mm and 4.8 mm at a CRL of 84 mm (distance between the rami in mm = 2.1315 + (0.1641 × CRL in mm), SD = 1.25810, $r = 0.735$, $P < 0.001$; maxillary depth in mm = 1.1068 + (0.0444 × CRL in mm), SD = 0.53833, $r = 0.564$, $P < 0.001$; Figures 3 and 4).

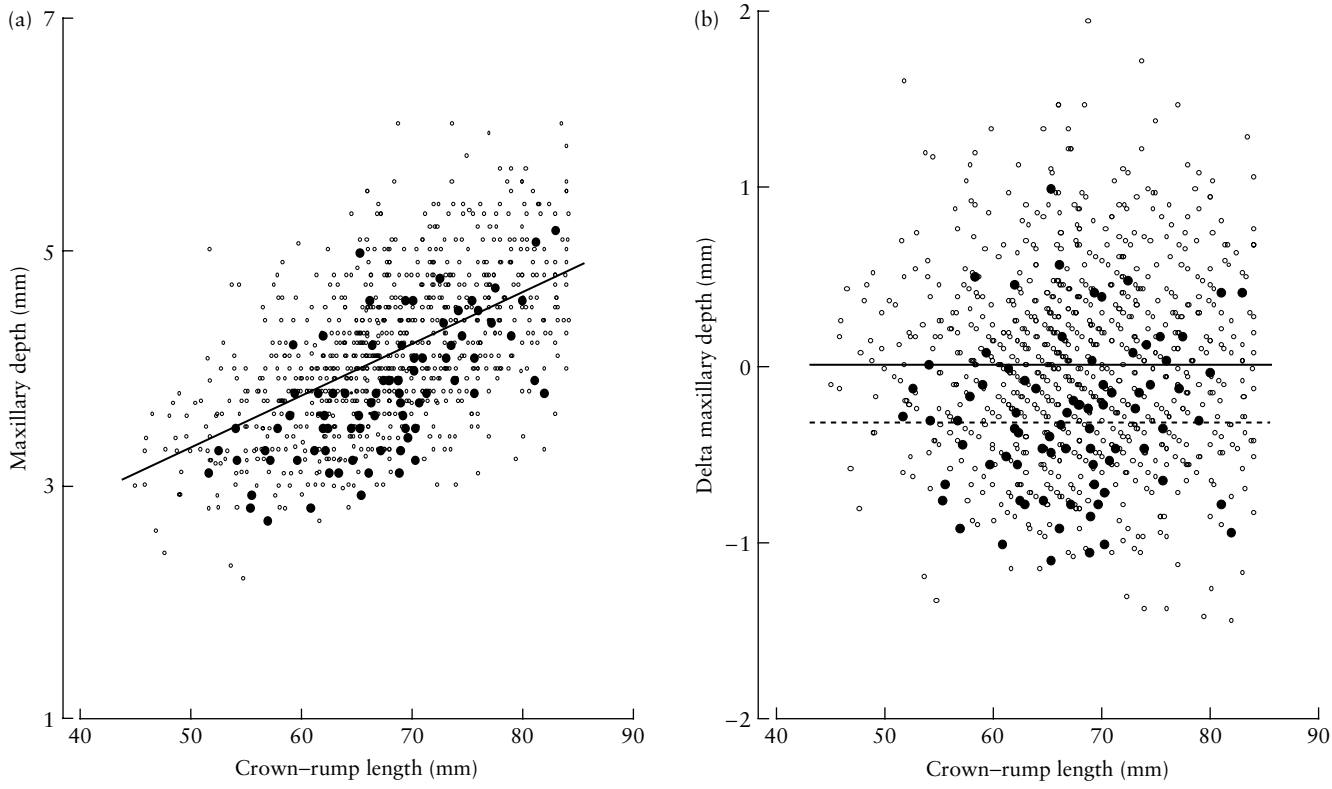


**Figure 4** (a) Maxillary depth in relation to crown–rump length (CRL) in chromosomally normal (open dots) and trisomy 21 (filled circles) fetuses. The diagonal line is the regression line for the chromosomally normal fetuses. (b) Plot of the difference of individual values from the normal mean for CRL (delta value). The solid horizontal line is the regression line for the chromosomally normal group and the dashed line is the regression line for the trisomy 21 group.

**Table 1** Findings of nasal bones in the chromosomally normal and trisomy 21 fetuses

| | *Fetal karyotype* (n) | |
|---|---|---|
| *Nasal bones* | *Normal* | *Trisomy 21* |
| Echogenic–echogenic | 835 | 32 |
| Echogenic–hypoechoic | 2 | 3 |
| Echogenic–sonolucent | 0 | 2 |
| Hypoechoic–hypoechoic | 15 | 11 |
| Hypoechoic–sonolucent | 0 | 2 |
| Sonolucent–sonolucent | 10 | 30 |

**Table 2** Mean percentage difference and the 95% limits of agreement between paired measurements by the same sonographer and between paired measurements by different observers

| | *Mean percentage difference and 95% CI* |
|---|---|
| Intraobserver | |
| Distance between rami | −0.79 [−6.88 (−8.80 to −4.95) to 5.29 (3.37 to 7.21)] |
| Maxillary depth | −0.33 [−10.06 (−13.13 to −6.98) to 9.40 (6.32 to 12.48)] |
| Interobserver | |
| Distance between rami | 1.43 [−6.16 (−8.56 to −3.76) to 9.02 (6.62 to 11.42)] |
| Maxillary depth | −2.08 [−7.90 (−11.05 to −4.74) to 12.05 (8.90 to 15.21)] |

In the fetuses with trisomy 21 the median delta maxillary depth was significantly smaller than the normal median for CRL (mean difference = −0.3 mm; 95% CI, −0.4 to −0.2 mm; $P < 0.001$) and it was below the median and the 5$^{th}$ centile of the normal range in 63 (78.8%) and 8 (10.0%) cases, respectively (Figure 4). There was no significant association between the delta maxillary depth and delta NT in either the trisomy 21 ($r = 0.067$, $P = 0.556$) or the chromosomally normal fetuses ($r = 0.001$, $P = 0.996$).

The nasal bone was considered to be hypoplastic in 60.0% (48/80) of fetuses with trisomy 21 and in 3.1% (27/862) of normal fetuses (Table 1). The findings for the first 31 of our 80 fetuses have been reported previously[13].

The maxillary depth was significantly smaller in fetuses with hypoplastic nasal bone than in fetuses with present nasal bone (mean difference = −0.2 mm; 95% CI, −0.3 to −0.1, $P = 0.001$).

The mean percentage difference and the 95% limits of agreement between paired measurements of the distance between the rami and maxillary depth by the same sonographer and between paired measurements by different observers are shown in Table 2.

## DISCUSSION

This 3D study has demonstrated that in chromosomally normal fetuses at 11 + 0 to 13 + 6 weeks' gestation both nasal bones are visible and their echogenicity is greater than that of the overlying skin in about 97% of cases. The increased echogenicity presumably reflects ossification of the bones. In the other 3% of cases there is impaired ossification of one or both nasal bones, as evidenced by their being either sonolucent or their echogenicity being the same or less than that of the overlying skin.

The finding that in about 60% of trisomy 21 fetuses there is impaired ossification of the nasal bones is compatible with previous reports from two-dimensional (2D) ultrasound studies[8,9]. In most previous studies the nasal bones were classified as normal or abnormal, but in this study we provide further details on the definition of impaired ossification. Thus, in two-thirds of our trisomy 21 fetuses with impaired ossification the bones were not visible and in one-third they were of the same or less echogenicity than the overlying skin. Furthermore, in about 10% of the cases with impaired ossification, the defect was unilateral. Two previous 3D ultrasound studies of mid-trimester fetuses with trisomy 21 have also reported that in some cases there is a unilateral defect of the nasal bones[14,15]. Thus, Gonçalves *et al.* examined 26 fetuses and reported bilateral and unilateral absence or hypoplasia of the nasal bones in 19 and one cases, respectively[14]. Benoit and Chaoui examined 20 fetuses and reported bilateral and unilateral absence of the nasal bones in six and three cases, respectively[15].

In this study we investigated two potential markers of impaired maxillary development, which is well documented in postnatal studies of patients with trisomy 21. In both the chromosomally normal and trisomy 21 fetuses the distance between the rami of the mandible and the maxillary depth increased linearly with CRL. In trisomy 21 fetuses, compared to normal fetuses, the distance between the rami was not significantly altered but the maxillary depth was smaller. Furthermore, the maxillary depth was smaller in fetuses demonstrating impaired ossification of the nasal bones than in those with normal bones.

The findings of maxillary depth are compatible with those of a previous study in which we measured maxillary length[10]. In that study we used 2D ultrasonography to obtain a mid-sagittal view of the fetal profile, after which the transducer was then gently angled laterally so that both the maxillary bone and mandible, including the ramus and condylar process, could be seen[10]. However, accurate measurement of the maxilla can be difficult and sometimes impossible, because the end of the maxilla often overlaps with the ramus and condylar process of the mandible. This problem has been overcome by the use of 3D ultrasonography and the decision to measure the depth, rather than the length, of the maxilla. This measurement relies on obtaining the correct transverse plane, which is facilitated by the multiplanar function of 3D ultrasound, and on the identification of three easily defined landmarks – the alveolus of the maxilla in the midline anteriorly and the two rami of the mandible posteriorly.

Measuring the maxillary depth of fetuses by 3D ultrasonography is probably not useful in identifying trisomy 21, because the value was below the 5$^{th}$ centile of the

normal range in only 10% of fetuses with trisomy 21, and the average difference in maxillary depth between normal and abnormal fetuses was 0.3 mm, which is within the axial resolution of the ultrasound system. Nevertheless, the finding that in a high proportion of fetuses with trisomy 21 there is sonographic evidence of mid-facial hypoplasia is compatible with the original observation of Langdon Down that in patients with trisomy 21 there is flattening of the face. Furthermore, we have documented that this phenotypic expression of the condition is evident from the third month of intrauterine life.

The development of the facial bones is intimately related to the migration of neuroectodermal cells from the crest of the neural tube. Cells arising from different regions of the neural tube migrate forwards and downwards towards, firstly, the mandible; secondly, the maxilla; and thirdly, the frontonasal region[16–18]. Previous studies suggested that many facial abnormalities may be the consequence of impaired migration or inadequate function of neural crest cells[17]. This could also be the underlying mechanism for the observed impairment in both the growth of the maxilla and the ossification of the nasal bones in trisomy 21.

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