

Prenasal thickness in trisomy-21 fetuses at 16–24 weeks of gestation

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ABSTRACT

Objective To construct a reference range for fetal prenasal thickness between 16 and 24 weeks of gestation and to evaluate the thickness in fetuses with trisomy 21.

Methods We acquired three-dimensional (3D) volumes of the fetal profile from 135 normal fetuses and 26 fetuses with trisomy 21 at 16–24 weeks' gestation. We used the multiplanar mode to obtain the exact mid-sagittal plane and measured the prenasal thickness as the shortest distance between the anterior edge of the lowest part of the frontal bone (at the junction with the nasal bone when present) and the skin anteriorly.

Results In the normal group prenasal thickness increased with gestation from a mean of 2.4 mm at 16 weeks to 4.6 mm at 24 weeks. Repeatability studies demonstrated that in 95% of the cases the difference between two measurements of prenasal thickness by the same operator and by different operators was less than 1 mm. In the trisomy-21 fetuses the mean prenasal thickness was significantly larger than in normal fetuses and in 19 (73.1%) cases it was above the 95th centile of the normal range. There was no significant difference in prenasal thickness between the trisomic fetuses with and without ventriculomegaly, nuchal edema, absent nasal bone or a cardiac defect.

Conclusions The fetal profile is routinely examined during the second-trimester scan and therefore the skill needed to obtain the view necessary for the measurement of prenasal thickness is widely available. If the finding of our study – that in more than 70% of fetuses with trisomy 21 prenasal thickness is above the 95th centile – is confirmed in prospective screening studies this measurement alone could prove a highly sensitive method of second-trimester screening for trisomy 21. Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

An excessive amount of skin is a common feature in individuals with trisomy 21, as originally described by Langdon Down in 1866¹. Extensive studies have documented this excessive amount of skin as increased nuchal translucency thickness in the first trimester and increased nuchal fold thickness in the second trimester^{2–5}. More recently Maymon *et al.* reported that in second-trimester trisomy-21 fetuses the prenasal skin thickness, between the frontonasal angle and the outer border of the skin edge, is increased⁶; in 58% of 21 fetuses with trisomy 21 at 14–27 weeks of gestation the prenasal thickness was above the 95th centile of 500 normal fetuses.

The aim of this three-dimensional (3D) ultrasound study was to construct a reference range for fetal prenasal thickness between 16 and 24 weeks' gestation and to evaluate further the thickness in fetuses with trisomy 21.

METHODS

We measured prenasal thickness using 3D volumes of the fetal face that had been acquired from two groups of patients. The first group comprised 135 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 16–24 weeks, and for this study we prospectively selected 15 consecutive cases per gestational week. The second group comprised 26 fetuses with trisomy 21 confirmed by chorionic villus sampling or amniocentesis, which were carried out because of a high suspicion for a chromosomal defect. In 14 (53.8%) 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 chromosomal defect, including mild ventriculomegaly ($n = 5$), nuchal edema ($n = 9$), absent

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nasal bone ($n = 7$), cardiac defect ($n = 11$), intracardiac echogenic focus ($n = 4$), hyperechogenic bowel ($n = 3$), collapsed stomach ($n = 2$), duodenal atresia ($n = 1$), mild hydronephrosis ($n = 3$), short femur ($n = 4$), talipes ($n = 2$), clinodactyly ($n = 2$), cleft lip and palate ($n = 1$), choroid plexus cyst ($n = 1$) and sandal gap ($n = 1$).

In each case transabdominal ultrasonography was carried out by sonographers with extensive experience in 3D ultrasound, using a RAB 4-8L probe (Voluson 730 Expert, GE Medical Systems, Milwaukee, WI, USA). A 3D volume of the fetal head was acquired in the mid-sagittal plane of the face with the transducer parallel to or within 30° of the long axis of the nose. The 3D volumes were examined off-line using the multiplanar mode to confirm the exact mid-sagittal plane and to make minor corrections from the original acquisition plane when necessary. The exact mid-sagittal plane was defined by the presence of the tip of the nose, the palate without the zygomatic bone and the translucent diencephalon at 16 weeks and the corpus callosum at 17–24 weeks. Prenasal thickness was defined as the shortest distance between the anterior edge of the lowest part of the frontal bone (at the junction with the nasal bone when present) and the facial skin anteriorly (Figure 1). This is essentially the same technique as that used in the study by Maymon *et al.*, who reported the distance between the skin and the junction between the frontal and nasal bone⁶, but we selected the lowest part of the frontal bone because the nasal bone is absent in about one-third of fetuses with trisomy 21.

All the measurements were made by sonographers who were not aware of the fetal karyotype. In addition one of the sonographers measured 30 randomly selected cases on two occasions, and in 30 cases the measurement was performed by two different operators to assess repeatability.

Statistical analysis

Regression analysis was used to determine the significance of the association between prenatal thickness and gestational age. The Kolmogorov–Smirnov test was used to confirm the normality of the distribution of the prenatal thickness measurement in chromosomally normal and trisomy-21 fetuses. The values of prenatal thickness were then expressed as a difference from the appropriate expected mean for gestation (delta value). The Kolmogorov–Smirnov test was used to confirm the normality of the distribution of the delta values in the normal and trisomy-21 fetuses. The Mann–Whitney *U*-test for independent samples was used to compare mean prenatal thickness delta values between normal fetuses and trisomy-21 fetuses, and it was also used to compare, within the trisomy-21 group, those with and without common defects (ventriculomegaly, nuchal edema, absent nasal bone and cardiac defect). Bland–Altman analysis was used to compare the measurement agreement and bias for a single examiner and between two examiners⁷. 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 to be statistically significant.

RESULTS

In the 135 normal fetuses the median maternal age was 32 (range, 16–44) years and the median gestational age (GA) was 20 (range, 16–24) weeks. Prenatal thickness increased with gestational age following a second order polynomial trend from 2.4 mm at 16 weeks to 4.6 mm at 24 weeks (prenatal thickness = $-12.000 + (1.315 \times \text{GA}) - (0.026 \times \text{GA}^2)$; $r = 0.781$, $P < 0.01$, $\text{SD} = 0.993$;

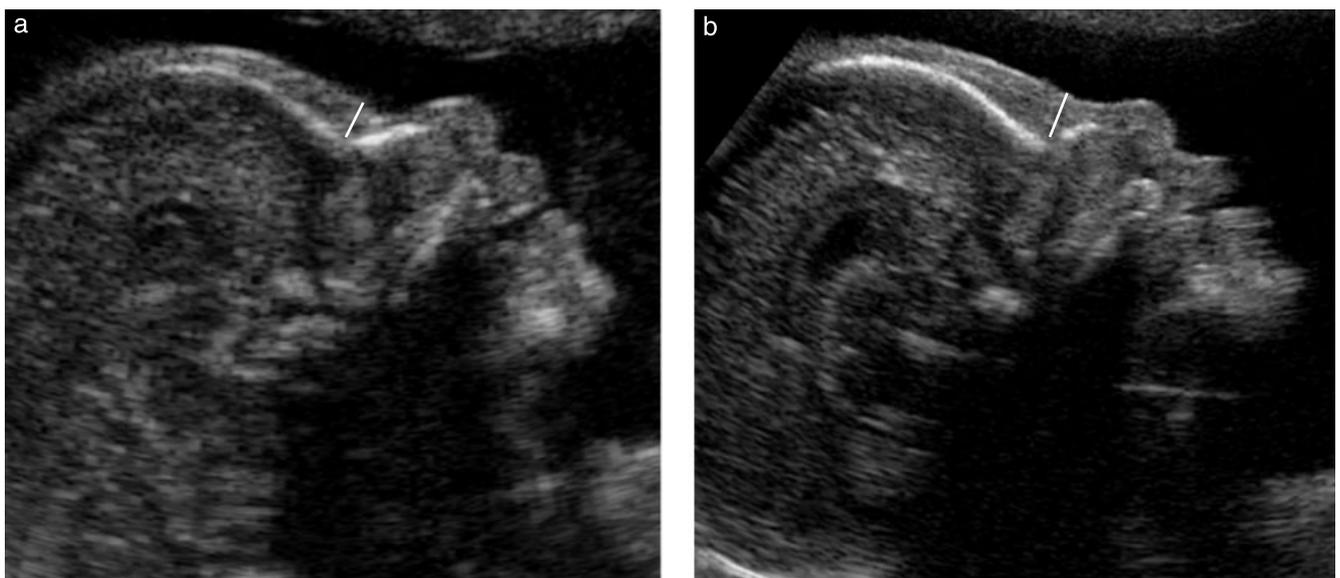


Figure 1 Ultrasound images of normal (a) and trisomy-21 (b) fetuses demonstrating the measurement of prenatal thickness as the shortest distance between the anterior edge of the lowest part of the frontal bone and the facial skin. Note that in the mid-sagittal plane the tip of the nose, the palate without the zygomatic bone and the corpus callosum are visible.

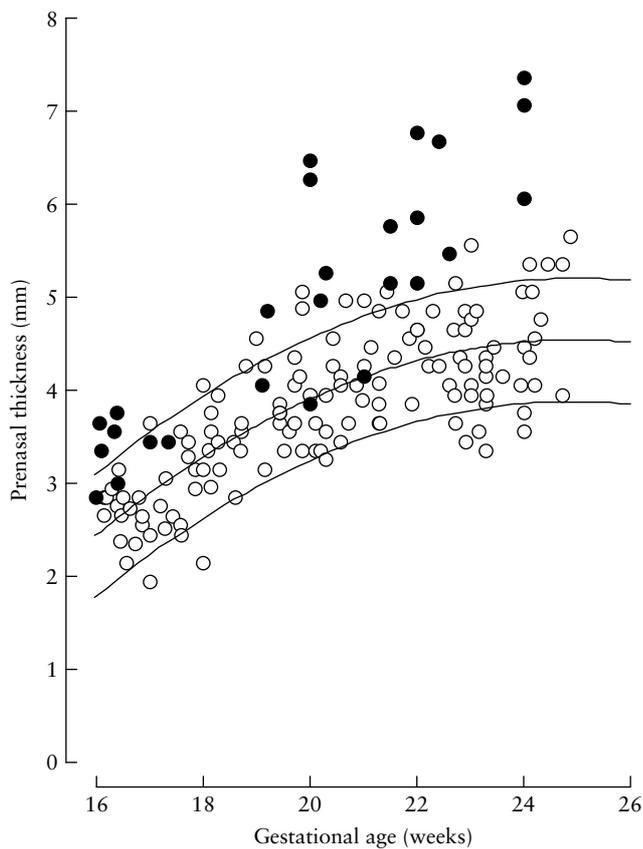


Figure 2 Variation of prenasal thickness with gestation in 135 normal fetuses (○) and 26 fetuses with trisomy 21 (●), plotted on the reference range (mean, 5th and 95th percentiles) of the normal fetuses.

Figure 2). The mean delta prenasal thickness was -0.166 (95% CI, -0.251 to -0.080) mm.

In the 26 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. Prenasal thickness was above the mean of the normal range in 25 (96.2%) and above the 95th centile of the normal range in 19 (73.1%) fetuses, respectively (Figure 2). In the trisomy-21 fetuses delta prenasal thickness was significantly greater than in the normal fetuses (mean 1.089 (95% CI, 0.767 – 1.412) mm; $P < 0.01$) and the delta prenasal thickness increased significantly with gestation ($r = 0.500$, $P < 0.01$). The nasal bone was present in all the 135 normal fetuses and absent in 7 (26.9%) of the 26 fetuses with trisomy 21. There was no significant difference in the mean delta prenasal thickness between those with and without ventriculomegaly ($P = 0.705$), nuchal edema ($P = 0.261$), absent nasal bone ($P = 0.279$) or cardiac defects ($P = 0.938$).

The mean difference and the 95% limits of agreement between paired measurements of prenasal thickness (mm) by the same observer were -0.063 (-0.489 (95% CI, -0.558 to -0.421) to 0.363 (95% CI, 0.294 to 0.431)) and the respective values in paired measurements by the two different observers were 0.090 (-0.360 (95% CI, -0.432 to -0.287) to 0.540 (95% CI, 0.467 to 0.612)) (Figure 3).

DISCUSSION

The findings of this study confirm that in fetuses with trisomy 21 during the second trimester of pregnancy there is increased prenasal thickness. In the normal fetuses prenasal thickness increased with gestation from a mean of 2.4 mm at 16 weeks to 4.6 mm at 24 weeks, which is similar to the reference range reported by Maymon *et al.*⁶. In their study the distribution of prenasal thickness was skewed and the values in both the normal and trisomy-21 groups were reported as multiples of the median. In our study the distribution of prenasal thickness with gestation was Gaussian, the SD did not change with gestation and we expressed the values in the normal and trisomy-21 groups as deltas (differences in mm from the normal mean for gestation). In the trisomy-21 group prenasal thickness was above the 95th centile of our normal range in 73.1% of our 26 fetuses, compared with 72% of the 18 fetuses reported by Maymon *et al.*⁶ at 18–24 weeks. The measurement of prenasal thickness is reproducible and in 95% of the cases the difference between two measurements by the same operator and by different operators was less than 1 mm.

In this study all the cases of trisomy 21 had been identified by prior screening through maternal age, second-trimester serum biochemistry or routine ultrasound examination, and in 25 of the 26 cases there was a fetal abnormality or sonographic marker of chromosomal defect. However, there was no significant association between prenasal thickness and any of the commonly detected defects, including nuchal edema. It is therefore reasonable to assume that our findings on prenasal thickness 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 β -human chorionic gonadotropin and pregnancy-associated plasma protein-A, with a detection rate of 90% for a false positive rate of 5%⁸. The incorporation of additional sonographic markers, such as nasal bone, frontomaxillary facial 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%⁸. In the second trimester screening by maternal age and maternal serum biochemistry has detection rates of 30% and 65%, respectively, for a false positive rate of 5%^{9,10}. 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 are observed in a minority of affected fetuses¹¹. If the finding of our study – that at 16–24 weeks prenasal thickness is above the 95th centile in more than 70% of trisomy-21 fetuses – is confirmed in prospective screening studies this measurement alone could prove the most sensitive method of second-trimester screening for trisomy 21.

The fetal profile is routinely examined during the second-trimester scan and therefore the skill needed to

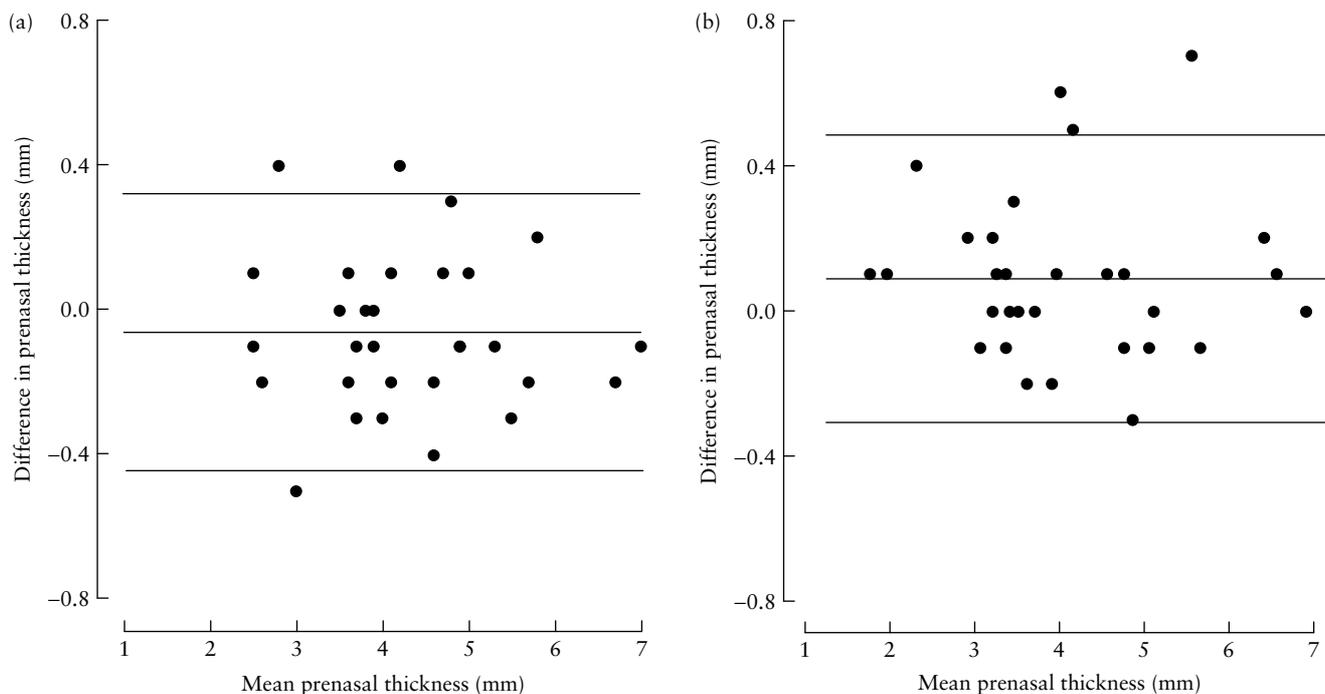


Figure 3 Mean difference and the 95% limits of agreement between paired measurements of the prenatal thickness by the same sonographer (a) and between paired measurements by two different observers (b).

obtain the view necessary for the measurement of prenatal thickness is widely available. Furthermore, the same view can be used for assessment of the nasal bone. The finding of this study that the nasal bone is absent in about 27% of trisomy-21 fetuses is compatible with the results of previous studies¹². The additional finding that in trisomy-21 fetuses prenatal thickness appears to be independent of the presence or absence of the nasal bone suggests that the two sonographic markers could be combined for an even higher detection rate of affected fetuses. A third promising sonographic marker that can be assessed in the same profile view is the frontomaxillary facial angle, which has recently been reported to be above the 95th centile in about 65% of fetuses with trisomy 21¹³.

In this study we used the multiplanar mode of 3D ultrasound to ensure accurate measurement of prenatal thickness in the exact mid-sagittal plane. However, the landmarks defining this plane, including the tip of the nose, the palate without the zygomatic bone and the diencephalon or corpus callosum, can easily be identified by two-dimensional ultrasonography. Large-scale prospective studies are now needed to determine the performance of second-trimester screening for trisomy 21 by prenatal thickness and combinations with the nasal bone and frontomaxillary facial angle as well as serum biochemistry.

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