

Sphenofrontal distance on three-dimensional ultrasound in euploid and trisomy-21 fetuses at 16–24 weeks' gestation

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KEYWORDS: 3D ultrasound; second trimester; sphenofrontal distance; trisomy 21

ABSTRACT

Objective To compare the distance between the sphenoid and frontal bones on three-dimensional (3D) ultrasound in euploid and trisomy-21 fetuses at 16–24 weeks' gestation.

Methods We acquired 3D volumes of the fetal profile from 80 normal and 30 trisomy-21 fetuses at 16–24 weeks' gestation. We used the multiplanar mode to obtain the mid-sagittal plane and measured the sphenofrontal distance as the shortest distance between the most anterior edge of the sphenoid bone and the lowest edge of the frontal bone.

Results In normal fetuses, the sphenofrontal distance increased linearly with gestational age, from 15.1 mm at 16 weeks to 18.2 mm at 24 weeks. In fetuses with trisomy 21, the mean sphenofrontal distance delta value was significantly smaller than in normal cases (-3.447 mm (95% CI, -5.684 to -1.211 mm); $P < 0.01$). The sphenofrontal distance was below the 5th and 1st percentiles of the normal range in 29 (96.7%) and 27 (90.0%) trisomy-21 fetuses, respectively.

Conclusions The sphenofrontal distance is shorter at 16–24 weeks' gestation in fetuses with trisomy 21 than in normal fetuses. A reduction in the growth of the anterior cranial base contributes to the mid-facial hypoplasia observed in fetuses with trisomy 21. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

Ultrasound examination of the fetal profile in the second and third trimesters of pregnancy enables the assessment of several facial measurements that are significantly different in fetuses with trisomy 21 from in those that

are chromosomally normal. Previous studies have shown that trisomy-21 fetuses have an increased prevalence of nasal bone absence or hypoplasia¹, prenatal thickening², wide frontomaxillary facial angle³, increased prenatal thickness (PT):nasal bone (NB) length ratio⁴ and high prefrontal space ratio (PFSR)⁵.

Postnatal radiological studies have shown that individuals with trisomy 21 also have growth reduction in the sagittal portion of the endocranium, mid-facial area, cranial base and frontal bone^{6–9}. These changes lead to vertical hypoplasia of the central structures of the cranium, lowering the position of the sella turcica and flattening the cranial base. It has been reported that children and infants with trisomy 21 have a significantly shorter anterior cranial base length than do normal controls^{8,9}.

The aim of this study was to compare the distance between the sphenoid and frontal bone on three-dimensional (3D) ultrasound, as a measure of the anterior cranial base length, in fetuses with trisomy 21 and in normal fetuses at 16–24 weeks' gestation.

METHODS

We examined the fetal profile using stored 3D ultrasound volumes of the fetal head that had been acquired from pregnant women undergoing an ultrasound examination for any indication at our fetal medicine units between 16 and 24 weeks' gestation. One operator selected the 3D volumes from two groups of patients. The first group comprised 80 appropriately growing fetuses with no sonographic evidence of fetal abnormality. The second group comprised 30 fetuses with trisomy 21, confirmed by chorionic villus sampling or amniocentesis that was carried out because of a high risk for aneuploidy. In 19 (63.3%) cases maternal age was 35 years or more and in 21 (70.0%) cases there was at least one fetal

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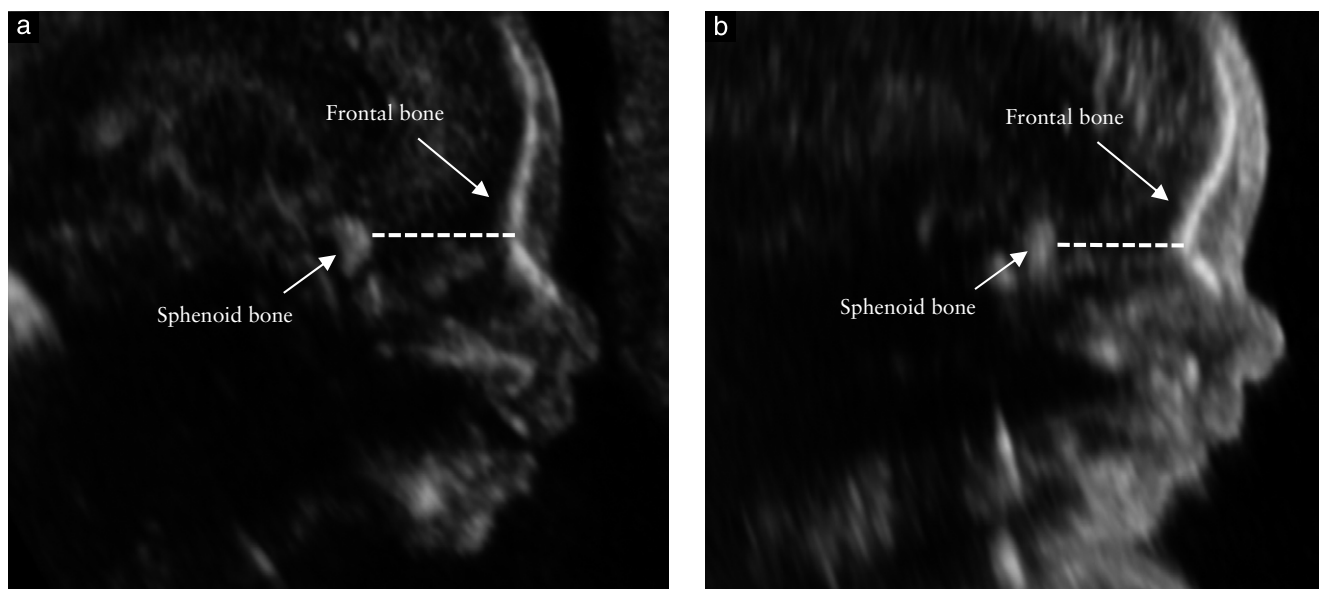


Figure 1 Ultrasound images of facial profile of a euploid fetus (a) and a fetus with trisomy 21 (b) at 20 weeks' gestation, showing measurement of sphenofrontal distance (-----).

abnormality or sonographic marker of chromosomal defect, including cardiac defects ($n = 7$), duodenal atresia ($n = 1$), facial cleft ($n = 1$), mild ventriculomegaly ($n = 4$), nuchal edema ($n = 10$), intracardiac echogenic focus ($n = 3$) and hyperechogenic bowel ($n = 4$).

Each 3D ultrasound volume of the fetal head was acquired transabdominally in the mid-sagittal plane using a RAB 4–8-MHz probe (Voulson 730 and E8 Expert, GE Medical Systems, Zipf, Austria), ensuring that the angle between the transducer and the long axis of the fetal nose was close to 45° . The 3D volumes were examined offline by an operator who was not aware of the clinical information or fetal karyotype, 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 nose, upper and lower lips, the maxilla (primary palate) and chin anteriorly, and by the presence of the secondary palate with the overlying vomeral bone posteriorly¹⁰. The anterior portion of the sphenoid bone was visualized on the image as an echogenic bony structure positioned dorsally and superiorly with respect to the posterior edge of the vomeral bone. The sphenofrontal distance was measured from the most anterior edge of the sphenoid bone to the lowest edge of the frontal bone using on-screen calipers (Figure 1).

In 50 randomly selected cases the sphenofrontal distance was measured independently by two operators to assess interobserver agreement, and in 60 randomly selected cases the distance was measured on two occasions by the same operator to assess intraobserver agreement.

Statistical analysis

Regression analysis was used to determine the significance of the association between sphenofrontal distance and

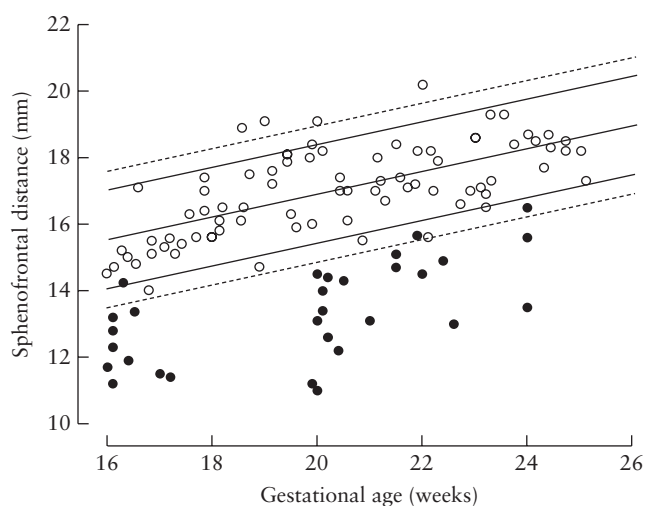


Figure 2 Sphenofrontal distance against gestational age in 80 euploid (○) and 30 trisomy-21 (●) fetuses, plotted on 5th, 50th and 95th (—) and 1st and 99th (-----) percentiles of normal range.

gestational age (GA). The Kolmogorov–Smirnov test was used to confirm the normality of the measurements in chromosomally normal and trisomy-21 fetuses. The values of sphenofrontal distance were then expressed as a difference from the appropriate expected mean for GA (delta value). Independent samples *t*-test was used to compare mean sphenofrontal distance delta values between normal and trisomy-21 fetuses. Bland–Altman analysis was used to compare the measurement agreement and bias for a single observer and between two observers¹¹.

The data were analyzed using the statistical package SPSS 19.0 (IBM Corp., Armonk, NY, USA) and Excel for Windows 2010 (Microsoft Corp., Redmond, WA, USA), and $P < 0.05$ was considered statistically significant.

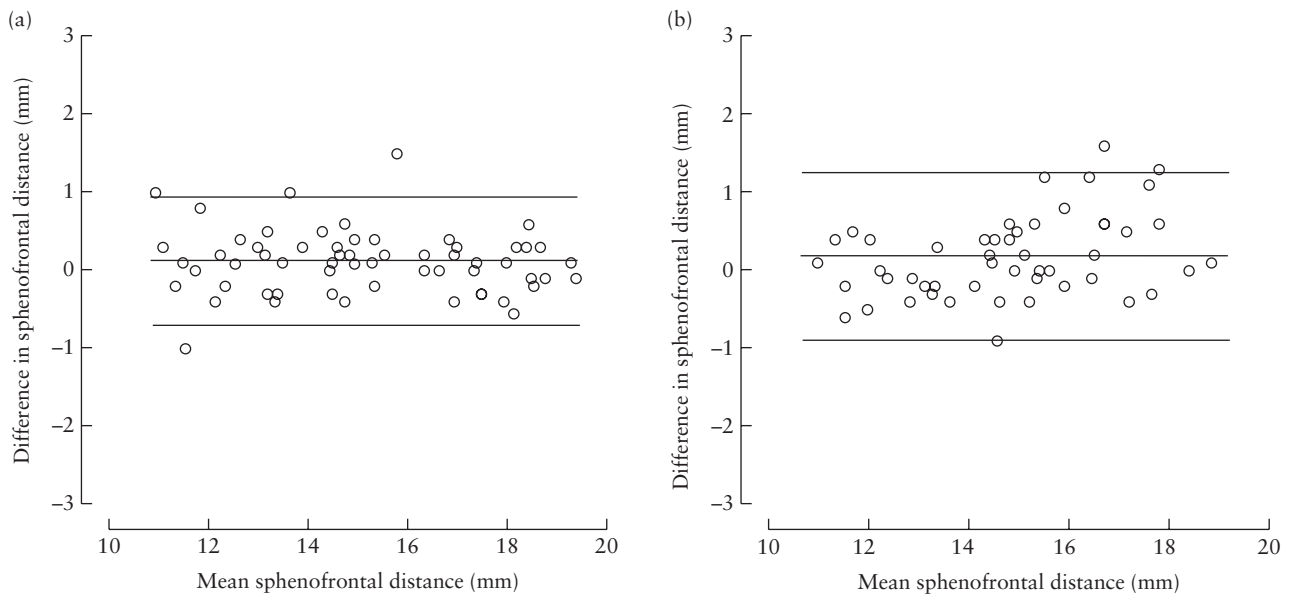


Figure 3 Mean difference and 95% limits of agreement between paired measurements of sphenofrontal distance at 16–24 weeks' gestation in fetuses with trisomy 21 and normal fetuses, obtained by same observer (a) and by two different observers (b).

RESULTS

In the 80 normal fetuses, median maternal age was 32 (range, 16–44) years and median GA at examination was 20 (range, 16–24) weeks. The median sphenofrontal distance increased linearly with GA, from 15.1 mm at 16 weeks to 18.2 mm at 24 weeks (sphenofrontal distance = $10.079 + (0.342 \times \text{GA})$; $r = 0.654$; $P < 0.01$; SD, 0.886).

In the 30 fetuses with trisomy 21, median maternal age was 36 (range, 20–44) years and median GA at examination was 20 (range, 16–24) weeks. In this group, mean sphenofrontal distance delta value was significantly smaller than that of normal fetuses (-3.447 mm (95% CI, -5.684 to -1.211 mm); $P < 0.01$). The sphenofrontal distance was below the 5th and 1st percentiles of the normal range in 29 (96.7%) and 27 (90.0%) fetuses, respectively (Figure 2).

The mean difference and 95% limits of agreement (LOA) between paired measurements of sphenofrontal distance made by the same observer were 0.113 mm (95% LOA, -0.674 to 0.901 mm) and the mean difference between paired measurements made by two different observers was 0.178 mm (95% LOA, -0.856 to 1.212 mm) (Figure 3).

DISCUSSION

The findings of this study provide evidence that the sphenofrontal distance is reduced at 16–24 weeks' gestation in fetuses with trisomy 21 compared with normal cases. Our results are consistent with those of previous postnatal studies examining cephalometric parameters in individuals with trisomy 21. Alio *et al.*⁸ measured the distance between the mid-point of the sella turcica and the nasion (S–N) on postnatal radiograms



Figure 4 Postnatal radiogram of skull of a normal child, showing measurement of anterior cranial base as distance (-----) between mid-point of sella turcica (S) and nasion (N).

(Figure 4) and they reported that this was significantly shorter in 47 subjects with trisomy 21 aged between 8 and 18 years than in 38 normal cases. Similarly, Suri *et al.*⁹ examined the S–N distance in 25 children with trisomy 21 and showed that the measurements were significantly smaller than in normal controls.

In this study, the landmarks used to measure the anterior cranial base length were different from those used in radiological studies. First, only a portion of the sphenoid bone can usually be visualized on obstetric ultrasound in the scanning plane required to obtain the fetal profile owing to shadowing from the anterior craniofacial bony structures. Therefore, for measurement of the sphenofrontal distance we selected the most anterior

border of the bone, which can be seen in most cases. Second, we used the lower edge of the frontal bone rather than the nasion because the frontal bone is more readily identified on fetal ultrasound, and this was reflected by good reproducibility of the measurements, which were within 1.2 mm in 95% of the cases assessed by two independent operators.

Previous sonographic studies have demonstrated that second- and third-trimester fetuses with trisomy 21 show signs of mid-facial hypoplasia, which can be assessed by measuring NB length¹, PT² and PFSR⁵. Our results suggest that a contribution to the flat face of fetuses with trisomy 21 is also provided by a shorter sphenofrontal distance, which could be due to dorsal displacement of the lower portion of the frontal bone (Figure 1).

A recent retrospective study compared the measurements of several ultrasound markers between a large number of fetuses with trisomy 21 and normal cases, showing that the most significant differences were observed for PT:NB ratio and PFSR¹². At a false-positive rate of 5%, PT:NB ratio and PFSR were abnormal in about 86% and 80% of trisomy-21 fetuses, respectively. Our results are not suitable for determining the performance of sonographic measurement of sphenofrontal distance in second-trimester screening for trisomy 21 because the measurements were undertaken on stored 3D volumes from two selected groups of patients. Therefore, larger studies would be required to define the clinical value of measuring the sphenofrontal distance in routine practice and to assess the feasibility and reproducibility of the measurements using two-dimensional ultrasound.

In the last 15 years, screening for trisomy 21 has seen a major shift in timing of screening towards the first trimester of pregnancy owing to the widespread introduction of combined testing at 11–13 weeks' gestation, which can detect about 90% of cases with trisomy 21 for a false-positive rate of about 5%¹³. More recently, it has been shown that cell-free DNA (cfDNA) testing of maternal blood from as early as 10 weeks' gestation can detect more than 99% of fetuses with trisomy 21, for a false-positive rate of about 0.1%¹⁴. Therefore, the prevalence of trisomy 21 in the second trimester of pregnancy in women who had prior screening

by combined and/or cfDNA testing is very low, and the routine use of sonographic soft-markers in these cases may produce a significant increase in the rate of invasive testing, especially if the 95th or 5th percentile of a given measurement is taken as the cut-off. However, second-trimester pregnancies that have not undergone prior testing can benefit from assessment of sonographic markers to calculate a patient-specific risk for trisomy 21, which can be obtained by multiplying the background maternal age-related risk by the positive or negative likelihood ratio for each of the examined markers¹⁵.

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