Spheno-frontal distance in euploid and trisomy 21 fetuses at 16-24 weeks’ gestation by three-dimensional ultrasound

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Running head: Spheno-frontal distance and trisomy 21

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Abstract

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

Methods: We acquired 3D volumes of the fetal profile from 80 normal and 30 trisomy 21 fetuses at 16-24 weeks. 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 the normal group, 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, 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). Sphenofrontal distance was below the 5th and the 1st percentile of the normal range in 29 (96.7%) and 27 (90.0%) fetuses, respectively.

Conclusion: The sphenofrontal distance is shorter in fetuses with trisomy 21 at 16 to 24 weeks’ gestation compared to normal cases. A reduction in the growth of the anterior cranial base contributes to the mid-facial hypoplasia observed in fetuses with trisomy 21.

Key words: sphenofrontal distance, 3D ultrasound, Trisomy 21, second trimester
Introduction

Ultrasound examination of the fetal profile in the second and third trimesters of pregnancy provides the ability to assess several facial measurements which are significantly different between trisomy 21 and chromosomally normal fetuses. Previous studies have shown that trisomy 21 fetuses have an increased prevalence of nasal bone absence or hypoplasia, prenasal thickening, wide fronto-maxillary facial angle, increased prenasal thickness-nasal bone length ratio and high prefrontal space ratio.

Postnatal radiologic studies have shown that individuals with trisomy 21 also have a growth reduction in the sagittal portion of the endocranium, the mid-facial area, the cranial base and the frontal bone. These changes lead to vertical hypoplasia of the central structures of the cranium, lowering the position of 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 compared to controls.

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

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 indications 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
included 80 appropriately growing fetuses with no sonographic evidence of fetal abnormality. The second group comprised 30 fetuses with trisomy 21, confirmed by chorionic villous sampling or amniocentesis, which were carried out because of a high risk for aneuploidies. In 19 (63.3%) cases the maternal age was 35 years or more and in 21 (70.0%) cases there was at least one fetal 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 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, Milwaukee, WI, USA), ensuring that the angle between the transducer and the long axis of the nose was close to 45°. The 3D volumes were examined off-line by an operator who was not aware of any 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 the chin anteriorly, and by the presence of the secondary palate with the overlying vomeral bone posteriorly. The anterior portion of the sphenoid bone was visualized in the image as an echogenic bony structure placed dorsally and superiorly with respect to the posterior edge of the vomeral bone. The spheno-frontal 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 sphenoid-frontal distance was measured independently by two operators and in 60 cases by the same operator on two occasions.

**Statistical analysis**

Regression analysis was used to determine the significance of the association between sphenoid-frontal distance and gestational age. The Kolmogorov-Smirnov test was used to confirm the normality of the measurements in chromosomally normal and trisomy 21 fetuses. The values of sphenoid-frontal distance were then expressed as a difference from the appropriate expected mean for gestation (delta value). Independent samples T-Test was used to compare mean sphenoid-frontal distance delta values between normal and trisomy 21 fetuses. The Bland-Altman analysis was used to compare the measurement agreement and bias for a single examiner and between two examiners.

The data were analysed using the statistical package IBM SPSS 19.0 (New York, USA) and Excel for Windows 2010 (Microsoft Corp., Redmond, WA, USA). A p value of less than 0.05 was considered statistically significant.

**Results**

In the 80 normal fetuses, the median maternal age was 32 (range 16-44) years and the median gestational age was 20 (range 16-24) weeks. Sphenoid-frontal distance increased linearly with gestational age from 15.1 mm at 16 weeks to 18.2 mm at 24 weeks (sphenoid-frontal distance = 10.079 + (0.342 x GA); r=0.654, p<0.01, standard deviation 0.886).
In the 30 fetuses with trisomy 21, the median maternal age was 36 (range 20-44) years and the median gestational age was 20 (range 16-24) weeks. In this group, mean spheno-frontal distance delta value was significantly smaller than in normal cases (-3.447 mm; 95% CI -5.684 to -1.211 mm; p<0.01). Spheno-frontal distance was below the 5th and the 1st percentile of the normal range in 29 (96.7%) and 27 (90.0%) fetuses, respectively (Figure 2).

The mean difference and the 95% limits of agreement between paired measurements of spheno-frontal distance by the same observer were in 0.113 mm (-0.674 to 0.901) and the respective values in paired measurements by the two different observers were 0.178 mm (-0.856 to 1.212) (Figure 3).

**Discussion**

The findings of this study provide evidence that the spheno-frontal distance is reduced in fetuses with trisomy 21 at 16 to 24 weeks’ gestation compared to normal cases. Our results are consistent with previous postnatal studies examining cephalometric parameters in individuals with trisomy 21. Alio et al. measured the distance between middle-point of the sella turcica and the nasion (S-N) on postnatal radiograms (Figure 4) and they reported that this was significantly shorter in 47 subjects with trisomy 21 with an age between 8 and 18 years, compared to 38 normal cases. Similarly, Suri et al. examined the S-N distance in 25 children with trisomy 21, showing that the measurements were significantly smaller compared to normal controls.
In this study, the landmarks used to measure the anterior cranial base length were different from those used in radiologic studies. First, only a portion of the sphenoid bone can be usually visualized on obstetric ultrasound in the scanning plane required to obtain the fetal profile, due to shadowing from the anterior cranio-facial bony structures. Therefore, for the measurement of 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 a 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 and that these can be assessed by measuring nasal bone (NB) length\(^1\), prenasal thickness\(^2\) (PT) and prefrontal space ratio\(^5\) (PFSR). 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 PFSR\(^12\). 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 to determine 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 spheno-frontal 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, due 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%\textsuperscript{13}. More recently, it has been shown that cell-free DNA (cfDNA) testing in the maternal blood from 10 weeks’ gestation can detect more than 99% of fetuses with trisomy 21, for a false positive rate of about 0.1%\textsuperscript{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 invasive testing rate, especially if the 95th or the 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 multiplying the background maternal age-related risk by the positive or negative likelihood ratio for each of the examined markers\textsuperscript{15}. 
References


Figure legends

Figure 1. Ultrasound images of the facial profile from a normal (a) and a trisomy 21 (b) fetus at 20 weeks showing the measurement of sphenofrontal distance (dashed line).

Figure 2. Sphenofrontal distance in normal (open circles) and trisomy 21 (closed circles) fetuses plotted on the 5th, 50th, 95th (continuous lines), 1st, 99th (dashed lines) percentiles of the normal range.

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

Figure 4. Postnatal radiogram of the skull showing the measurement of the anterior cranial base as the distance between the middle-point of the sella turcica (S) and the nasion (N).