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Metopic suture in fetuses with holoprosencephaly at 11 + 0 to 13 + 6 weeks of gestation

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KEYWORDS: 3D ultrasound; craniosynostosis; first trimester; holoprosencephaly; metopic suture

ABSTRACT

Objective *To investigate the development of the metopic suture in fetuses with holoprosencephaly at 11 + 0 to 13 + 6 weeks of gestation.*

Methods *Three-dimensional (3D) ultrasound was used to measure the height and gap between the frontal bones in 200 normal fetuses and in nine fetuses with holoprosencephaly at 11 + 0 to 13 + 6 (median, 12) weeks of gestation.*

Results *In the 200 normal fetuses, the height of the frontal bones increased significantly with gestation from a mean of 2.5 mm (5^{th} and 95^{th} centiles: 1.9 mm and 3.3 mm) at 11 weeks to 6.1 mm (5^{th} and 95^{th} centiles: 4.6 mm and 8.1 mm) at 13 + 6 weeks. The gap between the two frontal bones did not change significantly with gestation (mean: 1.5 mm; 5^{th} centile: 1.0 mm; 95^{th} centile: 2.0 mm). In fetuses with holoprosencephaly, the height of the frontal bones was significantly larger (mean difference, 5.6 SDs; range, 3.9–7.7 SDs; $P < 0.0001$) and the gap was significantly smaller (mean 0.2 mm, range 0–0.8 mm; $P < 0.0001$) than those in normal fetuses.*

Conclusions *Holoprosencephaly is associated with an accelerated development of the frontal bones and premature closure of the metopic suture. Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Three-dimensional (3D) ultrasound can provide useful information on the normal and abnormal development of the fetal cranial bones and sutures[1–3]. There is some evidence that growth and ossification of the skull may be influenced by the development of the underlying brain[4]. Holoprosencephaly, in which there is impaired cleavage of the embryonic forebrain, is commonly associated with midline facial abnormalities. Furthermore, a histological study in a fetus with holoprosencephaly at 18 weeks reported partial absence of the metopic suture[5].

The aim of this 3D ultrasound study was to investigate the development of the frontal bones and metopic suture in fetuses with holoprosencephaly at 11 + 0 to 13 + 6 weeks.

METHODS

A 3D volume of the fetal face was acquired at 11 + 0 to 13 + 6 weeks of gestation in 200 singleton pregnancies with no obvious fetal brain or other abnormalities and in nine with holoprosencephaly, including seven with trisomy 13 and two with a normal karyotype. All patients attended our center for first-trimester screening for trisomy 21 by a combination of maternal age and measurement of fetal nuchal translucency. The diagnosis of holoprosencephaly was made by routine two-dimensional (2D) ultrasound examination. The 3D volumes were obtained with the fetuses in the mid-sagittal plane, with the transducer being parallel to the direction of the nose. The 3D examinations were carried out transabdominally ($n = 199$) or transvaginally ($n = 10$) using a RAB 4-8L probe or a RIC 5-9H four-dimensional (4D) transvaginal probe (Voluson 730 Expert, GE Medical Systems, Milwaukee, WI, USA) by sonographers with extensive experience in 3D ultrasound.

For the analysis of the metopic suture height, the 3D volume was displayed in the three orthogonal planes that compose the multiplanar mode of image postprocessing (Figure 1a–c). The sagittal view showing the fetal profile was selected and the fetal face rotated until the frontal

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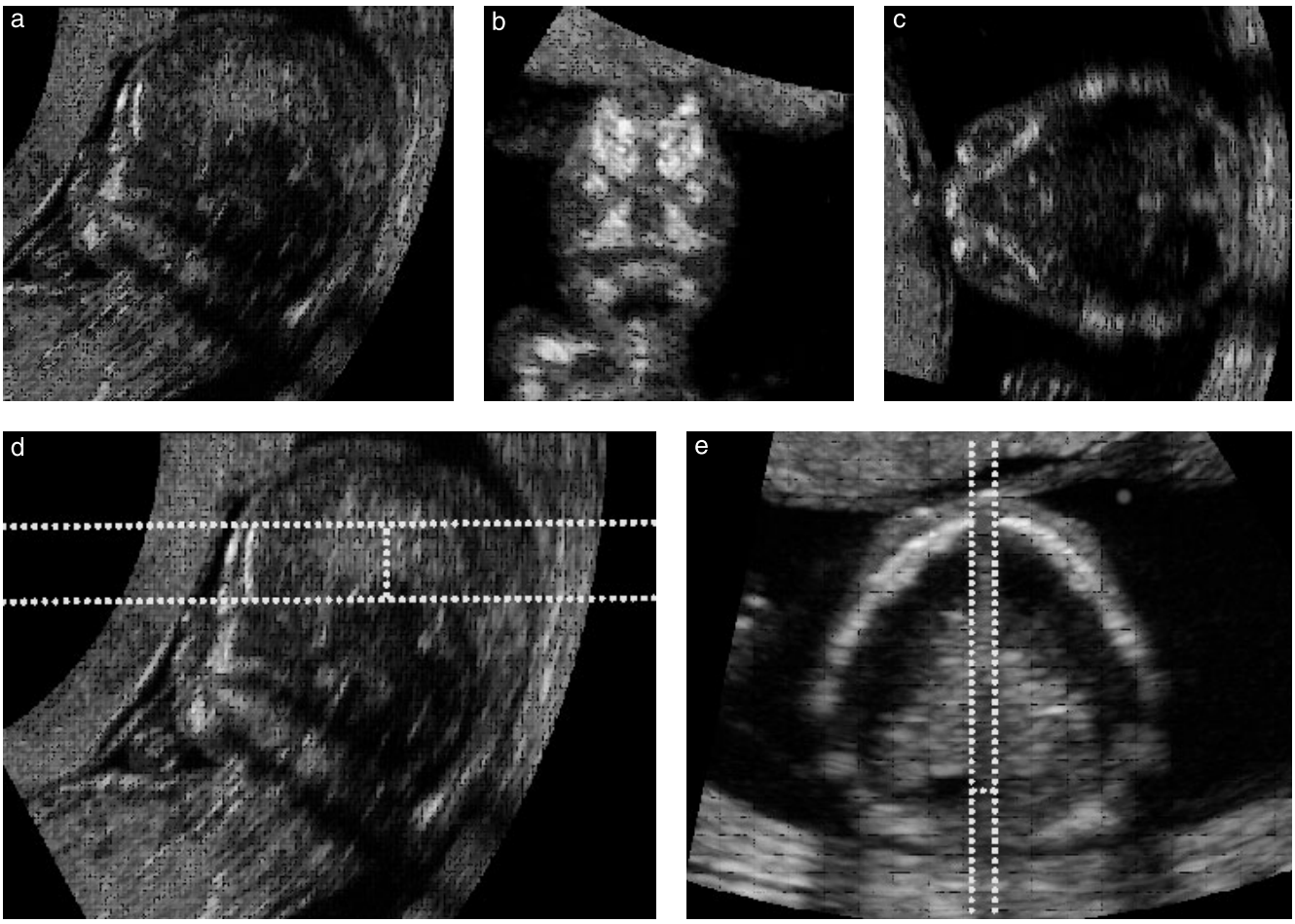


Figure 1 Three-dimensional ultrasound images of the fetal head displayed in the three orthogonal planes (a–c) and the measurement of the frontal bones' height (d) and transverse gap (e).

bones were aligned vertically with the *y*-axis. As this image was scrolled, starting from the midline, the frontal bones were identified as the first structures with the same echogenicity as that of the facial bones and then measured vertically (Figure 1d). The mean height from the right and left frontal bones was then used for the calculations. For the analysis of the gap between the frontal bones we used the volume contrast imaging (VCI) static postprocessing mode with 100% transparent maximum mode of display. A maximum thickness of 3 mm was used for the analysis of 3D volumes acquired transabdominally and 2 mm for those acquired transvaginally. The initial sagittal plane was selected and the image rotated until the frontal bone was aligned horizontally with the *x*-axis. Simultaneously the transverse view was shown on the B-plane. After selecting the transverse image, we examined a series of sections along the metopic suture and measured the smallest visible gap between the frontal bones (Figure 1e). Every measurement was carried out offline after the scan by the same operator.

In 40 arbitrarily selected cases, the vertical height and the transverse gap were measured by the same sonographer twice and also by a second sonographer once in order to compare the measurements and calculate intra- and interobserver agreement. In each case the second examiner was not aware of the results of the first examiner.

Statistical analysis

In the 200 normal fetuses, regression analysis was used to determine the significance of the association between height and gap of the frontal bones with crown–rump length (CRL). The Kolmogorov–Smirnov test demonstrated that the data for the height of the frontal bones were not normally distributed and therefore they were log-transformed to achieve a normal distribution. Each measurement of the log-transformed height was then expressed as a deviation in SD from the expected normal mean for gestation (delta value). The Mann–Whitney *U*-test was used to determine the significance of differences in the delta values between the normal and holoprosencephaly groups. In the case of the gap between the frontal bones in the normal fetuses the data were normally distributed and the Mann–Whitney *U*-test was used to determine the significance of differences in observed values between the normal and holoprosencephaly group. The reason for selecting the Mann–Whitney *U*-test was because the number of cases in the holoprosencephaly group was too small to assess the normality of their distribution.

The Bland–Altman analysis was used to compare the measurement of agreement and bias for a single examiner and between different examiners[6]. The analyses were

performed with SPSS 11.5 (SPSS, Chicago, Illinois, USA). $P < 0.05$ was considered to be statistically significant.

RESULTS

The median maternal age was 36 (range, 21–47) years, the median fetal CRL was 69 (range, 45–84) mm and the median gestation was 12 + 6 (range, 11 + 0 to 13 + 6) weeks. The height and the gap of the frontal bones were successfully measured in all cases.

In the normal fetuses, the height of the frontal bones increased significantly with gestation from a mean of 2.5 mm (5th and 95th centiles: 1.9 mm and 3.3 mm) at a CRL of 45 mm to 6.1 mm (5th and 95th centiles: 4.6 mm and 8.1 mm) at a CRL of 84 mm (ln height = 0.023 × CRL in mm −0.125, $r = 0.788$, $P < 0.0001$; Figure 2). The gap between the two frontal bones did not change significantly with gestation (mean: 1.5 mm; 5th centile: 1.0 mm; 95th centile: 2.0 mm; $r = 0.076$, $P = 0.282$; Figure 3).

In comparison with the normal fetuses, the height of the frontal bones of the fetuses with holoprosencephaly was significantly larger (mean difference, 5.6 SDs; range, 3.9–7.7 SDs; $P < 0.0001$) and the gap was significantly smaller (mean 0.2 mm, range 0–0.8 mm; $P < 0.0001$). In all fetuses with holoprosencephaly the gap was below the 5th centile and the height was above the 95th centile

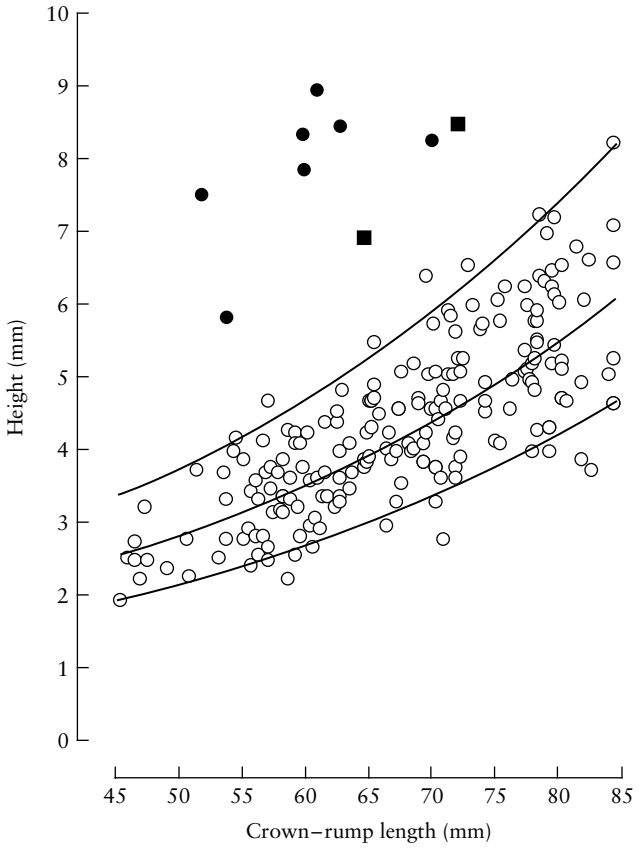


Figure 2 Mean height of the frontal bones in fetuses with holoprosencephaly (trisomy 13 (●); normal karyotype (■)) plotted on the reference range (mean, 95th and 5th centiles) with crown–rump length of the normal pregnancies (○).

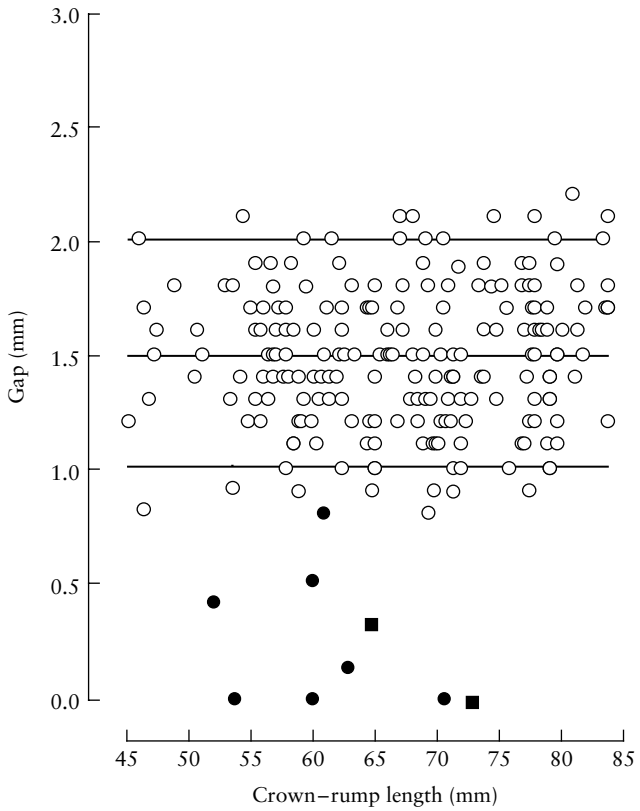


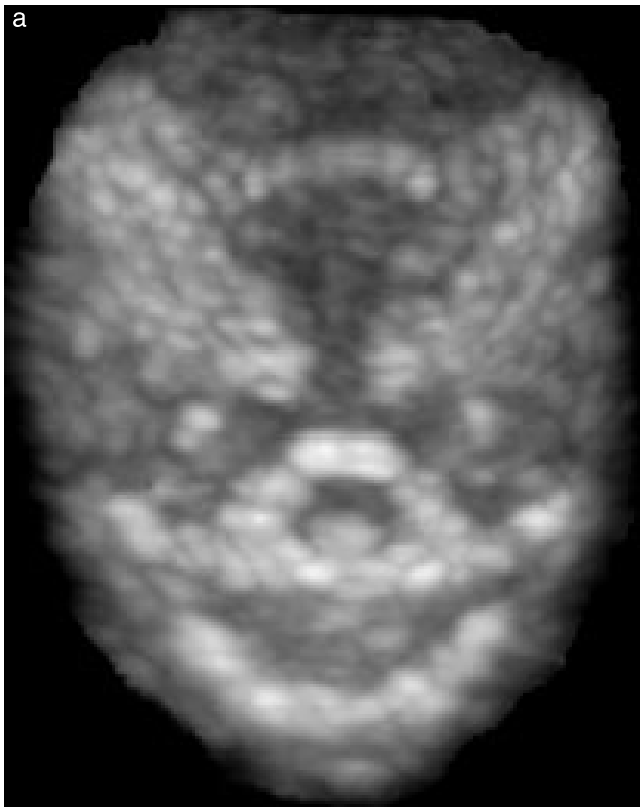
Figure 3 Mean gap between the frontal bones in fetuses with holoprosencephaly (trisomy 13 (●); normal karyotype (■)) plotted on the reference range (mean, 95th and 5th centiles) with crown–rump length of the normal pregnancies (○).

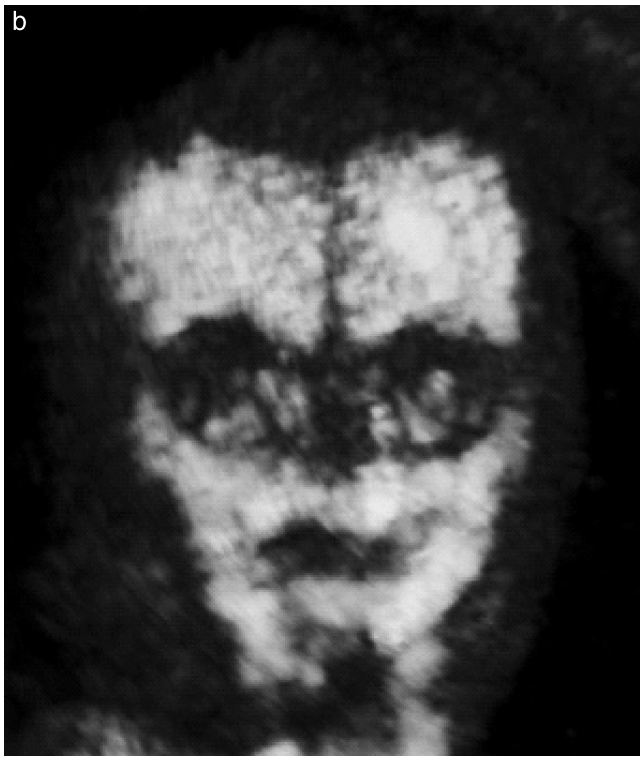
(Figures 2–4). There were no obvious differences in either the height or gap between the seven fetuses with trisomy 13 and the two with normal karyotype.

In the Bland–Altman plot, the mean difference between paired measurements of the height of the frontal bones by the same sonographer was −0.11 mm and the 95% limits of agreement were −0.73 mm (95% CI, −0.89 to −0.56 mm) to 0.51 mm (95% CI, 0.34 to 0.68 mm). The mean difference between paired measurements by two sonographers was 0.11 mm and the 95% limits of agreement were −0.59 mm (95% CI, −0.78 to −0.40 mm) to 0.80 mm (95% CI, 0.61 to 0.99 mm). The mean difference between paired measurements of the gap of the frontal bones by the same sonographer was −0.08 mm and the 95% limits of agreement were −0.45 mm (95% CI, −0.55 to −0.35 mm) to 0.30 mm (95% CI, 0.20 to 0.40 mm). The mean difference between paired measurements by two sonographers was 0.06 mm and the 95% limits of agreement were −0.39 mm (95% CI, −0.51 to −0.26 mm) to 0.50 mm (95% CI, 0.38 to 0.62 mm).

DISCUSSION

In this study we used 3D ultrasound to describe reproducible measurements of the height and gap between the frontal bones, which allow quantification of the development of these bones. The finding that in normal fetuses





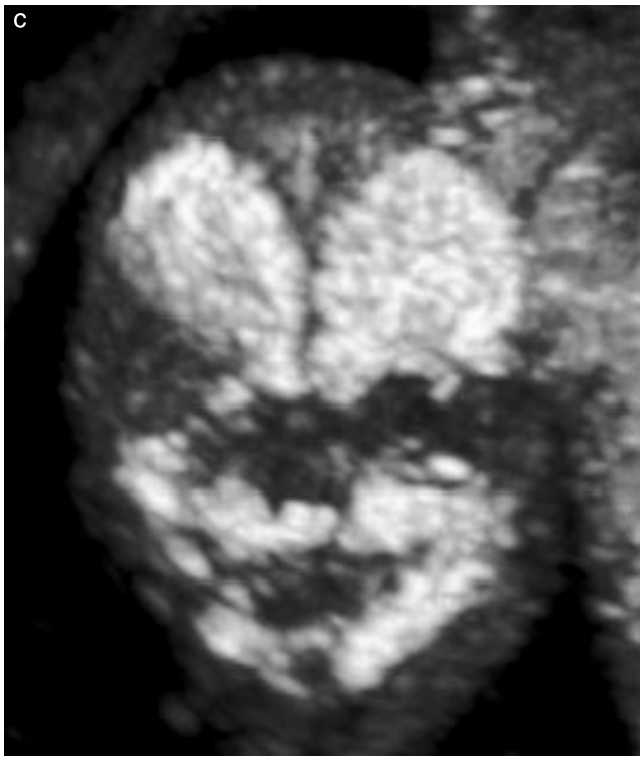


Figure 4 Fetal face in coronal view using volume contrast imaging static postprocessing mode with transparent maximum mode of display of a normal fetus (a), a fetus with holoprosencephaly and trisomy 13 (b) and a fetus with holoprosencephaly and normal karyotype (c) at 12 weeks of gestation.

at 11 + 0 to 13 + 6 weeks the height of the frontal bones increases with gestation, is compatible with data from histological and radiological studies that ossification of the frontal bones, which starts at around 9 weeks of gestation in the middle of each supraorbital region, spreads radially towards the coronal and metopic sutures[7,8]. We found that within the narrow gestational range of 11 + 0 to 13 + 6 weeks there is always a complete gap between the two frontal bones and the width of the gap does not decrease.

In fetuses with holoprosencephaly, irrespective of whether the karyotype is trisomy 13 or normal, the frontal bones at the metopic suture area were higher and the gap between the bones was smaller, suggesting an accelerated bone development and premature closure of the metopic suture. Indeed, in four of our nine cases there was no visible gap between the bones from as early as 12 weeks of gestation.

The sutures are believed to grow in response to the centrifugal pressure from the expanding brain and proximity of the dura to the suture is critical in maintaining its patency[4,9]. In a normal cranial suture there is an intense process of passive ossification and active reabsorption[10]. The dura supplies osteoinductive growth factors and cellular elements, such as osteoblast-like cells, to the overlying osteogenic fronts in the suture regulating the complex process of growth and fusion of that space[11–13]. In microcephaly, cranial sutures may be poorly defined or absent, because the lack of brain growth leads to an absence of normal stretch stimulus across the suture. Similarly, in shunted hydrocephaly the normal expansion of cranial contents is abruptly halted and the resultant lack of sutural stretch leads to craniosynostosis[14].

In holoprosencephaly, premature ossification of the frontal bones and closure of the metopic suture is associated with microcephaly and may be the consequence of the lack of brain growth and possible

abnormal or incomplete development of the dura. Normal development of the dura is dependent on the migration of neural crest cells to the nasofrontal field, which is the part of the face in between the eyes. In holoprosencephaly, the associated midfacial abnormalities, such as cyclopia or absent nose and facial cleft, may be the consequence of abnormal invasion of neural crest cells[15,16]. The same mechanism may be responsible for abnormal development of the dura mater and consequently premature closure of the metopic suture.

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