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Posterior brain in fetuses with open spina bifida at 11 to 13 weeks

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Objective To measure the changes in the posterior fossa in first-trimester fetuses with open spina bifida (OSB).

Methods The brain stem diameter and brain stem to occipital bone (BSOB) diameter were measured in stored images of the mid-sagittal view of the fetal face at 11^{+0} to 13^{+6} weeks from 30 fetuses with OSB and 1000 normal controls.

Results In the control group, the brain stem and BSOB diameter increased significantly with crown-rump length (CRL) and the brain stem to BSOB ratio decreased. In the spina bifida group, the brain stem diameter was above the 95th percentile of the control group in 29 (96.7%) cases, the BSOB diameter was below the 5th percentile in 26 (86.7%) and the brain stem to BSOB ratio was above the 95th percentile in all cases.

Conclusions At 11 to 13 weeks the majority of fetuses with OSB have measurable abnormalities in the posterior brain. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS: first-trimester screening; brain stem; spina bifida; neural tube defect; nuchal translucency

INTRODUCTION

Open spina bifida (OSB) is associated with the Arnold-Chiari II malformation which is thought to be the consequence of leakage of cerebrospinal fluid into the amniotic cavity and hypotension in the subarachnoid spaces, leading to caudal displacement of the brain stem and obliteration of the cistern magna. In the second trimester of pregnancy the sonographically detectable manifestations of the Arnold-Chiari II malformation are the lemon and banana signs (Nicolaides *et al.*, 1986; Van Den Hof *et al.*, 1990; Ghi *et al.*, 2006). There is some evidence that this malformation is also present in the first trimester and is manifested in the compression of the fourth ventricle with loss of the normal intracranial translucency which is visible in the same mid-sagittal view of the fetal face, as used routinely for measurement of nuchal translucency (NT) thickness in screening for aneuploidies (Chaoui *et al.*, 2009).

In the mid-sagittal view of the fetal face at 11 to 13 weeks, the lower part of the fetal brain between the sphenoid bone anteriorly and the occipital bone posteriorly can be divided into the brain stem in the front and a combination of the fourth ventricle and cisterna magna in the back (Figure 1). In some cases of OSB, we observed that the diameter of the brain stem appeared to be increased whereas the distance between the brain stem and the occipital bone (BSOB) appeared to be decreased.

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The aims of this study were firstly, to establish normal ranges of the brain stem and BSOB diameters and secondly, to examine whether in fetuses with OSB these diameters and their ratio are altered.

METHODS

The posterior brain was examined in stored images from 30 fetuses with OSB and 1000 normal controls scanned between November 2006 and March 2010. The cases and controls were obtained from centres providing routine first-trimester screening for chromosomal abnormalities by measurement of fetal NT thickness (Snijders *et al.*, 1998). The databases of the hospitals were searched to identify cases of OSB diagnosed during the first or second trimester of pregnancy which had stored images of the mid-sagittal view of the fetal face at 11^{+0} to 13^{+6} weeks of gestation. The controls were 1000 consecutively examined pregnancies at 11 to 13 weeks, which subsequently resulted in the live birth of healthy neonates or had a detailed ultrasound examination at 20 to 24 weeks that showed no fetal abnormalities. Approval for the study was obtained from the hospital Ethics Committee.

The stored images of the mid-sagittal view of the fetal face at 11^{+0} to 13^{+6} weeks of the cases of spina bifida and controls were placed in the same folder and were examined by a sonographer with extensive experience in first-trimester scanning who had obtained the Fetal Medicine Foundation Certificate of Competence in the 11 to 13 weeks scan. This sonographer, who was unaware of the pregnancy outcomes, examined the posterior brain and used the Software IQ-View 2.61 (Image

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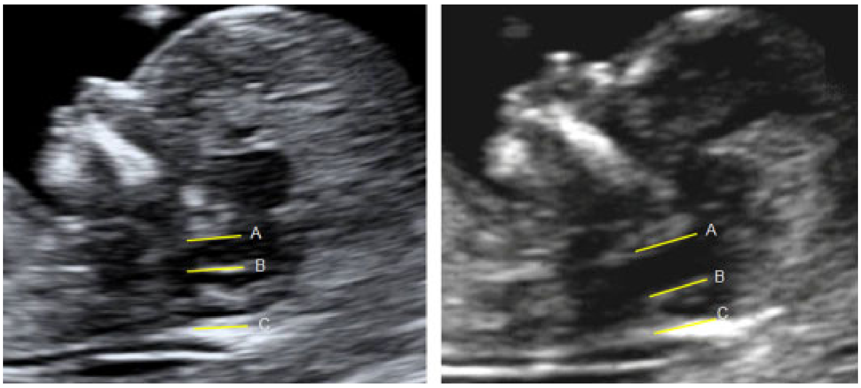

Figure 1—Mid-sagittal view of the fetal brain demonstrating the measurements of brain stem diameter and brain stem to occipital bone (BSOB) diameter. Three lines are drawn, along the posterior border of the sphenoid bone (line A), along the middle of the line produced by the posterior border of the brain stem and the anterior border of the fourth ventricle (line B) and along the anterior border of the occipital bone (line C). The vertical distances between lines A and B and between B and C are the brain stem diameter and BSOB diameter, respectively

Information Systems, Rostock, Germany) to draw three lines: firstly, along the posterior border of the sphenoid bone (line A), secondly, along the middle of the line produced by the posterior border of the brain stem and the anterior border of the fourth ventricle (line B), and thirdly, along the anterior border of the occipital bone (line C, Figure 1). Subsequently, a line vertical to line B was drawn and the distance between lines A and B and between B and C was measured and their ratio was calculated. Essentially, the first measurement is the vertical thickness of the brain stem and the second measurement is the vertical distance between the brain stem anteriorly and the occipital bone posteriorly (BSOB).

The agreement and bias for the measurements of brain stem diameter and BSOB diameter by a single examiner and between different examiners were investigated from the study of 100 images which were selected at random from the database. One operator (A) who made the original measurements repeated the measurements in the series of 100 pictures and a second operator (B) made the measurements once. The operators were not aware of the measurements of each other and operator A when making the measurements on the second occasion was not aware of his measurements on the first occasion.

Statistical analysis

In the control group, regression analysis was used to construct reference ranges with fetal CRL for brain stem diameter, BSOB diameter and brain stem diameter to BSOB diameter ratio. In each fetus in both the spina bifida and control groups, the measured diameters and their ratio were subtracted from the respective normal mean for CRL to calculate the delta value. The Kolmogorov-Smirnov test demonstrated that for brain stem diameter and BSOB diameter the distribution of delta values was normal in both the spina bifida and control groups and an independent sample t-test was used to determine the significance of differences in the mean delta values between the groups. The Mann–Whitney test was used to determine the significance of differences in the delta values of the brain stem diameter to BSOB diameter ratio in the cases and controls.

The Bland–Altman analysis was used to examine the degree agreement and bias between measurements by a single operator and two different operators for brain stem and BSOB diameters (Bland and Altman, 1986). Paired t-test was used to compare the significance of difference between these paired measurements. Significance was assessed at a P value of less that 0.05.

The statistical software packages SPSS 15.0 (SPSS, Chicago, Illinois, USA) and XLSTAT-Pro 2010 (Addinsoft, New York, USA) were used for data analyses.

RESULTS

The median CRL at the time of the first-trimester scan was 61 (range 45–84) mm for the controls and 62 (range 48–83) mm for the cases of OSB. The diagnosis of spina bifida was made at a median of 21 (range 13–23) weeks of gestation and in all cases the parents chose to have pregnancy termination. The spina bifida was thoracic in 3, lumbar in 6, lumbosacral in 15 and sacral in 6.

In the control group, there were always two horizontal lines between the sphenoid bone anteriorly and the occipital bone posteriorly: the first line was produced by the posterior border of the brain stem and the anterior border of the fourth ventricle and the second line was produced by the posterior border of the fourth ventricle and the anterior border of the cisterna magna. There was a significant increase with CRL in brain stem diameter ($0.8501 + 0.03537 \times$ CRL in mm, SD 0.30, $R^2 = 0.472$; Figure 2) and BSOB diameter ($-0.5712 + 0.087 \times$ CRL in mm, SD 0.47, $R^2 = 0.694$; Figure 3). The brain stem diameter to BSOB diameter ratio decreased with CRL ($0.8904–0.0040 \times$ CRL, SD 0.08, $R^2 = 0.140$; Figure 4).

In the fetuses with OSB, compared to the normal controls, the mean brain stem diameter was significantly increased and it was above the 95th percentile of the reference range for CRL in 29 (96.7%) of the 30 cases (Table1, Figure 2). The mean BSOB diameter was significantly decreased and it was below the 5th percentile in 26 (86.7%) cases (Table 1, Figure 3). The

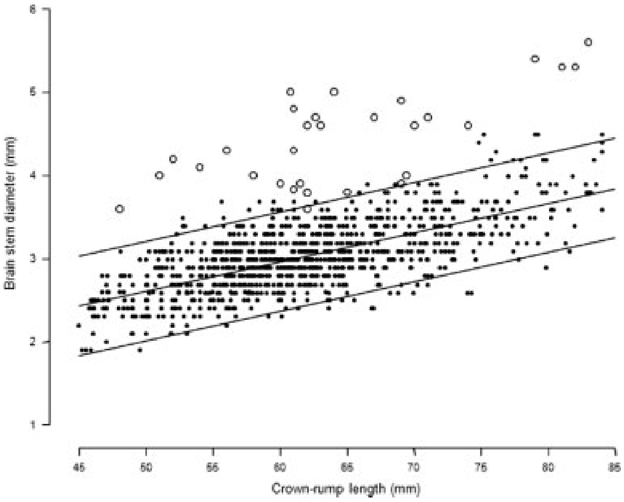

Figure 2—Individual measurements of brain stem diameter in fetuses with OSB (open circles) and normal controls (closed circles) plotted on the reference range for CRL (median, 5th and 95th percentiles)

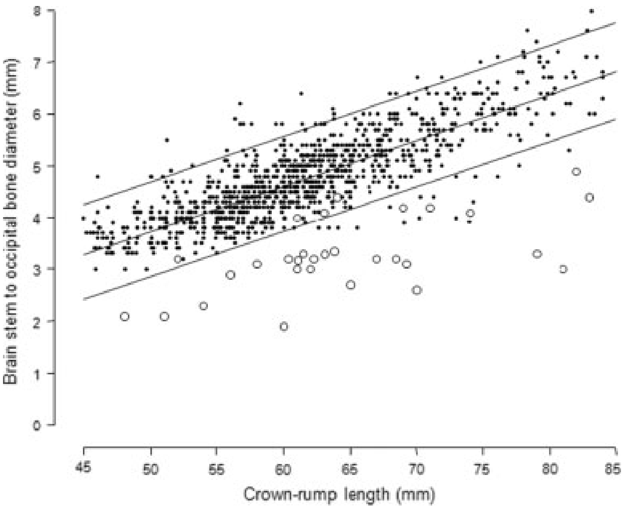

Figure 3—Individual measurements of BSOB diameter in fetuses with OSB (open circles) and normal controls (closed circles) plotted on the reference range for CRL (median, 5th and 95th percentiles)

mean brain stem diameter to BSOB diameter ratio was significantly increased and it was above the 95th percentile in all 30 cases (Table 1, Figure 4).

Intraobserver variability

The bias (mean difference) and 95% limits of agreement between paired measurements of the brain stem and BSOB diameters by the same operator are shown in Table 2. Paired t-test to assess the repeatability of measurements demonstrated that there was no significant difference in the measurement of either brain stem diameter ($P = 0.720$) or BSOB diameter ($P = 0.952$). The Pearson correlation coefficient between the difference and the mean of measurements by the same operator for brain stem diameter was 0.041 (95% CI −0.156 to 0.236) and for BSOB diameter was 0.149 (95% CI −0.049 to 0.335). There was no significant change with gestation in the intraobserver agreement in paired measurements (brain stem diameter: $r = 0.018$, $P = 0.858$; BSOB diameter: $r = -0.099$, $P = 0.326$).

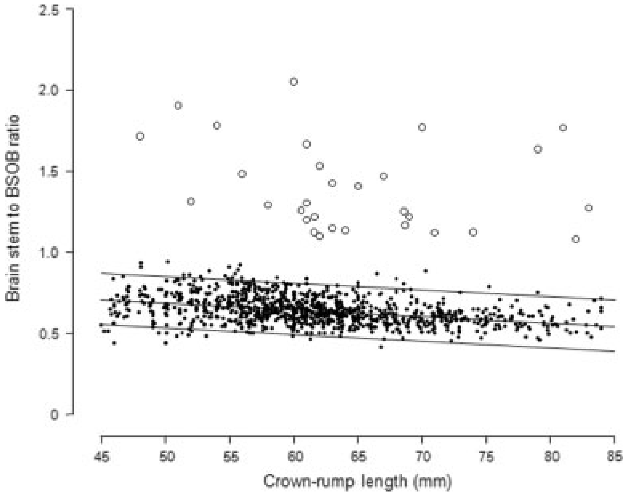

Figure 4—Individual measurements of the ratio between the brain stem diameter and BSOB diameter in fetuses with OSB (open circles) and normal controls (closed circles) plotted on the reference range for CRL (median, 5th and 95th percentiles)

Table 1—Comparison of mean delta values and standard deviation (SD) of brain stem diameter, brain stem to occipital bone (BSOB) diameter and the ratio of brain stem diameter to BSOB diameter in fetuses with open spina bifida and normal controls

Measurement	Control	Open spina bifida	P value
Delta brain stem diameter, mean (SD)	0.000 (0.303)	1.297 (0.420)	<0.0001
Delta BSOB diameter, mean (SD)	0.000 (0.468)	−1.772	<0.0001
Delta brain stem to BSOB ratio, mean (SD)	0.000 (0.081)	0.769 (0.265)	<0.0001

Interobserver variability

The bias (mean difference) and 95% limits of agreement between paired measurements of brain stem diameter by two different operators is shown in Table 2. The paired t-test to assess the repeatability of measurements demonstrated that there was no significant difference in the measurement of either brain stem diameter ($P = 0.755$) or BSOB diameter ($P = 0.652$). The Pearson correlation coefficient between the difference and the mean of measurements by two different operators for brain stem diameter was −0.09 (95% CI −0.281 to 0.108) and for BSOB diameter was 0.106 (95% CI −0.093 to 0.296). There was no significant change

Table 2—Mean difference and the 95% limits of agreement (bold numbers in brackets) with their 95% confidence interval (numbers in square brackets) between 100 paired measurements by the same sonographer and between 100 paired measurements by two sonographers in brain stem diameter and brain stem to occipital bone (BSOB) diameter

Measurement	Mean difference (95% LOA) [95% CI]
Brain stem diameter	
Intraobserver	**−0.01** (**−0.33** [−0.37 to −0.30], **0.32** [0.29–0.35])
Interobserver	**−0.01** (**−0.32** [−0.35 to −0.29], **0.31** [0.28–0.34])
Brain stem to occipital bone diameter	
Intraobserver	**0.00** (**−0.33** [−0.36 to −0.29], **0.33** [0.30–0.36])
Interobserver	**0.01** (**−0.34** [−0.37 to −0.30], **0.35** [0.32–0.39])

with gestation in the interobserver agreement in paired measurements (brain stem diameter: $r = 0.135$, $P = 0.180$; BSOB diameter: $r = -0.024$, $P = 0.810$).

DISCUSSION

The findings of this study demonstrate that in the mid-sagittal view of the fetal face at 11 to 13 weeks the brain stem and BSOB diameters normally increase and their ratio decreases with CRL. In fetuses with OSB, compared to normal fetuses, the brain stem diameter is higher, the BSOB diameter is lower and the brain stem to BSOB ratio is substantially higher. These findings are likely to be the consequence of caudal displacement of the brain stem and compression of the fourth ventricle–cisterna magna complex within the confined space between the sphenoid and occipital bones.

An inevitable limitation of this study is that although the sonographer performing the measurements was unaware of the pregnancy outcomes, the suspicion of spina bifida would have been raised by the presence of an abnormal appearance of the fourth ventricle–cisterna magna complex which could have introduced a bias in the measurements. However, there was a clear difference in measurements between normal and affected fetuses. The brain stem diameter was always smaller than the BSOB diameter in normal fetuses and the opposite was true in fetuses with OSB. In the mid-sagittal plane measurements, the brain stem diameter and the BSOB diameter were highly reproducible and in about 95% of cases the difference between two measurements by the same observer or measurements by different observers were within 11% of each other.

Examination of the mid-sagittal view of the fetal face is performed routinely for assessment of fetal NT and nasal bone in screening for aneuploidies. In this same view, the posterior brain can be examined and if this appears to be abnormal the sonographer can be alerted to the possibility of an underlying OSB. It would not be difficult or time consuming to routinely record the measurements of the brain stem and BSOB diameters so that the sonographers can document that they have indeed examined the posterior brain. It is likely that these measurements will improve the performance of early screening for OSB. Abnormal findings in the posterior brain should alert the sonographer to the possibility of OSB and encourage a detailed examination of the fetal spine. Such a detailed examination should identify an OSB at 11 to 13 weeks but if the views of the spine are inadequate another scan should be carried out in 2 to 3 weeks.

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