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ORIGINAL ARTICLE

# Posterior brain in fetuses with trisomy 18, trisomy 13 and triploidy at 11 to 13 weeks' gestation

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## ABSTRACT

**Objective** To measure changes in the posterior fossa of first-trimester fetuses with trisomy 18, trisomy 13 and triploidy.

**Methods** Brain stem (BS) diameter and BS to occipital bone (BSOB) diameter were measured in images of the midsagittal view of the face at $11^{+0}$ to $13^{+6}$ weeks from 45 trisomy 18, 21 trisomy 13 and 15 triploid fetuses and compared with values in 162 euploid fetuses.

**Results** In euploid fetuses BS and BSOB diameters increased significantly with crown–rum length and the BS to BSOB ratio decreased. In all three aneuploidies BSOB diameter was significantly higher than in euploid fetuses. In trisomy 18 and trisomy 13, the BS diameter and BS to BSOB ratio were decreased. The BS to BSOB ratio was below the $5^{th}$ percentile in 16 (35.6%), 17 (81.0%) and 5 (33.3%) of trisomy 18, trisomy 13 and triploidy, respectively. In 7 (8.6%) of the aneuploid fetuses there was open spina bifida and in all these cases the BS to BSOB ratio was above the $95^{th}$ percentile.

**Conclusions** At 11 to 13 weeks' gestation many fetuses with trisomy 18, trisomy 13 and triploidy have measurable abnormalities in the posterior brain. © 2012 John Wiley & Sons, Ltd.

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## INTRODUCTION

In the midsagittal view of the fetal face used for measurement of fetal nuchal translucency (NT) thickness in screening for aneuploidies at 11 to 13 weeks' gestation, there are measurable abnormalities in the posterior brain, which can lead to the diagnosis of open spina bifida.[1–5] In open spina bifida the brain stem (BS) diameter is increased, the BS to occipital bone (BSOB) diameter, containing the fourth ventricle and cisterna magna, is decreased and the BS to BSOB ratio is increased.[4]

A recent study reported that the anteroposterior diameter of the fourth ventricle, measured in the axial plane at 11 to 13 weeks' gestation, in fetuses with trisomy 18, trisomy 13 and triploidy, but not in trisomy 21, was higher than in euploid fetuses.[6] This increase was attributed to the association between these aneuploidies and the Dandy–Walker malformation spectrum, which is characterized by complete or partial agenesis of the vermis and cystic dilation of the fourth ventricle and the posterior cranial fossa.[7–10]

The aim of this study is to determine if in the midsagittal view of the fetal face fetuses with trisomy 18, trisomy 13 and triploidy at 11 to 13 weeks' gestation have alterations in the BS and BSOB diameters and their ratio.

## METHODS

The posterior fossa was examined in stored images of the midsagittal view of the fetal face at $11^{+0}$ to $13^{+6}$ weeks from fetuses with trisomy 18, trisomy 13 and triploidy and euploid controls. The images were obtained by transabdominal ultrasonography immediately before chorionic villous sampling for fetal karyotyping in pregnancies identified by first-trimester combined screening to be at high-risk for aneuploidies.[11] The ultrasound examination included measurement of fetal NT thickness and crown–rump length (CRL) and detailed examination of the fetal anatomy for the detection of major defects.[12] Gestational age was calculated from the fetal CRL.[13] Demographic characteristics and ultrasound findings were recorded in a fetal database at the time of the examination. A search of the database was carried out to identify all cases of trisomy 18, trisomy 13 and triploidy examined between December 2009 and January 2012. Each case of aneuploidy was matched with two euploid fetuses examined on the same day.

The stored images of cases 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 calipers of the ultrasound machine to measure the BS diameter as the distance between the posterior border of the sphenoid bone and the middle of the line produced by the posterior border of the brain stem and the anterior border of the fourth ventricle (A), and the BSOB diameter as the distance between A and the anterior border of the occipital bone, as previously described (Figure 1).[4] The BS to BSOB ratio was calculated.

### Statistical analysis

Continuous and categorical variables were compared using Mann–Whitney *U*-test and $\chi^2$-test, respectively, with post hoc Bonferroni correction.

In each euploid and aneuploid fetus the measured diameters and their ratio were subtracted from the respective mean for CRL from previously reported ranges derived from the study of 1000 normal fetuses[4] to calculate the delta value. Normality of delta values was assessed by inspection of probability plots and histograms. The Kolmogorov–Smirnov test showed that the delta values were not significantly different from Gaussian distribution for some but not all measurements in all groups. Consequently, Mann–Whitney test, with post hoc Bonferroni correction, was used to examine the significance of difference in median delta-values between each group of aneuploid and euploid fetuses.

The statistical software package SPSS 19.0 (SPSS Inc., Chicago, IL) was used for data analyses.

## RESULTS

The demographic and pregnancy characteristics of the study population are summarized in Table 1.

In euploid fetuses the median delta BS diameter was −0.039 (interquartile range (IQR) −0.229 to 0.146), delta BSOB diameter was −0.045 (IQR −0.406 to 0.286) and delta BS to BSOB ratio was −0.002 (IQR −0.058 to 0.042), which were not significantly different ($p=0.986$, $p=0.243$, $p=0.115$, respectively) from values in our previous study of 1000 normal fetuses (Figure 2).[4]

In all three aneuploidies the BSOB diameter was higher than in euploid fetuses (Table 2, Figure 3). In trisomy 18 and trisomy 13, the BS diameter and BS to BSOB ratio were significantly lower than in euploid fetuses. The BS to BSOB ratio was below the 5$^{th}$ percentile in 16 (35.6%), 17 (81.0%) and 5 (33.3%) of trisomy 18, trisomy 13 and triploidy.

Detailed ultrasound examination had demonstrated that in 7 (8.6%) of the aneuploid fetuses there was an open spina bifida, including 4 of the cases with trisomy 18, 1 of trisomy 13 and 2 of triploidy. In all 7 cases of open spina bifida the BS to BSOB ratio was above the 95$^{th}$ percentile (Figure 3).

## DISCUSSION

The findings of this study demonstrate that at 11 to 13 weeks' gestation many fetuses with trisomy 18, trisomy 13 and triploidy have measurable abnormalities in the posterior brain.

In aneuploid fetuses with open spina bifida, compared with normal fetuses, the BS diameter is higher, the BSOB diameter is lower and the BS to BSOB ratio is substantially higher. These findings are likely to be the consequence of the Chiari II malformation, which is thought to be due to leakage of cerebrospinal fluid into the amniotic cavity, hypotension in the cerebral ventricular system and subarachnoid spaces and caudal displacement of the hindbrain.[14,15] Such displacement results in compression of the fourth ventricle-cisterna magna complex within the confined space between the sphenoid and occipital bones.[4,5]

In all three aneuploidies the BSOB diameter was increased and the BS to BSOB ratio was below the 5$^{th}$ percentile in about one-third of fetuses with trisomy 18 and triploidy and in 81% of fetuses with trisomy 13. Possible explanations for the increased BSOB diameter in these aneuploidies are an underlying Dandy–Walker malformation or delayed development of the posterior fossa. Cystic malformations in the posterior fossa have been classified on the basis of their embryological origin into those of the rostral area with abnormal development of the cerebellum as in Dandy–Walker malformation and those of the caudal area with inadequate opening of the foramina of Magendie and Luschka, which are often transient and of no pathological significance.[16–19]

Sonographic studies have reported that a cyst in the posterior fossa in early pregnancy can be a transient finding in normal fetuses,[20,21] but it has also been described in association with subsequently diagnosed Dandy–Walker malformation.[22,23] A study involving ultrasound examination of the brain of 31 live births with trisomy 18 reported that the most common brain lesion was cerebellar hypoplasia, which was observed in 32% of the cases.[24] Another clinical and subsequent pathological

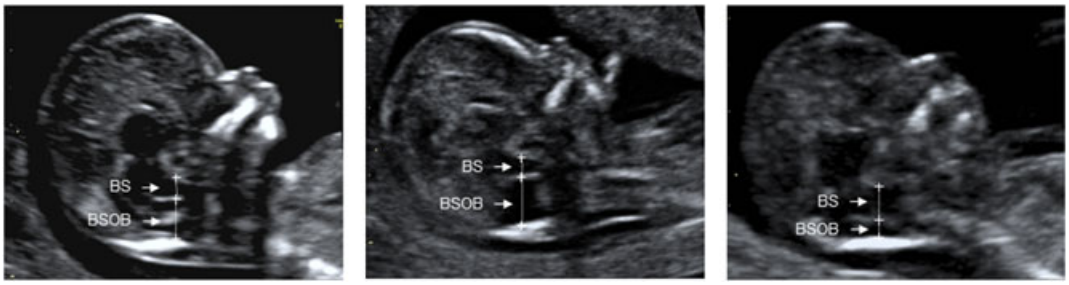


Figure 1 Midsagittal view of the fetal brain at 12 weeks' gestation demonstrating the measurements of BS diameter and BSOB diameter in a normal fetus (left), one with triploidy and a posterior fossa cyst (middle) and one with trisomy 18 and spina bifida (right)

Table 1 **Demographic and pregnancy characteristics of the study population. Each group is compared with the euploid fetuses**

| Measurement | Euploid fetuses ($n=162$) | Trisomy 18 ($n=45$) | Trisomy 13 ($n=21$) | Triploidy ($n=15$) |
|---|---|---|---|---|
| Maternal age in years, median (IQR) | 36.2 (31.2–39.6) | 38.6 (34.8–42.4)* | 32.9 (31.8–39.1) | 34.2 (25.4–38.0) |
| Maternal weight in kg, median (IQR) | 65.8 (58.1–72.4) | 64.0 (57.6–73.6) | 64.9 (57.7–71.0) | 64.0 (58.1–69.9) |
| Gestational age in days, median (IQR) | 91 (88–95) | 84 (82–88)** | 86 (83–89)** | 85 (81–89)** |
| Fetal crown rump length in mm, median (IQR) | 67.7 (60.9–76.1) | 54.8 (50.3–61.4)** | 58.3 (52.5–63.4)** | 56.0 (49.1–62.7)** |
| Fetal delta NT in mm, median (IQR) | 1.2 (1.0–1.5) | 3.7 (1.1–5.2)** | 3.7 (2.1–4.9)** | 1.4 (1.1–5.3) |
| Serum free ß-human chorionic gonadotrophin in MoM, median (IQR) | 1.703 (1.086–2.716) | 0.214 (0.127–0.352)** | 0.550 (0.258–0.965)** | 0.258 (0.113–10.438) |
| Serum pregnancy associated plasma protein-A in MoM, median (IQR) | 0.757 (0.459–1.147) | 0.168 (0.125–0.230)** | 0.283 (0.1667–0.310)** | 0.076 (0.043–0.652)** |
| *Ultrasound findings* | | | | |
| Absent nasal bone, *n* (%) | 21 (13.0%) | 33 (73.3%)** | 10 (47.6%)** | 8 (53.3%)** |
| Tricuspid regurgitation, *n* (%) | 30 (18.5%) | 26 (57.8%)** | 10 (47.6%)** | 7 (46.7%) |
| Reversed a-wave in ductus venosus, *n* (%) | 10 (6.2%) | 34 (75.6%)** | 7 (33.3%)** | 11 (73.3%)** |
| Holoprosencephaly, *n* (%) | — | — | 9 (42.9%)** | 3 (20.0%)** |
| Exomphalos, *n* (%) | 5 (3.1%) | 16 (35.6%)** | 10 (47.6%)** | 2 (13.3%) |
| Megacystis, *n* (%) | 3 (1.9%) | 4 (8.9%) | 1 (4.8%) | — |
| Spina bifida, *n* (%) | — | 4 (8.9%) | 1 (4.8%) | 2 (13.3%)* |
| Cardiac defects, *n* (%) | 6 (3.7%) | 21 (46.7%)** | 9 (42.9%)** | 5 (33.3%)** |

IQR, Interquartile range; MoM, multiple of the normal median; NT, nuchal translucency.
Comparisons by Mann–Whitney test for continuous variables, with post hoc Bonferroni correction for multiple comparisons.
Comparisons by $\chi^2$-test for categorical variables, with post hoc Bonferroni correction for multiple comparisons.
*$p<0.0167$, **$p<0.001$.

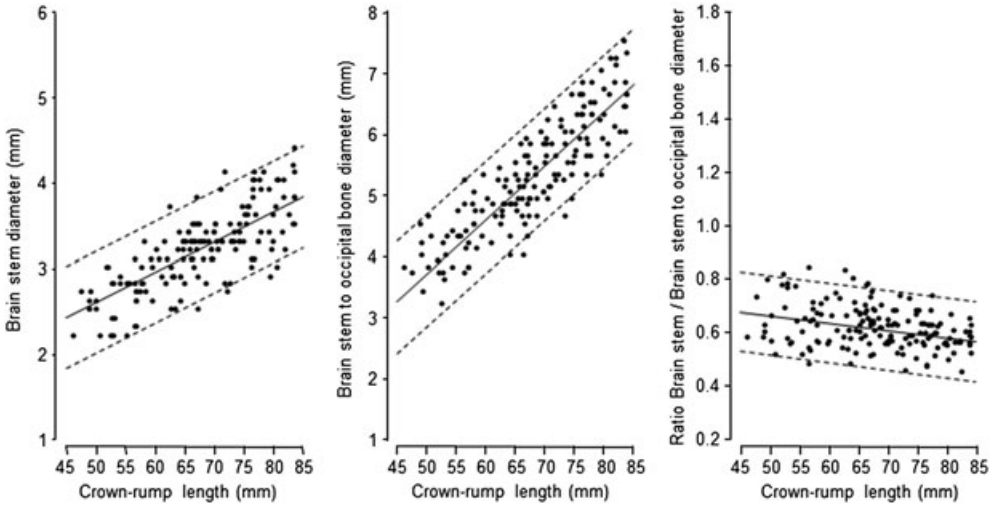


Figure 2 Individual measurements of BS diameter, BSOB diameter and BS to BSOB ratio in euploid fetuses plotted on the appropriate reference range for crown–rump length (median, 5th and 95th centiles) derived from the study of 1000 normal fetuses[4]

Table 2 Comparison of BS diameter, BSOB diameter and BS to BSOB ratio between euploid, trisomy 18, trisomy 13 and triploid fetuses from this study and 1000 normal fetuses in a previous study[4]

| Measurement | Euploid fetuses ($n=162$) | Trisomy 18 ($n=45$) | Trisomy 13 ($n=21$) | Triploidy ($n=15$) |
|---|---|---|---|---|
| Delta BS diameter in mm, median (IQR) | −0.039 (−0.229 to 0.146) | −0.525 (−0.634 to −0.07)** | −0.672 (−0.923 to −0.599)** | −0.144 (−0.557 to −0.469) |
| Delta BSOB diameter in mm, median (IQR) | −0.045 (−0.406 to 0.286) | 0.121 (−0.266 to 0.863)* | 0.577 (0.231 to 0.816)** | 0.669 (−0.857 to 1.330)* |
| Delta BS to BSOB ratio, median (IQR) | −0.002 (−0.058 to 0.042) | −0.132 (−0.234 to 0.003)** | −0.237 (−0.252 to −0.189)** | −0.149 (−0.213 to 0.166) |

IQR, interquartile range.
Comparisons by Mann–Whitney test, with post hoc Bonferroni correction for multiple comparisons.
*$p<0.0167$, **$p<0.001$

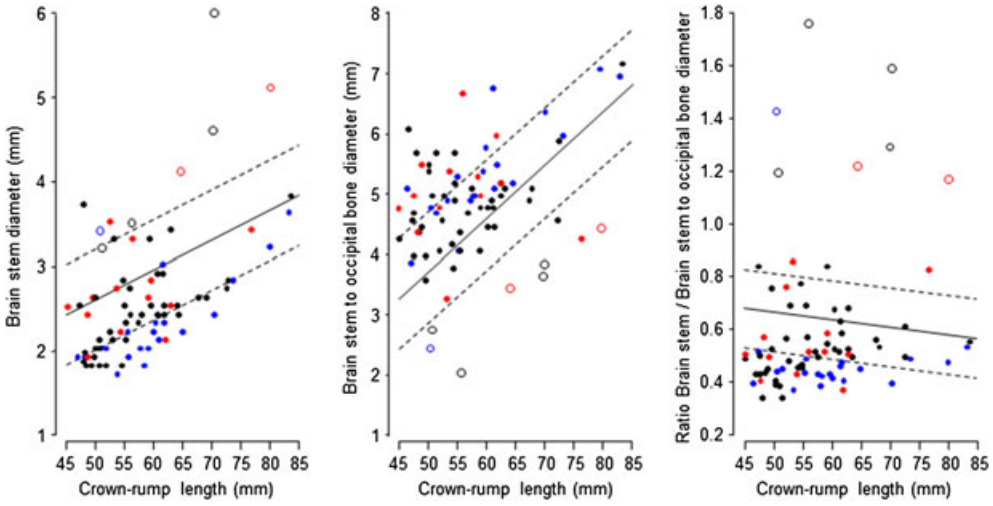


Figure 3 Individual measurements of BS diameter, BSOB diameter and BS to BSOB ratio in trisomy 18 (black circles), trisomy 13 (blue circles) and triploidy (red circles) plotted on the appropriate reference range for crown–rump length (median, 5th and 95th centiles) derived from the study of 1000 normal fetuses.[4] The open circles represent fetuses with open spina bifida

study of the brain of five neonates with trisomy 18 and two with trisomy 13 demonstrated hypoplasia of the cerebellar hemispheres and vermis with dilatation of the extracerebellar space in all cases.[25]

The findings of this study provide further support in favor of assessing the posterior fossa during the 11 to 13 weeks scan. The BS and BSOB can be measured in the same midsagittal view of the fetal face as the one obtained routinely for measurement of fetal NT. An increase in the BS to BSOB ratio raises the possibility of an underlying spina bifida and should stimulate the sonographer to undertake detailed examination of the fetal spine. A decrease in the BS to BSOB ratio raises the possibility of trisomy 18, trisomy 13 or triploidy and should stimulate the search for the other first trimester sonographic features of these aneuploidies.[11] The extent to which assessment of the posterior fossa is useful in early screening for Dandy–Walker malformation in euploid fetuses remains to be determined.

### WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- In open spina bifida at 11 to 13 weeks' gestation the BS diameter is increased, the BSOB diameter is decreased and the BS to BSOB ratio is increased.

### WHAT DOES THIS STUDY ADD?

- In trisomy 18 and trisomy 13 at 11 to 13 weeks BS diameter and BS to BSOB ratio are lower than in euploid fetuses.
- In trisomy 18, trisomy 13 and triploidy the BSOB diameter is increased.

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