

Lateral ventricles in fetuses with aneuploidies at 11–13 weeks' gestation

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ABSTRACT

Objective To examine the possible association between aneuploidies and fetal lateral cerebral ventriculomegaly in the first trimester of pregnancy.

Methods Three-dimensional brain volumes were acquired by transvaginal ultrasound examination at 11–13 weeks' gestation in 410 euploid fetuses and 63 fetuses with trisomy 21, 34 with trisomy 18 and seven with trisomy 13. Lateral ventricles were assessed in a transverse view, just above the roof of the third ventricle and measurements of the areas of the lateral ventricles and choroid plexuses were obtained. The ratio between choroid plexus and lateral ventricle areas (CLR) was calculated. Measurements in aneuploid fetuses were compared to those in euploid fetuses.

Results In euploid fetuses the lateral ventricle and choroid plexus areas increased, whereas the CLR decreased with fetal biparietal diameter. In fetuses with trisomy 21, lateral ventricle and choroid plexus areas were smaller but CLR was not significantly different from that in euploid fetuses. In trisomy 18 and 13 fetuses, CLR was significantly smaller than in euploid fetuses. The CLR was below the 5th centile of normal range in 11 (32.4%) fetuses with trisomy 18 and in six (85.7%) with trisomy 13.

Conclusion There is evidence of ventriculomegaly at 11–13 weeks' gestation in most fetuses with trisomy 13 and one third of fetuses with trisomy 18. Copyright © 2012 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Fetal cerebral ventriculomegaly may result from chromosomal and genetic defects, brain abnormalities, hemorrhage or infection, but in many cases no clear etiology is identified. In 14 published series in the 1980s and early

1990s concerning a combined total of 690 fetuses with ventriculomegaly during the second and third trimesters of pregnancy the mean incidence of aneuploidies was 13% and the commonest aneuploidies were trisomies 21, 18 and 13¹. It was noted also that the incidence of aneuploidies was inversely related to the severity of ventriculomegaly; in a series of 420 fetuses with ventriculomegaly the incidence of aneuploidies was 22% in those with mild to moderate ventriculomegaly and 6% in those with severe disease². The aim of this study was to examine the possible association between ventriculomegaly and aneuploidies in the first trimester of pregnancy.

METHODS

This study was part of a project investigating the fetal cerebral ventricular system at 11–13 weeks' gestation; the results concerning the fourth ventricle in fetuses with aneuploidies and all ventricles in fetuses with open spina bifida were published previously^{3,4}. The study was conducted in three university hospitals between October 2009 and December 2011. The control group consisted of 410 normal fetuses and the study group included 63 cases of trisomy 21, 34 of trisomy 18 and 11 of trisomy 13 (four cases of trisomy 13 were subsequently excluded because of holoprosencephaly). Gestational age was calculated from the fetal crown–rump length (CRL)⁵. The operator (L.T.) who performed all measurements was not aware of the fetal condition under investigation.

All patients underwent transvaginal sonography (transvaginal 5–9L probe, GE Voluson Expert 730, GE Voluson E8 or GE Voluson E6, GE Medical Systems, Zipf, Austria) and three-dimensional (3D) ultrasound brain volumes were acquired before chorionic villus sampling for fetal karyotyping. As a reference view, we used a transverse plane of the fetal head at the level of the thalamus and mesencephalon and the image was magnified to

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occupy the entire screen. The 3D sample box was placed to contain only the fetal head and the acquisition angle was 40–55°. To minimize movement artifacts, volume acquisition was done during fetal quiescence and took 3 seconds to complete. The resulting 3D volume was stored and processed offline, using 4D view software (GE Medical Systems, version 6.0). Using the multiplanar mode, the position of the brain was adjusted to obtain an exact vertical mid-sagittal view in Plane C. The landmark used for anteroposterior tilting was alignment of the roof of the third ventricle with the anterior border of the first cervical vertebra which are seen as echogenic dots at the middle of the fetal neck. The candle chrome map and speckle-reduction imaging features were used to improve the image. The reference views for measurements were identified in Plane A. The fetal biparietal diameter (BPD) was measured as previously described⁴. Lateral ventricles and the choroid plexus were assessed in a transverse view, just above the roof of the third ventricle and the caudate nucleus, which is a modified plane as compared to previously published data⁴ since, in this plane, the eminence created by the caudate nucleus is avoided (Figure 1). The area of each lateral ventricle and each choroid plexus was measured by tracing the border of these structures, and the average of two measurements was considered. The ratio of choroid plexus to lateral ventricle areas was then calculated. Demographic characteristics and ultrasound findings were recorded in a fetal database at the time of examination.

Statistical analysis

Continuous variables were compared using the Kruskal-Wallis test and each of the aneuploid groups was compared to the euploid group using the Mann-Whitney *U*-test with Bonferroni correction for multiple comparisons. In the euploid group regression analysis was used to examine whether each measurement changed with the

BPD and to determine whether the relationship was linear or non-linear. A reference range (5th, 50th and 95th centiles) for each measurement was constructed, based on the relationship with BPD. Measurements in the euploid fetuses and in those with a chromosomal abnormality were expressed as a difference from expected normal mean for BPD (delta value). The Kruskal-Wallis test was used to examine the significance of differences within the groups and, subsequently, each group of aneuploidy was compared to the euploid group using the Mann-Whitney *U*-test with Bonferroni correction for multiple comparisons. The statistical software package SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

RESULTS

Demographic and pregnancy characteristics of the study population are summarized in Table 1. Compared to euploid fetuses, the BPD and CRL values were smaller in fetuses with trisomy 18. In euploid fetuses the lateral ventricle and choroid plexus areas increased, whereas the ratio of choroid plexus area to lateral ventricle area decreased with fetal BPD (measured in mm) (Figures 2 and 3):

$$\text{Expected lateral ventricle area} = 0.578 + 0.068 \times \text{BPD}; \text{ adjusted } R^2 = 0.870;$$

$$\text{SD} = 0.08; P < 0.001.$$

$$\text{Expected choroid plexus area} = -1.004 + 0.116 \times \text{BPD} - 0.002 \times \text{BPD}^2;$$

$$\text{adjusted } R^2 = 0.740; \text{SD} = 0.07; P < 0.001.$$

$$\text{Expected choroid plexus lateral to ventricle ratio}$$

$$= 0.636 + 0.023 \times \text{BPD} - 0.001 \times \text{BPD}^2;$$

$$\text{adjusted } R^2 = 0.206; \text{SD} = 0.06; P < 0.001.$$

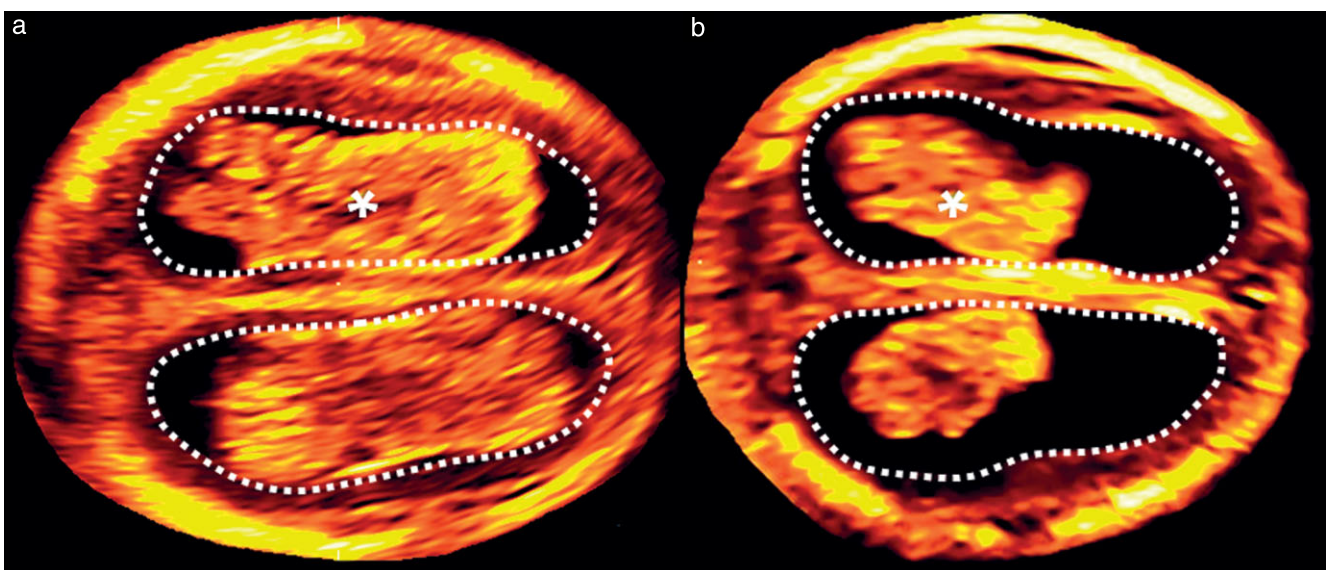


Figure 1 Axial view of fetal brain demonstrating lateral ventricles (dotted line) and choroid plexuses (*) in a euploid fetus (a) and in a fetus with trisomy 13 (b). In both fetuses the biparietal diameter was 24 mm.

Table 1 Demographic and pregnancy characteristics of the study population according to ploidy status

Characteristic	Euploid (n = 410)	Aneuploid		
		Trisomy 21 (n = 63)	Trisomy 18 (n = 34)	Trisomy 13 (n = 7)
Maternal age (years)	31.5 (28.0–35.0)	37.0 (34.0–40.0)*	37.0 (31.0–40.3)*	31.5 (24.0–36.3)
Gestational age (days)	87.6 (84.0–90.0)	88.0 (85.0–93.0)†	85.5 (83.0–90.5)	87.0 (84.0–91.8)
Fetal biparietal diameter (mm)	21.1 (19.1–23.4)	21.2 (18.9–23.1)	18.7 (17.2–20.9)*	19.3 (17.8–20.3)
Fetal crown–rump length (mm)	60.8 (55.5–66.3)	63.1 (56.6–71.4)	53.4 (49.5–62.7)†	57.4 (51.3–60.4)

Data are given as median (interquartile range). Comparisons were made using the Kruskal–Wallis test, with post-hoc Bonferroni correction for multiple comparisons. * $P < 0.001$. † $P < 0.05$.

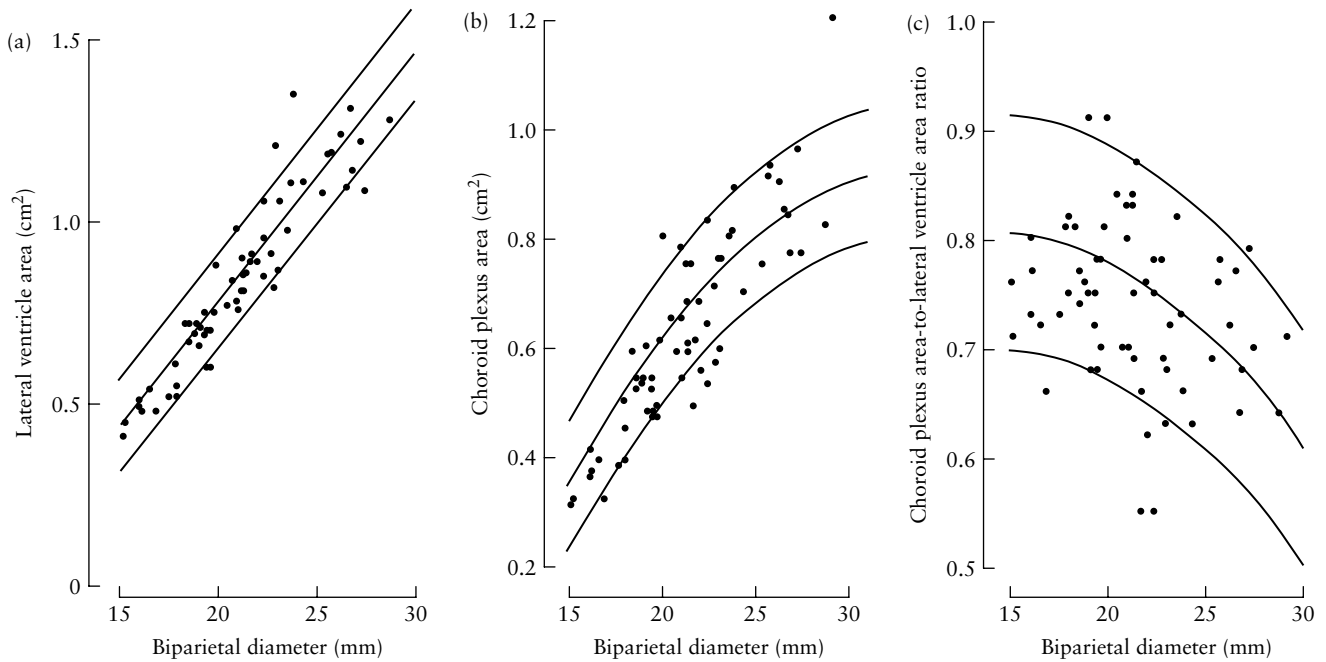


Figure 2 Lateral ventricle area (a), choroid plexus area (b) and ratio of choroid plexus area to lateral ventricle area (c) in relation to biparietal diameter in trisomy 21 fetuses at 11–13 weeks' gestation, plotted on reference range of euploid fetuses (5th, 50th and 95th centiles).

In fetuses with trisomy 21, the lateral ventricle and choroid plexus areas were significantly smaller than those in euploid fetuses (Figure 2, Table 2). In trisomy 18 fetuses, the ratio of choroid plexus area to lateral ventricle area was significantly smaller than that in euploid fetuses. In trisomy 13 fetuses, the choroid plexus and the ratio of choroid plexus area to lateral ventricle area were significantly smaller than those in euploid fetuses (Figure 3). The ratio of choroid plexus area to lateral ventricle area was below the 5th centile of the euploid fetuses in 11 (32.4%) of the 34 fetuses with trisomy 18 and in six (85.7%) of the seven fetuses with trisomy 13.

DISCUSSION

The findings of this study demonstrate that in normal fetuses at 11–13 weeks' gestation the areas of the lateral ventricles and choroid plexuses increase, whereas the ratio of choroid plexus area to lateral ventricle area decreases with fetal BPD. The area of both the lateral ventricles and the choroid plexuses was smaller in trisomy 21 fetuses

than in euploid fetuses and the ratio of choroid plexus to lateral ventricle was not significantly altered. In trisomy 18 and 13 fetuses, compared to euploid fetuses, the ratio of choroid plexus area to lateral ventricle area was smaller.

In the second and third trimesters of pregnancy, diagnosis of ventriculomegaly is based on demonstration of an increase in width of the lateral ventricular atrium in relation to the hemisphere^{1,6}. In the first trimester the cortex is very thin and it was therefore anticipated that, in fetuses with ventriculomegaly, the width of the ventricle may not be increased. Consequently, we measured the area of the ventricle to capture any possible distortion in shape. Additionally, we determined the area of the choroid plexuses relative to that of the ventricles, because an early sign of ventriculomegaly during the second trimester of pregnancy is apparent shrinkage of the choroid plexuses. Previous studies reported that at 14–21 weeks' gestation the choroid plexus normally fills the lateral cerebral ventricle from side to side⁷ and that, with development of ventricular dilatation, the choroid plexus separates from the medial wall of the lateral ventricle^{8,9}. A previous study

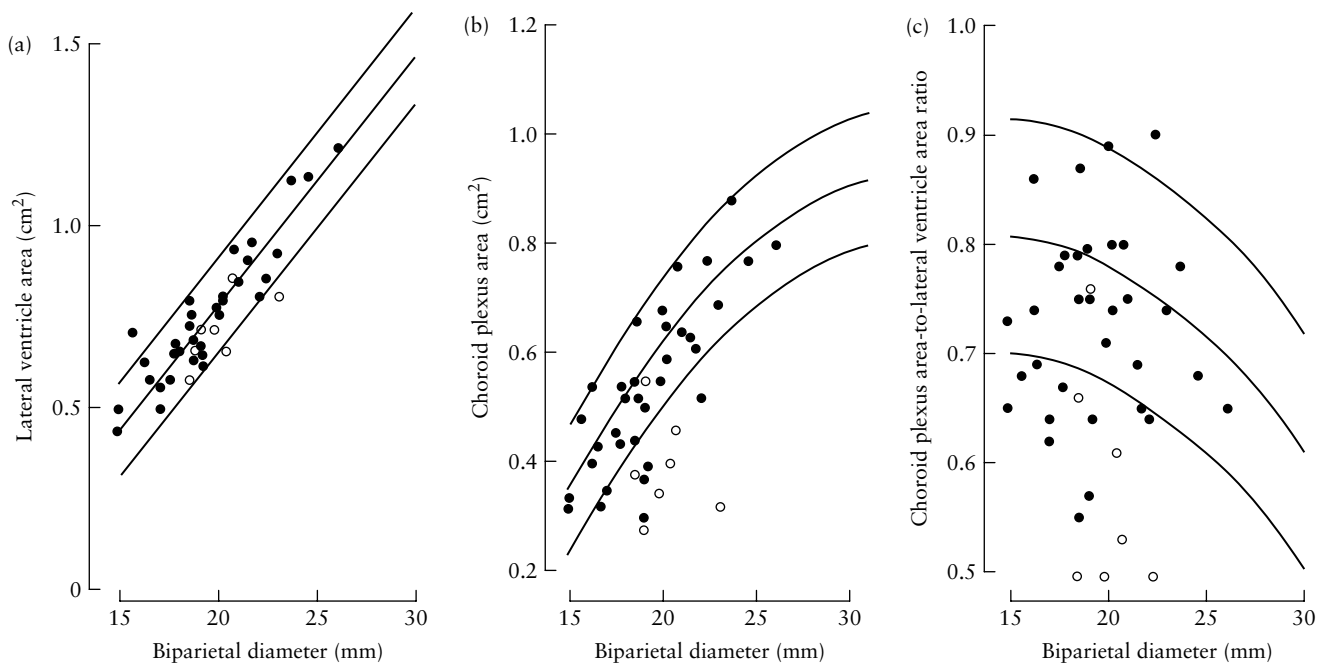


Figure 3 Lateral ventricle area (a), choroid plexus area (b) and ratio of choroid plexus area to lateral ventricle area (c) in relation to biparietal diameter in fetuses with trisomy 18 (●) and trisomy 13 (○) at 11–13 weeks' gestation, plotted on reference range of euploid fetuses (5th, 50th and 95th centiles).

Table 2 Area of lateral ventricles and choroid plexuses in euploid and aneuploid fetuses at 11–13 weeks' gestation, expressed as difference from euploid fetuses

Parameter	Euploid (n = 410)	Aneuploid		
		Trisomy 21 (n = 63)	Trisomy 18 (n = 34)	Trisomy 13 (n = 7)
Lateral ventricle area (delta (cm ²))	0.000 (−0.049 to 0.045)	−0.028 (−0.073 to 0.008)*	0.022 (−0.030 to 0.061)	−0.049 (−0.145 to 0.004)
Choroid plexus area (delta (cm ²))	−0.007 (−0.046 to 0.044)	−0.032 (−0.087 to 0.020)*	−0.023 (−0.060 to 0.041)	−0.229 (−0.272 to −0.156)†
Ratio of choroid plexus area to lateral ventricle area (delta)	0.002 (−0.039 to 0.042)	−0.020 (−0.071 to 0.029)	−0.048 (−0.123 to −0.002)†	−0.244 (−0.357 to −0.132)†

Data are given as median (interquartile range). Comparisons were made by Kruskal–Wallis test, with post hoc Bonferroni correction for multiple comparisons. * $P < 0.05$. † $P < 0.001$.

from 14 weeks' gestation onwards established a normal range for the ratio of occipital horn height to choroid plexus thickness and reported that it was above the 95th centile in 31 of 32 cases of confirmed ventriculomegaly¹⁰.

The observation that in trisomy 21 fetuses the areas of both lateral ventricles and choroid plexuses in relation to BPD were reduced could be the consequence of smaller brain volume and/or relative brachycephaly. There is supportive evidence for both findings from previous postnatal, prenatal and animal studies. A magnetic resonance imaging study in 16 patients with trisomy 21 reported that their brain volume was reduced¹¹. An anthropometric study in 199 patients with trisomy 21 between 6 months and 61 years of age reported the finding of brachycephaly due to shorter head length than head width¹². In two postmortem studies with a combined total of 415 fetuses with trisomy 21, aborted at 15–40 weeks'

gestation, the ratio of BPD to occipitofrontal diameter (OFD) or head circumference was significantly higher than that in normal fetuses^{13,14}. A 3D ultrasound study of 72 fetuses with trisomy 21 at 11–13 weeks' gestation reported that the fetal head volume was smaller than that in chromosomally normal fetuses¹⁵. Another 3D ultrasound study at 11–13 weeks' gestation reported that in 100 trisomy 21 fetuses, compared to 300 euploid fetuses, both BPD and OFD were smaller but the BPD to OFD ratio was higher¹⁶. In trisomy 16 mice, an animal model of trisomy 21, the brain is significantly smaller than in euploid mice during embryonic days 10–17, which corresponds to gestational weeks 7–18 in humans¹⁷.

The ratio of choroid plexus area to lateral ventricle area was below the 5th centile of normal range in 32% of fetuses with trisomy 18 and in 86% of those with trisomy 13. The pathophysiological significance

of this finding is uncertain. In all of our cases with aneuploidies the parents elected to terminate pregnancy, and it was therefore not possible to determine whether a low ratio of choroid plexus area to lateral ventricle area during the first trimester would have evolved into lateral ventriculomegaly during the second trimester. Previous studies during the second and third trimesters reported an association between ventriculomegaly and aneuploidies but the prevalence of ventriculomegaly in fetuses with trisomies 18 and 13 was only 4–15% and 3–39%, respectively^{2,18–20}. It could be postulated that a low ratio of choroid plexus area to lateral ventricle area at 11–13 weeks' gestation is a transient finding in some aneuploid fetuses and possibly is related to abnormal development of the ventricular system and the choroid plexuses, perturbed cellular function and decreased neurogenesis^{21–22}.

Cerebrospinal fluid (CSF) is primarily produced by choroid plexuses²³. There is evidence that the immature choroid plexus selectively transfers proteins from blood to CSF; thus, in the early brain, CSF has high concentrations of proteins including albumin, alpha-fetoprotein and proteoglycans^{24–26}. At 11–13 weeks' gestation the immature choroid plexus of the lateral ventricle is large and has abundant glycogen which is thought to have a nutritive and anabolic role^{27,28}. In the rat hydrocephalic model, changes in CSF content, including reduced proteoglycan, are detectable prior to morphological brain defects²⁹ and it is therefore possible that disturbed CSF regulation may be associated with abnormalities in brain ventricle structure. Aneuploidies are associated with altered maternal serum concentrations of various proteins produced by the fetal–placental unit³⁰ and it is likely that aneuploidies are associated with alterations concerning other proteins which could result in increased production of CSF and transient ventriculomegaly.

Ultrasound examination at 11–13 weeks' gestation is widely used in first-trimester combined screening for aneuploidies but also in early diagnosis of major defects³¹. Examination of the axial BPD plane of the fetal head, characterized by the butterfly image of the two choroid plexuses, is an integral part of the first-trimester scan and is useful in detection of acrania and alobar holoprosencephaly. The finding of a contracted choroid plexus should raise suspicion of ventricular dilatation and motivate the search for other defects associated with trisomies 18 and 13.

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