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Dilated Fourth Ventricle in Fetuses with Trisomy 18, Trisomy 13 and Triploidy at 11–13 Weeks' Gestation

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Key Words
Aneuploidy · Trisomy 21 · Neurosonography · First trimester ultrasound · Cerebral ventricles · Pyramid of pregnancy care

Abstract
Objective: To determine if in fetuses with aneuploidies the diameter of the fourth cerebral ventricle at 11–13 weeks' gestation is different from euploid fetuses. ***Methods:*** The fourth ventricle at 11–13 weeks' gestation was assessed in 62 cases of trisomy 21, 32 of trisomy 18, 10 of trisomy 13, and 12 of triploidy and compared to 410 normal euploid fetuses. Transvaginal sonography was carried out and 3D brain volumes were acquired. The fetal head was assessed in an axial plane and the diameter of the fourth ventricle was measured. Values in aneuploid and euploid fetuses were compared. ***Results:*** The diameter of the fourth ventricle in trisomy 18, trisomy 13 and triploidy, but not in trisomy 21, was significantly higher than in euploid fetuses. In the euploid fetuses the median diameter of the fourth ventricle was 1.9 mm and the 95th percentile was 2.5 mm. The measurements were above the median and the 95th percentile in 25 (78.1%) and 17 (53.1%) cases of trisomy 18, in 10 (100%) and 8 (80.0%) of trisomy 13, and in 10 (83.3%) and 10 (83.3%) of triploidy. ***Conclusions:*** In trisomy 18, trisomy 13 and triploidy the diameter of the fourth ventricle at 11–13 weeks' gestation is increased.

Introduction

Ultrasound examination at 11–13 weeks' gestation was originally introduced for measurement of fetal nuchal translucency (NT) thickness and crown-rump length (CRL) in screening for aneuploidies [1, 2]. However, it is now apparent that this scan can also lead to the diagnosis of many serious fetal defects and pregnancy complications [3, 4]. Recently, attention has focused on the early diagnosis of open spina bifida from demonstration of a decrease in the diameter of the fourth ventricle [5–8].

Ultrasound studies in the second trimester of pregnancy have reported an association between aneuploidies and the Dandy-Walker malformation (DWM) spectrum, which is characterized by complete or partial agenesis of the vermis and cystic dilation of the fourth ventricle and the posterior cranial fossa [9–12].

The aim of this study is to determine if in fetuses with aneuploidies there are alterations in the diameter of the fourth ventricle at 11–13 weeks' gestation.

Methods

The diameter of the fourth ventricle was measured in fetal head volumes, obtained by transvaginal 3D ultrasonography from 62 cases of trisomy 21, 32 of trisomy 18, 10 of trisomy 13, and 12 of triploidy at 11–13 weeks' gestation. Gestational age was cal-

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culated from the fetal CRL [13]. The study was part of a larger one in which the cerebral ventricular system was assessed in normal euploid fetuses, in aneuploid fetuses and in fetuses with open spina bifida. The operator (T.L.) who performed all measurements was not aware of the fetal condition under investigation. The values of this study on fetal aneuploidies were compared to those of 410 normal euploid fetuses that were previously reported [8]. We excluded cases with open spina bifida because the results of these cases were published previously [8].

The study was conducted in three university hospitals between October 2009 and December 2011. Transvaginal sonography was carried out and 3D brain volumes were acquired (transvaginal 5-9L probe, GE Voluson Expert 730, GE Voluson E8 or GE Voluson E6; GE Medical Systems, Milwaukee, Wisc., USA) before chorionic villous sampling for fetal karyotyping. The 3D sample box was placed in a way to contain only the fetal head and the acquisition plane was set at the level of the thalamus and mesencephalon, in a transverse view. The angle of acquisition was 40–55° depending on the distance between the transducer and the fetal head. Volume acquisition was during fetal quiescence and took 3 s to complete. The resulting 3D volume, which included the whole fetal head from crown to neck, was stored and studied off-line, using 4D view software (version 6.0; GE Medical Systems). The position of the brain was adjusted to obtain an exact mid-sagittal view in plane C. Different post-processing features to improve the quality of image were used, like candle chrome map and speckle-reduction imaging feature. Two axial planes of the brain were obtained as previously described [8]. In an axial plane characterized by the butterfly image of the two choroid plexuses with the roof of the third ventricle in the middle, we measured the biparietal diameter (BPD). The second plane was the suboccipitobregmatic one, below the cerebellum, where the largest anteroposterior diameter of the fourth ventricle was measured (fig. 1).

Demographic characteristics and ultrasound findings were recorded in a fetal database at the time of the examination.

Statistical Analysis

Continuous and categorical variables were compared using Mann-Whitney U test and χ^2 test or Fisher's exact test, respectively. In normal fetuses the diameter of the fourth ventricle did not change significantly with BPD and each value was expressed as a multiple of the normal median (MoM). Kruskal-Wallis test, with post hoc Bonferroni correction, was used to examine the significance of difference between each group of aneuploidies and euploid normal fetuses. The statistical software package SPSS 16.0 (SPSS Inc., Chicago, Ill., USA) was used for data analyses.

Results

The demographic and pregnancy characteristics of the study population are summarized in table 1. Compared to euploid pregnancies, in trisomy 18 the BPD was lower and in trisomy 18 and triploidy the CRL was lower.

In trisomy 21 the median MoM diameter of the fourth ventricle (1.0, interquartile range (IQR) 0.9–1.2) was not significantly different from euploid fetuses (1.0, IQR 0.9–1.2), but the diameter was significantly increased in trisomy 18 (1.4, IQR 1.1–1.6; $p < 0.05$), trisomy 13 (1.5, IQR 1.3–1.8; $p < 0.001$) and triploidy (2.1, IQR 1.8–2.0; $p < 0.001$).

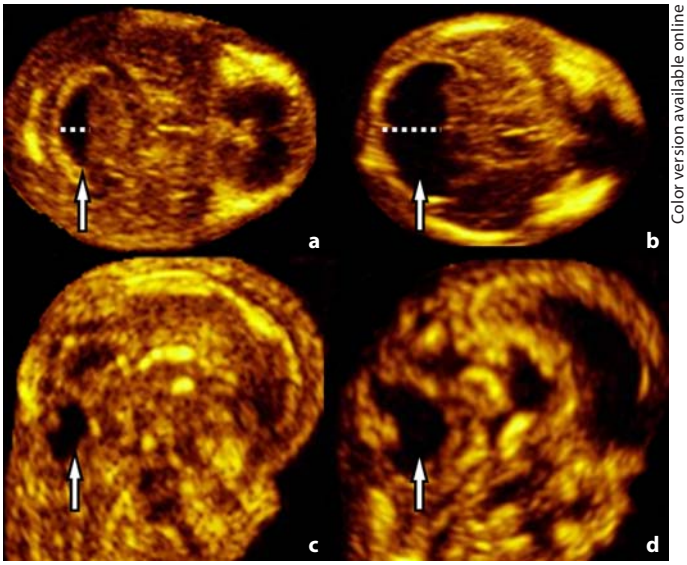

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Fig. 1. Axial (**a**, **b**) and sagittal (**c**, **d**) views of the fetal brain demonstrating the fourth ventricle (arrow) in a euploid fetus (left) and one with triploidy (right).

In the euploid fetuses the median diameter of the fourth ventricle was 1.9 mm and the 95th percentile was 2.5 mm. The diameter of the fourth ventricle was above the median and the 95th percentile in 25 (78.1%) and 17 (53.1%) of the 32 cases of trisomy 18, in 10 (100%) and 8 (80.0%) of the 10 cases of trisomy 13, and in 10 (83.3%) and 10 (83.3%) of the 12 cases of triploidy (fig. 2).

Discussion

The findings of this study demonstrate that at 11–13 weeks' gestation the anteroposterior diameter of the fourth ventricle in fetuses with trisomy 18, trisomy 13 and triploidy, but not in trisomy 21, is higher than in euploid fetuses. We measured the fourth ventricle in a suboccipitobregmatic plane, below the cerebellum, using 3D brain volumes which had been acquired by transvaginal ultrasound. This approach combined the advantages of good resolution and correct alignment of the small brain structures in three orthogonal planes.

In the second trimester the DWM is commonly associated with aneuploidies, mainly trisomy 18, trisomy 13

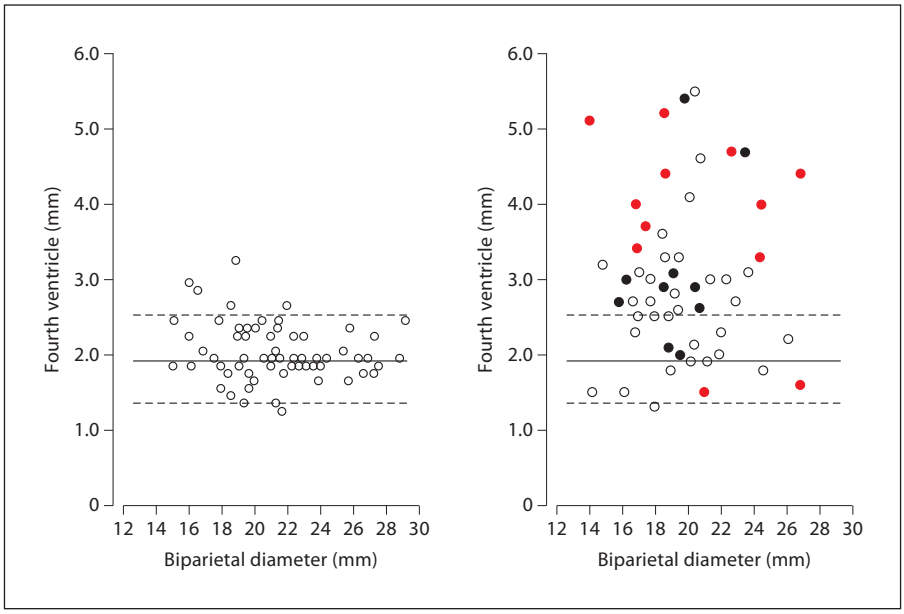

Fig. 2. Diameter of the fourth ventricle in fetuses with trisomy 21 (left) and trisomy 18 (open circles), trisomy 13 (black circles) and triploidy (red circles) (right) plotted on the normal range in euploid fetuses with BPD (5th, 50th and 95th percentiles).

Table 1. Demographic and pregnancy characteristics of the study population

Measurement	Euploid fetuses (n = 410)	Trisomy 21 (n = 62)	Trisomy 18 (n = 35)	Trisomy 13 (n = 10)	Triploidy (n = 12)
Maternal age, years					
Median (IQR)	31.5 (28.0–35.0)	37.0 (34.0–40.0)**	37.0 (30.0–40.5)**	32.0 (24.0–36.5)	30.5 (25.8–35.8)
Gestational age, days					
Median (IQR)	87.6 (84.8–90.4)	88.8 (85.5–93.0)	84.1 (81.3–88.7)*	86.0 (83.5–87.6)	83.2 (80.3–86.4)*
Fetal biparietal diameter, mm					
Median (IQR)	21.0 (19.1–23.4)	21.1 (18.9–23.2)	18.8 (17.6–21.1)**	19.3 (17.8–20.3)	19.5 (16.8–24.2)
Fetal CRL, mm					
Median (IQR)	60.8 (55.5–66.3)	62.9 (56.7–71.3)	54.2 (49.3–62.7)*	57.7 (53.1–60.7)	52.7 (47.6–58.5)*

Comparisons by Kruskal-Wallis test, with post hoc Bonferroni correction for multiple comparisons. * $p < 0.05$; ** $p < 0.001$.

and triploidy, but not trisomy 21 [9–12]. A previous study investigated the possible association between aneuploidies and the diameter of the fourth ventricle measured in the mid-sagittal view of the fetal profile at 11–14 weeks' gestation [14]. In 17 aneuploid fetuses, including 9 with trisomy 21, 3 of trisomy 18, 3 of trisomy 13, 1 of trisomy 20, and 1 of triploidy, the mean diameter of the fourth ventricle, corrected for CRL, was significantly increased. In our study an axial plane was used to obtain the largest diameter of this ventricle just below the cerebellum [8]. In trisomy 21 the diameter of the fourth ventricle was not significantly different from euploid fetuses but in trisomy 18, trisomy 13 and triploidy the diameter was increased.

At 8–9 weeks' gestation the roof of the fourth ventricle contains two areas lined by flattened ependymal cells: the anterior or rostral and posterior or caudal membranous areas separated by the plica choroidea, which subsequently develops into the choroid plexus [15]. 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 DWM 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 [16–18]. Consequently, possible explanations for the dilated fourth ventricle in trisomies 18 and 13 and triploidy are

delayed development of the posterior fossa or, in some cases, an underlying DWM. Sonographic studies have reported that a cyst in the posterior fossa in early pregnancy can be a transient finding in normal fetuses [19, 20]. Bronshtein et al. [19] described 21 fetuses with isolated enlargement of the fourth ventricle at 14–16 weeks' gestation which became normal on follow-up scans at 22–23 weeks. However, a posterior fossa cyst detected in the first trimester scan has also been described in association with subsequently diagnosed DWM [21, 22].

The effectiveness of ultrasound examination at 11–13 weeks' gestation and measurement of fetal NT thickness in early screening for aneuploidies is well established [23]. During this scan, systematic examination of the fetal anatomy can lead to the diagnosis of many serious fetal defects [3]. The finding of a small fourth ventricle can alert the ultrasonographer to the presence of open spina bifida [5–8]. As demonstrated in this study a large fourth ventricle is commonly found in fetuses with those aneuploidies which are associated with other brain defects, including the DWM. Trisomy 18, trisomy 13 and triploidy are associated with low serum free β-hCG and PAPP-A and several easily detectable sonographic features, including increased NT, early-onset growth restriction, tachycardia, holoprosencephaly, cardiac defects, exomphalos and megacystis. Assessment of the fourth ventricle may improve further the already high performance of first trimester biochemical and sonographic screening for these aneuploidies [23]. Further investigations are needed to determine the effectiveness of assessment of the fourth ventricle in first trimester screening for DWM in euploid fetuses.

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