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ORIGINAL ARTICLE

Subarachnoid space diameter in chromosomally abnormal fetuses at 11–13 weeks' gestation

Carolina Ferreira[a], Ana Lidia Rouxinol-Dias[b], Teresa Loureiro[a,c] and Kypros Nicolaides[d]

[a]Medical School, University of Porto, Porto, Portugal; [b]Center for Research in Health Technologies and Information Systems (CINTESIS), Medical School, University of Porto, Porto, Portugal; [c]Department of Obstetrics and Gynecology, S. João Hospital, Medical School, University of Porto, Porto, Portugal; [d]Fetal Medicine Research Institute, King's College Hospital, London, UK

ABSTRACT

Objectives: To examine the subarachnoid space diameters in chromosomally abnormal fetuses at 11–13 weeks' gestation.

Methods: Stored three-dimensional (3D) ultrasound volumes of the fetal head at 11–13 weeks' gestation from 407 euploid and 88 chromosomally abnormal fetuses (trisomy 21, $n = 40$; trisomy 18, $n = 19$; trisomy 13, $n = 7$; triploidy, $n = 14$; Turner syndrome, $n = 8$) were analyzed. The subarachnoid space diameters, measured in the sagittal and transverse planes of the fetal head, in relation to biparietal diameter (BPD) in each group of aneuploidies was compared to that in euploid fetuses. A total of 20 head volumes were randomly selected and all the measurements were recorded by two different observers to examine the interobserver variability in measurements.

Results: In euploid fetuses, the anteroposterior, transverse and sagittal diameters of the subarachnoid space increased with BPD. The median of the observed to expected diameters for BPD were significantly increased in triploidy and trisomy 13 but were not significantly altered in trisomies 21 and 18 or Turner syndrome. In triploidy, the subarachnoid space diameters for BPD were above the 95th centile of euploid fetuses in 92.9% (13 of 14) cases. The intraclass reliability or agreement was excellent for all three subarachnoid space diameters.

Conclusion: Most fetuses with triploidy at 11–13 weeks' gestation demonstrate increased subarachnoid space diameters.

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Aneuploidies; first-trimester screening; triploidy; subarachnoid space diameter

Introduction

Ultrasound examination at 11–13 weeks' gestation has been shown to be useful both in screening for aneuploidies and in the diagnosis of many fetal abnormalities [1,2]. Extensive studies have reported the application of three-dimensional (3D) ultrasound for first-trimester fetal neurosonography in describing normal and abnormal brain development [3–5]. In previous studies, we described the measurements of the different components of the cerebral ventricular system in normal fetuses at 11–13 weeks' gestation and how they relate to biparietal diameter (BPD); we found that the lateral ventricles area, choroid plexuses area and the third ventricle diameter increase with BPD, the width of the aqueduct of Sylvius decreases and the anteroposterior diameter of the fourth ventricle is stable at this stage of gestation [6]. Chromosomally abnormal fetuses demonstrated alterations in the development of the ventricular system, namely the fourth ventricle and lateral ventricles. The fourth ventricle diameter was significantly increased in fetuses with trisomy 18, trisomy 13 and triploidy but not in cases with trisomy 21 as compared to euploid fetuses [7]. We have also described a method to evaluate ventriculomegaly at 11–13 weeks' gestation by calculating the ratio between choroid plexus and lateral ventricle areas; we found that there was evidence of ventriculomegaly in most fetuses with trisomy 13 and in one-third of fetuses with trisomy 18 [8].

The objective of this study is to examine the subarachnoid space diameters between the superior surface of the cerebellum and mesencephalon in euploid and chromosomally abnormal fetuses at 11–13 weeks' gestation. This space, which is easily visible by ultrasound at 11–13 weeks' gestation, corresponds to the future vein of Galen cistern [9] and is influenced by the growth of the mesencephalon, corpus callosum and cerebellum; it was therefore hypothesized that the dimensions of this space could provide a measurable

CONTACT Teresa Loureiro tereloureiro@yahoo.com.br Serviço de Ginecologia e Obstetrícia, Centro Hospitalar S. João, Alameda, Porto 4200-319, Portugal

index of the effect of chromosomal abnormalities on brain development.

Materials and methods

Stored 3D ultrasound volumes of the fetal head at 11–13 weeks' gestation, collected for previous studies from patients undergoing first-trimester screening for aneuploidies [6–8], were used. These volumes included 407 from euploid and 88 from chromosomally abnormal fetuses (trisomy 21, $n = 40$; trisomy 18, $n = 19$; trisomy 13, $n = 7$; triploidy, $n = 14$; Turner syndrome, $n = 8$) were analyzed.

The anteroposterior, transverse and sagittal diameters of the subarachnoid space, in relation BPD in each group of aneuploidies were compared to those in euploid fetuses. Gestational age was calculated from the last menstrual period if cycles were regular, otherwise the crown-rump length (CRL) was used [10].

Essentially, transvaginal sonography was carried out and fetal brain volumes in the transverse plane were acquired (transvaginal 5–9 L probe, GE Voluson Expert 730, GE Voluson E8 or GE Voluson E6, GE Medical Systems, Milwaukee, WI). The fetal head image was magnified to occupy 75% of the screen. 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 the 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 (GE Medical System, version 6.0). During *off-line* manipulation, the BPD was measured in the axial plane characterized by the butterfly image of the two choroid plexuses with the roof of the third ventricle in the middle. The subarachnoid space was measured in the axial and sagittal planes, just above the aqueduct, at the anatomic region corresponding to the vein of Galen cistern and anteroposterior, transverse and sagittal diameters of the subarachnoid space were recorded (Figure 1).

A total of 20 head volumes were randomly selected and all the measurements were recorded by two different observers to examine the interobserver variability in measurements.

Statistical analysis

Normality of data distribution was assessed with Shapiro–Wilk normality test. None of the continuous variables showed a normal distribution for all outcomes. All continuous variables are reported as median (interquartile range), with tenths' approximation; all other categorical variables are reported as absolute or relative frequencies. Outliers outside three standard deviations for each group were excluded (total of five measurements). For comparisons of distributions between outcome groups, the Kruskal–Wallis test with Bonferroni correction for multiple comparisons was used for quantitative variables. To describe the correlation between parameters and BPD of euploid fetuses, Pearson's and Spearman's rank correlation coefficient were calculated. Regression analysis was used to examine whether each measurement changed with the BPD in euploid fetuses and whether the relationship was linear or nonlinear; a reference range (5th, 50th and 95th percentiles) for each measurement was constructed based on the relationship with BPD.

In the interobserver study, Bland–Altman analysis was used to compare the measurement agreement and bias between different examiners [11]. Intraclass correlation coefficient was also calculated. Intraclass agreement was classified according to intraclass correlation coefficient [<0.40 (poor), 0.40–0.59 (fair), 0.60–0.74 (good), and 0.75–1.00 (excellent)] [12].

Data analysis was performed using IBM SPSS Statistics 23 software and statistical software package R, version 3.3.2.

Results

The median maternal age in fetuses with trisomies 21 (38.0, range 23.0–43.2) and trisomy 18 (39.5, range 28.0–42.0) were higher and in Turner syndrome (29.0, range 20.0–33.0) was lower than in euploid fetuses (31.5, range 22.0–41.0); in trisomy 13 (31.0, range 19.0–37.0) and triploidy (32.0, range 22.0–38.0) it was not significantly different. Median BPD in fetuses with trisomy 18 was lower than in euploid fetuses; in the other chromosomal abnormalities, it was not significantly different (Table 1). Median CRL in fetuses with trisomy 18 and triploidy was lower than in euploid fetuses; in the other chromosomal abnormalities, it was not significantly different.

In euploid fetuses, CRL and each subarachnoid space diameter increased with BPD (Figure 2; Table 1). When compared to the expected measure of BPD for euploid fetuses, the CRL was increased in trisomy 21 fetuses and decreased in triploid fetuses; there was no significant difference for the other chromosomal abnormalities. Similarly, all subarachnoid space diameters were increased in triploid and trisomy 13 fetuses;

there was no significant difference for the other chromosomal abnormalities. In the 14 triploid fetuses the subarachnoid space diameters for BPD were above the 95th centile of euploid fetuses in 13 (93%) for the sagittal diameter, in 9 (64%) for the anteroposterior diameter and 11 (79%) for the transverse diameter. The respective values for the seven trisomies 13 fetuses were 4 (57%), 3 (43%) and 2 (28%).

In the interobserver study, the mean difference in subarachnoid space diameters and the 95% limits of

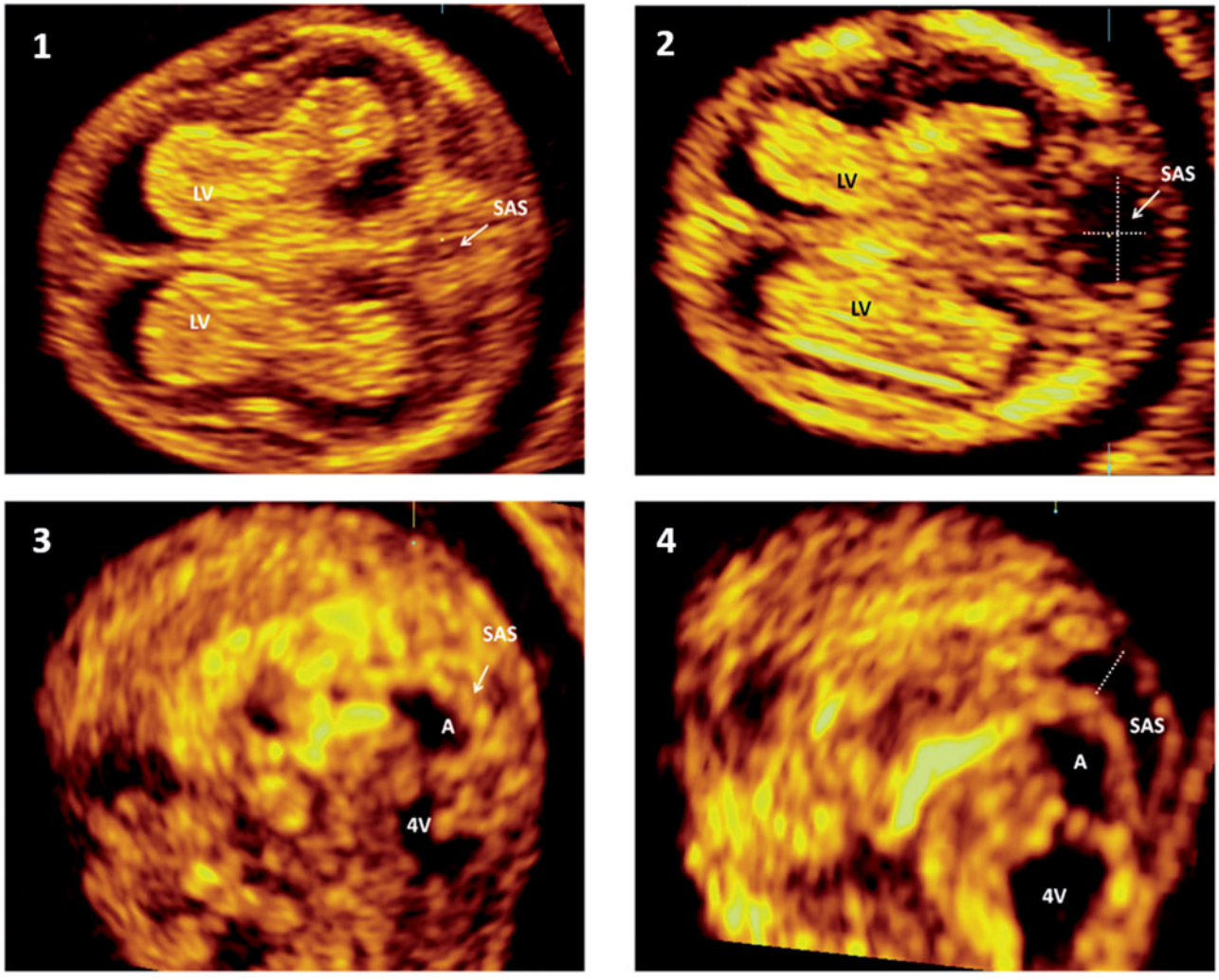

Figure 1. Subarachnoid space in transversal plane (1 and 2) and corresponding sagittal plane (3 and 4) in an euploid fetus (left) and in a triploid fetus (right). Footnote: LV: lateral ventricule; 4V: fourth ventricule; A: aqueduct; SAS: subarachnoid space.

Table 1. Median range of measurements of fetal crown-rump length, biparietal diameter (BPD) and subarachnoid space diameters for BPD in euploid and aneuploid fetuses.

	Euploidy	Trisomy 21	Trisomy 18	Trisomy 13	Triploidy	Turner
Measurements						
Biparietal diameter in mm	21.1 (16.7–26.0)	21.1 (16.1–27.3)	18.3 (14.0–25.9)*	18.9 (15.6–22.9)	22.0 (13.8–26.6)	21.0 (15.2–24.7)
Crown-rump length in mm	60.9 (48.1–76.7)	61.9 (49.3–82.8)	53.0 (41.5–73.4)*	57.0 (49.4–64.9)	49.0 (43.6–61.8)**	58.4 (45.9–71.1)
Difference of observed to expected						
Crown-rump length	−0.008 (4.07)	1.990 (4.32)*	0.667 (7.09)	0.025 (2.94)	−11.109 (10.62)**	−2.670 (3.91)
Anteroposterior SAS	−0.008 (0.42)	0.071 (0.44)	−0.057 (0.44)	1.055 (0.77)**	2.178 (1.20)**	0.066 (0.52)
Transverse SAS	−0.011 (0.63)	−0.084 (0.53)	0.021 (0.61)	1.035 (0.81)**	2.650 (1.43)**	0.303 (0.91)
Sagittal SAS	−0.007 (0.36)	0.068 (0.37)	−0.080 (0.29)	0.974 (0.66)**	1.924 (0.96)**	0.198 (0.49)

SAS: subarachnoid space diameter.
Values for biparietal diameter and crown-rump length are given as median (5th–95th percentile).
Values on the difference between the observed and expected measurement are given as mean difference (standard deviation) in mm.
Comparisons between each chromosomally abnormal group and euploid fetuses by Kruskal–Wallis test with Bonferroni correction for multiple comparisons.
*$p < .05$.
**$p < .001$.

agreement with their 95% confident interval between 20 paired measurements by two different observers and intraclass correlation coefficients are shown in Table 2. The intraclass reliability or agreement was excellent for all three subarachnoid space diameters.

Discussion

The findings of this study demonstrate the feasibility and reproducibility of using 3D ultrasound to measure fetal subarachnoid space diameters at 11–13 weeks' gestation. In euploid fetuses, the anteroposterior, transverse and sagittal diameters of the subarachnoid space increased with BPD. In fetuses with triploidy and less so for those with trisomy 13 the subarachnoid space diameters, corrected for BPD, were substantially higher than in euploid fetuses; in the other chromosomal abnormalities, the diameters were not significantly altered. The sagittal diameter of the subarachnoid space was above the 95th percentile of euploid fetuses for BPD in 13 of our 14 fetuses with triploidy.

Routine assessment of the posterior fossa, both in the sagittal and transverse section, of the fetal head during the 11–13 weeks scan has been advocated because of extensive evidence on the association between easily detectable features of the Chiari malformation type II in fetuses with open spina bifida [13,14]. The planes we used for our study are not the same as those for assessment for spina bifida, as they are at a level above the fourth ventricle, cerebellum and cisterna magna. The subarachnoid space measurement was performed specifically in its widest area corresponding to a cistern delineated superiorly by the tentorium cerebelli and inferiorly by the superior surface of the future cerebellum. This space extends laterally around the cerebral peduncles and corresponds anatomically to the future vein of Galen cistern [9]. At 11–13 weeks' gestation, the anatomy of this region and tentorium cerebelli differs considerably in shape and position from later development.

A previous study using high-resolution magnetic resonance images of 46 human fetuses proved that tentorium cerebelli rotates inferoposteriorly towards the foramen magnum from 10 to 29 gestational weeks in response to a normal disproportionate growth of the cerebrum, as most probably the consequence of increasing supratentorial volume in relation to posterior fossa volume [15]. These findings may support the impression that an increased volume in posterior fossa structures like the fourth ventricle or cisterna magna may affect the usual inferoposterior rotation of the

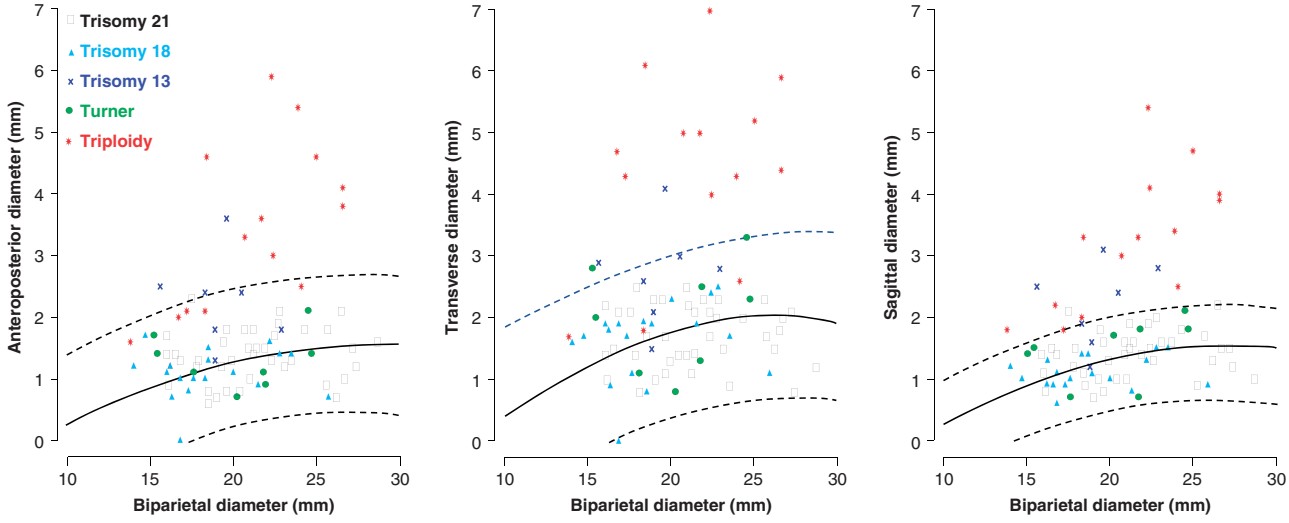

Figure 2. Anteroposterior (left), transverse (middle) and sagittal (right) subarachnoid space diameter in relation to biparietal diameter in chromosomally abnormal fetuses plotted on the reference range for euploid fetuses (5th, 50th and 95th percentiles).

Table 2. Mean difference of subarachnoid space diameters and the 95% limits of agreement with their 95% CI between 20 paired measurements between two observers.

Subarachnoid space diameter (mm)	Mean difference (95% limits of agreement) [95% CI]	Intraclass correlation coefficient for single measures (95% CI)
Anteroposterior	0.29 (−0.73 [−0.97; −0.50]; 1.32 [1.09; 1.56])	0.909 (0.739; 0.967)
Transverse	−0.29 (−1.17 [−1.37; −0.97]; 0.57 [0.37; 0.77])	0.840 (0.529; 0.942)
Sagittal	−0.01 (−1.05 [−1.29; −0.82]; 1.01 [0.78; 1.25])	0.837 (0.571; 0.938)

CI: confidence interval.

human fetal tentorium cerebelli. This would result in increased subarachnoid space around the cerebral peduncles. The finding of increased fourth ventricle dimensions in most of the fetuses with trisomy 13 and triploidy has been reported previously by our group. It was above the 95th percentile in 8 (80.0%) of the 10 cases of trisomy 13, and in 10 (83.3%) of the 12 cases of triploidy, probably related to the occurrence of delayed or abnormal development of the posterior fossa. It has been described previously that congenital malformations of the brain resulting in disproportionate increases of infratentorial size during development, such as Dandy–Walker malformation, can displace the tentorium and the confluence of sinuses superiorly [16].

Screening at 11–13 weeks by a combination of maternal age, fetal nuchal translucency thickness, fetal heart rate and maternal serum free β-hCG and PAPP-A can identify at least 90% of fetuses with the chromosomal abnormalities we examined in this study [1]. In this respect, it is unlikely that measurement of subarachnoid space diameters will improve the performance of the first trimester combined test. However, our findings provide some inside into early brain development in chromosomally abnormal fetuses.

Disclosure statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the paper.

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ORCID

Teresa Loureiro http://orcid.org/0000-0002-0998-4902

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