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Three-dimensional sonographic calculation of the volume of intracranial structures in growth-restricted and appropriate-for-gestational age fetuses

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KEYWORDS: 3D ultrasound; fetal brain; intrauterine growth restriction; volume calculation

ABSTRACT

Objectives *To evaluate the feasibility and reproducibility of volume segmentation of fetal intracranial structures using three-dimensional (3D) ultrasound imaging, and to estimate differences in the volume of intracranial structures between intrauterine growth-restricted (IUGR) and appropriate-for-gestational age (AGA) fetuses.*

Methods *Total intracranial, frontal, thalamic and cerebellar volumes were measured using 3D ultrasound imaging and Virtual Organ Computer-aided AnaLysis (VOCAL) in 39 IUGR and 39 AGA fetuses matched for gestational age, at 28–34 weeks of gestation. Volumes of, and ratios between, structures were estimated, and differences between IUGR and AGA fetuses were calculated. Volume measurements were performed by two observers, and interobserver and intraobserver intraclass correlation coefficients (ICCs) were calculated for each structure.*

Results *Volumes were satisfactorily obtained in all fetuses. All net volumes except those for the thalamus ($P = 0.23$) were significantly smaller ($P = 0.001$) in IUGR fetuses. After adjusting volumes for biparietal diameter the frontal volume was significantly smaller ($P = 0.02$) and the thalamic volume significantly greater ($P = 0.03$) in IUGR fetuses than in AGA fetuses. Significant intergroup differences in the ratios between structures were found only in those involving the frontal region. Interobserver ICCs were as follows: total intracranial 0.97 (95% CI, 0.92–0.98), cerebellar 0.69 (95% CI, 0.44–0.75), frontal 0.66 (95% CI, 0.42–0.79) and thalamic 0.54 (95% CI, 0.37–0.72).*

Conclusions *IUGR fetuses show differences in the volume of intracranial structures compared with AGA fetuses, with the largest difference found in the frontal region. These differences might be explained by* in-utero *processes of neural reorganization induced by chronic hypoxia. Copyright © 2009 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Although intrauterine growth-restricted (IUGR) fetuses develop protective mechanisms, such as increased blood flow and oxygen uptake, they have an increased risk of developing signs of brain damage at birth[1–3]. The brain is particularly sensitive to changes in oxygen and glucose concentration. Studies performed in neonates and in young adults born with intrauterine growth restriction have shown that signs of neurological damage can be manifested later in life as low scores in neurodevelopmental tests and reduced cognitive function[4–6]. Neonatal studies using brain biometry and volume segmentation have demonstrated the existence of selective growth restriction in certain brain regions[7,8], which could explain subsequent alterations in neurodevelopment. Whether these changes occur *in utero* is unknown.

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Prenatal assessment of the fetal head/brain is usually performed using two-dimensional (2D) ultrasound biometric measurements. Recently, 3D ultrasound imaging has been gradually introduced as a valuable complementary tool in fetal evaluation, offering the possibility of calculating fetal organ volumes and providing extra information on growth and maturation[9]. Virtual Organ Computer-aided AnaLysis (VOCAL) has been used to describe normal reference values for brain and cerebellar volumes throughout gestation[10,11]. However, no information has been reported on brain volume in IUGR fetuses and, apart from the cerebellum[11], there are no reports of segmentation of other fetal intracranial structures. The importance of this lack of information became apparent when studies in neonatal brain suggested that different intracranial areas could be selectively affected in intrauterine growth restriction[12].

Our group has previously demonstrated the existence of regional vascular redistribution processes in IUGR fetuses, as measured by pulsed Doppler ultrasound imaging of different brain arteries[13], and evaluation of brain blood perfusion by means of power Doppler ultrasound examination and fractional moving blood volume estimation[14]. We postulated that these changes might correlate with changes in growth and volume calculation of different brain regions. In the present study we aimed, first, to evaluate the feasibility and reproducibility of volume segmentation of fetal intracranial structures using 3D ultrasound imaging and, second, to analyze the possible existence of differences between IUGR and appropriate-for-gestational age (AGA) fetuses.

METHODS

A group of 39 IUGR and 39 AGA fetuses matched by gestational age (± 1 week) were studied. Intrauterine growth restriction was defined as an estimated fetal weight $< 10^{th}$ centile according to local standards[15] and a pulsatility index in the umbilical artery $> 95^{th}$ centile[16]. The protocol was approved by the ethics committees of the two participating centers and informed consent was obtained from the parents. Volume collection was done in the two centers and volume calculations were performed in Barcelona.

All ultrasound examinations were performed using a Voluson 730 Expert (GE Healthcare, Milwaukee, WI, USA) ultrasound machine with a 4–8-MHz curvilinear probe and an internal device for automatic acquisition of frames for volume reconstruction. Routine 2D ultrasound examination for fetal anatomical evaluation and standard fetal biometry, including biparietal diameter (BPD) and head circumference (HC), was performed.

Brain volumes were obtained by trained operators and were stored on digital devices for further analysis. The volume sample box was adjusted to include the complete fetal head and no zoom magnification was used. The volume sweep angle was set at 80° and the highest quality of acquisition was selected. Two brain volumes were acquired from each patient. The first was obtained from a cross-sectional view of the fetal skull at the level of the BPD plane. With this volume, a clear perspective of the frontal region, total intracranial region and thalamus was obtained. The second volume was obtained from the same axial plane with a discrete anterior inclination of 15–20° to avoid ultrasound shadowing of the petrous process and obtain a clear image of the cerebellum. All volumes were acquired in the axial view; thus, for the multiplanar display, Box A corresponded to the axial plane, Box B to the coronal plane and Box C to the sagittal plane. The acquisition process was repeated until the operator was satisfied with the volumes. Fetal brain scans were performed in the absence of maternal and fetal movements.

Volume calculations were made offline by two operators (one of whom was blinded to the clinical characteristics (J.F.-D.)). The total intracranial, frontal, thalamic and cerebellar volumes were segmented manually using 4D View offline analysis software and VOCAL (GE Healthcare). The total intracranial volume was selected as the standard with which to compare all other structures and to allow comparison of our results with those already published for normal fetuses[10]. The frontal lobe was selected because this region has previously been shown to be reduced in growth-restricted neonates[7]. The thalamus was selected for its importance in connecting almost all neural centers, and the cerebellum for its implication in motor control.

In 10 volumes of the frontal lobe three different levels of spacing for the rotational method were tested, 30° (six images), 15° (12 images) and 9° (20 images). We did not find differences in the volume calculation when 12 or 20 images were used (mean ± SD, 33.4 ± 13.6 cm^3 vs. 32.7 ± 11.7 cm^3), but the time for delineating 20 images was almost double that for 12 images (range, 3–5 min vs. 7–9 min). Using six images increased the variability of the volume calculation (mean ± SD, 38.4 ± 21.2 cm^3). Based on these findings, we opted for a rotation step of 15°. Figures 1 and 2 show the complete set of images used to construct and calculate the volume of the fontal lobe and the thalamus. The rotation process was started in an axial view at 0° and finished in the same plane at 180°, with an angle of 90° corresponding to a coronal view of the structure. The last image, corresponding to 180°, was not included in the volume calculation as it represents a mirror image of the 0° image (Figure 3).

The boundaries for the total intracranial volume were defined anteriorly, posteriorly and laterally by the inner wall of the skull and inferiorly by the floor of the skull. Frontal region boundaries were delineated anteriorly and laterally by the inner wall of the skull, inferiorly by the floor of the skull and posteriorly by the Sylvian fissure (lateral fissure). This structure can be recognized from an axial view of the fetal head at the level of the BPD and is considered as the posterior landmark for the frontal lobe[7,17]. To complete the posterior delineation of the frontal region, a transverse plane connecting the two lateral Sylvian fissures was drawn, excluding the thalami. The thalamus was defined by following its contours and crossing the midline at two points in

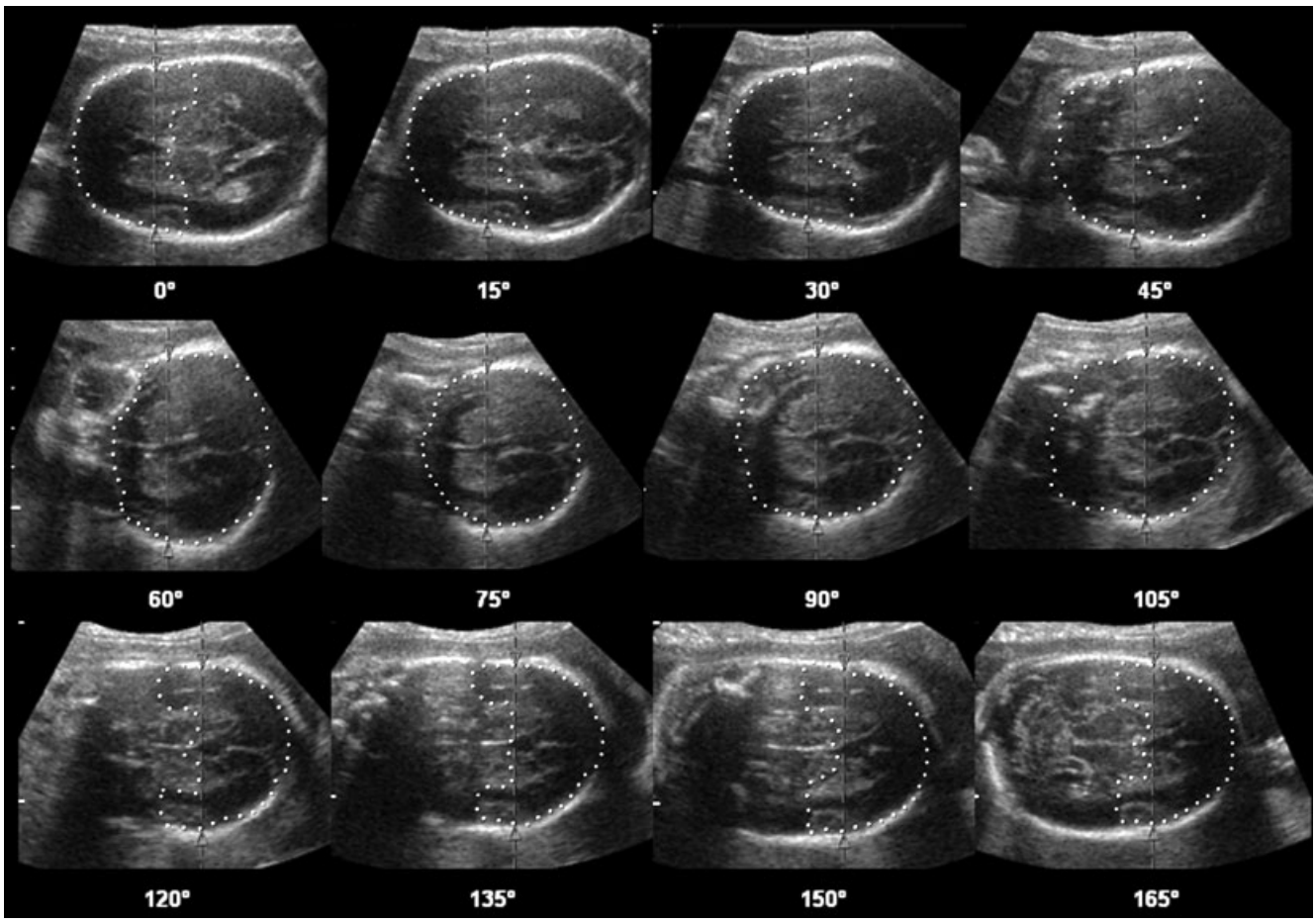

Figure 1 Images obtained with a rotation step of 15° using Virtual Organ Computer-aided AnaLysis (VOCAL) to delineate the frontal lobe for volume calculation and reconstruction.

order to obtain a single volume. The cerebellum was delineated by following the middle line and the contours of the cerebellar hemispheres (Figure 4). Volumes were expressed in cm^3. For each structure, the volume was estimated twice and the mean of these two measurements was considered as its representative value.

Ratios between the evaluated regions were calculated. Differences in net volumes were analyzed using Student's *t*-test and differences in ratios between IUGR and AGA fetuses were analyzed with the Mann–Whitney *U*-test.

To test the hypothesis that IUGR fetuses show smaller regional brain volumes than controls independently of head size, a multiple regression model was constructed for each region, in which the dependent variable was regional brain volume and the independent variable was a dichotomized IUGR variable. In addition, BPD was included in the model as a covariate to adjust for the effect of intrauterine growth restriction on overall head biometry. Thus, the model coefficient for the IUGR variable could be interpreted as the adjusted difference in regional brain volumes between cases and controls, assuming the same overall head size. Each regression model was checked for the assumptions of regression. $P < 0.05$ was considered significant.

To assess interobserver and intraobserver reliability, a two-way random and a two-way mixed model, respectively, were used and single-measure intraclass correlation coefficients (ICCs) for absolute agreement were calculated. The following benchmarks were used for ICC characterization: slight reliability (0–0.2), fair reliability (0.21–0.4), moderate reliability (0.41–0.6), substantial reliability (0.61–0.8) and almost perfect reliability (0.81–1.0)[18]. Statistical analysis was performed using Statistical Package for the Social Sciences version 14.0 (SPSS Inc., Chicago, IL, USA) and MedCalc version 8.0 (MedCalc Software, Mariakerke, Belgium) statistical software.

RESULTS

Volume measurements from all structures were obtained in all fetuses. The demographic characteristics of the groups studied are shown in Table 1. Low umbilical artery pH values and 5-min Apgar scores were more frequent in the IUGR group but these differences were not statistically significant.

There were three fetal and two neonatal deaths in the IUGR group. The three cases that resulted in fetal death had shown reversed atrial flow in the ductus venosus and, due to extreme prematurity, the parents had opted against the fetuses being delivered. The two cases that resulted in neonatal death had shown an increased pulsatility

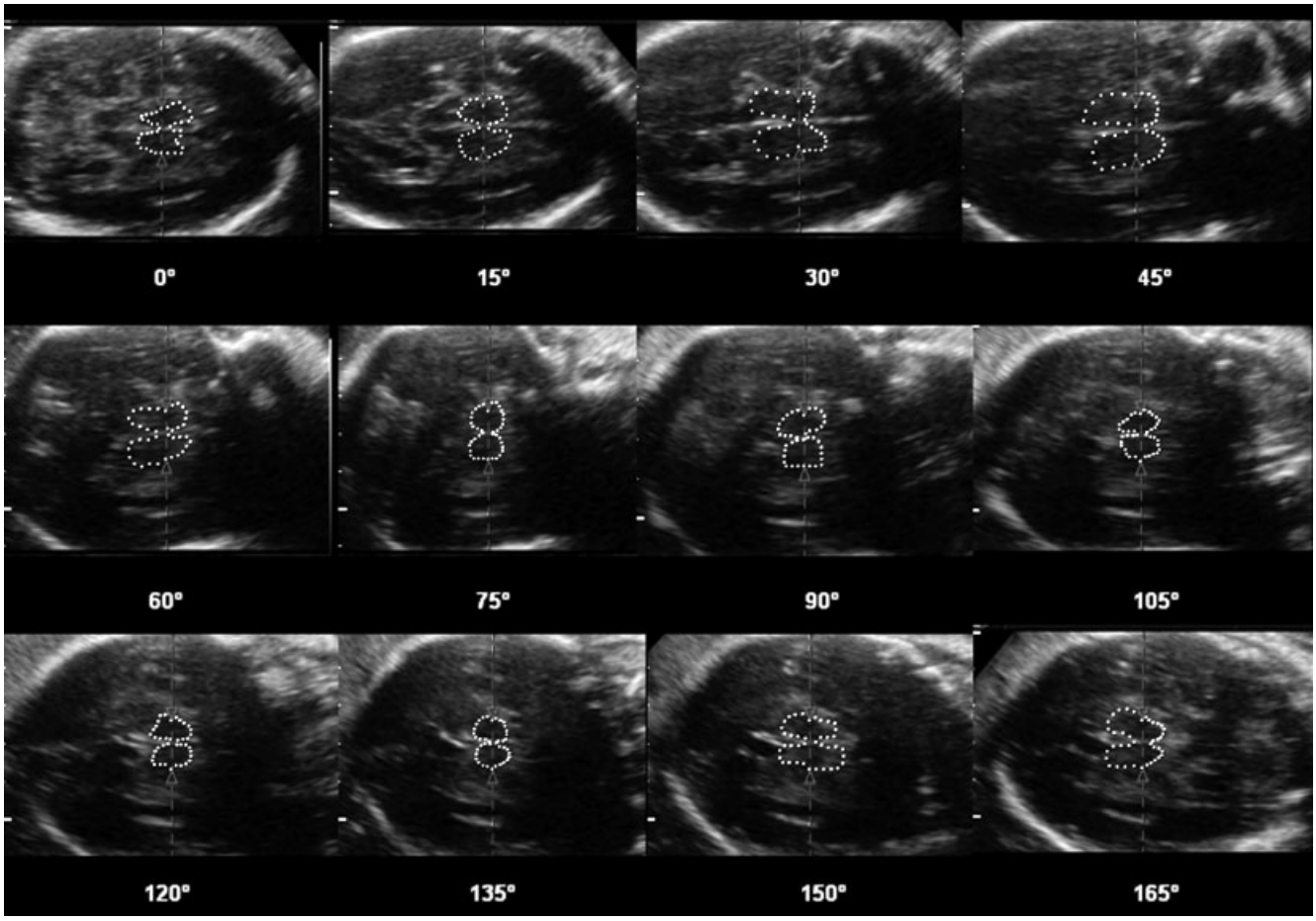

Figure 2 Images obtained with a rotation step of 15° using Virtual Organ Computer-aided AnaLysis (VOCAL) to delineate the thalamus for volume calculation and reconstruction.

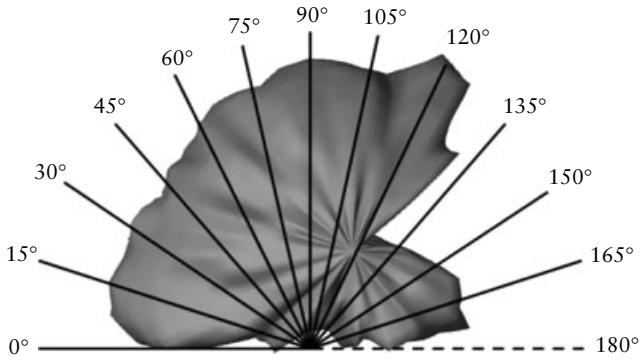

Figure 3 Diagram showing 15° rotation steps for measurement of the volume of the frontal lobe starting from the axial plane. Note that the starting image at 0° and the final one at 180° are mirror images, and so the last image (dashed line) is not included in the volume calculation.

index in the ductus venosus but present atrial flow. Both of these fetuses developed signs of intraventricular hemorrhage.

Substantial to almost perfect intraobserver reliability was observed for all regions. Total intracranial, frontal and cerebellar regions showed similar figures for interobserver reliability. The only structure showing moderate interobserver measurement reliability was the thalamus (Table 2).

The BPD and HC were significantly smaller in the IUGR group than in AGA fetuses (Table 3). No statistically significant differences were found in the HC/BPD ratio between the two groups. Differences in the net volumes of the studied structures are shown in Table 3. All volume estimations, except those for the thalamic area, were significantly reduced in the IUGR group.

Table 3 also illustrates the ratios between the different regions. In IUGR fetuses the frontal volume was reduced, and the thalamic volume was increased, in relation to the total intracranial volume. However, statistically significant differences were found only in ratios including the frontal volume.

After adjustment for BPD (Table 4), the thalamic volume was found to be significantly larger, and the frontal volume significantly smaller, in IUGR fetuses, whereas total intracranial and cerebellar volumes did not differ from those in AGA fetuses.

DISCUSSION

The results of this study suggest that fetuses with severe intrauterine growth restriction have reduced frontal and increased thalamic volumes in relation to the total intracranial volume. These differences persisted when the volumes were adjusted by the BPD of each fetus. The

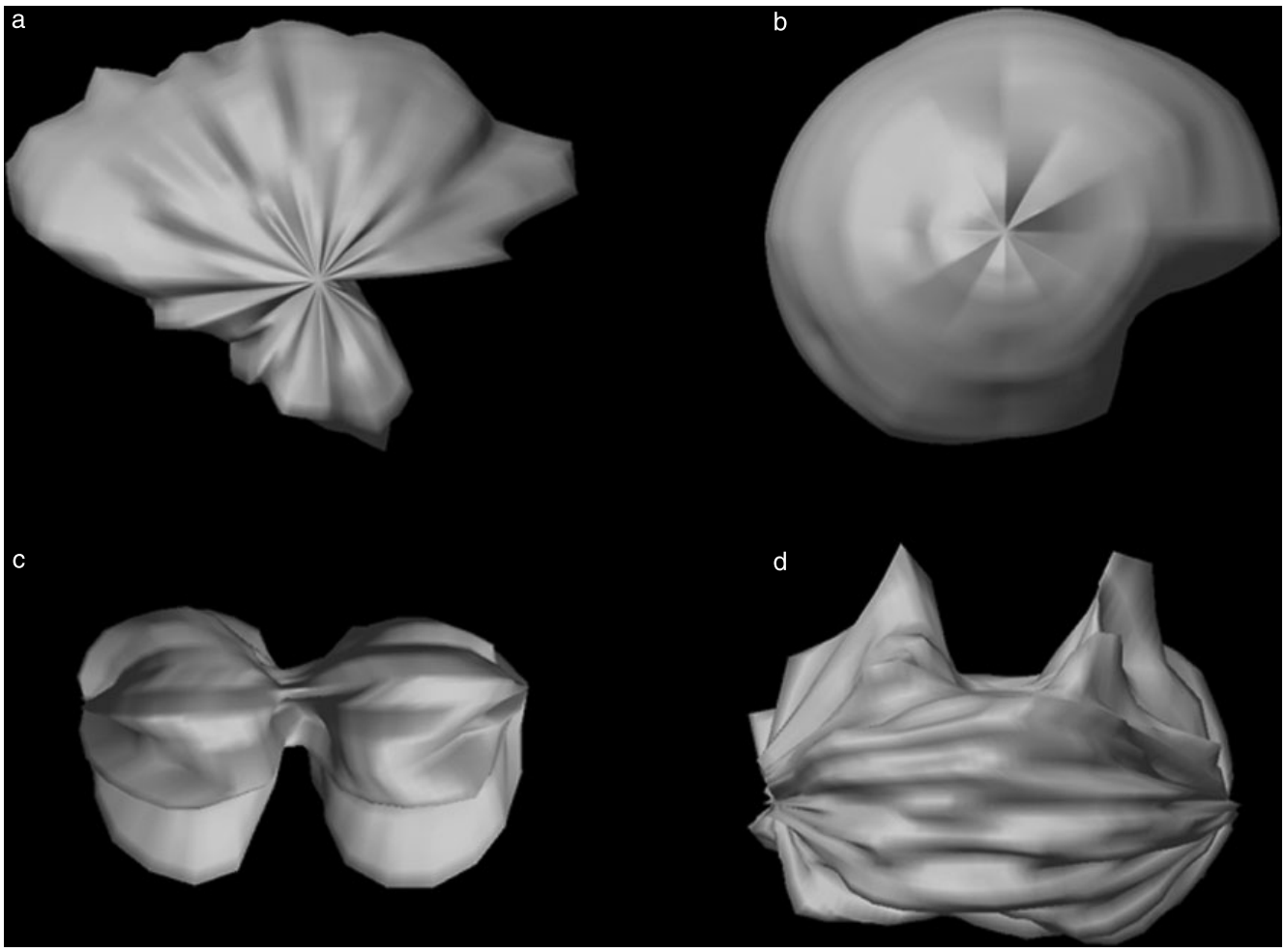

Figure 4 Final volume reconstructions of the frontal (a), total intracranial (b), thalamic (c) and cerebellar (d) regions using Virtual Organ Computer-aided AnaLysis (VOCAL).

Table 1 Clinical characteristics of appropriate-for-gestational age (AGA) and intrauterine growth-restricted (IUGR) fetuses

Variable	*AGA (n = 39)*	*IUGR (n = 39)*	P
Gestational age at examination (weeks + days)	28 + 1 (23 + 5 to 34 + 0)	28 + 3 (24 + 0 to 34 + 1)	NS
Maternal age (years)	27 (18–41)	29 (21–42)	NS
Gestational age at birth (weeks + days)	38 + 3 (36 + 2 to 40 + 5)	29 + 0 (25 + 2 to 34 + 6)	0.016
Birth weight (g)	3205 ± 455 (2610–3850)	1012 ± 394 (430–1808)	0.026
Survival rate	39/39 (100)	34/39 (87.2)	0.05
5-min Apgar score < 7	1	5	NS
Umbilical artery pH < 7.15	1	6	NS

Values are median (range), mean ± SD (range) or *n* (%). NS, not significant.

Table 2 Interobserver and intraobserver reliability of volume measurement of fetal intracranial structures expressed as intraclass correlation coefficients (ICCs)

	ICC (95% CI)	
Volume	*Interobserver*	*Intraobserver*
Intracranial	0.97 (0.92–0.98)	0.97 (0.95–0.98)
Cerebellar	0.69 (0.44–0.75)	0.76 (0.54–0.89)
Frontal	0.66 (0.42–0.79)	0.78 (0.55–0.86)
Thalamic	0.54 (0.37–0.72)	0.68 (0.48–0.84)

existence of regional brain volume variations in IUGR fetuses is in agreement with previous reports evaluating regional brain volumes with magnetic resonance imaging (MRI)[12], and brain areas calculated by sonographic biometric estimations[7] in IUGR preterm neonates. Our data are also in line with the concept of reorganization of the developing human brain in the context of pathological conditions or lesions[19–21].

The issue of whether brain reorganization is reflected in major changes in whole brain volume, at least in preterm IUGR fetuses, remains unclear. In agreement

Table 3 Cranial measurements, net volume calculations and volume ratios in appropriate-for-gestational age (AGA) and intrauterine growth-restricted (IUGR) fetuses

Parameter	*AGA (n = 39)*	*IUGR (n = 39)*	P
Biparietal diameter (cm)	7.1 ± 0.9	6.5 ± 0.9	< 0.0001
Head circumference (cm)	25.8 ± 3.0	23.6 ± 3.0	< 0.0001
Volume (cm^3)			
Total intracranial	194.2 ± 55.1 (96.3–328.0)	157.3 ± 51.9 (79.17–287.3)	0.001
Frontal	32.2 ± 11.6 (11.2–62.0)	22.9 ± 9.9 (7.8–43.8)	0.001
Thalamic	1.5 ± 0.9 (0.8–4.5)	1.3 ± 0.8 (0.5–4.2)	0.23
Cerebellar	6.0 ± 2.1 (2.8–11.3)	5.0 ± 1.7 (1.7–8.6)	0.001
Ratio between structures			
Intracranial/thalamic	129.46	121.00	0.2
Intracranial/cerebellar	32.36	31.46	0.8
Intracranial/frontal	6.03	6.86	0.001
Frontal/thalamic	21.46	17.61	0.001
Frontal/cerebellar	5.36	4.58	0.0122
Thalamic/cerebellar	0.25	0.26	0.289

Values are mean, mean ± SD or mean ± SD (range).

Table 4 Differences in regional brain volume adjusted by biparietal diameter between intrauterine growth-restricted (IUGR) and appropriate-for-gestational age (AGA) fetuses

Brain region	Δ *volume (95% CI)*	P
Frontal	−3.61 (−6.67 to −0.55)	0.02
Thalamic	0.28 (0.03–0.54)	0.03
Intracranial	−4.59 (−14.78 to 5.60)	0.37
Cerebellar	0.23 (−0.32 to 0.77)	0.41

Δ volume, volume difference (IUGR − AGA).

with the present study, Tolsa *et al*. failed to demonstrate a reduction in the total brain volume adjusted by HC in premature infants who were growth-restricted *in utero* compared with AGA neonates, as measured by MRI[12]. In contrast, Duncan *et al*. showed a significant reduction in the total brain volume in mildly growth-restricted neonates born near to term, although these authors did not adjust by cranial measurements[8]. The differences between these studies might therefore be explained by the different methods used for calculation, but could also reflect the distinct impact of the frontal lobe on total brain volume between early gestational ages and those at the end of pregnancy, when the frontal lobe comprises almost one-third of the total brain volume[7].

Our results in the frontal region are in agreement with those of another study by Makhoul *et al*., which found significant differences in the frontal lobe area between IUGR and AGA neonates, also with measurements obtained using ultrasound imaging[7]. Furthermore, our findings are also in line with long-term follow-up studies of children with intrauterine growth restriction showing abnormal neurological functions typically or partly associated with frontal networking, such as creativity and language, and memory performance and learning abilities[22]. These alterations have been reported to be strongly associated with impaired frontal lobe function and abnormal neural connections with the hippocampus[22]. Other abnormalities associated with a reduction in the frontal lobe are trisomy 21[23], epilepsy[24], severe mental retardation[25], schizophrenia[26] and fragile-X gene syndrome[27].

The second interesting finding of this study was the relative increase in thalamic volume in relation to other intracranial structures in IUGR fetuses. To our knowledge, there are no previous reports on volume estimation of this structure in fetuses. The thalamus is a gray matter structure made up of myelinated fibers from which most sensory information reaches the cerebral cortex. Using MRI segmentation, Zacharia *et al*. found that the relative volume of the basal ganglia and thalamus was higher in preterm than in term-born infants[28]. These data are in agreement with neonatal observations reported by Tolsa *et al*., who concluded that intrauterine growth restriction affects mainly the cortical white matter rather than the subcortical gray matter[12]. The observed differences in the thalamic volume in IUGR and AGA fetuses, despite being encouraging, should be interpreted with caution. Despite obtaining acceptable reliability results, a considerable source of error should be expected when tracing this area manually. Further studies with a larger population and using other methods of segmentation or imaging modalities are needed to confirm these results.

There are several possible explanations for the distinct size of intracranial structures in IUGR fetuses. Studies using animal models and voxel-based morphometry have demonstrated that early brain insults often lead to extensive neural reorganization of the gray and white brain matter, which can be expressed as an increment or reduction in specific brain areas[19,21,29]. These changes may reflect the existence of regional differences in susceptibility to brain insults[19]. Alternatively, or in combination, hemodynamic brain redistribution could be a major pathophysiological mechanism behind regional reorganization of the brain[12,14]. IUGR fetuses show significant temporal differences in the blood flow patterns

of different brain arteries in the vasodilatory response to hypoxia[13,30]. This mechanism has been further demonstrated by regional differences in brain blood flow perfusion related to the severity and progression of the growth restriction insult[14]. Whereas IUGR fetuses at early stages of deterioration show an overall increment in blood flow perfusion, mainly manifested in the frontal lobe, those at later stages shift this increment to the basal ganglia.

Several methodological issues and potential limitations in this study deserve mention. The present study provides evidence that segmentation of fetal brain structures obtained by 3D ultrasound examination can be achieved with reasonable reproducibility. The intracranial regions studied were chosen on the basis of previous reports in neonates with growth restriction[7,12]; however, as experience is gained and image resolution improves, further areas could be studied. These relatively ill defined structures have been delineated following anatomical descriptions and in accordance with reports using MRI. Owing to the lack of 'gold standards', the accuracy of the calculations performed cannot be assessed.

However, this study did not intend to calculate absolute values of intracranial structures but rather to assess the existence of differences in relative volume between cases and controls. Total intracranial volume calculations in AGA fetuses and reproducibility scores were in agreement with those reported by Roelfsema *et al.*[31]. One major factor that can affect volume calculations is the method used for segmentation of the intracranial structures. Methods for total automatic segmentation in 3D ultrasound volumes are lacking. In this study we used VOCAL, which provides a semiautomatic delineation that frequently requires manual adjustments by the operator. VOCAL was selected instead of a multiplanar technique because this method requires less time to calculate volumes and has acceptable reproducibility[9]. However, the possibility that the use of a multiplanar technique might provide greater accuracy in the calculation of absolute volumes cannot be excluded.

The results of this study suggest that the fetal brain, exposed to a specific injury, does not respond in the same manner in all of its regions. It should be considered as a dynamic structure, which varies in its response depending on the onset, duration and intensity of the injury. These different responses might have different neurological manifestations. The study also shows that different fetal brain regions can be reliably delineated and analyzed. The combination of morphological and hemodynamic changes might help to identify specific patterns of neural damage, and could allow implementation of optimal clinical management to reduce or avoid possible abnormal neurodevelopment later in life.

In conclusion, when adjusted for overall head biometry, IUGR fetuses show a reduction in the frontal and an increment in the thalamic volumes compared with AGA fetuses matched by gestational age. These results illustrate the modifications induced by *in-utero* growth restriction in the anatomical configuration of the fetal brain. The differences may be due to the neural reorganization processes produced by regional changes in blood flow redistribution to these areas, among other mechanisms. Future studies on 3D ultrasound volume calculations of these and other intracranial fetal structures could provide valuable information on how these changes may be correlated with long-term neurodevelopment.

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