Three-Dimensional Sonographic Calculation of Brain and Cerebellar Volume in Growth-Restricted Fetuses

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Abstract: Objective: This study evaluates fetal brain and cerebellum volumes in fetuses with asymmetrical intrauterine growth-restriction (IUGR) in comparison to appropriate-for-gestational age (AGA) fetuses using three-dimensional (3D) ultrasound imaging. **Patients and Method:** This cross sectional studyinvolved 2 groups of women with singleton pregnancy with a gestational age (GA) between 32 and 36 weeks; group A (n = 36) of fetuses with IUGR and group B (n = 36) with AGA fetuses. Fetuses were examined with ultrasonography for measurement of biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL) in addition to 3D volume estimation of frontal lobe, thalamus and cerebellum. **Results:** The BPD and HC were slightly smaller in the IUGR group (p = 0.079, p = 0.124, respectively. IUGR group had significantly smaller FL and AC (p< 0.001). IUGR group had significantly smaller volume of frontal lobe and cerebellum (p< 0.001) and comparable thalamic volume (p = 0.669). The regional difference between the two groups was the highest in the frontal lobe. **Conclusion:** Using 3D ultrasound volume calculations, IUGR fetuses have reduced frontal and cerebellar volumes (p< 0.001) and comparable thalamic volume (p = 0.669) compared with AGA fetuses.

[Ali Farid Mohamed, Noha Hamed Rabei, Amr Mohamed El-Helaly and Marwa Saber. **Three-Dimensional Sonographic Calculation of Brain and Cerebellar Volume in Growth-Restricted Fetuses.** *Life Sci J* 2014;11(3):1-5]. (ISSN:1097-8135). http://www.lifesciencesite.com. 1

Key wards: Three dimentional ultrasonography, Asymmetrical intrauterine growth restriction

1.Introduction:

Intrauterine growth restriction (IUGR) is a common and complex problem in modern obstetrics that causes perinatal mortality and morbidity. It affects about 7% to 15% of pregnancies worldwide.[1] It is characterized by a pathologic restriction in fetal capability to grow due to anatomical and/or functional disorder affecting the fetoplacental-maternal system. [2]. IUGR is diagnosed when the fetus is at or below the 10th percentile of weight for his gestational age.[3]

IUGR is classified as symmetric when head circumference, length, and weight are proportionally small for gestational age (SGA) and asymmetrical when head circumference is appropriate for gestational age (AGA), but length and weight are reduced. In asymmetrical IUGR, the fetus directs most of its energy to maintain growth of vital organs; the brain and heart and is associated with maternal vascular disease or poor maternal nutrition.[4]

Infants with asymmetric IUGR have reduced body weight and relatively normal head growth.[5,6] The main concept in asymmetrical growth restriction is what is called “brain sparing” effect; which is a hemodynamic adaptation by redistribution of blood flow to the brain. However, hypoxia and diminished nutrition progress with ongoing pathology that causes IUGR, e.g. placental insufficiency.[7] Doppler studies of the middle cerebral arteries indicated a relative decrease in blood flow in the frontal areas in favor of the basal ganglia.[8] Moreover, fetuses with IUGR are at an increased risk of developing signs of brain damage at birth.[9-11]

The brain is largely sensitive to changes in oxygen and glucose concentration. Studies of neonates and children born with IUGR reported that signs of neurological damage can be manifested later in life in the form of reduced cognitive function and low scores in the neurodevelopmental tests.[12-14] Additionally, neonatal studies revealed selective growth restriction in certain brain areas.[15,16]. There was evidence that IUGR causes reduction in IQ, memory and higher order verbal skills. The neuropsychological pattern is consistent with increased susceptibility in brain growth, particularly development of frontal lobe systems.[17]

Prenatal evaluation of fetal head and brain is classically performed with two-dimensional (2D) ultrasound biometric measurements. More recently, 3D ultrasound imaging is increasingly presented to be a complementary tool for fetal evaluation especially in fetal organ volume calculation including brain and cerebellum.[18]

It has been suggested that fetal brain might be affected in cases of intrauterine growth restriction.[19] Thus, this study was done for assessment of fetal brain and cerebellum in fetuses with asymmetrical intrauterine growth-restriction (IUGR) in comparison to appropriate-for-gestational age (AGA) fetuses using three-dimensional (3D) ultrasound imaging.

2.Patients and Method:

This cross sectional studywas conducted at Fetal Care Unit of Maternity hospital in Ain-Shams University in the period from January 2011 to May 2013 after approval by the local ethical committee. All women have given an informed consent for participation in the study.The study involved 2 groups of women with singleton pregnancy with a gestational age (GA) between 32 and 36 weeks. Group A involved 36 women their fetuses have asymmetrical IUGR and group B involved 36 women with AGA fetuses. Evaluation of fetal growth was done according to the local standard. IUGR was defined as an ultrasound estimated fetal weight < 10^{th} centile of the local standard. Date of the last menstrual period (LMP) was determined using sure dating or documented 1^{st} trimester ultrasonography. Fetuses with evident congenital anomalies were excluded from the study.

For all participants, full history taking and general examination were done before ultrasound examinations using a MedisonSonoAce X8 Ultrasound Machine (MEDISON Co. Ltd., Seoul, South Korea) with a 4-8-MHz curvilinear probe and an internal device for automatic acquisition of frames for volume reconstruction.

Ultrasound Examination:

1. Routine two dimensional (2D) examination:

Fetuses were evaluated anatomically then standard fetal biometry was done to measure biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL).

2. Three-dimensional (3D) examination:

Brain volumes were obtained and stored on digital devices for further analyses. Fetal brain scans were performed in the absence of maternal and fetal movements. The volume sample box was adjusted to include the complete fetal head without zoom magnification. The volume sweep angle was set at 80° and the highest quality of acquisition was selected.Two volumes were measured for each fetus. The first was obtained from across-sectional view of the fetal skull at the level of the BPD plane. With this volume, a clear perspective of the frontal 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 to obtain a clear image of the cerebellum. All volumes were estimated twice and the mean of these two measurements was considered as its representative value. The frontal, thalamic and cerebellar volumes were segmented manually using VOCAL (Virtual Organ Computer-Aided Analysis).

The Fontal region was delineated anteriorly and laterally by the inner wall of the skull and inferiorly by the floor of the skull and posteriorly by the sylvain fissure (lateral fissure). This structure can be recognized from the axial view of the fetal head at the level of the BPD and is considered as the posterior land mark for the frontal lobe.The thalamus was defined by following its contours and crossing the midline at two points in order to obtain a single volume. The cerebellum was delineated by the contours of the cerebellar hemispheres.

Statistical Methods:

Data was analyzed using IBM SPSS Advanced Statistics version 20.0 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Comparison between the two groups was done using independent sample t-test or Mann-Whitney test. Pearson product-moment was used to estimate correlation between numerical variables. A p-value < 0.05 was considered significant.

3.Results:

The two groups were comparable in gestational age (p = 0.590). The BPD and HC were slightly smaller in the IUGR group (p = 0.079, p = 0.124, respectively). Otherwise, the IUGR group had significantly smaller FL and AC (Table 1). The IUGR group had significantly smaller volume of frontal lobe and cerebellum but comparable thalamic volume (p = 0.669). The frontal/thalamic and frontal/cerebellar ratios were significantly smaller in IUGR group, while the thalamic/cerebellar ratio was significantly smallerin AGA group.

Table 1: Comparison between the two studied groups regarding gestational age, fetal biometry and brain volume measurements

	IUGR Group (n = 36)	AGA Group (n = 36)	*p* value
GA (weeks)	34.4±1.4	34.2±1.2	0.590
BPD (mm)	82.3±5.5	84.4±4.6	0.079
HC (mm)	297.2±11.1	301.8±15.1	0.124
FL (mm)	58.7±8.6	66.9±2.9	< 0.001
AC (mm)	269.9±20.0	304.0±25.0	< 0.001
Frontal lobe volume (cm^3)	65.1±11.5	84.2±7.8	< 0.001
Thalamus volume (cm^3)	4.4±0.6	4.4±0.5	0.669
Cerebellum volume (cm^3)	8.6±0.7	10.0±0.8	< 0.001
Frontal/thalamic ratio	14.7±1.6	19.3±1.0	< 0.001
Frontal/cerebellar ratio	7.6±1.0	8.4±0.5	< 0.001
Thalamic/cerebellar ratio	0.5±0.0	0.4±0.0	< 0.001

GA: gestational age; BPD:biparietal diameter; HC: head circumference; FL: femur length; AC: abdominal circumference

Table 2: Correlation coefficient (r) between brain structure volumes and gestational age and 2D fetal biometric measurements

	Frontal lobe volume	Thalamic volume	Cerebellum volume
GA	0.571	0.837	0.540
BPD	0.792	0.884	0.730
HC	0.835	0.797	0.752
FL	0.699	0.421	0.674
AC	0.905	0.709	0.926

GA: gestational age; BPD:biparietal diameter; HC:head circumference; FL: femur length; AC: abdominal circumference

Table 2 shows correlation coefficient (r) between brain structure volumes and gestational age and 2D fetal biometric measurements. The volumes of frontal lobe, thalamus and cerebellum were positively correlated with gestational age and all biometric measurements (*p* value for all correlations was < 0.001). Table 3 shows that the regional difference between the two groups was the highest in the frontal lobe.

Table 3: Differences in volumes of frontal lobe, thalamus and cerebellum between intrauterine growth-restricted (IUGR) andappropriate-for-gestational age (AGA) groups

	Mean difference	95% Confidence Interval		*p* value
		Lower	Upper	
Frontal lobe volume (cm^3)	-19.09	-23.71	-14.48	< 0.001
Thalamus volume (cm^3)	0.06	-0.20	0.31	0.669
Cerebellum volume (cm^3)	-1.45	-1.82	-1.08	< 0.001

4.Discussion:

This study demonstrated a significant reduction in the volume of frontal lobe of the brain of intrauterine growth restricted fetuses compared appropriate-for-gestational age fetuses ($p< 0.001$) with a mean difference of -19.1 (95% CI: -23.7 to -14.5). Similar reduction but to a lesser degree was observed in the cerebellar volume ($p< 0.001$). Meanwhile, thalamic volume was not affected in cases of IUGR. Regional brain volumes were positively correlated with biparietal diameter and head circumference. These finding supports the suggested brain microstructural changes in growth restricted fetuses.[20]

Several studies suggested an association between abnormal neurobehavior and impaired volumetric brain growth.[21] Many of these studies used magnetic resonance imaging(MRI) for evaluation of regional brain volumes.[19,22] Fewer number of studies resorted to sonographic estimations.[15,23] Other studies concentrated on cerebellar volume evaluation by means of 3-D ultrasound.[24]

Nowadays, thanks to recent advances in technology, three-dimensional(3D) ultrasound has become an integral partof most ultrasound systems. It enables theacquisition of a fetal volume over a short period of timewith minimal motion artifact. These volume data can be stored and manipulated later on apart from the effects of further fetalmovements. Moreover, multiplanar reconstruction views of obtained volumes permit their re-slicing to attain the most optimal plane to minimize measurement errors.[25]

The results of the current study are in line with previous studies that showed regional brain volume variations in fetuses with IUGR. Using an advanced quantitative volumetric 3D MRI technique, Tolsa*et al.*[19] measured brain volumein 14 premature infants with placental insufficiency. They found reduction in intracranial volume and in cerebral cortical gray matter in infants with IUGR. Behavioral assessment at term showed a significantly less mature score in attention-interaction availability.

Makhoul*et al.*[15] performed sonographic biometry of the frontal lobe at birth of 218 newborn infants. They concluded that frontal lobe measures increased significantly between 24 and 43 wk of gestationand were strongly correlated with HC. Small-for gestational age fetuses had growth restriction of the fetal frontal lobe.Duncan *et al.*[16] compared ultrasound biometry and magnetic

resonance imaging measurement of brain volume to predict fetal growth restriction.Ultrasonic head circumference demonstrated brain sparing, but MRI found an overall reduction of brain volume in fetal growth restriction.

Another study used volume segmentation of fetal brain with 3Dultrasound to compare IUGRand AGA fetuses. In agreement with the current study, frontal lobe and cerebellum volume were significantly smaller in IUGRfetuses, and conversely thalamic volume was significantly greater inIUGR fetuses compared to AGA fetuses.[23]

The current study found major reduction in frontal lobe volume. These findings might explain abnormal neurological functions typically associated with frontal networking previously reported in long-term follow-up studies of children born with IUGR. These changes usually involve creativity and language skills, memory performance andlearning abilities.[26]

Relevant to these long-term follow-up studies, Ramenghi*et al.*[27] evaluated cerebral maturation in IUGRand AGAneonatesUsing MRI. They observed no difference in the level of cerebral maturation between the two groups. Meanwhile, myelination was significantly reduced in IUGR neonates with brain sparing compared to IUGR neonates with normal Doppler of middle cerebral artery.

The comparable thalamic volume in the current study goes in concordance with findings that intrauterine growth restriction affects mainly the corticalwhite matter rather than the subcortical gray matter.[19]

Olivier *et al.*[28] studied rat pups with prenatal growth restriction induced by unilateral ligation of the uterine artery. Pups with severe GR exhibited white-matter damage that persisted to adulthood. Pups with moderate growth restriction showed diffuse white-matter lesions, microglial activation, and astrogliosis.

In conclusion, by means of 3D ultrasound volume calculations,IUGR fetuses appear to have reduced frontal and cerebellar volumes ($p< 0.001$) compared with AGAfetuses of equivalent gestational age, while the thalamic volumes were not significantly different ($p = 0.669$). These results suggest anatomical restructuring of the fetal brain associated with asymmetrical growth restriction in spite of the relatively unaffected fetal head biometry.

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1/26/2014