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Article

Ultrasonographic evaluation of cerebral cortical development in growth-restricted versus matched average gestational age fetuses, a prospective cohort study

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Abstract

Background: Fetal growth restriction (FGR) contributes significantly to prenatal and long-term morbidity, including neurological impairments. *Objective:* Assessment of cortical development in FGR fetuses in pregnancies complicated by preeclampsia compared to uncomplicated pregnancies using two-and three-dimensional ultrasonography. *Methods:* Observational prospective cohort study involving 300 pregnant women (25–37 gestational weeks); 150 had pre-eclampsia with FGR, and 150 had normal pregnancies with average gestational age (AGA) fetuses matched by gestational age at fetal neurosonography (±2weeks). Fetal Doppler and fetal biometry were done. In the axial transventricular plane, the insula and sylvian fissure depths were measured. Using two- or three-dimensional ultrasonography, the corpus callosum's length and thickness were measured in the mid-sagittal plane. Using two- or three-dimensional ultrasonography, the depths of the calcarine fissure in the coronal trans-cerebellar plane and the cingulate fissure in the transcaudal plane were measured. *Results:* These 300 pregnancies were separated into 6 groups according to gestational age using a 2 week gap.

Regarding age, BMI, gravidity, parity, and abortion, the study groups were comparable. Cases complicated by PE and FGR displayed a distinct pattern of fetal cortical development on fetal neurosonography, as evidenced by significantly shallower sylvian fissure measurements in each group of FGR compared to AGA fetuses. There was no statistically significant difference in insula depth between the two groups, although the FGR group's corrected insula depth (Insula depth (mm) /BPD) was deeper than AGA group's. The corpus callosum length was shorter in the FGR groups than in the AGA groups. There was no statistically significant difference between the two groups for the anterior, middle, and posterior measurements of corpus callosum thickness. Between study groups, there were no discernible variations in calcarine and cingulate fissure depth. *Conclusion:* In FGR fetuses, neurosonography appears to be a sensitive method for identifying subtle anatomical variations in brain development.

Keywords: Cortical development, neurosonography, fetal growth restriction, corpus callosum, sylvian fissure, insula, cingulate fissure, calcarine fissure.

Introduction

In perinatal medicine, fetal growth restriction (FGR) is a common disorder that affects roughly 5-8% of live newborn babies.(1) FGR contributes significantly to prenatal and long-term morbidity (2-4) including neurological impairments, which are among the sequelae that are most frequently observed in this population.(5-7) When a fetus' estimated weight falls below the 10th centile, it is regarded as small in medical practice,(8) in the absence of genetic syndromes or fetal infections.

The term "brain sparing effect" in fetal growth restriction refers to a shift in the fetus's oxygenation pattern brought on by a redistribution of cerebroplacental blood flow caused by placental insufficiency as detected by Doppler ultrasound.(9) Cerebral development is delayed as a result of these aberrant blood flow and oxygen patterns. (9-13)

Throughout pregnancy, the fetal brain develops in a complex yet well-organized progressive manner, with sporadic periods of rapid brain development (most notably at 26–28 weeks of gestation). (14-17).

Cortical expansion in thickness and surface area is linked to the process of new neuron development and neuronal migration towards the outer brain surface.(18) This stress-induced transformation of the cortex's smooth surface into a complex network of sulci and gyri, known as cortical folding, begins at about 18 weeks of gestational age (GA) and is closely connected with GA.(19)

Prenatal ultrasonography examination of fetal sulcus development to comprehend cortical maturation and development has become prevalent. To evaluate the development of the fetal cerebral sulcus, trans-abdominal two-dimensional ultrasonography has traditionally been the primary technique.(20) Recent studies have detailed the use of magnetic resonance imaging (MRI) and three-dimensional ultrasonography to evaluate the development of cerebral fissures in fetuses. (21-23)

The current study aimed to assess cortical development in fetal growth restricted and matched average gestational age fetuses using two-and three-dimensional ultrasonography.

Methods

Study population

The current study was an observational prospective cohort study conducted in Alexandria, Egypt, in the ultrasonography department of El Shatby Maternity Hospital between December 2019 and May 2022. After explaining the purpose of the study and getting everyone's informed consent.

The study involved 300 pregnant women, with gestational ages ranging from 25 to 37 gestational weeks. Of these, 150 had pre-eclampsia and fetal growth restriction, (with at least one of the following criteria; abnormal umbilical artery PI,(24) abnormal cerebro-placental ratio,(25) abnormal uterine artery PI(26)or the estimated fetal weight less than 3rd centile for gestational age) and 150 low-risk pregnant women with average gestational age fetuses (AGA) who were matched with cases according to gestational age at the time of fetal neurosonography (±2weeks) after signing their informed consents. The local ethics committee gave its approval to the study protocol and patients who agreed to participate did so voluntarily. Multiple pregnancies, chromosomal anomalies, and congenital defects were excluded from the study. AGA was defined as birth weight ≥10th centile, whereas FGR was considered if birth weight was <10th centile.(27) Based on the length of the crown-rump in the first trimester or the last menstrual period, gestational age was determined for each pregnancy.(28)

Data collection and study protocol

Maternal age, body mass index (BMI), maternal medical history (autoimmune and/or chronic illness presence), and obstetric history were all reported at enrollment (gravidity, parity, abortion). At (25-37 weeks' gestation), an estimated fetal weight and fetoplacental Doppler were recorded. Fetoplacental Doppler measurements included evaluation of the uterine arteries,(26) umbilical artery(29) and middle cerebral artery(29) as well as determination of the cerebroplacental ratio.(25)

Neurosonography

Detailed neurosonographic examination at 25–37weeks' gestation was performed using a Voluson P8 (GE Healthcare Ultrasound, Zipf, Austria) ultrasound device equipped with a RAB 2-6-D probe. Following the recommendations of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), we conducted all measurements in the brain hemisphere that was further away from the probe, regardless of the fetal side, to avoid shadowing from the fetal skull bones,(30)

using a transabdominal technique, incorporating transthalamic and transventricular planes.

Insular depth was measured in the axial transventricular plane, with the anterior horns, cavum septum pellucidum, atrium, posterior horn of the lateral ventricle, and choroid plexus serving as anatomical landmarks. The insula's depth was then determined by drawing a perpendicular line from the midline to the upper border of the insular cortex at its highest prominence.(31)

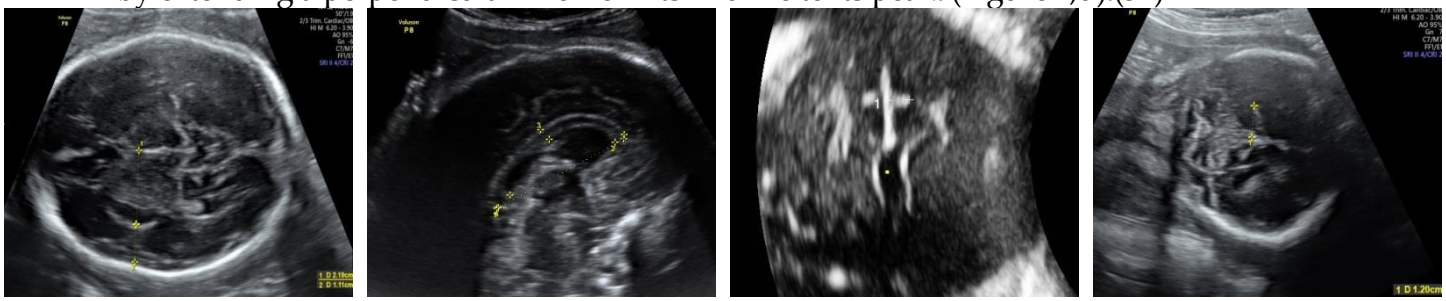
The depth of the sylvian fissure was measured in the same plane as previously described, with a continuous line extending from the outermost border of the insular cortex (perpendicular to the midline) in the direction of the inner table of the parietal bone. (as shown in figure 1,a). (31)

The length of corpus callosum was determined from the most anterior part of the genu to the most posterior part of the splenium tracing a straight rostrocaudal line between the two points.(32)

The anterior, middle, and posterior parts of the corpus callosum, which correlate to the genu, body, and splenium thickness, were measured. (figure 1,b).(33)

In the mid-coronal plane (transcaudal plane), the cingulate fissure was measured by tracing a perpendicular line from the midline to its tip. (Figure 1,c).(23)

The depth of the calcarine fissure was measured in the coronal trans-cerebellar plane by extending a perpendicular line from its midline to its peak. (Figure 1,d).(31)



(A) **(B)** **(C)** **(D)**

Figure 1 (a–d) Fetal neurosonographic images obtained in normal fetus, showing the study measurements. (a) Axial transventricular plane and measurements of insula depth and Sylvian fissure depth. (b) Measurement of corpus callosum length and thickness using 2 D ultrasound mid-sagittal plane. (c) Coronal transthalamic plane showing measurement of the cingulate fissure depth. (d) Coronal transcerebellar plane, showing measurement of the calcarine fissure depth.

3D neurosonography:

The sweep angle of the two brain volumes during acquisition was chosen between 45° and 80° depending on gestational age. The two brain volumes were recorded in the axial transventricular plane and transcerebellar plane. Both maternal respiration and fetal movements were absent throughout acquisition. In three orthogonal planes, the volumes were represented.(34)

To align the orthogonal planes into a common orientation, systemic volume manipulation was carried out in the multiplanar display mode. The axial plane of the brain was depicted in Plane A, the coronal plane in Plane B, and the mid-sagittal plane of the brain in Plane C (Figure 2).

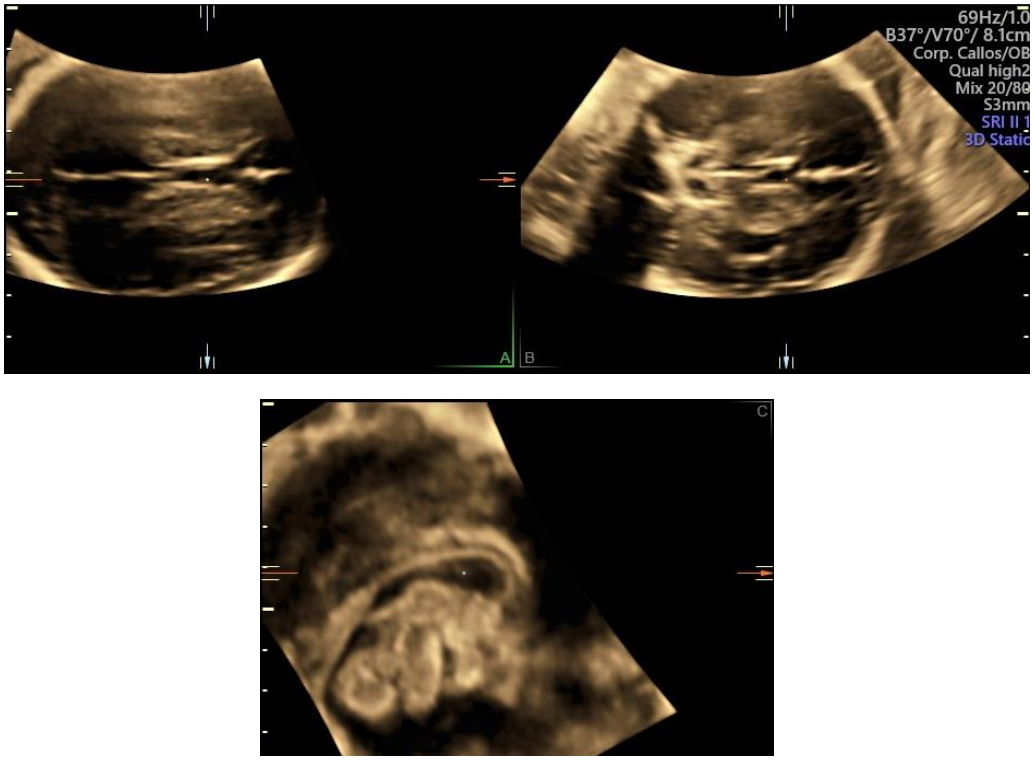


Figure (2): Three-dimensional (3D) ultrasound image of the transventricular plane showing the three orthogonal planes and multiplanar view. Plane A is the axial plane, Plane B the coronal plane and Plane C is the mid-sagittal plane of the fetal brain.

Brain volume in the axial transventricular plane:

In the midsagittal plane, the whole corpus callosum could be seen, and morphological examination was carried out in respect to the axial and coronal planes, including the rostrum, genu, body, and splenium (Figure 2).

The length of corpus callosum was determined from the most anterior part of the genu to the most posterior part of the splenium by tracing a straight rostrocaudal line between the two points.(32) Corpus callosum thickness was measured in its anterior, middle and posterior portions corresponding to the genu, body and splenium thickness.(33)

In the coronal plane, the cingulate fissure was visible, and morphological analysis was carried out with respect to the axial and midsagittal planes. By drawing a perpendicular line from the midline to the apex of the cingulate fissure, the cingulate fissure was measured.(23)

Brain volume in the axial transcerebellar plane:

In the coronal plane, the calcarine fissure could be seen, and morphological analysis was done with respect to the axial and midsagittal planes. By drawing a perpendicular line from the midline to the apex of the calcarine fissure, the depth of the calcarine fissure was calculated.(31)

All measurements were expressed in mm and after that adjusted by fetal head size ; Insula, Sylvian fissure, cingulate fissure and calcarine fissure depths were adjusted by biparietal diameter (BPD),(35) and corpus callosum length and thickness were adjusted by cephalic index (CI).(36) CI was calculated dividing BPD by occipitofrontal diameter (OFD), using the formula: CI=BPD/OFD×100. BPD and OFD were measured in the transthalamic plane following ISUOG guidelines.(37)

Statistical analysis: The data was evaluated statistically using IBM SPSS software, version 20.0.IBM Corporation, Armonk, New York. Numbers and percentages were used to describe qualitative data. The normality of the distribution was examined using the Kolmogorov-Smirnov test. The range (minimum and maximum), mean, standard deviation, median, and interquartile range were used to characterize quantitative data (IQR). $P< 0.05$ was regarded as significant for the analysis.

The chi-square test was employed for categorical variables and group comparisons. A Student t-test was used to compare two groups under study for quantitative variables with normally distributed distributions. Use the Mann-Whitney test to compare two groups under study with improperly distributed quantitative variables.

RESULTS

A total of 300 pregnancies made up the cohort, 150 of which were PE with FGR (25–37 gestational weeks) and 150 of which were uncomplicated low risk pregnancies. According to the gestational age at neurosonography, they were divided into 6 groups, each with a 2 week gap. Table 1 displays the baseline characteristics and fetoplacental Doppler of the study population.

Table (1): Comparison between the two studied groups according to basic parameters.

	FGR (n = 150)	AGA(n = 150)	Test of Sig.	p
Age				
Mean ± SD.	27.25 ± 5.86	28.29 ± 4.54	t=	0.085
Median (Min. – Max.)	26.50 (23.0 – 31.0)	28.0 (25.0 – 32.0)	1.731	
BMI				
Mean ± SD.	28.76 ± 4.70	28.92 ± 4.0	t=	0.746
Median (Min. – Max.)	28.0 (25.70– 31.60)	29.10 (20.10 – 37.90)	0.324	
Gravidity				
Primary	73 (48.7%)	60 (40.0%)	χ^2=	0.131
Multi	77 (51.3%)	90 (60.0%)	2.283	
Mean ± SD.	2.11 ± 1.48	2.14 ± 1.23	U=	0.318
Median (Min. – Max.)	2.0 (1.0 – 3.0)	2.0 (1.0 – 3.0)	10541.0	
Parity				
Null para	85 (56.7%)	68 (45.3%)		
Primary para	34 (22.7%)	41 (41.3%)	χ^2= 3.931	0.140
Multi para	31 (20.7%)	41 (41.3%)		
Mean ± SD.	0.73 ± 1.01	0.90 ± 0.99	U= 9964.5	0.063
Median (Min. – Max.)	0.0 (0.0 – 1.0)	1.0 (0.0 – 2.0)		
Abortion				
No	113 (75.3%)	124 (82.7%)		
1	28 (18.7%)	20 (13.3%)	χ^2= 2.444	0.295
2+	9 (6.0%)	9 (4.0%)		
Mean ± SD.	0.39 ± 0.90	0.23 ± 0.60	U= 10408.5	0.114
Median (Min. – Max.)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)		
Umbilical PI				
Mean ± SD.	1.44 ± 0.55	0.95 ± 0.19	U=	<0.001*
Median (Min. – Max.)	1.39 (1.20 – 1.59)	0.94 (0.85 – 1.0)	2187.5*	
MCA PI				
Mean ± SD.	1.57 ± 0.36	2.19 ± 0.78	U=	<0.001*
Median (Min. – Max.)	1.59 (1.30 – 1.80)	2.0 (1.70 – 2.50)	4398.0*	
CPR Centile				
Mean ± SD.	5.39 ± 9.51	70.25 ± 23.40	U=	<0.001*
Median (Min. – Max.)	3.0 (1.0 – 6.0)	81.0 (64.0 – 81.0)	276.5*	
Mean uterine PI				
Mean ± SD.	1.32 ± 0.37	0.77 ± 0.15	t=	<0.001*
Median (Min. – Max.)	1.24 (1.0 – 1.56)	0.79 (0.66 – 0.89)	16.833*	
Uterine PI Centile				
Mean ± SD.	97.53 ± 4.42	55.09 ± 27.84	U=	<0.001*
Median (Min. – Max.)	99.0 (97.0 – 99.0)	60.0 (34.0 – 81.0)	237.5*	

SD: **Standard deviation** **t: Student t-test** **U: Mann Whitney test** χ^2: **Chi square test**
p: p value for comparing between the studied groups *: Statistically significant at $p \leq 0.05$

The study groups were similar in terms of maternal characteristics (age, BMI, gravidity, parity and abortion).
All patients with PE had proteinuria. Fetoplacental Doppler characteristics in the FGR group were significantly different from those in the AGA group.

According to fetal neurosonography, as shown in Tables 2 and 3, patients complicated by PE and FGR showed a distinct pattern of fetal cortical development from AGA. When compared to AGA, FGR fetuses in each group of patients had significantly shallower sylvian fissure ($P < 0.05$).

Furthermore, the FGR group's sylvian fissure (mm)/BPD adjusted value was shallower than that of the AGA group. For insula depth measures, there was no statistically significant difference between the two groups.

However, the adjusted insula depth (insula depth (mm)/BPD) of the FGR group was deeper than that of the AGA group. The corpus callosum is shorter in the FGR group than in the AGA group, and there was a statistically significant difference in corpus callosum length measurements between the two groups.

Moreover, the adjusted measurement (CC length (mm)/CI) for the FGR group was lower than that for the AGA group. The anterior, middle, and posterior measurements of corpus callosum thickness and the adjusted values showed no statistically significant difference between the two groups. There were no obvious differences in calcarine and cingulate fissure depth across study groups.

Table (2): Comparison between the two studied groups according to neurosonopraphic parameters.

	Gestational age											
	25 – 26 weeks&6ds		27 - 28weeks&6ds		29 - 30 weeks&6ds		31 - 32 weeks&6ds		33 - 34 weeks&6ds		35 – 37 weeks	
	FGR 13(8.7%)	AGA 16 (10.7%)	FGR 15 (10.0%)	AGA 16 (10.7%)	FGR 22 (14.7%)	AGA 21 (14.0%)	FGR 25 (16.7%)	AGA 25 (16.7%)	FGR 33 (22.0%)	AGA 34 (22.7%)	FGR 42 (28.0%)	AGA 38 (25.3%)
Sylvian Fissure	8.292 ± 0.501	10.30 ± 1.205	8.95 ± 0.728	10.737 ± 1.284	10.209 ± 1.444	12.338 ± 1.163	11.588 ± 1.077	14.020 ± 1.321	13.164 ± 1.50	15.353 ± 1.576	14.181 ± 1.504	16.355 ± 1.468
t,p	**t=6.052*,p<0.001***		**t=4.815*,p<0.001***		**t=5.310*,p<0.001***		**t=7.133*,p<0.001***		**t=5.821*,p<0.001***		**t=6.531*,p<0.001***	
Sylvian Fissure (mm)/BPD	0.139 ± 0.012	0.154 ± 0.019	0.138 ± 0.011	0.150 ± 0.015	0.147 ± 0.022	0.165 ± 0.012	0.152 ± 0.014	0.172 ± 0.015	0.165 ± 0.023	0.181 ± 0.019	0.172 ± 0.021	0.183 ± 0.015
t,p	**t=2.455*,p=0.021***		**t=2.617*,p=0.014***		**t=3.238*,p=0.003***		**t=4.966*,p<0.001***		**t=3.183*,p=0.002***		**t=2.761*,p=0.007***	
Insula depth (mm)	20.085 ± 0.926	19.594 ± 1.195	21.593 ± 1.113	20.994 ± 1.285	22.245 ± 1.664	22.143 ± 1.153	22.944 ± 2.625	23.036 ± 1.410	24.988 ± 2.029	24.965 ± 1.592	25.888 ± 1.473	25.797 ± 1.734
t,p	**t=1.213,p=0.236**		**t=1.385,p=0.177**		**t=0.234,p=0.816**		**t=0.154,p=0.878**		**t=0.052,p=0.959**		**t=0.253,p=0.801**	
Insula depth (mm) /BPD	0.337 ± 0.024	0.292 ± 0.019	0.333 ± 0.028	0.293 ± 0.017	0.320 ± 0.025	0.296 ± 0.017	0.301 ± 0.035	0.283 ± 0.015	0.311 ± 0.023	0.295 ± 0.019	0.314 ± 0.017	0.289 ± 0.020
t,p	**t=5.579*,p<0.001***		**t=4.807*,p<0.001***		**t=3.708*,p=0.001***		**t=2.368*,p=0.022***		**t=3.236*,p=0.002***		**t=5.829*,p<0.001***	
Cingulate fissure (mm)	1.908 ± 0.284	2.194 ± 0.624	2.120 ± 0.208	2.306 ± 0.404	2.723 ± 0.350	2.786 ± 0.460	3.316 ± 0.208	3.444 ± 0.272	4.061 ± 0.375	4.082 ± 0.373	4.719 ± 0.427	4.858 ± 0.625
t,p	**t=-1.524,p=0.139**		**t=1.628,p=0.117**		**t=0.507,p=0.615**		**t=1.869,p=0.068**		**t=0.238,p=0.813**		**t=1.169,p=0.246**	
Cingulate fissure (mm) /BPD	0.032 ± 0.005	0.033 ± 0.009	0.033 ± 0.004	0.032 ± 0.006	0.039 ± 0.006	0.037 ± 0.006	0.044 ± 0.003	0.042 ± 0.004	0.051 ± 0.007	0.048 ± 0.005	0.057 ± 0.006	0.055 ± 0.007
t,p	**t=0.223,p=0.825**		**t=0.262,p=0.795**		**t=1.118,p=0.270**		**t=1.178,p=0.245**		**t=1.770,p=0.082**		**t=1.912,p=0.060**	
Calcarine fissure (mm)	7.469 ± 0.633	8.075 ± 1.443	9.173 ± 0.808	9.475 ± 0.820	10.455 ± 1.720	10.876 ± 1.404	12.496 ± 0.617	13.004 ± 1.106	14.052 ± 1.392	14.253 ± 1.720	15.269 ± 1.487	15.855 ± 1.720
t,p	**t=1.510,p=0.146**		**t=1.031,p=0.311**		**t=0.878,p=0.385**		**t=2.005,p=0.052**		**t=0.526,p=0.601**		**t=-1.635,p=0.106**	
Calcarine fissure (mm) /BPD	0.126 ± 0.016	0.120 ± 0.020	0.141 ± 0.014	0.133 ± 0.014	0.151 ± 0.028	0.145 ± 0.019	0.164 ± 0.005	0.160 ± 0.012	0.176 ± 0.022	0.168 ± 0.021	0.185 ± 0.023	0.178 ± 0.020
t,p	**t=0.805,p=0.428**		**t=1.780,p=0.086**		**t=0.791,p=0.434**		**t=1.583,p=0.123**		**t=1.419,p=0.161**		**t=1.567,p=0.121**	

SD: **Standard deviation** **t: Student t-test** p: p value for comparing between the studied groups *: Statistically significant at $p \leq 0.05$

Table (3): Comparison between the two studied groups according to neurosonopraphic parameters.

	Gestational age											
	25 - 26 weeks&6ds		**27 - 28 weeks&6ds**		**29 - 30 weeks&6ds**		**31 - 32 weeks&6ds**		**33 - 34 weeks&6ds**		**35 – 37 weeks**	
	FGR	**AGA**	**FGR**	**AGA**	**FGR**	**AGA**	**FGR**	**AGA**	**FGR**	**AGA**	**FGR**	**AGA**
	13 (8.7%)	**16 (10.7%)**	**15 (10.0%)**	**16 (10.7%)**	**22 (14.7%)**	**21 (14.0%)**	**25 (16.7%)**	**25 (16.7%)**	**33 (22.0%)**	**34 (22.7%)**	**42 (28.0%)**	**38 (25.3%)**
CC length (mm)	30.831 ± 3.094	33.956 ± 2.543	33.133 ± 2.743	35.219 ± 1.929	34.809 ± 2.625	37.176 ± 2.233	37.072 ± 1.871	38.804 ± 2.712	40.358 ± 2.333	42.494 ± 2.324	41.317 ± 3.440	45.184 ± 2.946
t,p	**t=-2.988*,p=0.006***		**t=-2.462*,p=0.020***		**t=3.178*,p=0.003***		**t=2.628*,p=0.012***		**t=3.755*,p<0.001***		**t=5.373*,p<0.001***	
CC length (mm)/CI	0.402 ± 0.043	0.449 ± 0.041	0.423 ± 0.023	0.459 ± 0.037	0.448 ± 0.052	0.496 ± 0.042	0.473 ± 0.037	0.510 ± 0.042	0.520 ± 0.034	0.551 ± 0.034	0.535 ± 0.056	0.581 ± 0.046
t,p	**t=3.008*,p=0.006***		**t=3.212*,p=0.003***		**t=3.360*,p=0.002***		**t=3.296*,p=0.002***		**t=3.805,p<0.001***		**t=4.044*,p<0.001***	
CC Thickness (mm)												
Anterior	2.846 ± 0.326	2.894 ± 0.489	3.033 ± 0.297	2.956 ± 0.320	3.232 ± 0.320	3.252 ± 0.343	3.360 ± 0.413	3.428 ± 0.518	3.915 ± 0.331	3.90 ± 0.470	4.107 ± 0.281	4.082 ± 0.445
t,p	**t=0.300,p=0.766**		**t=0.694,p=0.493**		**t=0.203,p=0.840**		**t=0.513,p=0.610**		**t=0.152,p=0.880**		**t=0.304,p=0.763**	
Middle	1.623 ± 0.159	1.638 ± 0.131	1.720 ± 0.246	1.675 ± 0.267	1.809 ± 0.258	1.795 ± 0.136	2.112 ± 0.274	2.020 ± 0.318	2.273 ± 0.297	2.347 ± 0.248	2.421 ± 0.272	2.468 ± 0.336
t,p	**t=0.268,p=0.791**		**t=0.487,p=0.630**		**t=0.222,p=0.826**		**t=1.096,p=0.278**		**t=-1.114,p=0.270**		**t=0.690,p=0.492**	
Posterior	2.215 ± 0.182	2.463 ± 0.506	2.633 ± 0.333	2.519 ± 0.304	2.927 ± 0.411	2.810 ± 0.417	3.004 ± 0.413	2.996 ± 0.510	3.318 ± 0.356	3.485 ± 0.413	3.707 ± 0.388	3.721 ± 0.466
t,p	**t=1.815,p=0.085**		**t=1.002,p=0.325**		**t=0.933,p=0.356**		**t=0.061,p=0.952**		**t=-1.773,p=0.081**		**t=0.145,p=0.885**	
CC Thickness (mm)/ CI												
Anterior	0.037 ± 0.005	0.038 ± 0.007	0.039 ± 0.004	0.039 ± 0.005	0.042 ± 0.006	0.043 ± 0.006	0.043 ± 0.006	0.045 ± 0.007	0.050 ± 0.005	0.051 ± 0.006	0.053 ± 0.005	0.053 ± 0.006
t,p	**t=0.511,p=0.614**		**t=0.176,p=0.861**		**t=1.047,p=0.301**		**t=1.150,p=0.256**		**t=0.108,p=0.914**		**t=0.475,p=0.636**	
Middle	0.021 ± 0.002	0.022 ± 0.002	0.022 ± 0.003	0.022 ± 0.004	0.023 ± 0.003	0.024 ± 0.002	0.027 ± 0.004	0.027 ± 0.004	0.029 ± 0.004	0.030 ± 0.003	0.031 ± 0.004	0.032 ± 0.004
t,p	**t=0.611,p=0.546**		**t=0.125,p=0.901**		**t=0.986,p=0.330**		**t=0.356,p=0.723**		**t=1.306,p=0.196**		**t=0.412,p=0.681**	
Posterior	0.029 ± 0.002	0.033 ± 0.007	0.034 ± 0.005	0.033 ± 0.004	0.038 ± 0.006	0.038 ± 0.006	0.038 ± 0.006	0.039 ± 0.007	0.043 ± 0.005	0.045 ± 0.006	0.048 ± 0.005	0.048 ± 0.006
t,p	**t=1.981,p=0.063**		**t=0.574,p=0.570**		**t=0.017,p=0.987**		**t=0.564,p=0.576**		**t=1.970,p=0.053**		**t=0.031,p=0.975**	

SD: **Standard deviation** **t: Student t-test**

p: p value for comparing between the studied groups

DISCUSSION

This study offers evidence that, in comparison to low risk AGA fetuses, fetuses from women with PE who have FGR show a distinct pattern of prenatal cortical development, with significantly reduced sylvian fissure depth and corrected deeper insula depth.

Numerous studies have found a connection between PE and worse than ideal neurodevelopment in the offspring. Children of PE mothers have higher incidence of neurobehavioral disorders, worse neurocognitive function, and impaired early language development, according to follow-up research. (35, 38) Population-based research using information from national registries or parents' recollections from the past provides support for these observations.(39, 40) The possible impact of confounders, particularly preterm and FGR, which are present in 60–100% and 10–90% of patients, respectively, when reported, is an issue regarding the relationship between PE and neurodevelopment. (41-43)

Functionally, it is well-known that the insula is essential for emotional wellness and plays a significant role in the processing of sensory information.(44) Autism, anxiety, and changes in the insula's grey matter volumes have all been linked to these conditions. (44, 45) Reduced perfusion and oxidative stress from placental insufficiency may lead to inadequate nutrition and oxygen availability, which may have an impact on the developing brain.(46)

Additionally, the current study reports FGR cases with shorter corpus callosum length. These outcomes are in line with those of earlier MRI and neurosonography studies.(36, 38, 47) The complex process of brain development involves the formation and myelination of white matter connections between different brain regions as well as the maturation and functional specialization of grey matter regions.(48-50) White matter matures throughout the first few years following birth, starting in the third trimester, and is particularly sensitive to hypoxia.(50) The primary commissure is the corpus callosum, which links the brain hemispheres. In the hippocampus primordium, callosal connections begin to develop more centrally and in both directions, with anterior growth becoming more apparent.(51) It has been demonstrated that the corpus callosum's development is impacted by the immature oligodendrocytes' and callosal fibres' intrinsic susceptibility to prolonged hypoxia (52, 53) and myelination deficits in the corpus callosum of rats exposed to hypoxia, resulting in a smaller corpus callosum. (54)

We acknowledge that one of the limitations was that, beyond 36 weeks, increasing skull calcification and shadowing make cortical developmental assessment more challenging. A further limitation was that the postnatal neurodevelopmental outcome was not evaluated, which prevented us from assessing any correlation between the altered pattern of fetal cortical development observed and the outcome.

Our results support the use of neurosonography to assess neurodevelopment in FGR fetuses, making them clinically significant. Because small fetuses are so common and because of the effects they have on neurodevelopment, (6, 55) evaluating fetal cortical development and the corpus callosum could be helpful to detect small fetuses with brain reorganization in order to provide early neurodevelopmental interventions.

To evaluate the postnatal performance following fetal neurosonography in FGR fetuses, additional research is necessary.

Conclusion

Neurosonography might be used to identify minute variations in the brains of fetuses who have experienced fetal smallness. It specifically allowed us to pinpoint important variations in corpus callosum and brain development.

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Conflicts of interest

The authors declare no conflicts of interest.

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Data availability

The data are available upon request.

Conflict of interest

None

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