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Impact of Intrauterine Growth Restriction on Fetal Cortical Brain Development: A Neurosonographic Assessment at 28-36 Weeks of Gestation

Behrokh Sahebdel [1], Reihaneh Mortazavi Ardestani [2], Setareh Soltani [3], Mohammad Hossein Golezar [4], Fatemeh Golshahi [1], Nafiseh Saedi [1], Fatemeh Rahimi Sharbaf [1], Mahboobeh Shirazi [1], Nooshin Faraji [1], Mohadese Dashtkoohi [5], Zohreh Heidary [5], Masoumeh Aslanpour [1*]

1- Department of Obstetrics and Gynecology, Fetal an d Neonatal Research Center, Yas Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
2- Department of Radiology, Tehran University of Medical Sciences, Tehran, Iran
3- Clinical Research Development Center, Taleghani and Imam Ali Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran
4- Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Medical Imaging Center, Tehran University of Medical Sciences, Tehran, Iran
5- Vali-E-Asr Reproductive Health Research Center, Family Health Research Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran

** Corresponding Author:*
Masoumeh Aslanpour, Department of Obstetrics and Gynecology, Fetal and Neonatal Research Center, Yas Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
E-mail:
drmasiiii20@gmail.com

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Abstract

Background: Cortical folding during fetal brain development reflects neural maturation. Fetal growth restriction (FGR) may disrupt this process, potentially affecting neurodevelopmental outcomes. Although ultrasound enables noninvasive sulcal assessment, so normative data and objective tools are lacking. The purpose of the current study was to assess the impact of FGR on fetal cortical development using neurosonography and establish a third-trimester nomogram for cortical maturation.

Methods: This prospective study included 425 singleton pregnancies (330 appropriate-for-gestational-age [AGA], 54 symmetrical FGR, and 41 asymmetrical FGR) at 28–36 weeks. Conducted at a Tehran tertiary center (2023–2024), the study included cases with normal anatomy and negative aneuploidy screening. Neurosonographic parameters including Sylvian fissure (SF), insula, parieto-occipital fissure (POF), cavum septum pellucidum (CSP) width, and ventricular diameter were measured and the ratios calculated relative to biparietal diameter (BPD). ANOVA and post-hoc tests were applied and statistical significance was set at $p<0.05$.

Results: No significant differences in neurosonographic ratios (*e.g.*, SF/Insula, POF/BPD, CSPW/BPD) were found between AGA and FGR groups. However, unadjusted SF and insular depths were reduced in symmetrical FGR fetuses with head circumference (HC) <10th percentile. Asymmetrical FGR showed no differences. A gestational-age-based nomogram was developed for AGA fetuses.

Conclusion: While absolute sulcal measurements vary with head size in FGR, biometric adjustments (*e.g.*, BPD ratios) improve cortical maturation assessment. The study supports ratio-based neurosonography and provides normative data for objective fetal brain evaluation.

Keywords: Cortical maturation, Fetal brain development, Fetal ultrasound, Insula, Intrauterine growth restriction, Neurosonography, Nomogram, Sylvian fissure.
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Introduction

Fetal brain development progresses through three key stages: cell proliferation, neuronal migration, and cortical organization. During the cortical organization stage, occurring between the 20th and 35th weeks of gestation, the brain's surface evolves from a smooth surface at around

18 weeks of gestational age into a complex structure of sulci and gyri, called cortical folding that closely resembles the adult brain by the end of gestation (1-5). The development of these sulci is a critical sign of cortical maturation. The timing of these sulci's appearance is so accurate that it is used by neuropathologists to estimate gestational age and assess fetal brain development (1, 6-9). Fetal growth restriction can influence both short-term fetal development and long-term offspring health. However, brain development is a complex process shaped by genetic, epigenetic, environmental, and experiential factors, as well as events like vascular accidents or infections, making it difficult to pinpoint the exact effect of a single exposure on brain development (10-13). Fetal smallness, defined as birth weight below the 10th percentile, affects approximately 6–10% of pregnancies (14, 15) and increases the risk of neurodevelopmental issues like autism, ADHD, and schizophrenia (5, 18, 19)

In FGR, the "brain-sparing effect", caused by altered blood flow due to placental insufficiency, changes fetal oxygen levels (5, 20), suggesting that these changes may raise the risk of brain abnormalities and neurodevelopmental disorders in FGR pregnancies (5, 22). Although some studies have reported significantly deeper insular and left cingulate sulci, reduced brain volume, thinner insular cortex, smaller insula volume, decreased cortical grey matter, and altered cortical maturation in cases of FGR (5, 16, 18, 20), others have found no significant differences in fetal brain maturation in FGR fetuses (5, 14-16, 18, 20).

While prenatal ultrasound is a valuable tool for assessing fetal sulcus development and cortical maturation, there is a notable lack of comprehensive descriptions of normal gyration and growth charts for cortical development. In this study, the impact of fetal growth restriction on the development of key fetal brain sulci was evaluated to improve predictions of future neurodevelopmental outcomes. Additionally, an effort was made to propose a nomogram for objective assessment of normal cortical development, moving away from subjective evaluations.

Methods

Study design and population: This study involved 425 pregnant women who attended the perinatology clinic at YAS Hospital, a referral center affiliated with Tehran University of Medical Sciences. All participants underwent third-trimester ultrasound examinations between 28 and 36 weeks of gestation, from September 2023 to September 2024. The inclusion criteria comprised singleton pregnancies with normal aneuploidy screening results and no structural abnormalities detected on ultrasound. Prior to the ultrasound assessments, a comprehensive maternal history was recorded in the study database, and pregnancies with any maternal comorbidities, including diabetes, hypertension, thyroid disorders, cardiovascular diseases, renal diseases, neurological and immunological disorders, and infectious diseases, were excluded to minimize potential confounding factors. The study population was categorized into three groups based on biometric indices: appropriately grown for gestational age (AGA), symmetric FGR, and asymmetric FGR. Symmetric FGR fetuses had both BPD and HC measurements below the 10th percentile, while asymmetric FGR fetuses had BPD and HC measurements within the 10th to 90th percentile range. The classification followed the 2021 practice bulletin guidelines issued by the American College of Obstetricians and Gynecologists (ACOG).

Ultrasound measurements: All participants underwent transabdominal ultrasonography using a Voluson E8 ultrasound system (GE Healthcare, USA). The ultrasound assessment included the measurement of several brain parameters: HC, BPD, insular depth, SF depth, POF depth, and CSP width. Each patient was assessed three times by an experienced sonographer, and all measurements were independently checked by a second examiner to ensure accuracy and reliability. To reduce shadowing artifacts from the fetal skull, all measurements were acquired from the hemisphere contralateral to the ultrasound probe, regardless of fetal orientation. Several derived ratios were calculated, including SF/Insula, POF/Insula, POF/BPD, SF/BPD, Insula/BPD, ventricle diameter/BPD, and CSP width/BPD.

Measurement protocol: A standard transthalamic plane of the fetal head was used as the initial imaging plane for measuring BPD and HC. In this plane, the depths of the insula and Sylvian fissure were recorded (Figure 1). Subsequently, the probe was cranially adjusted to acquire a transventricular plane, where the depths of the POF, lateral ventricle, and the CSP width were measured (Figure 2).

Statistical analysis: Comparisons of HC, BPD, and brain fissure depths among the three groups

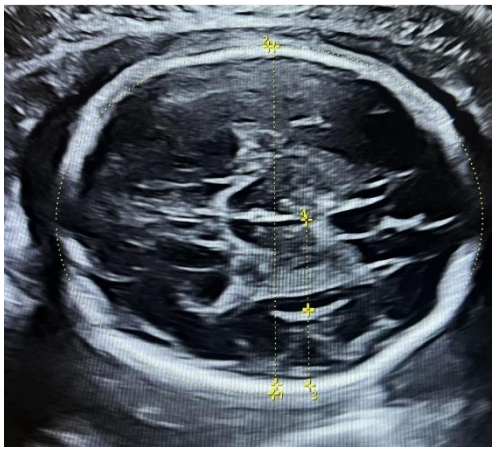

Figure 1. Transthalamic plane showing measurement of (1) HC, (2) BPD, (3) SF, and (4) insula

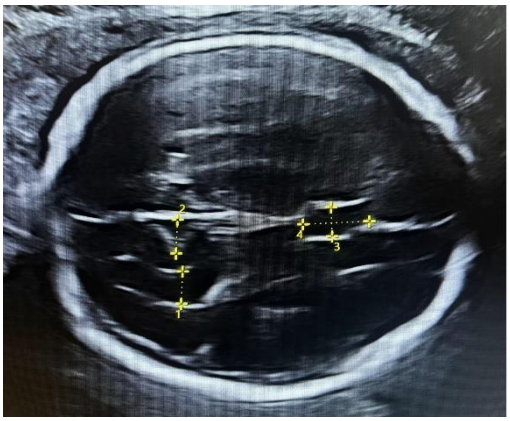

Figure 2. Transventricular plane showing measurement of (1) ventricular diameter, (2) POF, and (3) CSPW

(AGA, symmetric FGR, and asymmetric FGR) were performed using one-way ANOVA, applying Fisher's or Welch's tests depending on homogeneity of variances. For post-hoc comparisons, Tukey's Honestly Significant Difference (HSD) test was utilized when homogeneity of variances was confirmed, and the Games-Howell test when it was violated. The Shapiro-Wilk test was applied to evaluate the normality of data distributions. Statistical analyses were conducted using R and SPSS version 27 software (IBM, USA), and a $p< 0.05$ was considered statistically significant.

This study was approved by the Medical Ethics Committee of Tehran University of Medical Sciences under ethics code IR.TUMS.MEDICINE.REC.1402.719. Written informed consent was obtained from all participants and their partners prior to enrollment and ultrasound examination.

Results

The study included a total of 425 pregnancies, with 330 cases classified as AGA in which BPD and HC measurements fell between the 10th and 90th percentiles. Additionally, there were 95 cases identified as FGR, all of which exhibited normal brain Doppler indices. Among the FGR cases, 54 were categorized as symmetrical, while 41 were asymmetrical (Table 1).

The study presents a detailed analysis of various brain sonographic indices and ratios in AGA and FGR fetuses, focusing on gestational weeks 28 to 36. According to the findings, there were no significant differences in the measured ratios (SF/Insula, POF/Insula, POF/BPD, SF/BPD, Insula/BPD, ventricle diameter/BPD, and CSP width/BPD) between AGA and both symmetrical and asymmetrical FGR fetuses in all categories of gestational weeks ($p<0.05$) (Table 2).

However, when examining unadjusted measurements, significant differences were observed between AGA and symmetrical FGR fetuses with a head size below the 10% percentile. At certain gestational ages, Sylvian and insular depths were significantly smaller in these two study groups ($p<0.05$) (Table 3). Sylvian fissure depth between 30 and 35 weeks of gestation and insular depth between 28 and 35 weeks were significantly smaller in FGR fetuses compared to AGA fetuses. Conversely, no significant differences were found in the measured indices between AGA and asymmetrical FGR fetuses with normal head sizes ($p> 0.05$) (Table 4).

This suggests that smaller head sizes in FGR fetuses may impact these specific measurements and using adjusted ratios provides more accurate results in the interpretation of brain cortical development. It also highlights the importance of considering head size when interpreting brain sonographic measurements in the context of growth restrictions.

Discussion

In this study, a standardized method was used for assessing the main fetal brain sonographic indices including the insula, Sylvian fissure, parieto-occipital fissure, diameter of the lateral ventricle, and CSP width, consistent with methods used in other similar studies (1, 21, 22). The main benefit of these methods is that the measurements can be taken from standard ultrasound planes used for

Table 1. Nomogram of fetal neurosonographic parameters across gestational ages in AGA fetuses

Variables	Percentile	28-29 (n=74)	30-31 (n=46)	32-33 (n=67)	34-35 (n=71)	36 (n=72)
SV/Insula	5	0.40	0.42	0.38	0.43	0.42
	50	0.56	0.58	0.58	0.60	0.56
	95	0.78	0.81	0.80	0.87	0.72
POF/Insula	5	0.18	0.20	0.21	0.20	0.20
	50	0.32	0.28	0.29	0.29	0.30
	95	0.46	0.45	0.46	0.41	0.41
POF/BPD	5	0.06	0.07	0.07	0.06	0.06
	50	0.09	0.08	0.09	0.09	0.09
	95	0.14	0.13	0.13	0.11	0.12
SV/BPD	5	0.12	0.13	0.13	0.14	0.13
	50	0.16	0.17	0.17	0.17	0.17
	95	0.21	0.22	0.21	0.22	0.20
Insula/BPD	5	0.25	0.26	0.24	0.24	0.26
	50	0.29	0.30	0.30	0.30	0.30
	95	0.34	0.34	0.35	0.34	0.34
Ventricle/BPD	5	0.05	0.05	0.05	0.05	0.05
	50	0.08	0.07	0.07	0.07	0.07
	95	0.12	0.11	0.10	0.11	0.09
CSPW/BPD	5	0.11	0.12	0.11	0.12	0.11
	50	0.16	0.15	0.16	0.15	0.15
	95	0.21	0.18	0.19	0.18	0.19
SV	5	7.70	9.61	10.42	11.50	11.61
	50	11.70	13.50	14.00	14.70	15.20
	95	14.83	17.62	17.68	18.20	17.74
Insula	5	17.03	19.75	19.28	20.30	22.76
	50	20.00	23.05	24.50	25.80	26.50
	95	24.05	27.36	28.84	29.04	30.00
POF	5	4.00	5.07	5.64	5.36	5.43
	50	6.45	6.75	7.30	7.50	8.15
	95	9.70	10.10	10.42	9.64	11.00
CSPW	5	4.18	4.60	4.50	4.46	4.77
	50	5.80	6.30	6.70	6.60	6.70
	95	8.43	8.60	8.80	8.54	8.77

All parameters are expressed as ratios unless otherwise stated (in *mm*).
SV: Sylvian Fissure, POF: Parieto-Occipital Fissure, BPD: Biparietal Diameter, CSPW: Cavum Septum Pellucidum Width.
Percentiles indicate the 5th, 50th (median), and 95th percentiles for each gestational age group

biometric assessments. Since the measurement landmarks were easily identifiable, fetal maturation could be effectively evaluated during routine scans.

Certain sulci serve as gestational age landmarks, with previous research indicating that the insula, SF, POF, and calcarine fissure (CF) deepen between 19 and 30 weeks of gestation (22, 23). In atypical fetal cases, such as those with congenital heart disease, agenesis of the corpus callosum, or central nervous system abnormalities, the process of sulcus development is delayed (24, 26).

Many studies have attempted to identify the effect of maternal or fetal factors on sulcus formation and maturation. For example, some studies on fetal cortical development in pregnancies affected by FGR and small-for-gestational-age (SGA) conditions have shown no significant differences in the depth of the POF. They observed no notable differences in the depths of the POF,

Table 2. Comparison of fetal neurosonographic parameter ratios in three groups (AGA, symmetric FGR, and asymmetric FGR)

Parameters		N	Mean	Std. deviation	Minimum	Maximum	p-value
SV/Insula	AGA	330	0.58	0.12	0.24	0.99	0.226
	SYM	54	0.55	0.14	0.35	0.90	
	ASYM	41	0.55	0.12	0.31	0.90	
POF/Insula	AGA	330	0.31	0.07	0.15	0.56	0.191
	SYM	54	0.31	0.06	0.18	0.51	
	ASYM	41	0.29	0.06	0.18	0.42	
POF/BPD	AGA	330	0.09	0.02	0.05	0.2	0.279
	SYM	54	0.09	0.01	0.05	0.13	
	ASYM	41	0.09	0.02	0.06	0.13	
SV/BPD	AGA	330	0.17	0.02	0.07	0.33	0.193
	SYM	54	0.16	0.03	0.11	0.25	
	ASYM	41	0.16	0.02	0.09	0.25	
Insula/BPD	AGA	330	0.30	0.03	0.2	0.52	0.678
	SYM	54	0.30	0.03	0.24	0.43	
	ASYM	41	0.30	0.02	0.23	0.35	
Ventricle/BPD	AGA	330	0.07	0.02	0.04	0.17	0.58
	SYM	54	0.08	0.02	0.05	0.13	
	ASYM	41	0.07	0.01	0.05	0.11	
CSPW/BPD	AGA	330	0.15	0.02	0.05	0.3	0.456
	SYM	54	0.15	0.03	0.04	0.21	
	ASYM	41	0.15	0.02	0.1	0.18	

Group abbreviations: AGA: Appropriate for Gestational Age, SYM: Symmetric FGR, ASYM: Asymmetric FGR
Ratios are calculated relative to BPD or insula as indicated. Statistical significance was assessed using ANOVA

Table 3. Comparison of fetal neurosonographic parameters in different gestational ages in AGA and symmetric FGR groups

Variables	Group	28-29	30-31	32-33	34-35	36
SV	AGA	11.67±2.07	13.50±2.26	14.03±1.88	14.88±2.3	14.95±2.05
	SYM	10.64±2.53	10.85±2.9	12.58±1.76	12.95±2.03	14.14±2.82
	p-value	0.207	0.002	0.008	0.026	0.222
Insula	AGA	20.37±1.99	13.50±1.96	24.38±2.69	25.33±2.5	26.80±2.54
	SYM	19.65±4.85	10.85±1.97	22.42±2.27	23.32±1.82	25.96±3.36
	p-value	0.045	<0.001	0.011	0.031	0.301
POF	AGA	6.49±1.61	6.91±1.46	7.47±1.42	7.54±1.28	8.06±1.6
	SYM	5.67±0.88	6.73±1.14	7.14±0.93	7.28±1.12	7.45±0.89
	p-value	0.191	0.714	0.395	0.362	0.059
CSPW	AGA	5.96±1.17	6.4±1.13	6.63±1.3	6.61±1.26	6.66±1.08
	SYM	5.87±0.74	6.08±0.94	6.22±0.86	6.4±1.03	6.43±0.96
	p-value	0.841	0.466	0.2460	0.648	0.302

Values are presented as mean ± standard deviation. Statistically significant differences (p<0.05) are bolded

cingulate sulcus, and calcarine sulcus when compared to uncomplicated pregnancies (15, 27). Another study by Putra et al. reported that fetuses with an estimated fetal weight below the 10th percentile showed smaller Sylvian fissure depths, larger insular depths, and increased hypoechoic insular zone circumferences compared to normally grown controls. The insula plays a critical role in sensorimotor integration, affective regulation, and higher-order cognitive functions. Due to its high sensitivity to hypoxic conditions, it serves as a particularly specific marker of reduced fetal

Table 4. Comparison of fetal neurosonographic parameters in different gestational ages in AGA and asymmetric FGR groups

Variables	Groups	28-29	30-31	32-33	34-35	36
SV	AGA	11.68±2.01	13.51±2.26	14.04±1.88	14.88±2.30	14.96±2.05
	ASYM	10.92±1.33	12.00±2.69	13.16±0.99	13.72±2.38	14.80±2.44
	p-value	0.395	0.097	0.202	0.140	0.819
Insula	AGA	20.38±1.99	23.31±1.96	24.38±2.69	25.33±2.50	26.80±2.54
	ASYM	19.98±1.61	23.75±1.74	23.48±1.04	24.14±2.45	26.53±3.02
	p-value	0.690	0.430	0.230	0.120	0.900
POF	AGA	6.49±1.61	6.91±1.46	7.47±1.42	7.54±1.28	8.07±1.60
	ASYM	5.80±1.70	7.09±1.32	6.90±1.87	6.90±1.25	7.39±1.53
	p-value	0.400	0.660	0.260	0.230	0.230
CSPW	AGA	5.96±1.17	6.40±1.13	6.63±1.30	6.61±1.26	6.67±1.08
	ASYM	5.13±0.97	6.55±0.62	6.84±1.40	6.56±0.78	6.75±1.38
	p-value	0.170	0.640	0.640	0.770	0.920

Values are presented as mean ± standard deviation. No statistically significant differences were observed between AGA and ASYM groups across gestational ages.

oxygen saturation. Alterations in the cortical morphology of the insula have been observed in fetuses with FGR. A novel parameter for assessing insular development is the hypoechoic insular zone circumference, defined as an echo-poor region bordered laterally by the Sylvian fissure and medially by portions of the basal ganglia. A larger hypoechoic insular zone circumference was strongly linked to poorer neurodevelopmental outcomes in early childhood. It is hypothesized that the enlargement of this region may indicate accelerated neuronal maturation in growth-restricted fetuses experiencing mild hypoxia (28). Research on insular development in small fetuses has produced varied results: some studies show underdeveloped insular cortices (14, 18, 29), while others indicate more developed insular cortices (15, 16), and some find no difference (5).

Abe et al. reported no differences in cortical gyrus and sulcus formation in FGR fetuses between 28 and 39 weeks of gestation (30). Another study revealed that FGR fetuses exhibited a slower growth trajectory of the right Sylvian fissure compared to controls. These findings remained consistent after adjusting for various factors such as head circumference and gestational age. No significant differences were observed in the growth patterns of the insula, POF, or left Sylvian fissure. Additionally, head circumference was positively linked to all brain fissures in both unadjusted and adjusted analyses (31).

The inconsistent findings reported in the literature regarding fetal sulcal depth in FGR versus AGA fetuses may stem from several methodological and clinical differences across studies. First, variation in study design and sample size could influence the power to detect subtle cortical changes. Second, the gestational age at which neurosonographic assessments were performed differs among studies, and given the rapid and dynamic nature of cortical brain development in the third trimester, even small differences in timing may significantly impact measurements. Third, discrepancies in the definition and classification of FGR such as inclusion of different severity levels, Doppler flow patterns, or growth percentile thresholds may contribute to variability in reported outcomes. Additionally, technical factors such as differences in ultrasound equipment, imaging planes, and measurement protocols may introduce inter-study variability. Lastly, population characteristics, including maternal health status, genetic background, and environmental influences may modulate fetal brain development and further explain the heterogeneity observed across studies.

The gyral formation is often used to assess brain maturation, along with methods like cortical surface area, sulcal organization, cortical curvature, and shape indices (32). However, no standardized approach exists due to individual structural variability. This may explain why some of the studies found no differences in gyral formation (33).

Brain sparing can be characterized by increased pulsatility in middle cerebral artery (MCA) or by alterations in specific Doppler-derived ratios.

Pathological findings include a cerebroplacental ratio (CPR) below 1 or below the 5th percentile, as well as, an umbilical-cerebral ratio (UCR) exceeding 0.72. Additionally, MCA pulsatility index values falling below the 5th percentile are also considered indicative of abnormal cerebral hemodynamics. The association between Doppler abnormalities and perinatal outcomes is well-documented. Although neurological and long-term developmental consequences have been explored, the evidence remains inconclusive. Brain sparing is traditionally characterized as a compensatory mechanism through which cerebral perfusion is prioritized to support optimal brain development and function under conditions of fetal hypoxia or nutrient deprivation. In response to these adverse intrauterine conditions, cerebral vasodilation occurs, facilitating increased blood flow to the brain to ensure an adequate supply of oxygen and nutrients. Nevertheless, this adaptive response may not confer complete neuroprotection. Evidence suggests that the presence of brain sparing in growth-restricted fetuses is associated with reduced head circumference and diminished brain volume at birth, potentially impacting neurocognitive development in later life (34). In our study, all of the FGR fetuses had normal brain Doppler indices. Therefore, the effect of abnormal color Doppler findings on fetal brain sulcal development could not be evaluated among FGR fetuses.

In this study, the challenges associated with comparing brain maturation between AGA and FGR fetuses were addressed. In fact, FGR fetuses often exhibit smaller BPD and HC, which can skew brain sonographic index measurements. By adjusting for these variables, no significant differences in brain maturation indicators were found between AGA and FGR fetuses among the 425 cases analyzed. This adjustment allowed us to establish normative data for the defined ratios. The clinical significance of smaller unadjusted SF and insular depths in symmetrical FGR is still underexplored. It is unclear how these findings might relate to neurodevelopmental outcomes, and what their implications for clinical practice would be.

Furthermore, it is essential to conduct future studies that differentiate between early-onset and late-onset FGR, as well as to evaluate the impact of abnormal brain Doppler indices and other maternal and fetal parameters on developmental growth. Longitudinal follow-up of neonatal outcomes related to these factors will also be critical for a comprehensive understanding of the implications of FGR on brain development.

The integration of nomogram percentile curves for SF/BPD and Insula/BPD into routine prenatal imaging protocols holds potential for enhancing the radiologic assessment of fetal brain maturation, particularly in fetuses at risk for intrauterine growth restriction or hypoxic injury. To facilitate their clinical utility, external validation across diverse populations and imaging environments is essential to ensure reproducibility and reliability. Given the sensitivity of these cortical measurements to gestational age, operator technique, and equipment resolution, multicenter studies are warranted to establish normative references and population-specific thresholds. Incorporating these indices into standardized fetal neurosonography protocols could support early detection of atypical cortical development, while future correlative studies linking prenatal imaging findings with postnatal neurodevelopmental outcomes will be critical to confirming their diagnostic and prognostic value in radiologic practice.

Conclusion

In this study, an effort was made to explore whether brain cortical development could be more effectively assessed using specific brain structure-to-BPD ratios. Our findings suggest that there are no significant differences in these ratios between AGA fetuses and those with FGR. These results indicate that the sulcus-to-BPD ratio may not be a sensitive marker for detecting subtle cortical developmental delays in FGR fetuses. Further high-quality, prospective studies are needed to validate these findings and refine neurosonographic assessment methods. In further investigations, measurement of corpus callosum length and also diameter of vermis and cerebellum should be considered to better evaluate the posterior fossa differences between FGR and normal fetuses.

Conflict of Interest

Authors declare no conflict of interest.

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