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Fetal frontal lobe development in gestational diabetes mellitus: a cross-sectional neurosonographic study

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Abstract

Objectives: To evaluate the impact of gestational diabetes mellitus (GDM) on fetal frontal lobe development, as assessed by the anteroposterior frontal diameter (APFD) and its relationships with standard cranial biometric parameters.

Methods: This case–control study included 257 singleton pregnancies between 20 and 38 + 6 week's gestation. Participants were divided into two groups: uncomplicated pregnancies (n=152) and pregnancies complicated by GDM (n=105). Ultrasound images were retrospectively analyzed to obtain APFD, occipitofrontal diameter (OFD), head circumference (HC), and transverse cerebellar diameter (TCD), as well as derived ratios (APFD/OFD, APFD/HC, and APFD/TCD). Clinical, metabolic, and perinatal data were collected.

Results: No significant differences were observed between groups in APFD (36.9 vs. 35.5 mm, p=0.086), TCD (40.1 vs. 38.6 mm, p=0.206), or in any of the evaluated ratios, including APFD/OFD (p=0.897), APFD/HC (p=0.702), and APFD/TCD (p=0.602). These findings remained consistent after stratification by type of glycemic control (diet vs. insulin). In contrast, the GDM group exhibited higher body mass index, fasting glucose levels, estimated fetal weight, and abdominal circumference (all p<0.05), as well as lower uterine and umbilical artery pulsatility indices. No clinically relevant differences were observed in head circumference or Apgar scores.

Conclusions: GDM was not associated with detectable alterations in fetal frontal lobe morphometry or its proportional relationships with global cranial measurements. These findings indicate no detectable differences in fetal frontal lobe morphometry using ultrasound parameters. However, no conclusions can be drawn regarding functional or neurodevelopmental outcomes.

Keywords: fetus; frontal lobe; ultrasound; gestational diabetes mellitus

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Introduction

Fetal neurodevelopment is a highly sensitive process influenced by intrauterine metabolic conditions. Maternal hyperglycemia has been associated with alterations in fetal brain structure and maturation, including reduced corpus callosum length, changes in cerebellar development, and modifications in cortical fissuration patterns [1, 2]. These findings suggest that gestational diabetes mellitus (GDM) may interfere with early brain organization, although results remain heterogeneous and may depend on glycemic control and disease severity.

In addition to structural findings, some studies have reported associations between intrauterine exposure to hyperglycemia and neurodevelopmental outcomes later in life, including language delay, behavioral disorders, autism spectrum disorder, and attention-deficit/hyperactivity disorder [3–7]. However, these associations are derived from longitudinal and epidemiological studies and cannot be inferred from fetal biometric assessments alone.

The frontal lobe, which plays a central role in higher cognitive and executive functions, may be particularly vulnerable to metabolic disturbances during fetal life. Recent studies suggest that GDM may affect frontal lobe development, as reflected by alterations in ultrasound-derived parameters such as the anteroposterior frontal diameter (APFD) and its relationship with global cranial measurements [8]. However, data on this topic remain limited and inconsistent, particularly regarding whether these changes represent true alterations in brain development or variations in overall fetal growth.

In this context, our objective in this study was to evaluate the impact of gestational diabetes mellitus on fetal intracranial measurements, with particular emphasis on frontal lobe development, using standardized neurosonographic parameters.

Patiens and methods

This was a case–control study conducted at Federal University of Triângulo Mineiro (UFTM), the Mário Palmério University Hospital of University of Uberaba (UNIUBE), and Sabin Medical Diagnostics, all three in the city of Uberaba, Brazil. Fetal cephalic pole images were selected from institutional image databases. Available images were retrieved from October 2025 to April 2026, with a total study duration of seven months. The study protocol was submitted to the UFTM Research Ethics Committee (CAAE: 91546225.0.0000.8667).

We included: Singleton pregnancy with a live fetus and no structural abnormalities; gestational age between 20 weeks and 38 weeks + 6 days, determined by last menstrual period and confirmed by ultrasound performed up to 13 weeks + 6 days; and pregnant women diagnosed with gestational diabetes. Exclusion criteria included: maternal diseases at the time of examination that could affect fetal growth, such as chronic hypertension, preeclampsia, connective tissue diseases, or other vasculopathies; and pregnancies complicated with fetal growth restriction.

Patients were randomly selected from the image database. All ultrasound examinations were performed by a single examiner, certified in Fetal Medicine by the Brazilian Federation of Gynecology and Obstetrics Associations, with vast experience in ultrasonography. Fetal cephalic pole and central nervous system assessments were conducted during routine obstetric ultrasound examinations at the Fetal Medicine outpatient clinics of UFTM and UNIUBE. The ultrasound equipment used included the Aplio 400 (Canon Medical Systems, Otawara, Japan) and Voluson E6 (General Electric Healthcare, Zipf, Austria).

Clinical data were collected from the electronic medical record system AGHUx (Application for Management of University Hospitals, Brazilian Hospital Services Company – EBSERH, Brasília, Brazil), including: maternal age, ethnicity, smoking status, alcohol consumption, maternal weight, height, body mass index (BMI), number of pregnancies, number of deliveries, number of miscarriages, diagnosis of gestational diabetes, and insulin use. Ultrasound data collected included: gestational age at examination, estimated fetal weight (EFW), EFW percentile, biparietal diameter (BPD), occipitofrontal diameter (OFD), head circumference (HC), transverse cerebellar diameter (TCD), APFD, APFD/OFD ratio, APFD/HC ratio, and APFD/TCD ratio. Perinatal data included: gestational age at delivery, birth weight, birth weight percentile, mode of delivery, Apgar score at 1st minute and 5th minutes, and neonatal complications.

During routine ultrasound evaluation, biometric measurements were obtained, including BPD, HC, abdominal circumference (AC), femur length (FL), humerus length (HL), TCD, and structural assessment. All fetal biometric and structural evaluations were performed in accordance with the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines [9]. Estimated fetal weight was calculated using BPD, HC, AC, and FL. Fetal weight and percentiles were estimated using the Hadlock formula [10], while EFW percentiles were calculated according to Yudkin et al. [11], and other biometric percentiles according to Snijders and Nicolaides [12]. Birth weight percentiles were calculated as described by Nicolaides et al. [13].

APFD and OFD measurements were obtained retrospectively from stored ultrasound images in the transventricular plane, according to previously described methodology (Figure 1) [14]. The posterior margin of the cavum septi pellucidi (CSP) represents the boundary between the frontal lobe and the remaining brain structures. APFD was measured from the inner table of the frontal bone to the posterior border of the CSP along the midline of the fetal brain. OFD was measured as the distance between the inner margins of the frontal and occipital bones. The following ratios were calculated: APFD/OFD=100 × APFD/OFD, APFD/HC=100 × APFD/HC, and APFD/TCD=100 × APFD/TCD.

The use of proportional indices was intended to account for overall fetal and cranial size, allowing a more reliable interpretation of regional brain measurements. This approach is consistent with previous studies demonstrating that normalization of neurosonographic parameters to head

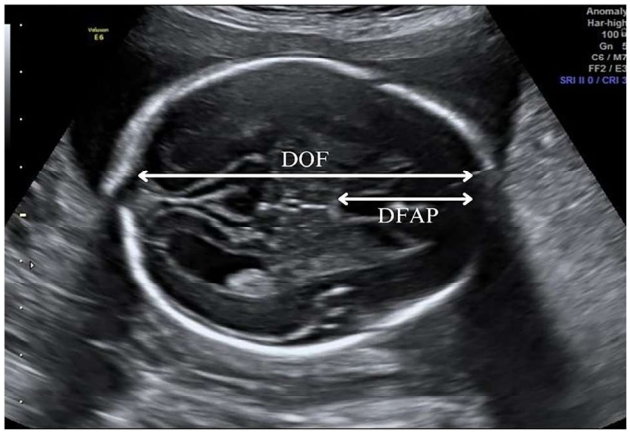

Figure 1: Ultrasound axial view of the fetal head at the transventricular plane demonstrating the measurement of the anteroposterior frontal diameter (DFAP) and occipitofrontal diameter (DOF).

size, particularly head circumference, improves the assessment of fetal brain development and reduces the potential confounding effect of global fetal growth [15].

GDM was defined as fasting plasma glucose ≥92 mg/dL, 1-h value ≥180 mg/dL, or 2-h value ≥153 mg/dL after a 75 g oral glucose tolerance test (OGTT), according to the American Diabetes Association [16]. Pre-gestational diabetes refers to diabetes mellitus (type 1, type 2, or monogenic forms) present before conception or first diagnosed during pregnancy due to routine prenatal screening (overt diabetes), according to the same guideline [16].

Images were analyzed through direct access to ultrasound image storage systems at UFTM and UNIUBE (Pacs Aurora 2025, Pixeon). Measurements were recorded directly into the study database. Clinical data were extracted from electronic medical records and entered into the same database. No images or clinical data were downloaded or stored on external electronic devices.

Sample size calculation

Sample size was calculated using G*Power 3.1 [17]. To evaluate the effect of the study group on APFD, APFD/OFD, APFD/HC, and APFD/TCD measurements, a total of 153 patients without comorbidities and 77 patients with the studied comorbidity were required, considering an effect size of 0.35, statistical power of 80 %, and a significance level of <0.05.

Statistical analysis

Data were entered into an Excel 2010 spreadsheet (Microsoft Corp., Redmond, WA, USA) and analyzed using PASW Statistics (version 18.0, SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 5.0, GraphPad Software, San Diego, CA, USA).

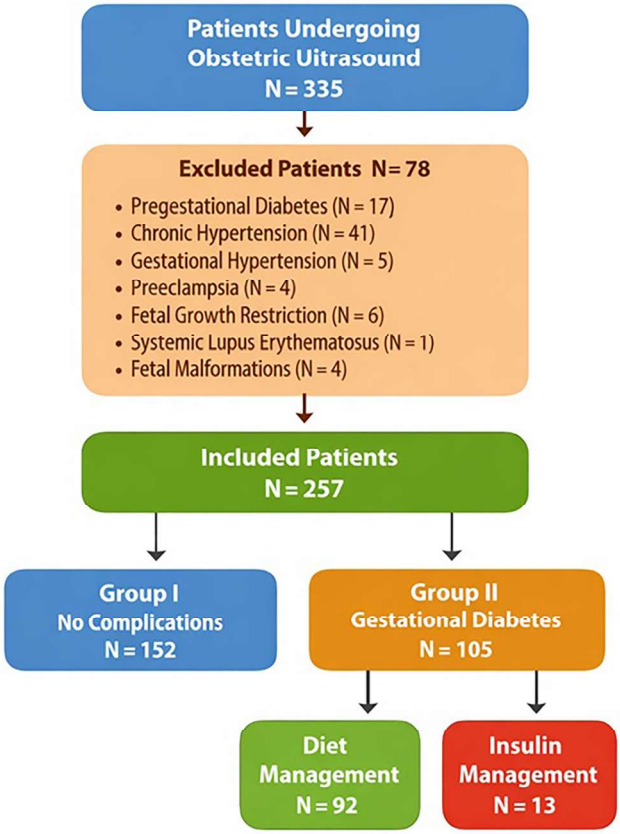

Figure 2: Flowchart of patient selection and distribution of the study population.

Continuous variables were expressed as mean, median, standard deviation (SD), and minimum and maximum values. Categorical variables were expressed as absolute frequency and percentages. The Mann–Whitney and Kruskal–Wallis tests were used to evaluate the effect of the study groups on APFD, APFD/OFD, APFD/HC, and APFD/TCD. The chi-square test was used to assess associations between categorical variables. Statistical significance was $p<0.05$.

Results

Between October 2025 and April 2026, a total of 335 pregnant women undergoing obstetric ultrasound examinations. Seventy-eight patients were excluded due to pregestational diabetes mellitus (n=17), chronic hypertension (n=41), gestational hypertension (n=5), preeclampsia (n=4), fetal growth restriction (n=6), systemic lupus erythematosus (n=1), and fetal malformations (n=4). A total of 257 patients were included in the final statistical analysis and divided into two groups: Group I – uncomplicated pregnancies (n=152), and Group II – pregnancies complicated by GDM (n=105). Among patients with GDM, 13 required insulin therapy, while 92 achieved glycemic control through diet alone (Figure 2).

Table 1: Clinical and epidemiological characteristics of the study population.

Variable	Group I (n=152)	Group II (n=105)	p-Value
Age, years	32 (20–40)	28.5 (18–43)	0.830ʃ
Ethnicity			<0.001∂
White	62.5 % (95/152)	40.0 % (42/105)	
Black	10.5 % (16/152)	5.7 % (6/105)	
Mixed	27.0 % (41/152)	54.3 % (57/105)	
Alcohol use	2.0 % (3/152)	3.8 % (4/105)	0.374∂
Smoking	3.9 % (6/152)	8.6 % (9/105)	0.120∂
BMI, kg/m^2	28.2 (22.8–36.9)	31.0 (19.9–53.0)	<0.001ʃ
Gravidity	1.0 (1.0–2.0)	3.0 (1.0–6.0)	0.018ʃ
Parity	0.0 (0.0–1.0)	1.0 (0.0–4.0)	0.002ʃ
Miscarriages	0.0 (0.0–0.0)	0.0 (0.0–3.0)	0.694ʃ
Fasting glucose, mg/dL	76.0 (69.0–97.0)	96.0 (66.0–123.0)	<0.001ʃ
Glycated hemoglobin, %	5.0 (4.9–5.4)	5.1 (4.3–6.6)	0.558ʃ
Gestational age at delivery, weeks	39.0 (38.7–39.7)	39.0 (33.7–40.4)	0.073ʃ
Birth weight, g	3,196.0 (3,105.0–3,495.0)	3,270.0 (1860.0–4,110.0)	<0.001ʃ
Mode of delivery			0.369∂
Vaginal	34.9 % (53/152)	29.5 % (31/105)	
Cesarean section	65.1 % (99/152)	70.5 % (74/105)	
Forceps	0.0 % (0/152)	0.0 % (0/105)	
Apgar score, 1st min	8.0 (4.0–9.0)	8.0 (4.0–9.0)	0.799ʃ
Apgar score, 5th min	9.0 (9.0–10.0)	9.0 (7.0–10.0)	0.822ʃ

Group I: uncomplicated pregnancies; Group II: gestational diabetes mellitus (GDM). ʃ Mann–Whitney test: median (min–max); ∂ Chi-square test: % (n/n). p<0.05.

Table 2: Ultrasound characteristics of the study population.

Variable	Group I (n=152)	Group II (n=105)	p-Value
Gestational age, weeks	32.3 (27.6–37.7)	32.5 (25.6–38.0)	0.065
BPD, mm	84.6 (67.0–100.3)	84.5 (66.0–101.9)	0.129
OFD, mm	97.0 (78.2–118.6)	97.5 (74.6–114.5)	0.050
HC, mm	295.5 (241.9–344.9)	295.6 (115.8–341.6)	0.042
AC, mm	279.2 (37.6–589.6)	286.0 (66.3–357.6)	0.011
FL, mm	60.8 (49.4–72.8)	61.8 (28.6–76.5)	0.041
Deepest vertical pocket, cm	4.8 (2.5–8.3)	4.4 (2.2–11.1)	0.926
EFW, g	1925.9 (566.6)	2045.0 (707.9)	0.026
Mean uterine artery PI	0.73 (0.43–1.98)	0.66 (0.42–1.36)	0.010
Umbilical artery PI	0.97 (0.60–1.96)	0.91 (0.51–1.29)	0.044
Middle cerebral artery PI	2.0 (1.27–2.95)	1.98 (1.14–2.70)	0.155

Group I: uncomplicated pregnancies; Group II: GDM. BPD, biparietal diameter; OFD, occipitofrontal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length; EFW, estimated fetal weight. Mann–Whitney test: median (min–max). p<0.05.

The clinical and demographic characteristics of the study population are presented in Table 1. Regarding anthropometric profile, Group II exhibited a higher BMI (31.0 vs. 28.2 kg/m^2, p<0.001), a greater number of pregnancies (3.0 vs. 1.0, p=0.018), and a higher parity (1.0 vs. 0.0, p=0.0002) compared to Group I. In terms of metabolic parameters, fasting plasma glucose levels were significantly higher in Group II (96.0 vs. 76.0 mg/dL, p<0.001), whereas glycated hemoglobin levels were similar between groups (5.1 vs. 5.0 %, p=0.558).Regarding perinatal outcomes, no significant difference was observed in the mode of delivery (p=0.369), although cesarean section rates were high in both

Table 3: Comparison of fetal frontal lobe anteroposterior diameter, transverse cerebellar diameter, and their ratios in fetuses of women with and without gestational diabetes.

Variable	Group I (n=152)	Group II (n=105)	p-Value
TCD, mm	38.6 (20.0–98.7)	40.1 (21.0–84.3)	0.206
APFD, mm	35.5 (16.4–46.8)	36.9 (19.9–48.2)	0.086
APFD/OFD	0.40 (0.20–0.50)	0.40 (0.30–0.50)	0.897
APFD/HC	0.10 (0.10–0.20)	0.10 (0.10–0.40)	0.702
APFD/TCD	1.0 (0.40–1.30)	0.90 (0.40–1.30)	0.602

Group I: uncomplicated pregnancies; Group II: GDM. TCD, transverse cerebellar diameter; APFD, anteroposterior frontal diameter; OFD, occipitofrontal diameter; HC, head circumference. Mann–Whitney test: median (min–max). p<0.05.

groups (70.5 % in Group II and 65.1 % in Group I). Median birth weight was higher in Group II (3,270 vs. 3,196 g, p<0.001). No clinically relevant differences were observed in Apgar scores at 1 min (p=0.799) and 5 min (p=0.822) (Table 1).

Fetal biometric parameters and maternal–fetal Doppler findings are presented in Table 2. There was no significant difference in gestational age at the time of ultrasound evaluation between groups (p=0.065). Regarding cranial growth, no statistically significant differences were observed in BPD (p=0.129) or OFD (p=0.050). Although HC was statistically higher in Group II (295.6 vs. 295.5 mm, p=0.011), this difference is not clinically meaningful. AC (286.0 vs. 279.2 mm, p=0.011) and EFW (2045 vs. 1925.9 g, p=0.026) were significantly higher in Group II compared to Group I. Fetal well-being and placental function were assessed by Doppler analysis. The umbilical artery PI (0.91 vs. 0.97, p=0.044) and mean uterine artery PI (0.66 vs. 0.73, p=0.010) were significantly lower in Group II. No significant differences were observed in middle cerebral artery PI (p=0.155) or deepest vertical pocket of amniotic fluid (p=0.926).

The impact of GDM on fetal intracranial measurements and their ratios is detailed in Table 3. No statistically significant differences were identified between Group I and Group II in any of the analyzed brain morphometry variables. Measurements of APFD (36.9 vs. 35.5 mm, p=0.086) and TCD (40.1 vs. 38.6 mm, p=0.206) did not differ significantly between groups. Ratios reflecting the relationship between the frontal lobe and overall cranial biometry were also comparable. APFD/OFD (p=0.897) and APFD/HC (p=0.702) remained stable, with median values of 0.40 and 0.10, respectively, in both groups. Similarly, the APFD/TCD ratio showed no significant difference (p=0.602).

Table 4 presents the comparison of fasting plasma glucose and glycated hemoglobin levels among patients with uncomplicated pregnancies and those with GDM managed with diet or insulin. A significant difference was observed in fasting glucose levels (p<0.001), whereas glycated hemoglobin levels did not differ significantly between groups (p=0.506). Pairwise comparisons demonstrated significant differences in fasting glucose levels between uncomplicated pregnancies and GDM controlled by diet (p<0.001), as well as between uncomplicated pregnancies and GDM requiring insulin (p<0.001). No significant difference was observed between diet-controlled and insulin-treated GDM groups (p=0.478).

Table 5 shows the comparison of fetal neurosonographic and biometric measurements stratified by type of maternal glycemic control (diet vs. insulin) compared with the uncomplicated group. No statistically significant differences were observed among the three groups for any of the analyzed brain morphometry variables.

Table 4: Comparison of fasting glucose and glycated hemoglobin among uncomplicated pregnancies and GDM (diet- and insulin-controlled).

Variable	Normal (n=152)	GDM – diet (n=92)	GDM – insulin (n=13)	p-Value
Fasting glucose, mg/dL	76.0 (69.0–97.0) a,b	96.0 (66.0–123.0) c	101.0 (93.0–111.0)	<0.001
Glycated hemoglobin, %	5.0 (4.9–5.4)	5.1 (4.3–6.5)	5.1 (4.3–6.6)	0.506

GDM, gestational diabetes mellitus. Kruskal–Wallis test: median (min–max). (a) Normal vs. GDM, diet; (b) Normal vs. GDM, insulin; (c) GDM, diet vs. GDM, insulin. p<0.05.

Discussion

The present study did not demonstrate a significant impact of GDM on fetal frontal lobe morphometry, as assessed by the APFD and its ratios with OFD, HC, and TCD in fetuses between 20 weeks and 38 weeks of gestation.

Despite relevant clinical and metabolic differences observed in the GDM group – including higher body mass index, increased gravidity and parity, and elevated fasting glucose levels – no statistically significant differences were identified in APFD measurements or their proportional relationships to global cranial biometry. Notably, these findings remained consistent even after stratification according to glycemic control (diet vs. insulin), reinforcing the robustness of the observed lack of association.

In contrast, fetuses in the GDM group exhibited expected alterations in somatic growth, including increased estimated fetal weight and abdominal circumference, as well as significant differences in maternal–fetal Doppler indices, suggesting hemodynamic adaptations. However,

Table 5: Comparison of fetal cranial biometric measurements and brain ratios according to maternal glycemic control.

Variable	Normal (n=152)	GDM – diet (n=92)	GDM – insulin (n=13)	p-Value
TCD, mm	38.6 (20.0–98.7)	39.7 (21.0–84.3)	42.5 (22.8–54.8)	0.224
APFD, mm	35.5 (16.4–46.8)	36.8 (19.9–48.2)	37.0 (23.3–42.8)	0.366
BPD, mm	84.6 (67.0–100.3)	82.6 (50.7–101.9)	88.7 (55.7–94.8)	0.133
OFD, mm	97.0 (78.2–118.6)	95.7 (58.8–114.5)	101.4 (62.9–119.7)	0.085
HC, mm	295.5 (241.9–344.9)	290.8 (115.8–349.6)	313.3 (197.8–349.7)	0.055
APFD/OFD	0.40 (0.20–0.50)	0.40 (0.30–0.50)	0.40 (0.30–0.40)	0.356
APFD/HC	0.10 (0.10–0.20)	0.10 (0.10–0.40)	0.10 (0.10–0.10)	0.779
APFD/TCD	1.0 (0.40–1.30)	0.90 (0.40–1.30)	0.90 (0.60–1.00)	0.296

APFD, anteroposterior frontal diameter; TCD, transverse cerebellar diameter; GDM, gestational diabetes mellitus; BPD, biparietal diameter; OFD, occipitofrontal diameter; HC, head circumference. Kruskal–Wallis test: median (min–max). $p<0.05$.

these changes were not accompanied by detectable differences in intracranial morphometric parameters. This dissociation may suggest that, within the limits of ultrasound-based biometric assessment, no measurable differences in frontal lobe size were identified. However, this finding should not be interpreted as evidence of preserved brain development, as functional, microstructural, or histopathological alterations cannot be assessed using the parameters applied in this study.

These findings should be interpreted in the context of existing literature, which has reported heterogeneous results regarding the impact of GDM on fetal brain development. While some neurosonographic studies have described alterations in cortical maturation and frontal lobe proportions, others have failed to demonstrate significant structural differences, particularly in populations with adequate glycemic control [1, 2]. Our results align with the latter and suggest that, under contemporary prenatal care conditions, GDM may not lead to measurable changes in fetal brain biometry using conventional ultrasound techniques.

Several mechanisms may explain the absence of detectable differences in our study. First, glycemic control appears to play a central role. Evidence suggests that appropriate management of maternal glucose levels, through dietary measures or insulin therapy, can mitigate the potential impact of hyperglycemia on fetal brain development [1, 2]. In our cohort, although metabolic differences were present, the lack of difference in glycated hemoglobin between groups supports the hypothesis of relatively adequate glycemic control.

Second, the timing of exposure to hyperglycemia may be critical. Early gestational exposure is more strongly associated with disturbances in organogenesis and neurodevelopment, whereas later exposure tends to influence fetal growth and metabolic outcomes rather than structural brain development [5]. Given that GDM is typically diagnosed in the second half of pregnancy, the window of exposure in our population may not have been sufficient to induce detectable structural alterations.

Third, the inherent limitations of ultrasound-based measurements must be considered. Although ultrasound is the standard tool for fetal neurosonographic assessment, it may lack sensitivity for detecting subtle or microstructural brain changes. Advanced imaging modalities, such as fetal and neonatal magnetic resonance imaging, have demonstrated alterations in brain microstructure, metabolism, and connectivity in offspring exposed to maternal diabetes, even in the absence of gross anatomical differences [3–5]. Therefore, the absence of differences in our study should be interpreted with caution, as ultrasound-based measurements are limited to gross anatomical assessment and do not allow evaluation of microstructural brain organization or prediction of postnatal neurodevelopmental outcomes.

The strengths of this study include a relatively large sample size, the use of standardized measurement protocols, and the evaluation of both absolute and proportional cranial parameters. The use of a single experienced operator also minimizes interobserver variability and enhances measurement consistency. However, limitations should be acknowledged. The retrospective design introduces potential selection bias, and the cross-sectional nature of the analysis limits the assessment of longitudinal brain development. Additionally, glycemic control was assessed using limited clinical parameters, and more detailed metabolic profiling could provide further insights. Finally, the absence of postnatal neurodevelopmental follow-up precludes correlation between imaging findings and functional outcomes. Importantly, this study was not designed to assess neurodevelopmental outcomes, and no conclusions can be drawn regarding the functional or cognitive implications of the findings. In addition, the use of ratios between frontal lobe measurements and global cranial parameters represents a methodological strength, as it allows adjustment for fetal

size, in line with previous studies showing that head size–adjusted measurements provide a more accurate representation of cortical development. Another limitation of this study is that fetal sex was not included in the analysis. Previous studies have shown that fetal sex may influence cortical development, with male fetuses demonstrating greater fissure depth compared to females, particularly in later gestational ages, even after adjustment for head circumference [18]. Therefore, sex-related differences in brain development may represent a potential confounding factor that was not accounted for in the present analysis.

Conclusions

In conclusion, within the parameters and methods adopted in this study, gestational diabetes mellitus was not associated with detectable alterations in fetal frontal lobe morphometry or its proportional relationships with other cranial measurements. These findings indicate that no differences were detected in fetal frontal lobe morphometry using ultrasound-based parameters. However, these results should not be interpreted as evidence of preserved neurodevelopment, as functional and microstructural outcomes were not assessed. Future studies incorporating longitudinal designs, advanced neuroimaging techniques, and long-term neurodevelopmental assessment are warranted to better elucidate the potential subtle effects of GDM on fetal brain development.

Research ethics: Our investigations were carried out following the rules of the Declaration of Helsinki of 1975, revised in 2013. The study protocol was submitted to the UFTM Research Ethics Committee (CAAE: 91546225.0.0000.8667).
Informed consent: Not applicable. It was a retrospecrive case control study and informed consent form was not required.
Author contributions: Conceptualization, ABP, YRA; methodology, ACMR, and FBA; validation, AB and EAJ; formal analysis, GYC and ABP; investigation, ACNRB, YRA, and ACMR; resources, EAJ; data curation, FBA and ACNRB; writing – original draft preparation, GYC, and YRA; writing – review and editing, EAJ and AB; visualization, ABP, YRA, ACMR, FBA, AB, EAJ, GYC, ACNRB; supervision, EAJ; project administration, ABP. All authors have read and agreed to the published version of the manuscript.
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Conflict of interest: The authors state no conflict of interest.
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Data availability: The data presented in this study are available on request from the corresponding author.

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