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Integrated Ultrasound Assessment of the 'Placenta-Brain Unit': Correlating Uteroplacental Doppler with Fetal Neurosonography Findings in Diabetic Pregnancies

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ABSTRACT

Objective: To investigate the relationship between utero-placental Doppler indices and detailed fetal neurosonographic findings in pregnancies complicated by pre-gestational and gestational diabetes mellitus (GDM). Methods: A prospective cohort study was conducted on 150 diabetic pregnancies (75 pre-gestational, 75 GDM) and 75 matched healthy controls between 28-32 weeks of gestation. All participants underwent pulsed-wave Doppler assessment of the uterine arteries (UtA) to determine the pulsatility index (PI) and the presence of an early diastolic notch. Subsequently, a dedicated fetal neurosonography was performed to measure the transcerebellar diameter (TCD), Sylvian fissure depth, and lateral ventricle width, and to assess the development of the corpus callosum and cortical sulcation. Results: The diabetic cohort, particularly the pre-gestational subgroup, demonstrated significantly higher mean UtA-PI values and a higher prevalence of bilateral notching compared to controls ($p < 0.01$). Neurosonography revealed significant alterations in the diabetic groups, including a larger transcerebellar diameter ($p < 0.05$), abnormal Sylvian fissure maturation, and delayed opercularization compared to the control group ($p < 0.01$). A significant inverse correlation was observed between UtA-PI and transcerebellar diameter ($r = -0.45$, $p < 0.001$), and a positive correlation with Sylvian fissure depth ($r = 0.52$, $p < 0.001$) in the pre-gestational diabetes group. Conclusion: This study demonstrates a significant correlation between impaired utero-placental hemodynamics and alterations in fetal brain development in diabetic pregnancies, supporting the concept of a "placenta-brain unit". Integrated ultrasound assessment of this unit may serve as an early biomarker for identifying fetuses at risk for neurodevelopmental morbidity, enabling potential early intervention strategies.

Keywords: Diabetic Pregnancy, Fetal Neurosonography, Uterine Artery Doppler, Placenta-Brain Unit, Fetal Brain Development.

1. Introduction

Diabetes in pregnancy, encompassing both pre-gestational diabetes mellitus (PGDM) and gestational diabetes mellitus (GDM), represents a major metabolic challenge to the developing fetus [1]. While the macroscopic complications, such as macrosomia and cardiac anomalies, are well-documented, the subtler impacts on the developing central nervous system are an area of growing concern [2]. Offspring of diabetic mothers are at an increased risk for long-term neurodevelopmental disorders, including deficits in motor skills, language, and social behavior, suggesting an in-utero origin for these abnormalities [3].

The fetal environment is critically dependent on optimal placental function, which acts as the primary interface for nutrient and oxygen transfer. In diabetic pregnancies, placental structure and function can

be compromised by hyperglycemia-induced oxidative stress and altered angiogenesis, often manifesting as impaired uteroplacental blood flow [4]. Uterine artery Doppler ultrasonography is a established tool for the non-invasive assessment of utero-placental circulation, with increased pulsatility index (PI) and the presence of an early diastolic notch being indicators of increased impedance to flow [5].

Concurrently, advances in high-resolution ultrasonography have enabled detailed in-utero assessment of the fetal brain, known as fetal neurosonography. This technique allows for the precise evaluation of brain biometry, including the transcerebellar diameter (TCD), and the qualitative assessment of sulcation and opercularization, which are markers of cerebral maturation. Altered brain biometry and delayed cortical development have been anecdotally observed in fetuses of diabetic mothers, but a systematic evaluation linking these findings to placental health is lacking [6,7].

We hypothesize that the placental dysfunction evident in diabetic pregnancies, quantified by uterine artery Doppler, is directly correlated with deviations in fetal brain maturation, as visualized by neurosonography. This integrated approach, which we term the "placenta-brain unit" assessment, may provide a comprehensive understanding of the pathophysiological link between maternal diabetes and fetal neurodevelopment [8]. The primary aim of this study is to correlate uterine artery Doppler indices with detailed fetal neurosonographic parameters in a cohort of women with diabetic pregnancies compared to healthy controls.

2. Methodology

2.1. Study Design and Population

A prospective cohort study was conducted at a tertiary care teaching hospital between January 2023 and December 2024. The study protocol was approved by the Institutional Ethics Committee of Thi-Qar college of medicine, and written informed consent was obtained from all participants.

A total of 225 singleton pregnant women were recruited and divided into three groups:

- **Group 1 (PGDM):** 75 women with pre-gestational diabetes (Type 1 or Type 2).
- **Group 2 (GDM):** 75 women with gestational diabetes diagnosed by a 75g oral glucose tolerance test at 24-28 weeks, according to IADPSG criteria [9].
- **Group 3 (Control):** 75 normoglycemic, low-risk pregnant women matched for gestational age, maternal age, and body mass index.

Exclusion criteria included multiple pregnancies, known fetal chromosomal or structural anomalies (excluding those related to diabetes), maternal autoimmune disease, pre-eclampsia, substance abuse, and inadequate ultrasound visualization.

2.2. Ultrasound and Doppler Examination

All ultrasound examinations were performed transabdominally between 28 and 32 weeks of gestation using a Voluson E6 system (GE Healthcare, USA) equipped with a 2-5 MHz curvilinear transducer by a single fetal medicine specialist (M.S.) with over 10 years of experience to minimize inter-observer variability.

- **Uterine Artery Doppler:** The uterine arteries were identified at the crossover point with the external iliac arteries using color Doppler. Pulsed-wave Doppler was used to obtain velocity waveforms. The pulsatility index (PI) was automatically calculated from three consecutive waveforms from each artery, and the mean UtA-PI was recorded. The presence of an early diastolic notch was assessed bilaterally and classified as unilateral or bilateral [10].
- **Fetal Neurosonography:** A dedicated fetal neurosonography was performed following a standardized protocol [11]. The following parameters were assessed:
    1. **Transcerebellar Diameter (TCD):** Measured in the transcerebellar plane.
    2. **Sylvian Fissure Depth:** Measured in the axial plane from the insular surface to the inner table of the skull.
    3. **Lateral Ventricle Atrial Width:** Measured in the axial plane at the level of the glomus of the choroid plexus.
    4. **Corpus Callosum:** Visualized in the midsagittal plane and its length was measured.
    5. **Opercularization and Cortical Sulcation:** Qualitative assessment of the development of the Sylvian fissure and the presence of primary sulci (pre-central, central, and calcarine) was performed and graded as 'normal for age' or 'delayed' [12].

2.3. Statistical Analysis

Data were analyzed using SPSS Statistics Version 28.0. Continuous variables were expressed as mean ± standard deviation and compared using one-way ANOVA with post-hoc Tukey test. Categorical variables were expressed as numbers (percentages) and compared using the Chi-square test or Fisher's exact test as appropriate. Pearson's correlation coefficient was used to assess the relationship between UtA-PI and neurosonographic parameters. A p-value of < 0.05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics

The three groups were well-matched for maternal age, gestational age at scan, and parity as shown in Figure 1. As expected, pre-gestational body mass index and HbA1c levels at the time of scan were significantly higher in the PGDM and GDM groups compared to the control group ($p < 0.01$) (Table 1).

Table 1. Baseline and Doppler Characteristics of the Study Population

Characteristic	PGDM (n=75)	GDM (n=75)	Control (n=75)	p-value
Maternal Age (years)	31.4 ± 4.2	30.8 ± 3.9	30.1 ± 4.5	0.15
Gestational Age at Scan (weeks)	30.1 ± 1.2	30.3 ± 1.1	30.0 ± 1.3	0.28
Pre-gestational BMI (kg/m²)	28.5 ± 3.1*	27.8 ± 2.9*	24.1 ± 2.4	<0.01
HbA1c at scan (%)	6.5 ± 0.8*	5.4 ± 0.4*	4.9 ± 0.3	<0.01
Mean UtA-PI	1.25 ± 0.28*	1.02 ± 0.21	0.95 ± 0.18	<0.01
Bilateral Notch, n (%)	18 (24.0%)*	5 (6.7%)	3 (4.0%)	<0.01
p<0.05 vs. Control group				

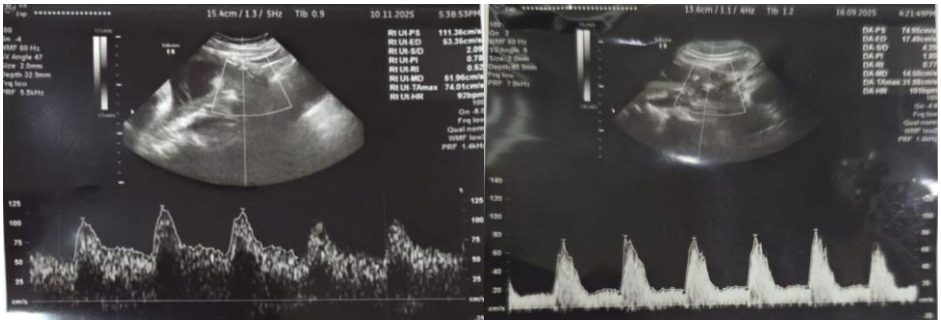

Figure 1. Representative images of Uterine Artery Doppler wave forms:

Normal wave form with low PI and no early diastolic notch.

Abnormal waveform from a PGDM patient showing high PI and early diastolic notch.

3.2. Uterine Artery Doppler Findings

The PGDM group demonstrated a significantly higher mean UtA-PI (1.25 ± 0.28) compared to both the GDM (1.02 ± 0.21, $p<0.01$) and control groups (0.95 ± 0.18, $p<0.01$) [6]. The prevalence of bilateral diastolic notching was also significantly higher in the PGDM group (24.0%) compared to the GDM (6.7%) and control (4.0%) groups ($p < 0.01$). There was no significant difference in UtA-PI or notching between the GDM and control groups as shown in Figure 2.

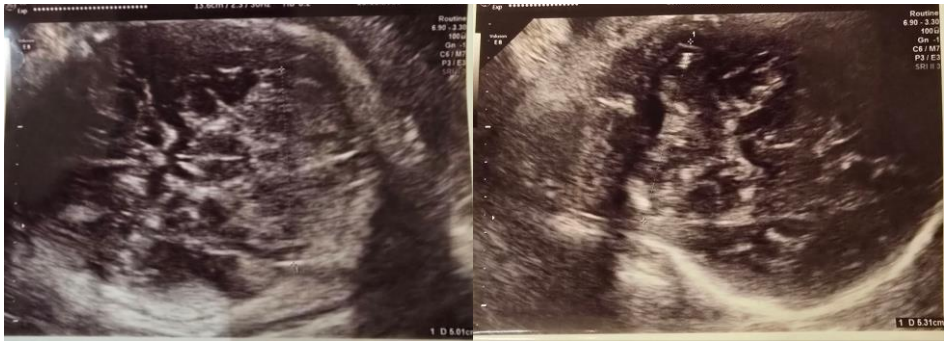

Figure 2. Representative neurosonography images in axial plane- TCD :

Normal TCD at 31 week control group

Abnormal TCD at 30 week in PGDM group

3.3. Fetal Neurosonography Findings

The neurosonographic parameters are summarized in Table 2. The transcerebellar diameter (TCD) was significantly larger in the PGDM group (53.2 ± 3.1 mm) compared to the control group (50.1 ± 2.8 mm, $p<0.05$), suggesting macroscopic cerebellar overgrowth. The Sylvian fissure was significantly deeper in the PGDM group (5.8 ± 1.1 mm) compared to controls (4.2 ± 0.9 mm, $p<0.01$), indicating delayed

opercularization. A higher proportion of fetuses in the PGDM group were graded as having 'delayed' cortical sulcation (29.3%) compared to the GDM (12.0%) and control (5.3%) groups ($p < 0.01$). No significant differences were found in the lateral ventricle width or corpus callosum length among the groups.

Table 2. Fetal Neurosonography Parameters

Neurosonographic Parameter	PGDM (n=75)	GDM (n=75)	Control (n=75)	p-value
Transcerebellar Diameter (mm)	53.2 ± 3.1*	51.5 ± 2.9	50.1 ± 2.8	<0.05
Sylvian Fissure Depth (mm)	5.8 ± 1.1*	4.7 ± 1.0	4.2 ± 0.9	<0.01
Lateral Ventricle Width (mm)	7.1 ± 0.8	6.9 ± 0.7	6.8 ± 0.6	0.10
Corpus Callosum Length (mm)	38.5 ± 2.5	39.1 ± 2.3	38.8 ± 2.4	0.35
Delayed Sulcation, n (%)	22 (29.3%)*	9 (12.0%)	4 (5.3%)	<0.01
p<0.05 vs. Control group				

3.4. Correlation Analysis

In the PGDM group, a significant moderate inverse correlation was found between the mean UtA-PI and the transcerebellar diameter ($r = -0.45$, $p < 0.001$), meaning that higher placental resistance was associated with a relatively smaller TCD, though still larger than controls overall. A stronger positive correlation was observed between mean UtA-PI and Sylvian fissure depth ($r = 0.52$, $p < 0.001$), indicating that worse placental perfusion was linked to more pronounced delays in opercularization. These correlations were weak and non-significant in the GDM and control groups as shown in Figure 3.

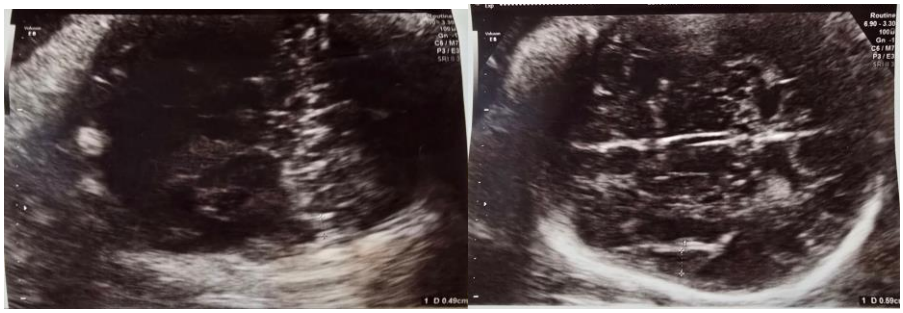

Figure 3. Representative neurosonography images in the axial plane-Sylvian fissure depth

Normal Sylvian fissure at 30 weeks.

Deep/immature Sylvian fissure from a fetus in the PGDM group at 31 weeks .

4. Discussion

This prospective study provides compelling evidence for the existence of a functional "placenta-brain unit" in diabetic pregnancies. Our findings demonstrate that impaired utero-placental hemodynamics, particularly in pre-gestational diabetes, are significantly correlated with distinct alterations in fetal brain development as visualized by advanced neurosonography [13].

The significantly higher UtA-PI and prevalence of bilateral notching in the PGDM group confirm the presence of underlying placental vasculopathy [14]. This is likely a consequence of hyperglycemia-mediated endothelial dysfunction and inadequate trophoblastic invasion, leading to increased impedance in the maternal uterine circulation [15]. The absence of such significant changes in the GDM group suggests that the severity and duration of hyperglycemia play a critical role in the development of placental dysfunction.

The neurosonographic findings are particularly insightful. The larger transcerebellar diameter observed in the PGDM group aligns with the concept of fetal overgrowth, a well-known consequence of maternal diabetes, but specifically localized to the cerebellum [16]. However, the inverse correlation with UtA-PI suggests a complex interaction where placental insufficiency may paradoxically modulate the effects of hyperglycemia-driven growth. More critically, the deeper Sylvian fissure and higher incidence of delayed sulcation and opercularization are strong indicators of altered neuronal migration and cortical maturation [17]. The significant positive correlation between UtA-PI and Sylvian fissure depth provides a direct link: poorer placental blood flow is associated with greater immaturity of the fetal cerebral cortex. This may be due to chronic, subtle fluctuations in oxygen and nutrient delivery or the passage of inflammatory cytokines across the compromised placenta, affecting the vulnerable process of gyration and sulcation [18].

The integrated assessment proposed here moves beyond evaluating the placenta and fetus in isolation. By correlating a functional placental parameter (UtA Doppler) with a detailed structural brain assessment, we can identify fetuses who are not only exposed to a diabetic milieu but are also showing early signs of neurological adaptation or compromise [19]. This has profound clinical implications. While current antenatal care focuses on glycemic control and monitoring fetal growth, our findings suggest that a combined Doppler and neurosonography exam at 28-32 weeks could stratify risk for neurodevelopmental delay. Fetuses showing evidence of both high UtA-PI and abnormal cortical maturation, as in our PGDM cohort, could be targeted for enhanced postnatal developmental follow-up and early intervention programs [20].

"Our findings, which link impaired utero-placental blood flow to specific alterations in fetal brain maturation, are supported by recent literature that also documents brain changes in diabetic pregnancies. A 2025 systematic review by Oikonomou et al. confirmed that fetuses of mothers with GDM exhibit significant neurosonographic changes, including larger cavum septum pellucidum and lateral ventricle widths compared to controls . However, while their review successfully identified structural brain markers for GDM, it did not incorporate an assessment of uteroplacental hemodynamics. Therefore, our study extends this existing evidence by demonstrating that these brain changes are part of a broader pathophysiology involving the 'placenta-brain unit,' and provides a more direct link between placental function and fetal brain development." [8]

4.1. Strengths and Limitations

A key strength of this study is its prospective design and the use of a standardized, comprehensive neurosonographic protocol performed by a single expert, ensuring data consistency. The inclusion of both PGDM and GDM groups allowed for the analysis of a spectrum of disease severity.

This study is limited by its sample size from a single center. Furthermore, the neurodevelopmental outcomes of the children were not available, as this is an ongoing longitudinal study. The findings, therefore, demonstrate an association between placental function and fetal brain structure, and long-term follow-up is needed to confirm the predictive value of these findings for postnatal neurodevelopmental disorders.

5. Conclusion

This study establishes a significant correlation between impaired utero-placental blood flow, assessed by Doppler, and alterations in fetal brain maturation, visualized by neurosonography, in diabetic pregnancies. We propose the "placenta-brain unit" as a critical conceptual framework for understanding how the diabetic intrauterine environment shapes fetal neurodevelopment [20]. The integration of uterine artery Doppler with dedicated fetal neurosonography between 28-32 weeks of gestation provides a powerful, non-invasive tool to identify fetuses at highest risk for neurological sequelae. This approach warrants further validation in larger, multi-center studies with long-term neurodevelopmental follow-up to solidify its role in clinical practice for improving the long-term outcomes of children born to diabetic mothers.

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Conflict of interest statement: The authors have no conflict of interest with respect to the publication of this article.

Ethical Consideration: The ethical committee approved the study at University of Thi-Qar, Al-Nasiriyah, Iraq.

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