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The cerebro-placental-uterine ratio in predicting adverse perinatal outcomes in gestational diabetes: a prospective cohort study

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ABSTRACT

Aims: The primary aim of the study was to evaluate Doppler parameters focusing on fetal cerebral and placental circulation in gestational diabetes mellitus (GDM) and to investigate their relationship with maternal glycemic profiles.

Methods: A prospective cohort study was conducted involving 52 pregnant women diagnosed with GDM and 55 control participants. Doppler ultrasonography was performed between 34 and 37 weeks of gestation to evaluate key fetal hemodynamic parameters, including the umbilical artery (UA) systolic/diastolic (S/D) ratio, UA pulsatility index (PI), middle cerebral artery (MCA) S/D ratio and PI, uterine artery S/D ratio and PI, cerebro-placental ratio (CPR), and cerebro-placental uterine ratio (CPUR). Statistical analyses were performed to compare Doppler parameters between groups and to evaluate their predictive value for adverse perinatal outcomes.

Results: Both the MCA PI (p=0.019) and MCA S/D (p=0.011) differed significantly between the GDM and control groups. The median MCA PI was 1.60 in the GDM group and 1.46 in the control group. No statistically significant differences were observed in other parameters, including UA PI, CPR, or CPUR. A positive correlation was found between the CPUR and the second-hour 100-gram oral glucose tolerance test (OGTT) result (r=0.375; p=0.022). However, none of the Doppler parameters reliably predicted adverse perinatal outcomes.

Conclusion: The st udy found that fetal Doppler parameters were significantly associated only with MCA S/D and MCA PI. Perinatal outcomes were not correlated with UA, CPR, or CPUR. A positive correlation was observed between CPUR and the second-hour glucose value from the 100 g OGTT.

Keywords: Cerebroplacental-uterine ratio, cerebroplacental ratio, doppler parameters, gestational diabetes

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most prevalent endocrinological conditions during pregnancy.[1] GDM is associated with several fetal complications, including macrosomia, birth trauma, and intrauterine growth restriction, as well as maternal complications, particularly an increased rate of operative deliveries.[2-4] Therefore, early diagnosis and close monitoring of GDM are crucial. The oral glucose tolerance test (OGTT) is still the gold standard for diagnosing GDM, despite clinicians' efforts to take preventative measures by trying to identify the condition in the first trimester.[5] Consequently, several international pregnancy organizations, including the International Association of Diabetes and Pregnancy Study Groups (IADPSG) and the World Health Organization (WHO), recommend screening pregnant women using a one- or two-step OGTT.[6]

Studies have demonstrated that Doppler ultrasound performed in pregnant women can effectively indicate adverse fetal conditions.[7] The cerebroplacental ratio (CPR), calculated by dividing the fetal middle cerebral artery (MCA) pulsatility index (PI) by the umbilical artery (UA) PI, is commonly used alongside UA Doppler evaluation to identify fetuses at risk for unfavorable perinatal outcomes.[8] It has been demonstrated that the Doppler parameter most strongly associated with placental insufficiency in intrauterine growth retardation is the cerebro-placental uterine ratio (CPUR), which is the ratio of CPR to uterine artery PI.[9] Pregnant women with GDM are believed to have higher plasma viscosity than those without the condition due to elevated blood glucose levels. This results in increased blood flow resistance and reduced flow rates, which can impair blood perfusion.[10] During pregnancy, placental villi rely on interstitial perfusion to eliminate metabolic waste products and deliver essential nutrients for

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placental growth.[11] Maternal arterial blood perfusion is the primary source of interstitial perfusion for the placental villi. Decreased placental blood perfusion due to GDM may result in inadequate fetal nutrient uptake and impair fetal development. Under unfavorable conditions in pregnant women with GDM, increased uterine and UA resistance and decreased MCA resistance are expected.

The use of color Doppler ultrasound to determine arterial hemodynamic parameters in pregnant women may serve to detect abnormal perfusion of the placenta in a timely manner and effectively predict the outcome of pregnancy. This study aimed to investigate the potential role of CPUR as a novel Doppler parameter reflecting dysregulated blood glucose levels in pregnant women with GDM. Additionally, we sought to evaluate its predictive capacity for adverse perinatal outcomes and its utility in fetal well-being assessment.

METHODS

Between April 2022 and December 2022, this prospective cohort study was conducted at the Perinatology Clinic of Etlik Zübeyde Hanım Gynecology and Obstetrics Training and Research Hospital. The study was conducted with the permission of Etlik Zübeyde Hanım Gynaecology and Obstetrics Training and Research Hospital Clinical Practice Ethics Committee (Date: 31/03/2022, Decision No: 2022/37). The study was conducted in compliance with the Declaration of Helsinki, and all patients provided their informed consent for the Doppler examination after being made aware of the research study design.

Pregnant women between 34 and 37 weeks of gestation underwent obstetric examinations. 52 pregnant women with a GDM diagnosis and 55 control pregnant women without a GDM diagnosis were involved in the study. The two-step IADPSG criteria served as the basis for the GDM diagnosis. Based on these standards, all pregnant women between 24 and 28 weeks of gestation underwent a 50-g OGTT without first undergoing a fasting blood glucose test. Unless the initial value was already diagnostic for GDM (>200 mg/dl), women whose blood glucose levels reached 140 mg/dl or above in the first hour were then given a 100-g OGTT.[13] Gestational diabetes was identified in patients who met two of the Carpenter and Coustan criteria.[14,15] At first, diet control was used to treat these people. Insulin therapy was started if, after two weeks of monitoring fasting and postprandial blood glucose levels, there was no improvement. Thus, the study covered both diet-controlled and insulin-controlled diabetes. The study excluded participants with multiple pregnancies, intrauterine growth restriction, fetal abnormalities, and other systemic disorders (such as hypertension, diabetes mellitus, and cardiovascular diseases).

The study and control groups' Doppler parameters were compared, and any discrepancies between them were investigated. Then, a subgroup analysis was performed on GDM patients, dividing them into those who were on a diet only and those who required insulin, and the groups were evaluated in terms of Doppler parameters. The ability of these measures to forecast worse perinatal outcomes in the group with gestational diabetes was evaluated as a secondary result.

The occurrence of at least one poor event, such as a 5-minute APGAR score less than 7, admission to the newborn intensive care unit (NICU), umbilical cord blood pH less than 7.2, or perinatal mortality, was referred to as composite adverse perinatal outcomes (CAPO). The ratio of the MCA PI to the UA PI was used to determine the CPR. By dividing the CPR by the uterine artery PI, CPUR values were determined. At an angle of less than thirty degrees, MCA PI values were obtained from the proximal one-third of the arteries that emerged from the Circle of Willis. In the absence of fetal respiration, the UA's free loop was used to calculate the PI. At least three successive waveforms were averaged to record Doppler readings. CPR or CPUR data were recorded but not shared with the team before delivery to avoid compromising follow-up and delivery procedures. Neonatal outcomes were documented in the patient records. Pregnancy outcomes, delivery method, birth weight, and adverse perinatal outcomes were also assessed.

Statistical Analysis

All data were entered, cleaned, organized, and analyzed using IBM SPSS version 25 (IBM Corp.), USA. The Shapiro-Wilk test was used to assess the normality of data distribution. For normally distributed variables, independent Samples t-tests were performed, and data were presented as mean±standard deviation (mean±SD). For non-normally distributed variables, the median (Q1-Q3) was used, and group comparisons were conducted using the Mann-Whitney U test. The link between continuous parameters that followed the normal distribution was examined using Pearson's correlation coefficient, while values that did not were examined using Spearman's correlation coefficient. The threshold value for differentiating between the GDM and control groups was determined using the ROC analysis. A significant threshold of $p<0.050$ was established. The sample size was determined using a power analysis based on earlier research by Perez Martin et al.[16] The effect size and α-value were found to be 0.6957011 and 0.05, respectively, using the independent-samples t test; with 92 participants, the power (1-β) was computed to be 0.95. It was determined that 46 patients in each group would be sufficient to reach this power. We assume that our study's power is higher because our sample size is larger than these numbers.

RESULTS

This study included 107 pregnant women in total. There were fifty-two patients in the study group and fifty-five in the control group. The pregnant women who took part in the study had a median age of 29 (25-35). The BMI readings ranged from 27 to 35 kg/m^2, with 29 being the median. Table 1 compares the clinical features of the two groups. Accordingly, there was no significant difference between the two groups in BMI, gestational week of examination, smoking, neonatal birth weight, cesarean section (C/S) birth rates, and APGAR scores. While the median week of birth score in the GDM group was 38, it was 39 in the control group (p=0.020). As anticipated, the study group's 50g OGTT readings increased statistically significantly (p<0.001). The groups' median values for the MCA S/D and MCA PI parameters differed statistically significantly (p=0.011, p=0.019). The control group's median MCA PI parameter value was 1.46, whereas the GDM group's was 1.60 (Table 2). The distributions of the other parameters

Table 1. Clinical and disease characteristics of patients and control group

	Study group n=52	Control group n=55	p
Age (years) median (Q1-Q3)	32 (27-38)	27 (25-32)	<0.001*
Gravida median (Q1-Q3)	3 (2-4)	1 (1-3)	<0.001*
Body-mass index (kg/m²) median (Q1-Q3)	32 (27-37)	29 (27-32)	0.031*
Smoking	3 (5.9%)	2 (3.6%)	0.670‡
Gestational week at examination median (Q1-Q3)	36 (34-36)	36 (35-36)	0.296*
50 g-OGTT results (mg/dl) median (Q1-Q3)	156 (147-183)	109 (94-115)	<0.001*
Weight during pregnancy (kg) median (Q1-Q3)	10 (6-12)	15 (10-18)	<0.001*
Gestational age at delivery median (Q1-Q3)	38 (37-39)	39 (38-39)	0.020*
Neonatal birthweight (grams) mean±SD	3175.06±458.38	3216.81±452.9	0.638†
Cesarean delivery (n, %)	45 (68.6%)	33 (60.0%)	0.511‡
APGAR 1. minute median (Q1-Q3)	9 (9-9)	9 (9-9)	0.771*
APGAR 5. minute median (Q1-Q3)	10 (10-10)	10 (10-10)	0.394*
Neonatal intensive care unit admission (n, %)	13 (25.5%)	8(14.5%)	0.243‡
Perinatal death	0	0	NA
CAPO	14 (26%)	9 (16%)	0.183

SD: Standard deviation, Q1-Q3: "First quartile - third quartile, OGTT: Oral glucose tolerance test, CAPO: Composite adverse perinatal outcome, *Mann-Whitney U test ; † Independent Two Sample-t test; ‡: Chi-square test

Table 2. Comparison of Doppler parameters in study groups

	Study group n=52	Control group n=55	p
Umbilical S/D median (Q1-Q3)	2.36 (2.14-2.71)	2.18 (2.09-2.66)	0.073
Umbİlical PI median (Q1-Q3)	0.86 (0.77-0.96)	0.79 (0.71-0.94)	0.139
MCA S/D median (Q1-Q3)	4.62 (3.81-6.09)	4.00 (3.27-5.00)	0.011
MCA PI median (Q1-Q3)	1.60 (1.40-1.84)	1.46 (1.22-1.69)	0.019
Uterine S/D median (Q1-Q3)	1.91 (1.69-2.50)	1.98 (1.57- 2.40)	0.676
Uterine PI median (Q1-Q3)	0.70 (0.57-1.04)	0.80 (0.50-1.02)	0.978
CPR median (Q1-Q3)	1.90 (1.54-2.19)	1.62 (1.46-2.16)	0.152
CPUR median (Q1-Q3)	2.45 (1.65-3.65)	2.32 (1.57- 3.43)	0.667

S/D: Systolic/diastolic, PI: Pulsatility index, CPR: Cerebro-placental ratio, CPUR: Cerebro-placental-uterine ratio

by group did not differ statistically significantly (p>0.050). **Table 3** displays if there is a correlation between CPUR values and clinical features. The OGTT value of the second hour (100 g) and the CPUR among the parameters under study thus only showed a slight, statistically significant positive connection (r=0.342; p=0.017). The CPUR parameter and other parameters did not show any statistically significant correlation (p>0.050). The CPR parameter and other parameters did not exhibit a statistically significant connection (p>0.050). Neither CRP nor CPUR had any significant cut-off values that could be used to identify the GDM group (CRP: AUC=0.580, p=0.156; CPUR: AUC=0.524, p=0.669). **Table 4** shows that neither CRP nor CPUR had any significant cut-off values to differentiate CAPO (CRP: AUC=0.521, p=0.777; CPUR: AUC=0.532, p=0.620). Other than uterine artery S/D and uterine PI (p=0.001, p=0.007), subgroup analysis between insulin users and those with diet-regulated GDM revealed no significant differences (**Table 5**).

Table 3. Examining the relationship between CPR and CPUR parameters and quantitative parameters

	CPR		CPUR	
	r	p	r†	p†
Birthweight (gr)	0.149†	0.126†	0.064	0.510
50 gr OGTT hour	-0.042†	0.670†	-0.045	0.647
100g OGTT (FBG)	0.071†	0.630†	-0.080	0.589
100 gr OGTT (1. hour)	0.094†	0.523†	0.023	0.876
100 gr OGTT (2. hour)	0.166†	0.260†	0.342	0.017
OGTT (3. hour)	-0.111*	0.475*	-0.132	0.395

*Pearson correlation coefficient; †Spearman's correlation coefficient, CPR: Cerebro-placental ratio, CPUR: Cerebro-placental-uterine ratio, OGTT: Oral glucose tolerance, FBG: Fasting blood glucose

DISCUSSION

This study highlights the importance of fetal Doppler parameters in predicting pregnancy outcomes in women diagnosed with GDM, providing new insights into their potential prognostic value. The only fetal Doppler parameter that was statistically different between the two groups of patients (with and without GDM) was the MCA PI. Perinatal outcomes showed no correlation with UA, CPR, CPUR. However, a positive correlation was observed between CPUR and the 100-g OGTT value.

In perinatal practice, UA Doppler is commonly used to assess downstream circulatory impedance (i.e. flow resistance).[17] Unlike systemic arteries, the umbilical vasculature lacks innervation. Instead, vasoactive substances regulate the contractile mechanism of the UA.[18] End diastolic velocity decreases and Doppler indices rise with pregnancy issues such fetal growth retardation and preeclampsia, which are

Table 4. ROC analysis results in distinguishing study and control groups and composite adverse perinatal outcomes

	Cut-off	Sensitivity	Specificity	AUC	p	Analysis type
CPR	>1.61	75	49	0.580	0.156	GDM & control groups
CPUR	>1.15	92	20	0.524	0.669	GDM & control groups
CPR	>1.82	57	56	0.521	0.774	CAPO
CPUR	>1.49	87	25	0.532	0.270	CAPO

ROC: Receiver operator characteristic, CPR: Cerebro-placental ratio, CPUR: Cerebro-placental-uterine ratio, CAPO: Composite adverse perinatal outcome, GDM: Gestational diabetes mellitus

Table 5. Comparison of Doppler indices between DRGDM and IRGDM groups

	DRGDM (n=34)	IRGDM (n=18)	p
Umbilical S/D median (Q1-Q3)	2.38 (2.12-2.80)	2.38 (2.23-2.68)	0.939
Umbilical PI median (Q1-Q3)	0.87 (0.78-1.03)	0.88 (0.77-0.92)	0.780
MCA S/D median (Q1-Q3)	4.87 (3.74-6.13)	4.56 (4.19-5.94)	0.962
MCA PI median (Q1-Q3)	1.68 (1.44-1.90)	1.60 (1.27-1.70)	0.204
Uterine S/D median (Q1-Q3)	2.12 (1.90-2.97)	1.71 (1.47-1.90)	0.001
Uterine PI median (Q1-Q3)	0.801 (0.65-1.11)	0.63 (0.49-0.70)	0.007
CPR median (Q1-Q3)	1.94 (1.70-2.18)	1.78 (1.32-2.28)	0.519
CPUR median (Q1-Q3)	2.27 (1.49-2.91)	2.56 (1.93-4.72)	0.098

DRGDM: Diet-regulated gestational diabetes mellitus, IRGDM: Insulin- regulated gestational diabetes mellitus, S/D: Systolic/diastolic, PI: Pulsatility index, CPR: Cerebro-placental ratio, CPUR: Cerebro-placental-uterine ratio

marked by increased resistance in the fetoplacental vascular bed.[19] Doppler indices are used for fetal monitoring on the basis of this. But as the weeks of pregnancy go by, end-diastolic velocity rises, which is in line with the gradual reduction in fetoplacental blood flow impedance brought on by fetal and placental vascular and hemodynamic alterations.[20] This is demonstrated by the steady decline in PI and the systolic/diastolic (S/D) ratio over the course of pregnancy. When fetal growth restriction (FGR) and/or hypertension complicate a pregnancy, UA Doppler testing is especially helpful. For these pregnancies, Doppler ultrasonography is advised as the main monitoring method.[21,22] Doppler examination reveals the cardiovascular response of the fetus to progressive hypoxia and acidosis and helps distinguish small but structurally normal fetuses from those compromised by placental insufficiency. In general, a Doppler index for gestational age> of 95% should not be considered reassuring. Low CPR indicates redistribution of fetal blood flow (brain protective). Several thresholds for CPR have been proposed to predict an unfavorable outcome (<1, <1.05, ≤1.08).[23] In the PORTO study, which included singleton pregnancies with FGR, the rate of serious neonatal outcomes with low CPR (<1) was 18 percent (27 of 146) versus 2 percent (14 of 735).[24] However, fetuses of mothers with GDM exhibit expanded placental vasculature, increased UA diameter, and aberrant Wharton's jelly, leading to a reduction in the connective tissue component. As a result, there is a notable reduction in flow impedance in the UA and UA PI.[25] These results may support the following hypothesis: CPR as a ratio between MCA and UA PI is not predictive of perinatal outcome, which is due to the possible influence of GDM on birth. On the other hand, regular assessment of CPR or MCA in a low-risk cohort with a minimal occurrence of adverse outcomes is not advisable, as it would result in a significant number of false-negative and false-positive findings, consequently leading to an escalation of unnecessary and potentially detrimental interventions.[23] A meta-analysis has demonstrated that CPR is associated with adverse perinatal outcomes in pregnancies complicated by GDM. However, the same study emphasized that CPR should not be considered a universal screening tool for pregnancy complications.[26]

The literature suggests that Doppler indices can predict high-risk pregnancies and their fetuses that are small for their age, especially with regard to maternal hypertensive states.[27] However, there are confounding results on Doppler indices of pregnant women with GDM who fall into the high-risk category and are diagnosed and treated without placental insufficiency. Therefore, Doppler ultrasound measurements are important for an accurate understanding of the existing literature regarding prognostic accuracy and prediction of adverse perinatal outcomes due to GDM.

The optimal timing of delivery in GDM remains a matter of debate. Prolonging pregnancy beyond 38 weeks may increase the risk of shoulder dystocia, while its impact on cesarean delivery rates remains unclear.[28] WHO recommends that patients in whom GDM is the only abnormality should be delivered by 41 weeks of gestation. However, fetal well-being testing is recommended by physicians for this procedure.[29] The clinical outcomes of our investigation contribute to the evaluation of fetal well-being at term in high-risk pregnancies. This study also investigated the CPUR value for GDM among Doppler indices. Previous studies have shown that CPUR score at >40+0 weeks is predictive of adverse perinatal outcomes and invasive deliveries in low-risk pregnancies.[30] In a study evaluated along with GDM, some Doppler parameter was found to be associated with high blood glucose.[16] However, the extent to which CPUR can be used to optimize labor management needs further investigation in prospective interventional studies.

Limitations

One of limitations was although our study has a sample size higher than the minimum required to achieve a power of 0.95, further studies with larger cohorts may help to more robustly confirm the validity of our findings. However, the association between MCA PI was statistically significant even in a small cohort. The benefit is limited in patients with

GDM when it comes to making decisions about timing and mode of delivery. Further evaluation of the use of Doppler in pregnancies complicated by diabetes mellitus requires the use of standardized protocols.

CONCLUSION

This study investigated the impact of fetal Doppler parameters on pregnancy outcomes in women with GDM. The findings revealed that MCA PI was the only Doppler parameter that significantly differed between GDM and control groups. No correlation was observed between perinatal outcomes and other Doppler indices, including UA, CPR, and CPUR. However, CPUR was positively correlated with the second-hour 100-g OGTT result. While Doppler ultrasound is a valuable tool for monitoring high-risk pregnancies, its application in GDM should be approached with caution. Further research is needed to better understand the influence of GDM on fetal Doppler indices and refine clinical decision-making in this population.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Etlik Zübeyde Hanım Gynaecology and Obstetrics Training and Research Hospital Clinical Practice Ethics Committee (Date: 31/03/2022, Decision No: 2022/37).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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