Original Article

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Comparison of Doppler Flow Parameters of Foetal Middle Cerebral Artery in Pregnancy with Gestational Diabetes versus Normal Pregnancy: A Cohort Study

Obstetrics and Gynaecology Section

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ABSTRACT

Introduction: Gestational Diabetes Mellitus (GDM) affects maternal placental blood flow. As a compensatory mechanism for placental haemodynamic changes, blood flow is redistributed from peripheral vessels to the brain. This re-distribution can be evaluated using doppler Ultrasonography (USG) measurements of the umbilical arteries and foetal middle cerebral arteries.

Aim: To compare doppler flow parameters {Pulsatility Index (PI), Resistance Index (RI), Peak Systolic Velocity (PSV), Systolic-To-Diastolic (S/D)} of the foetal Middle Cerebral Artery (MCA) in pregnancy with gestational diabetes versus normal pregnancy, and to compare pregnancy outcomes in GDM versus non-GDM women.

Materials and Methods: A prospective cohort study was conducted from November 2019 to November 2021 at the Department of Obstetrics and Gynaecology, Department of Radiology, and Department of Paediatrics in Tertiary care centre of New Delhi, India. All pregnant women attending the Antenatal Care Outpatient Department (ANC OPD) upto 34 weeks with an Oral Glucose Tolerance Test (OGTT) ≥140 mg/dL were defined as cases, and those with OGTT <140 mg/dL were taken as controls. All patients underwent doppler USG after 34 completed weeks, and doppler flow parameters (PI, RI, PSV, S/D ratio) were noted. Patient outcomes were recorded, including maternal outcomes such as mode of delivery, pregnancy-induced hypertension, polyhydramnios, stillbirth, and Intrauterine Death (IUD). Foetal outcomes such as APGAR (Activity Pulse Grimace Appearance Respiration) score, hypoglycemia, hyperbilirubinemia, admission to the Neonatal Intensive Care Unit (NICU), Respiratory Distress Syndrome (RDS), and neonatal death were also documented. Appropriate statistical tests were used for the statistical analysis (Chi-square test, Fisher's exact test and Wilcoxon-Mann-Whitney test).

Results: The mean age of GDM and non-GDM women was 27.40±3.57 years and 26.20±3.29 years, respectively. Among GDM women, 14 patients (31.1%) were primigravida, while there were 15 patients (33.3%) who were primigravida among non-GDM women. MCA PI was significantly higher in cases (1.79±0.36) compared to controls (1.65±0.19) (p-value=0.023), whereas MCA PSV was significantly lower in cases (45.86±2.17) than in controls (50.10±1.62) (p-value=0.001). Pregnancy-induced hypertension was observed in 28.9% of GDM women and 6.7% of non-GDM women, with the difference being statistically significant (p-value=0.006). There was a statistically significant difference between APGAR scores at 1 minute (p-value=0.030). However, there was no statistically significant difference in the APGAR scores at 5 minutes (p-value=0.242).

Conclusion: Foetal MCA PI on doppler velocimetry was significantly higher in the GDM group, and MCA PSV was significantly lower in the study group, while MCA RI and MCA S/D ratio were not significantly different. Maternal complications were more common in GDM compared to non-GDM.

Keywords: Blood flow, Pregnancy-induced hypertension, Pulsatility index, Resistance index

INTRODUCTION

The GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [1]. It is the most common medical complication and metabolic disorder of pregnancy, occurring in 1-14% of pregnant women depending on the population and diagnostic criteria used [2].

A study has shown that higher cord serum erythropoietin levels in amniotic fluid are associated with foetal hypoxia in conditions such as Pre-Eclampsia (PE), diabetes, and isoimmunised high-risk gestations [3]. In GDM, chronic intrauterine hypoxia can lead to polycythemia, a condition characterised by increased red blood cell production outside the bone marrow. Polycythaemia results in decreased foetal blood flow velocity due to increased blood viscosity. Therefore, changes in MCA-PSV are expected in women with GDM, reflecting a decrease in foetal blood flow velocity [4].

Hyperglycaemia during pregnancy can affect maternal placental blood flow. As a compensatory mechanism to placental haemodynamic changes, blood flow is re-distributed from peripheral vessels to the brain. This re-distribution can be evaluated using doppler USG measurements of the umbilical arteries and foetal middle cerebral arteries [5]. Changes in doppler USG findings may occur in conditions such as intrauterine growth restriction, anaemia, hypoxemia, and pre-eclampsia [6]. However, the assessment of such changes in GDM patients has produced controversial results [7].

The objective of the present study was to compare doppler flow parameters (PI, RI, PSV, SD ratio) of the foetal MCA between pregnancies with gestational diabetes and normal pregnancies.

MATERIALS AND METHODS

A prospective cohort study was conducted from November 2019 to November 2021 at the Department of Obstetrics and Gynaecology, Department of Radiology, and Department of Paediatrics of the University College of Medical Sciences, New Delhi, India. Ethical clearance was obtained from the Institutional Ethics Committee (IEC-HR/2019/41/77), and informed written consent was taken from all participants.

Inclusion criteria: Antenatal patients coming to the Outpatient Department (OPD) for registration were included in this study. Cases

were defined as pregnant women up to 34 weeks of gestation (POG) with an OGTT result of ≥140 mg/dL. Controls were defined as all pregnant women up to 34 weeks of gestation with an OGTT result of <140 mg/dL.

The following criteria were applied for inclusion:

1. Pregnant women aged 18 or older with a gestational age of up to 34 weeks.
2. Singleton pregnancy.
3. Absence of foetal malformation or anomaly.
4. No maternal conditions affecting uteroplacental blood flow, such as smoking or hypertension.

Exclusion criteria: Those pregnant women with a previous history of Type 2 diabetes mellitus or chronic hypertension, history of any acute medical illness, such as fever, infection, or evidence of ongoing inflammation were excluded from the study.

Procedure

The OGTT was conducted during the first prenatal visit, and a repeat test was performed at 24-28 weeks if the initial test was negative. All antenatal patients diagnosed with GDM were followed-up at two-week intervals until 32 weeks, and then at weekly intervals until delivery. Antenatal patients in the control group were followed-up at four-week intervals until 32 weeks, then at two-week intervals until 36 weeks, and finally at weekly intervals after 36 weeks.

Doppler ultrasonographic assessment: To evaluate various blood flow indices in the MCA, all recruited women underwent doppler USG after completing 34 weeks of gestation. The 2D ultrasound examinations were performed using a colour doppler flow ultrasound machine, model ECUBE 7® by Alpinion, Korea. The transabdominal USG employed a convex transducer with a frequency of 16 MHz. The axial section of the foetal brain was focused on, and the MCA closer to the probe was identified in each case. Doppler parameters such as PI, PSV, RI, and S/D ratio were determined. Foetal biometry was also assessed using colour flow mapping in the transverse view of the foetal brain. The doppler beam was directed along the MCA, and the sample volume was placed on the proximal section with an angle of insonation <30°. Recordings were made in the absence of foetal breathing or body movements. PI and RI were measured both manually and using the auto mode over three consecutive cycles. A single radiologist with more than 15 years of experience took all measurements. Each measurement was taken twice, and the average of both readings was considered. Patient outcomes were noted, including maternal outcomes such as the mode of delivery, pregnancy-induced hypertension, polyhydramnios, stillbirth/IUD. Foetal outcomes such as APGAR score, hypoglycemia, hyperbilirubinemia, admission to NICU, RDS, and neonatal death were also recorded.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 10.1, SPSS Inc., Chicago, IL, USA) and MedCalc 8.0 (Broekstraat, Belgium) statistical software. An appropriate statistical test was used for the analysis, including the Chi-square test, Fisher's exact test, and Wilcoxon Mann-Whitney test.

RESULTS

A total of 45 pregnant women with OGTT values greater than or equal to 140 mg/dL were diagnosed with GDM and labeled as cases (n=45). An equal number of pregnant women with OGTT values less than 140 mg/dL were labeled as the control group (n=45). The mean age of GDM and non-GDM women was 27.40±3.57 years and 26.20±3.29 years, respectively. A significantly higher BMI was noted in cases compared to controls, with a p-value of 0.001. In 10 cases (10/45), a past history of GDM was present compared to controls (3/45), although the p-value was not significant [Table/Fig-1].

Characteristics	GDM women (Cases) n=45	Non-GDM Women (Control) n=45	p-value (Chi-square test)
Maternal age (years)	Mean age 27.40±3.57	Mean age 26.20±3.29	0.170
Multiparity ≥2	16 (35.6%)	6 (13.4%)	0.082
Body Mass Index(BMI) (kg/m^2)	22.25±1.91	20.71±1.65	**0.001**
Past history of GDM	10 (22.2%)	3 (6.7%)	**0.036**
Family history of GDM	12 (26.7%)	6 (13.3%)	0.114

[Table/Fig-1]: Comparison of demographics between GDM and non-GDM.

Out of all the USG doppler parameters measured, MCA PI and MCA PSV showed statistically significant differences between the two groups. However, other parameters like MCA RI and MCA S/D ratio showed no statistically significant difference between the groups, but MCA RI values were higher in cases, and MCA S/D ratio values were lower in cases compared to controls [Table/Fig-2].

Parameters	Cases n=45	Controls n=45	p-value	Test performed
MCA PI Mean±SD	1.79±0.36	1.65±0.19	**0.0234**	Wilcoxon Mann Whitney U test
MCA RI Mean±SD	0.78±0.15	0.76±0.20	0.593	Wilcoxon Mann Whitney U test
MCA PSV (cm/sec) Mean±SD	45.86±2.17	50.10±1.62	**<0.001**	Wilcoxon Mann Whitney U test
MCA S/D ratio Mean±SD)	4.36±0.95	4.65±0.74	0.1098	Wilcoxon Mann Whitney U test

[Table/Fig-2]: Distribution of USG Doppler parameters of fetal MCA in cases and controls.

Pregnancy-induced hypertension was observed in 28.9% of GDM women and 6.7% of non-GDM women (p-value=0.006). Premature rupture of membranes was observed in 33.3% of GDM women, whereas the incidence among non-GDM women was 8.9% (p-value=0.004) [Table/Fig-3].

Outcome	Cases	Controls	Total	p-value	Test performed
PIH					
Yes	13 (28.9%)	3 (6.7%)	16 (17.8%)	**0.006**	Chi-Squared Test
No	32 (71.1%)	42 (93.3%)	74 (82.2%)		
PROM					
Yes	15 (33.3%)	4 (8.9%)	19 (21.1%)	**0.004**	
No	30 (66.7%)	41 (91.1%)	71 (78.9%)		
Polyhydramnios					Fisher's-Exact Test
Yes	5 (11.1%)	0 (0.0%)	5 (5.6%)	**0.056**	
No	40 (88.9%)	45 (100.0%)	85 (94.4%)		
Macrosomia					
Yes	4 (8.9%)	0 (0.0%)	4 (4.4%)	**0.117**	
No	41 (91.1%)	45 (100.0%)	86 (95.6%)		
Stillbirth/Intra-uterine Death (IUD)					
Yes	1 (2.2%)	0 (0.0%)	1 (1.1%)	1.000	
No	44 (97.8%)	45 (100.0%)	89 (98.9%)		
Postpartum complications					
Atonic PPH	3 (6.7%)	3 (6.7%)	6 (6.7%)	1.000	Fisher's-Exact Test
No	42 (93.3%)	42 (93.3%)	84 (93.3%)		

[Table/Fig-3]: Comparison of maternal outcomes in cases and controls.

There was no statistically significant difference (p-value=0.064) in the mode of termination of pregnancy between the two groups [Table/Fig-4]. In the GDM group, 18 out of 45 participants (40%) required induction of labour, whereas in the control group, 11 out of 45 participants (24.4%) required induction of labour.

Additionally, in the GDM group, eight out of 45 participants (17.8%) had an APGAR score of less than seven at one minute compared to only one out of 45 participants (2.2%) in the control group [Table/Fig-5].

MOD	Group			Chi-squared test	
	Case	Control	Total	$\chi 2$	p-value
NVD	9 (20.0%)	13 (28.9%)	22 (24.4%)	5.501	0.064
NVD with Episiotomy	22 (48.9%)	27 (60.0%)	49 (54.4%)		
LSCS	14 (31.1%)	5 (11.1%)	19 (21.1%)		
Total	45 (100.0%)	45 (100.0%)	90 (100.0%)		

[Table/Fig-4]: Comparison of mode of delivery in cases and controls.
NVD: Normal vaginal delivery ; LSCS: Lower section caesarean surgery

Neonatal outcomes	GDM	Non-GDM	Total	p-value	Test used
APGAR score at 1 minute					
</=7	8 (17.8%)	1 (2.2%)	9 (10.0%)	**0.030**	Wilcoxon Mann Whitney U Test
>7	37 (82.2%)	44 (97.8%)	81 (90.0%)		
APGAR score at 5 minutes					
</=7	3 (6.7%)	0 (0.0%)	3 (3.3%)	0.242	Wilcoxon Mann Whitney U Test
>7	42 (93.3%)	45 (100.0%)	87 (96.7%)		
Adverse outcomes					
NICU admission	14 (31.1%)	11 (24.4%)	25 (27.8%)	0.480	Chi-square Test
Hypoglycemia	12 (26.7%)	0 (0.0%)	12 (13.3%)	**<0.001**	
Hyperbilirubinemia	3 (6.7%)	0 (0.0%)	3 (3.3%)	0.242	Fisher's-Exact Test
Neonatal death	0	0	0	0	
Respiratory Distress Syndrome (RDS)	2 (4.4%)	0	2 (2.2%)	0.32	

[Table/Fig-5]: Comparison of other neonatal outcomes between GDM and non-GDM.

DISCUSSION

Gestational Diabetes Mellitus (GDM) is one of the most common complications in pregnancies. Doppler velocimetry is an important method in the management of gestational diabetes as it relies on the oxygen metabolism in the maternal-placental-foetal balance [8]. However, studies on GDM have reported varied results regarding the application of doppler indices in the assessment of diabetes-associated pregnancies [9,10]. In the present study, there was no significant difference in age between the two groups. A study conducted by Liu X et al., reported a higher risk of developing gestational diabetes in advanced age groups (35-39 years and ≥40 years) compared to women in the 25-29 years age group [11].

Among women with GDM, 35.6% were multiparous, while only 13.4% of non-GDM women were multiparous. A cross-sectional study by Tian Y et al., involving 14,196 women, showed that fasting plasma glucose levels increased with an increased number of live births (p<0.001), and multiparity was associated with an increased risk of GDM [12]. There was a significant difference between the two groups in terms of BMI (kg/m^2) (t=4.085, p<0.001), with the mean BMI (kg/m^2) being highest in the case group. Fatthy WM et al., showed that a BMI >30 was significantly associated with the risk of developing GDM [13]. A systematic review and meta-analysis identified a history of macrosomia, stillbirth, and GDM as the most common risk factors for GDM [14].

In the doppler flow parameters, the mean (SD) MCA PI was higher in the study group compared to the control group (p-value=0.0234). This finding is consistent with the study conducted by Shabani Zanjani M et al., in which the left foetal MCA PI was significantly higher in the GDM group (2.07, SD=0.07) compared to the normal pregnant women group (1.85, SD=0.74) [5]. Another study by Wei Z et al., also showed a significantly higher MCA PI in the experimental group (p-value≤0.001) [15]. D'Ambrosi F et al., similarly concluded that MCA PI was significantly higher in the GDM group compared to the non-GDM group [16]. These findings contrast with a study that failed to show any association between maternal diabetes and abnormal doppler indices in foetuses [17]. In normal pregnancy, the MCA PI value should decrease with advancing gestational age, so a higher MCA PI in these various studies reflects a foetal brain-sparing effect due to placental insufficiency [18].

In the current study, the MCA RI was higher in cases, but no significant difference (p-value=0.593) was noted between the two groups. These findings contrast with the study conducted by Liu F et al., in which significantly lower values of MCA RI were noted in the GDM group than in normal controls {0.70 (SD=0.06) vs 0.78 (SD=0.02, p-value≤0.001)} [19]. They suggested that lower resistance in MCA is the result of the brain-sparing effect in pregnancy complicated by GDM. Another study conducted by Fatihoglu E et al., in 60 GDM patients showed no difference in the MCA RI value between both groups [20]. In 2019, Refaat MM et al., conducted a colour doppler evaluation of cerebral-umbilical pulsatility indices and ratio among 40 patients with high-risk pregnancies classified into two groups: PE and diabetic groups. They concluded that in a relatively well-controlled diabetic pregnancy not complicated by PE or FGR, the values of colour doppler indices are similar to those in a normal pregnancy [21].

In the present study, although the MCA PSV was much lower in cases than in controls (45.86±2.17 cm/sec in GDM and 50.10±1.62 in non-GDM patients), it had a p-value of <0.001, which was statistically significant. Dantas AMA et al., conducted a study and noted that the median MCA PSV was 1.02 in the GDM group and 1.08 in the control group. The doppler USG measurement for MCA PSV was lower in the GDM group, although no statistically significant difference was found [22]. Fatihoglu E et al., also noted that MCA PSV was significantly lower in the GDM group (28 cm/s vs. 32 cm/s, p-value=0.037), and a value <35.5 cm/s can predict GDM with a sensitivity of 41% and specificity of 78.3% [20]. The low MCA PSV in the GDM group, as seen in the current study, reflects the development of hyperviscosity due to polycythaemia in response to hypoxia. However, in a study of 169 GDM pregnancies conducted by Leung WC et al., the usefulness of doppler parameters in predicting abnormal pregnancy outcomes was not found [4].

The authors found no significant difference in the MCA S/D ratio between the GDM and non-GDM groups. This concurs with the findings of another study, which also showed no difference in the S/D ratio between the two groups [20]. In the present study, 8.9% of GDM women had macrosomia, but it was not statistically significant (p-value=0.117). Additionally, Dantas AMA et al., concluded that there was no correlation between MCA PSV and maternal hyperglycaemia and foetal macrosomia [22]. The authors were unable to establish any correlation, as larger studies are needed to associate doppler parameters with predicting polyhydramnios and intrauterine death.

Fadda GM et al., conducted a PI assessment of the umbilical artery, foetal descending thoracic aorta, and foetal MCA and noted a correlation of neonatal hypoglycaemia (p-value≤0.001) with abnormal doppler measurements [23]. This finding was consistent with the current study, which also established a positive association of neonatal hypoglycaemia in GDM women compared to non-GDM women. Fadda GM et al., found a significant association of neonatal hyperbilirubinemia (p-value≤0.001) in the GDM group with abnormal PI doppler values [23].

In a cohort study on 103 diabetic women to compare MCA and UA doppler assessments for evaluating foetal well-being in pre-gestational or GDM pregnancies, although both umbilical and MCA doppler had some association with neonatal outcomes, the sensitivity for predicting adverse neonatal outcomes was found to be low. This study concluded that the UA doppler assessment is a better predictor of neonatal outcomes than the MCA doppler [24].

However, this study contributes to the limited body of literature comparing foetal brain haemodynamic indices in GDM and non-GDM pregnancies using doppler changes in the MCA and their effect on pregnancy outcomes.

Limitation(s)

The present study has several limitations that should be acknowledged. Firstly, the sample size was small, which resulted in low statistical power for some analyses. Therefore, further research with a larger sample size is necessary to confirm and strengthen the findings. Secondly, the doppler assessment of the foetus was conducted in patients with GDM who were under treatment, and the results may vary depending on the level of glycaemic control achieved by the patients. It is important to consider this factor when interpreting the results.

CONCLUSION(S)

The findings suggest a potential role for doppler assessment of the MCA in predicting adverse outcomes in GDM pregnancies. Therefore, the authors recommend that antenatal assessments of gestational diabetic pregnancies should include doppler parameters in the third trimester. However, further studies with a larger sample size are needed to validate the role of doppler velocimetry and identify adverse haemodynamic parameters in diabetic pregnancies.

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