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Original article

Doppler flow parameters of fetal middle cerebral artery in gestational diabetes: a comparative analysis with normal pregnancy and correlation with pregnancy outcome

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Abstract

Background: The objectives of this study were to compare Doppler flow parameters of the fetal middle cerebral artery in pregnancy with gestational diabetes versus normal pregnancy, and to study the correlation of Doppler flow parameters of fetal middle cerebral artery (MCA) with pregnancy outcome in gestational diabetes mellitus.

Methods: All pregnant women attending antenatal care (ANC) up to 34 weeks with oral glucose tolerance test (OGTT) ≥ 140mg/dl were defined as cases, and those with OGTT < 140 mg/dl were taken as controls. All patients underwent Doppler ultrasound after 34 completed weeks, and Doppler flow parameters [Pulsatility Index (PI), Resistance Index (RI), peak systolic velocity (PSV), and Systolic Diastolic (S/D) ratio] were noted. Pregnancy outcomes among were noted.

Results: MCA PI and MCA PSV showed a statistically significant difference between both groups with p= 0.0234 and P <0.001, respectively. MCA PI was significantly higher in cases compared to controls, whereas MCA PSV was significantly lower in cases than in controls. MCA RI values were higher in cases. In addition, MCA S/D ratio values were lower in controls compared to cases. Fetal MCA PI on Doppler velocimetry were significantly higher in the GDM group, and MCA PSV was significantly lower in the study group, MCA RI and MCA S/D ratio were not significantly different. Maternal complications were found to be more frequent in GDM compared to non-GDM. MCA PSV was significantly associated with development of PIH in GDM. The rate of NICU admission, RDS, & hypoglycemia were significantly higher in babies of GDM mothers.

Conclusion: Our findings suggest a potential role for Doppler assessment of MCA in predicting adverse outcomes in GDM pregnancies. Therefore, we recommend that antenatal assessments of gestational diabetic pregnancies should include Doppler parameters in the third trimester.

Keywords: Gestational diabetes; Blood flow, Doppler Fetus, Middle cerebral artery, Pulsatility Index

Introduction

Gestational Diabetes Mellitus (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).

Studies have shown that higher cord serum erythropoietin levels in amniotic fluid are associated with fetal hypoxia in conditions such as Pre-eclampsia (PE), diabetes, and iso-immunized high-risk gestations (3). In GDM chronic intrauterine hypoxia can lead to polycythemia, a condition characterized by increased red blood cell productions outside the bone marrow. Polycythemia results in decreased fetal blood flow velocity due to increased blood viscosity. Therefore, changes in middle cerebral artery peak systolic velocity (MCA- PSV) are expected in women with GDM, reflecting a decrease in fetal blood flow velocity (4).

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suggesting that interactions may influence endometrial responsiveness (6, 7).

Hyperglycaemia during pregnancy can affect maternal placental blood flow. As a compensatory mechanism to placental hemodynamic changes, blood flow is redistributed from peripheral vessels to the brain. This redistribution can be evaluated using Doppler ultrasonography (USG) measurements of the umbilical arteries and fetal middle cerebral arteries (5) Changes in Doppler USG findings may occur in conditions such as intrauterine growth restriction, anemia, hypoxemia and preeclampsia (6). However, the assessment of such changes in GDM patients has produced controversial results (7).

The objective of the present study is to compare Doppler flow parameters [Pulsatility Index (PI), Resistance Index (RI), PSV, Systolic Diastolic (S/D) ratio] of the fetal middle cerebral artery between pregnancies with gestational diabetes and normal pregnancies. Additionally, the correlation between Doppler flow parameters of the fetal MCA and pregnancy outcomes in gestational diabetes mellitus is also investigated.

Materials & Methods

This study was a Case-Control Study. Ethical clearance was obtained from the institutional Ethics Committee, and informed written consent was taken from all participants.

Cases were defined as pregnant women up to 34 weeks of gestation with an oral glucose tolerance test (OGTT) result of ≥140 mg/dl. Controls were defined as all pregnant women up to 34weeks of gestation with an OGTT result of <140 mg/dl. The inclusion following criteria included pregnant women aged 18 or older with gestational age of up to 34 weeks, singleton pregnancy, Absence of fetal malformation or anomaly, and no maternal conditions affecting uteroplacental blood flow, such as smoking or hypertension. Pregnant women with a previous history of Type 2 diabetes mellitus or chronic hypertension and women with history of any acute medical illness, such as fever, infection, or evidence of ongoing inflammation were excluded.

To evaluate various blood flow indices in MCA, all recruited women underwent Doppler USG after completing 34 weeks of gestation. 2D ultrasound examinations were performed using a color Doppler flow ultrasound machine, model ECUBE 7®; Alpinion, Korea. The transabdominal ultrasonography employed a convex transducer with a frequency of 16 MHz. The axial section of the fetal brain was focused, 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. Fetal biometry was also assessed using color flow mapping in the transverse view of the fetal brain. The Doppler beam was directed along the MCA, and the sample volume was placed on the proximal section with an angle of insolation <30°. Recordings were made in the absence of fetal breathing or body movements. PI and RI were measured both manually as well as using the auto mode over three consecutive cycles. Patient outcomes were noted, including maternal outcomes such as mode of delivery, pregnancy induced hypertension, polyhydramnios, stillbirth, and intrauterine death (IUD). Fetal outcomes such as birth weight, APGAR score, hypoglycemia, hyperbilirubinemia, admission to neonatal intensive care unit (NICU) respiratory distress syndrome (RDS) and neonatal death were also recorded.

Results

From November 2019 to November 2021, a total of 45 pregnant women with OGTT values greater than or equal to 140 mg/dl were diagnosed with GDM and labelled as cases (n=45), while an equal number of pregnant women with OGTT values less than 140 mg/dl were labelled as control group (n=45). Various demographic characteristic parameters between the two study groups are compared in Table 1.

Table 1. Comparison of demographics in pregnant women with oral glucose tolerance test result of ≥140 mg/dl (case) and pregnant women with an OGTT result of <140 mg/dl (control).

Characteristics	**Cases (n=45) Mean ± SD**	**Controls (n=45) Mean ± SD**	**P value**
Maternal age	27.4 ±3.5	26.20 ±3.2	0.17
BMI* (kg/m^2)	22.2± 1.9	20.7± 1.6	0.001
Past history of GDM**, n (%)	10 (22.2)	3 (6.7)	0.03
Multiparity ≥2, n (%)	16 (35.6)	6 (13.4)	0.08

*BMI, Body mass index;**GDM, Gestational diabetes.

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USG Doppler parameters for fetal MCA were performed on both GDM and non-GDM women after 34 completed weeks. Parameters such PI, RI, PSV, and S/D ratios were measured. Out of all the USG Doppler parameters measured, MCA PI and MCA PSV showed statistically significant differences between the two groups, with p-values of 0.023 and <0.001, respectively. MCA PI was significantly higher in the cases compared to controls. 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 2).

Pregnancy-induced hypertension was seen in 28.9% of GDM women and 6.7% of non-GDM women, and the difference was statistically significant (p=0.006) between the two groups. Premature rupture of membranes was seen in 33.3% of GDM women, whereas the incidence among non GDM women was 8.9% which, was statistically significant (p value= 0.004). 11.1% of the GDM women had polyhydramnios, whereas none of the non-GDM women had polyhydramnios. There was no statistically significant difference (p=0.056) between the two groups. Macrosomia and stillbirth were only seen in 8.9% and 2.2% of GDM women (Table 3).

Table 2. Distribution of USG Doppler parameters of fetal Middle Cerebral Artery in pregnant women with oral glucose tolerance test result of ≥140 mg/dl (case) and pregnant women with an OGTT result of <140 mg/dl (control).

	Cases (n=45) Mean± SD	Control (n= 45) Mean± SD	P value
Middle Cerebral Artery Pulsatility Index	1.8±0.4	1.7± 0.2	0.023
Middle Cerebral Artery Resistance Index	0.8±0.2	0.8±0.2	0.593
Middle Cerebral Artery Resistance systolic velocity (cm/sec)	45.9±2.2	50.1±1.6	<0.001
Middle Cerebral Artery Systolic Diastolic ratio	4.4± 0.9	4.7± 0.7	0.109

Table 4. Comparison of maternal outcomes in pregnant women with oral glucose tolerance test result of ≥140 mg/dl (case) and pregnant women with an OGTT result of <140 mg/dl (control).

	Cases n (%)	**Controls n (%)**	**Total n (%)**	**P value**
Pregnancy Induced Hypertension				
Yes	13 (28.9)	3 (6.7)	16 (17.8)	0.006
No	32 (71.1)	42 (93.3)	74 (82.2)	
Premature Rupture Of Membranes				
Yes	15 (33.3)	4 (8.9)	19 (21.1)	0.004
No	30 (66.7)	41 (91.1)	71 (78.9)	
Polyhydramnios				
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/ 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
No	42 (93.3)	42 (93.3)	84 (93.3)	

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Table 5. Comparison of other neonatal outcomes in pregnant women with oral glucose tolerance test result of ≥140 mg/dl (case) and pregnant women with an OGTT result of <140 mg/dl (control).

	Cases n (%)	Control n (%)	P value
APGAR (score at 1 minute)			
</=7	8(17.8)	1(2.2)	0.03
>7	37 (82)	44 (97.8)	
APGAR (score at 5 minutes)			
</=7	3(6.7)	0 (0)	0.24
>7	42(93.3)	45(100)	
Adverse outcomes			
NICU* admission	14(31.)	11 (24.4)	0.48
Hypoglycemia	12(26.7)	0 (0)	<0.001
Hyperbilirubinemia	3 (6.7)	0 (0)	0.24

* NICU, neonatal intensive care unit

88.9% of non-GDM women had a normal delivery, and only 21.1% had a caesarean section. 31.1 % of GDM women underwent caesarean section. There was no statistically significant difference (p=0.064) in the mode of termination of pregnancy between the two groups. 40.0% of the participants in the GDM group required Induction of labour compared to 24.4% of the participants in the control group (Table 4). 17.8% of GDM women had an APGAR score of less than 7 at 1 minute for their neonates, whereas only 2.2 % of non-GDM women had an APGAR score of less than 7 at 1

Minute.

There was a statistically significant difference between APGAR scores at 1 minute (p=0.030). However, there was no statistically significant difference in the APGAR scores at 5 minutes (p= 0.242). 27.8% of all neonates were admitted to NICU.

Among the neonates of GDM women, 31.1% were admitted to NICU while 24.4% of neonates of non-GDM women were admitted to NICU. No statistically significant difference (p=0.480) was found between the NICU admission of the neonates in the two groups (p<0.001). 6.7% of neonates of GDM women had hyperbilirubinemia, whereas none of the neonates of non-GDM women developed hyperbilirubinemia. No statistically significant difference (p=0.24) was found in the occurrence of hyperbilirubinemia between the two groups (Table 5).

Discussion

Gestational diabetes mellitus is one of the most common complications in pregnancies. Previous studies have highlighted significant changes in blood flow velocity in the umbilical artery (UA) and fetal.

MCA in conditions such as intrauterine growth restriction, anemia, hypoxemia, and pre-eclampsia. Doppler velocimetry is an important method in the management of gestational diabetes, as it relies on the oxygen metabolism in the maternal-placental-fetal balance (8) However, studies on GDM have reported varied results regarding the application of Doppler indices in the assessing of diabetes-associated pregnancy (9, 10).

The objective of our case-control study was to establish a correlation between Doppler flow parameters of the fetal middle cerebral artery and gestational diabetes mellitus after 34weeks of gestation. The mean age of GDM women was 27.4 ± 3.6 yrs, while the mean age of non-GDM women was 26.2 ± 3.3 yrs. 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 25-29 years' age group (11).

Among GDM women 35.6% were multiparous, while only 13.4% of non-GDM women were multiparous. Although the difference between the two groups was not statistically significant (p=0.082), a cross-sectional study by Tian 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

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(Kg/m²) (t = 4.085, p = <0.001), with the mean BMI (Kg/m²) being highest in the case group. Fatthy et al showed that BMI> 30 was significantly associated with the risk of developing GDM (13) In the GDM group, 22.2% of women had a previous history of GDM compared to only 6.7% of the non-GDM women, with a statistically significant difference (p=0.036) between the two groups. 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 (1.8 ± 0.4) in the study group compared to control group (1.7 ± 0.2) and this difference was significant (p value=0.0234). This finding is consistent with the study conducted by Zanjani et al in which left fetal MCA PI was significantly higher in the GDM group (2.1, SD=0.1) compared to the normal pregnant women group (1.9, SD=0.7). 5 Another study by Wei et al in 2021 also a significantly higher MCA PI in the experimental group (p=<0.001) (15). D'Ambrosi et al similarly concluded that MCA PI was significantly higher in the GDM group compared to the non-GDM group (16) interestingly, the results of a multivariate analysis confirmed that an MCA PI above the 90th percentile of the normal value was almost 11 times more common. These findings contrast with randomized control studies that failed to show any association between maternal diabetes and abnormal Doppler indices in fetuses. (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 fetal brain-sparing effect due to placental insufficiency (18).

In the current study, the MCA RI was higher in cases but had no significant difference (p=0.593) with a mean (SD) of 0.78 (0.2) in the study group and 0.76 (0.2) in the control group. These findings contrast with the study conducted by Fang et al in which significantly lower values of MCA RI were noted in the GDM group than in normal controls [0.70 (SD=0.1) vs 0.8 (SD=0.1, p=<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, Medhat and et al, conducted a color Doppler evaluation of cerebral-umbilical pulsatility indices and ratio among 40 patients with a high-risk pregnancies classified into two groups: preeclampsia and diabetic group. They concluded that in a relatively well-controlled diabetic pregnancy not complicated by preeclampsia or FGR, the values of color Doppler indices are similar to those in a normal pregnancy (21).

In our study although MCA PSV was much lower in cases than in controls (45.9 ± 2.2 cm/sec in GDM and 50.1 ± 1.6 in non-GDM patients), It had a p value of <0.001, which was statistically significant. Dantas et al conducted a study and noted that the median MCA PSV was 1.0 in the GDM group and 1.1 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 et al also noted that MCA PSV was significantly lower in the GDM group (28 cm/s vs 32 cm/s p=0.037), and a value <35.5 cm/s can predict GDM with a sensitivity of 41% and specificity of 78.3% Low MCA PSV in the GDM group as seen in the current study reflects the development of hyper viscosity due to polycythemia in response to hypoxia. However, in a study of 169 GDM pregnancies conducted by Leuing et al, the usefulness of Doppler parameters in predicting abnormal pregnancy outcomes was not found (4).

We found no significant difference in the MCA S/D ratio between the GDM and non-GDM groups. This concurs with 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=0.117). Additionally, Dantas et al. concluded that there was no correlation between MCA PSV and maternal hyperglycaemia and fetal macrosomia (22). We were unable to establish any correlation, as larger studies are needed to associate Doppler parameters with predicting polyhydramnios and intra-uterine death. There was no significant difference noted between GDM and non-GDM groups for polyhydramnios (p=0.056) and IUD (p=1.00). Therefore, no correlation of Doppler parameters of fetal MCA was found with polyhydramnios and IUD in GDM pregnancies.

Fadda et al. conducted a PI assessment of the umbilical artery, fetal descending thoracic aorta and fetal MCA and noted a correlation of neonatal hypoglycemia (p=<0.001) with abnormal Doppler measurements (23). This finding was consistent with

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the current study, which also establish a positive correlation of neonatal hypoglycemia in GDM women compared to non-GDM women. In the present study, MCA PI had a sensitivity of 100% but very low specificity of 33%, resulting in a very low diagnostic accuracy of 51%. Although all parameters of MCA were insignificant in predicting neonatal hypoglycemia, MCA PSV had better specificity and diagnostic accuracy of 61% and 62%, respectively, albeit with a low sensitivity of 67%.

In predicting NICU admissions, MCA PI had the highest sensitivity of 93% but a specificity of 36%. Regarding neonatal hyperbilirubinemia, it was not statistically significant in GDM women. However, 6.7% of the GDM group had neonatal hyperbilirubinemia, and it was better predicted by MCA PSV. The sensitivity of MCA PSV in predicting neonatal hyperbilirubinemia was 67% with a specificity of 93%, which was the highest among all other parameters of MCA. Hence, MCA PSV had a good diagnostic accuracy of 91%. However, other MCA parameters (PI, RI, S/D ratio) had low specificity and low diagnostic accuracy. Similarly, in the study conducted by Fadda et al., there was a significant association of neonatal hyperbilirubinemia ($p=< 0.001$) 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 fetal well-being in pre-gestational or gestational diabetes mellitus pregnancies, although both umbilical & middle cerebral artery Doppler had some association with neonatal outcomes, the sensitivity for predicting adverse neonatal outcome was found to be low. This study concluded that the UA Doppler assessment is a better predictor of neonatal outcome than the MCA Doppler (24).

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 fetus was conducted in patients with GDM who were under treatment and the results may vary depending on the level of glycemic control achieved by the patients. It is important to consider this factor when interpreting the results. However, our study contributes to the limited body of literature comparing fetal brain hemodynamic indices in GDM and non-GDM pregnancies using Doppler changes in the MCA and their effect on pregnancy outcomes.

Conclusion

Our study demonstrated that fetal MCA PI on Doppler velocimetry was significantly higher in the GDM group, while MCA PSV was significantly lower in the study group. However, no significant differences were observed in MCA RI and MCA S/D ratios. Maternal complications such as polyhydramnios, premature rupture of membranes (PROM), and pregnancy-induced hypertension were more common in GDM compared to non-GDM pregnancies, although the results were not statistically significant except for PIH and PROM. MCA PSV was significantly associated with the development of pregnancy induced hypertension in GDM women. Furthermore, the rate of NICU admission was significantly higher in babies born to GDM mothers compared to non-GDM mothers, and these babies were also more likely to experience complications such as RDS, hypoglycemia, and macrosomia.

Our findings suggest a potential role for Doppler assessment of MCA in predicting adverse outcomes in GDM pregnancies. Therefore, we 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 hemodynamic parameters in diabetic pregnancies.

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Conflicts of Interest

The authors declare no conflict of interest.

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