Effect of pregestational diabetes mellitus on fetal cerebral artery Doppler changes and its correlation with fetal weight

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Background

Pregestational diabetes mellitus (PDM) is one of the causes of many gestational complications. This study aimed to review the effect of maternal pregestational diabetes on fetal cerebral circulation through assessment of fetal middle cerebral artery (MCA) and vertebral artery (VA) Doppler study as well as cerebroplacental ratio using MCA pulsatility index (PI)/uterine artery PI and VA PI/uterine artery PI, and to find its correlation with fetal weight.

Patients and methods

This prospective study was conducted on 40 cases, comprising 20 pregestational diabetic women and 20 comparison pregnant nondiabetic women (comparison cases). Fetal Doppler studies were done twice for pregestational diabetic patients and the comparison group. The Doppler indices such as fetal MCA, VA, and umbilical artery were assessed along with the routine obstetric ultrasound examination.

Results

Statistically significant differences were detected between pregestational diabetic and comparison cases regarding MCA peak systolic volume and VA resistivity index at mid/end of the second trimester and VA resistivity index, VA PI, and VA cerebroplacental ratio at the beginning of the third trimester. There was no correlation in PDM cases between Doppler indices and fetal weight.

Conclusion

PDM was associated with VA and MCA Doppler changes. VA Doppler is recommended along with MCA Doppler in fetal screening in high-risk pregnancies.

Keywords:

cerebroplacental ratio, fetal Doppler, maternal pregestational diabetes, middle cerebral artery, peak systolic velocity, pulsatility index, resistance index, vertebral artery

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Introduction

Babies of mothers with pregestational diabetes mellitus (PDM) have higher rates of still and preterm births, high birth-weight, low Apgar scores, high rate of admission to neonatal ICU, and longer stay in the hospital than babies of mothers with gestational diabetes mellitus or normal pregnancies [1].

The vertebral artery (VA) and internal carotid artery with its main branch, middle cerebral artery (MCA), are the major arteries that supply blood to the fetal brain [2]. Both fetal MCA and VA participate in the brain-sparing phenomenon [3]. Placental vascular resistance is assessed by umbilical artery (Umb A) Doppler, which is affected by intrauterine growth restriction (IUGR) and placental insufficiency [4].

Doppler ultrasound (US) is a well-established noninvasive technique used for diagnosing problems during pregnancy and assessing the fetal well-being [5]. Umb A Doppler and MCA Doppler, or the combination of both to produce a cerebroplacental ratio (CPR), have been widely used to assess fetal stress in growth-restricted fetuses and fetal anemia [6].

Maternal hyperglycemia produced perceptible reduction in cardiac output, with redistribution to fetal heart, renal, adrenal, and splanchnic circulation. The fetuses also developed systemic hypoxemia and mixed acidemia, which were correlated with the changes in fetal brain perfusion [7].

This study aimed to compare Doppler indices of fetal brain hemodynamic between PDM and normal pregnancies and to assess the blood velocimetry of the MCA and VA along with Umb A.

Patients and methods

This prospective cohort study included 40 pregnant women [20 women with PDM and 20 normal nondiabetic women (comparison group)] for obstetric assessment. Cases with any associated medical disorders, any congenital anomalies, or multiple gestations and any other causes that could affect the Doppler assessment other than PDM were excluded. The research protocol was approved by the Institutional Human Research Ethics Committee. A written informed consent was taken from the participating patients.

Each case was subjected to the following: full history was obtained, fasting blood glucose analysis was conducted to differentiate between the PDM and comparison groups, and obstetric US was performed twice (the first at around 20–24 weeks of gestation and the second at around 30–34 weeks of gestation), including Doppler assessment. The choice of timing of Doppler surveillance was made according to the National Institute for Health and Care Excellence guidelines [8]. Then, fetal biometry was performed for all cases, including measurements of biparietal diameter, abdominal circumference (AC), and femur length, and fetal biophysical profile score (BPS) and Doppler study of Umb A, MCAs, and VAs was conducted for all cases.

The Doppler study was conducted on MCA, VA, and Umb A for both groups twice: the first time at the middle to the end of the second trimester [20–24 weeks of gestation (time A)] and the second time at the beginning of the third trimester [30–34 weeks of gestation (time B)].

Fetuses were diagnosed as having IUGR based on the estimated fetal weight (EFW) and AC measured by US being below the 10th percentile for gestational age. Fetuses were diagnosed as having macrosomia based on EFW and AC measured by US being above the 90th percentile for gestational age.

The US machines used were Toshiba XarioTM 200 (Toshiba Medical Systems Corporation, Otawara City, Tochigi Prefecture, Japan) and DC-8 (Shenzhen Mindray Bio-Medical Electronics Co. Ltd, Shenzhen, China).

Doppler studies on the Umb A were obtained from a free loop of the umbilical cord, MCA by the sphenoid wing close to the circle of Willis, and VA during fetal apnea in the space between the first cervical vertebra and the occipital bone, at the anatomical point where the artery runs nearly perpendicular to its previous direction through the transverse foramen surrounding the lateral mass of the atlas vertebra.

Measurement of indices

The Doppler waveform was automatically traced, and the peak systolic velocity (PSV), pulsatility index (PI), and resistance index (RI) were calculated according to the Gosling–King formula for both MCA and VA. The MCA CPR was calculated as the ratio between the MCA PI and Umb A PI. The VA CPR was calculated as the ratio between the VA PI and Umb A PI.

After between-group comparisons of the crude measurements, the PSV, PI, and CPR values for MCA and VA were reassessed based on the reference percentiles for these indices in normal fetuses with different gestational ages, presented by Morales Rosello *et al.* [2].

Statistical analysis

Statistical analysis was conducted employing data management using Statistical Package for the Social Sciences, version 21 (IBM Corporation New Orchard Road, Armonk, NY 10504 Produced in the United States of America). *P* value less than 0.05 was considered statistically significant.

Results

This study included 40 pregnant women who were categorized as group I (comparison group) with 20 non-PDM cases and group II (PDM group) with 20 PDM cases.

All of the pregnancies were singleton, with the mean age of all females being 28.1±7.4 years (range, 19–35 years old). PDM and non-PDM cases had the mean ages of 31.5±4.5 and 25.3±5.4 years, respectively. The mean number of gravidity and parity was significantly higher in the PDM group. Other demographic and baseline characteristics of women in both study groups are presented in Table 1. The fetal Doppler indices

Table 1 Comparison of demographics and baseline characteristics of the women in the two study groups

Characteristics (mean±SD)	PDM + (*N*=20)	PDM − (*N*=20)
Maternal age (year old)	31.5±4.5	25.3±5.4
GA (time A) (weeks)	23.0±2.4	23.4±2.13
GA (time B) (weeks)	32.6±2.16	33.2±2.58
Gravidity	3.02±1.6	1.52±1.6
Parity	2.07±1.25	1.15±0.50
Abortion	1.00±0.63	0.70±0.00
FBS	110.30±23.02	75.34±11.61

FBS, fasting blood sugar; GA, gestational age; PDM, pregestational diabetes mellitus.

of the PDM group compared with those of the comparison group at time A are presented in Table 2 and at time B in Table 3.

Group comparison of fetal weight

At time A, there was one (5%) case of IUGR in group I versus two (10%) cases in group II and two (10%) cases of macrosomia in group I versus eight (40%) cases in group II. At time B, there was one (5%) case of IUGR in group I versus three (15%) cases in group II and two (10%) cases of macrosomia in group I versus nine (45%) cases in group II (Fig. 1).

No significant differences were observed in EFW at time A (P=0.056), whereas there was a significant difference at time B (P=0.013). In group I, there were no changes in the number of cases of macrosomia or IUGR, whereas in group II, there was an increase in the number of cases of both macrosomia and IUGR.

Correlation of brain color Doppler hemodynamics with fetal weight

In terms of the importance of EFW in relation to fetal hemodynamics, probable correlations between fetal

Table 2 Estimated fetal weight correlation of fetal brain hemodynamics

	EFW	
	P value	Correlation coefficient (*r*)
Umbilical artery		
Peak systolic velocity (cm/s)	0.861	0.029
End-diastolic velocity (cm/s)	0.879	0.025
Systolic/diastolic ratio	0.376	0.144
Resistance index	0.35	0.152
Pulsatility index	0.894	0.022
Middle cerebral artery		
Peak systolic velocity (cm/s)	0.197	0.208
End-diastolic velocity (cm/s)	0.338	0.157
Systolic/diastolic ratio	0.227	0.198
Resistance index	0.856	0.03
Pulsatility index	0.855	–0.03
Cerebroplacental ratio	0.582	–0.091
Vertebral artery		
Peak systolic velocity (cm/s)	0.466	0.12
End-diastolic velocity(cm/s)	0.042*	0.327*
Systolic/diastolic ratio	0.524	– 0.107
Resistance index	0.118	– 0.254
Pulsatility index	0.614	–0.083
Cerebroplacental ratio	0.581	–0.091

EFW, estimated fetal weight. *Significance, *P* value less than 0.05.

Table 3 Comparison of fetus Doppler characteristics in pregestational diabetes mellitus versus normal pregnancy group at time A (all values are presented as mean±SD)

Time A	PDM + (*N*=20)	PDM – (*N*=20)	*P* value
EFW (g)	719.3±305.88	663.2±263.24	0.056
Umbilical artery			
Peak systolic velocity (cm/s)	39.84±17.06	35.88±8.6	0.247
Resistance index	0.75±0.1	0.70±0.05	0.302
Pulsatility index	1.33±0.3	1.21±0.09	0.315
Middle cerebral artery (Figs 2, 3)			
Peak systolic velocity (cm/s)	36.68±13.87	26.62±6.03	0.035*
Resistance index	0.80±0.08	0.79±0.12	1.00
Pulsatility index	1.67±0.87	1.79±0.67	NA
Cerebroplacental ratio	1.32±0.35	1.47±0.24	NA
Vertebral artery (Figs 3, 4)			
Peak systolic velocity (cm/s)	25.44±8.99	19.24±4.24	1.00
Resistance index	0.83±0.106	0.80±0.05	0.02*
Pulsatility index	1.70±0.42	1.695±0.29	0.23
Cerebroplacental ratio	1.33±0.37	1.38±0.22	NA

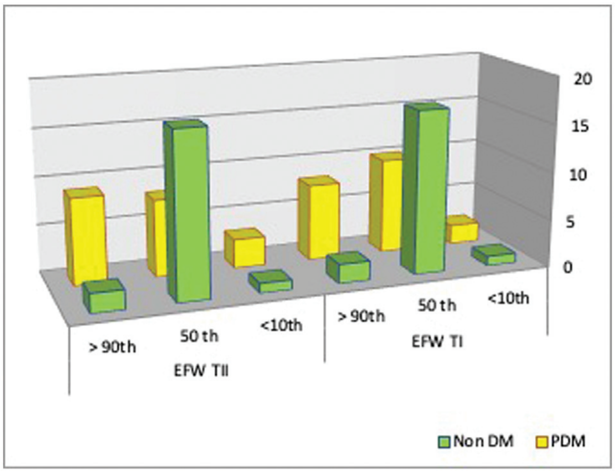
EFW, estimated fetal weight; NA, not applicable; PDM, pregestational diabetes mellitus. *P* value less than 0.05. *Significance.

weight and hemodynamic indices were further evaluated (Table 1). The results of the Pearson correlation indicated that end-diastolic velocity of fetal VA directly correlated with EFW in PDM and normal pregnancy groups (Pearson r=0.327, P=0.042).

Between-group comparison of the fetal middle cerebral artery indices

The Doppler indices of MCA (MCA PSV, MCA RI, and MCA PI) column chart of their values in time A and time B according to percentiles reference values represented in Fig. 2. There was no correlation between them and EFW either at time A (Table 3) or time B (Table 4) and either in the non-PDM or in the PDM group. Moreover, elevated MCA PSV (in four cases at time A in the PDM group) was not associated with any abnormality in EFW (IUGR or macrosomia) or other abnormality in Doppler indices of VA or Umb A.

Figure 1



Comparison between EFW at time A and time B. EFW, estimated fetal weight.

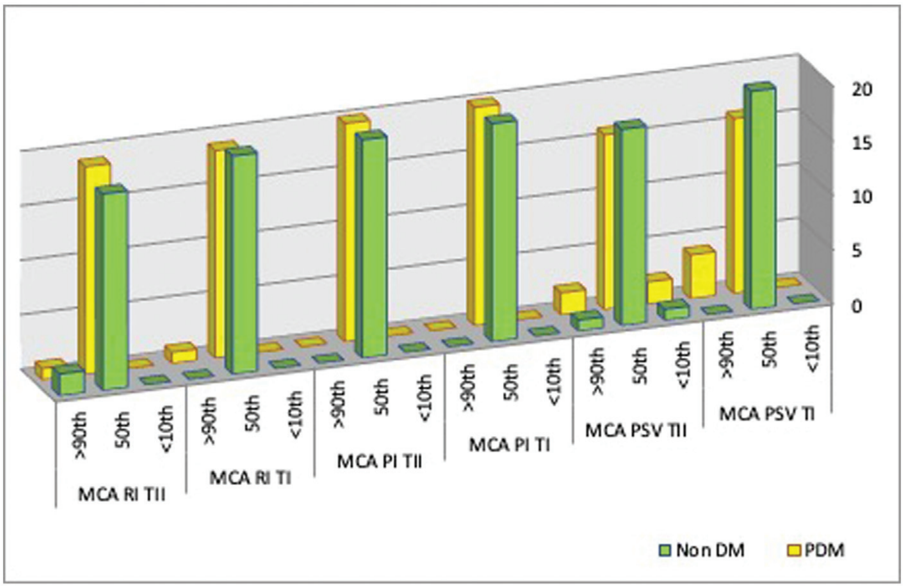
Between-group comparison of the fetal vertebral artery indices

The dopple indices values of MCA (MCA PSV, MCA RI, MCA PI) column chart in time A, and time B according to percentiles reference values represented in Fig. 3. There was no correlation between them and EFW either at time A (Table 3) or time B (Table 4) and either in the non-PDM or in the PDM group. In addition, the abnormal Doppler indices, including elevated VA RI (in six cases at time A in the PDM group), elevated VA RI (in seven cases at time B in PDM group), and elevated VA PI (in five cases at time B in PDM group), indicated no correlation between these indices and abnormality in EFW [IUGR (<10th percentile and >5th percentile) or macrosomia (>90th percentile)] or other abnormality in the Doppler indices of MCA or Umb A (Fig. 3).

Between-group comparison of middle cerebral artery cerebroplacental ratio and vertebral artery cerebroplacental ratio

A column chart of their values in time A and time B according to percentiles reference values is represented in Fig. 4. At time A, MCA CPR and VA CPR in all cases of non-PDM and PDM groups were at the 50th

Figure 2



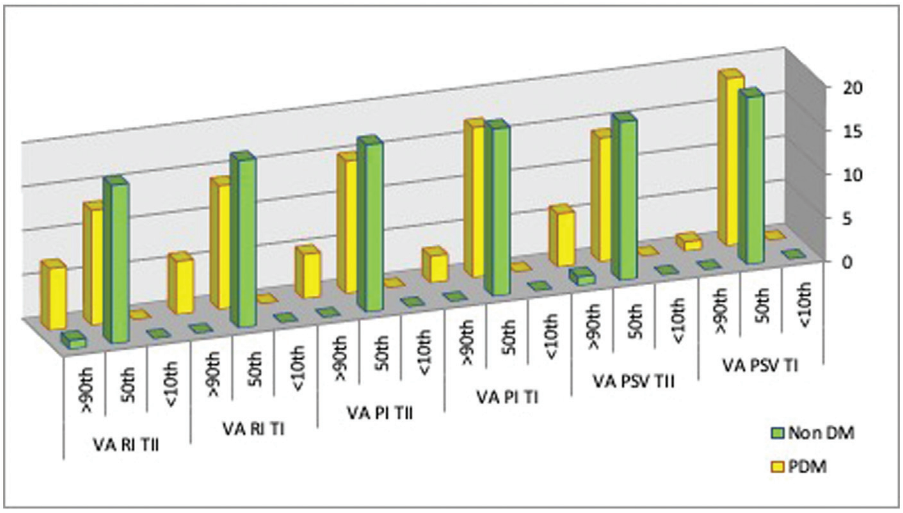
Comparison of hemodynamic indices of the fetal MCA at time A and time B between the non-PDM and PDM groups indicated no significant difference between both groups. MCA, middle cerebral artery; PDM, pregestational diabetes mellitus.

Table 4 Comparison of fetus Doppler characteristics in pregestational diabetes mellitus versus normal pregnancy group at time B (all values are presented as mean±SD)

Time B	PDM + (*N*=20)	PDM − (*N*=20)	*P* value
EFW (g)	2114.6±694.91	2336.9±595.95	0.013*
Umbilical artery			
Peak systolic velocity (cm/s)	45.63±11.4	38.94±9.94	0.114
Resistance index	0.71±0.08	0.63±0.05	0.360
Pulsatility index	2.32±4.8	1.97±0.12	0.215
Middle cerebral artery (Figs 2, 3)			
Peak systolic velocity (cm/s)	42.27±14.24	39.85±12.70	NA
Resistance index	0.83±0.10	0.77±0.07	1.000
Pulsatility index	1.96±0.56	1.67±0.33	NA
Cerebroplacental ratio	1.47±1.04	1.73±0.39	1.000
Vertebral artery (Figs 3, 4)			
Peak systolic velocity (cm/s)	38.60±12.02	32.83±6.48	0.0544
Resistance index	0.83±0.11	0.80±0.04	0.02*
Pulsatility index	2.24±0.94	1.89±0.36	0.047*
Cerebroplacental ratio	1.98±1.09	1.66±0.58	0.04*

EFW, estimated fetal weight; N/A, Not applicable; PDM, pregestational diabetes mellitus. *Statistical significance ($P<0.05$).

Figure 3



Comparison of hemodynamic indices of the fetal VA at time A and time B between the non-PDM and PDM groups indicated no significant difference between both groups. PDM, pregestational diabetes mellitus; VA, vertebral artery.

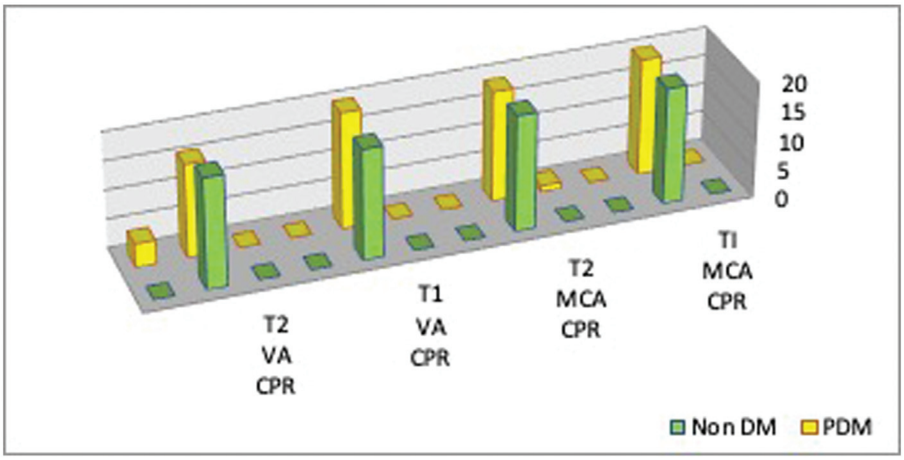
percentile. At time B, there was one (5%) case below the 10th percentile, and the rest of the cases were within the 50th percentile. There were four (20%) cases above the 90th percentile. The VA CPR of the rest of the cases was within the 50th percentile. The MCA CPR and VA CPR indicated no correlation between them and EFW either at time A (Table 3) or time B (Table 4) and either in the non-PDM or in the PDM group. At time B, low MCA CPR in one case in the PDM group and high VA CPR in four cases in the PDM group were not associated with an abnormality in EFW [either IUGR (<10th percentile and >5th percentile) or macrosomia (>90th percentile) or other abnormality in Doppler indices of MCA, VA, or Umb A].

Discussion

Doppler US assessment of the placental and fetal circulations is a widely used noninvasive method for evaluating fetal well-being. It has been proven to have significant efficacy in the diagnosis of neonatal outcomes in high-risk pregnancy; however, a few studies have investigated their effectiveness in improving perinatal outcomes in diabetic women [9].

This study aimed to review the effect of maternal PDM on the fetal cerebral circulation, for which complete fetal MCA and VA Doppler tests were conducted twice (first at the middle to the end of the second trimester and second at the beginning of the third

Figure 4



Comparison of MCA CPR and VA CPR between time A and time B. CPR, cerebroplacental ratio; MCA, middle cerebral artery; VA, vertebral artery.

trimester) for every case to rule out any abnormalities in Doppler changes. PI, RI, and CPR were used as functional tools for assessing overall fetal circulation (Umb A) and fetal cerebral circulation (MCAs and VAs). In addition, the aforementioned tests were conducted to display the impedance of flow and to identify the high-risk groups.

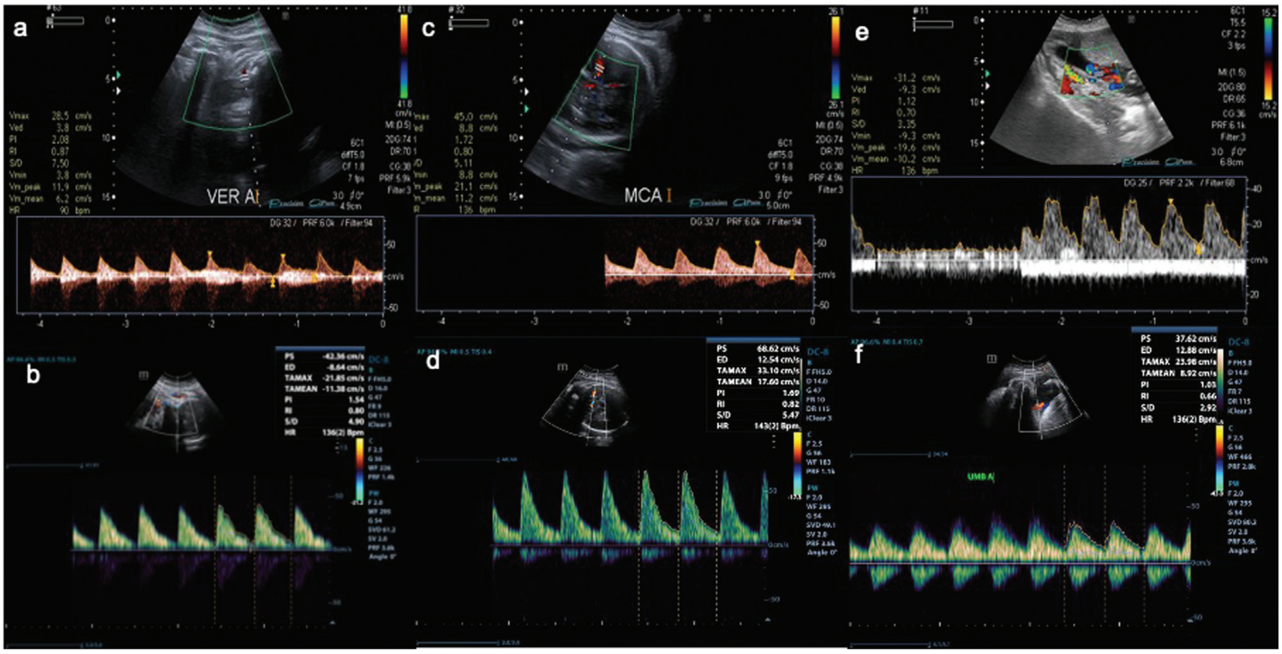
No significant time interval changes between Doppler values in times A and B in both groups were observed. Our results failed to indicate any association between them and an abnormality in EFW [either IUGR (<10th percentile and >5th percentile) or macrosomia (>90th percentile)]. Furthermore, these abnormal Doppler indices failed to indicate a correlation between them (MCA, VA, and Umb A). A study by Dantas *et al.* [5] on gestational diabetes mellitus also found no association between MCA PSV and excessive fetal weight gain or macrosomia.

Some randomized studies that supported the use of Umb A Doppler only performed multiple Umb A systolic/diastolic ratio measurements in 35 insulin-dependent diabetic women, who have pregnancies complicated by hypertensive diseases, severe fetal growth restriction, or vasculopathy [6,10]. In these studies, significantly elevated mean second and third trimester systolic/diastolic ratio values in women with vasculopathy compared with these values in women without complications were observed (4.34±0.7 and 3.2±0.65 vs. 3.72±0.42 and 2.55±0.32, respectively; $P<0.001$). The elevated ratio preceded the development of preeclampsia and severe fetal growth restriction. We had a different study group in this study, and the Umb A Doppler studies revealed no differences between the complicated and noncomplicated PDM group and non-PDM groups.

No significant difference was observed in the Doppler indices of MCA (including MCA PI, RI, and CPR, either in the middle of the second trimester or at the beginning of the third trimester), except for MCA PSV in the middle of the second trimester in the PDM group compared with the non-PDM group. However, it failed to indicate an association with an abnormality in EFW (either IUGR or macrosomia) (Fig. 5). This finding is in agreement with that of Abdella *et al.* [11], who reported no significant difference in CPR in cases with macrosomia and a significant relationship between macrosomia and MCA PI and MCA RI: with a cutoff value for MCA PI of 1.2450, a sensitivity of 48% and a specificity of 71%, and a cutoff value for MCA RI of 0.705, a sensitivity of 54% and a specificity of 64%. Therefore, they concluded that in the case of macrosomia, the MCA Doppler indices (MCA PI and RI) are the only significant parameters; however, the CPR and uterine artery (UA) Doppler indices are not significant parameters.

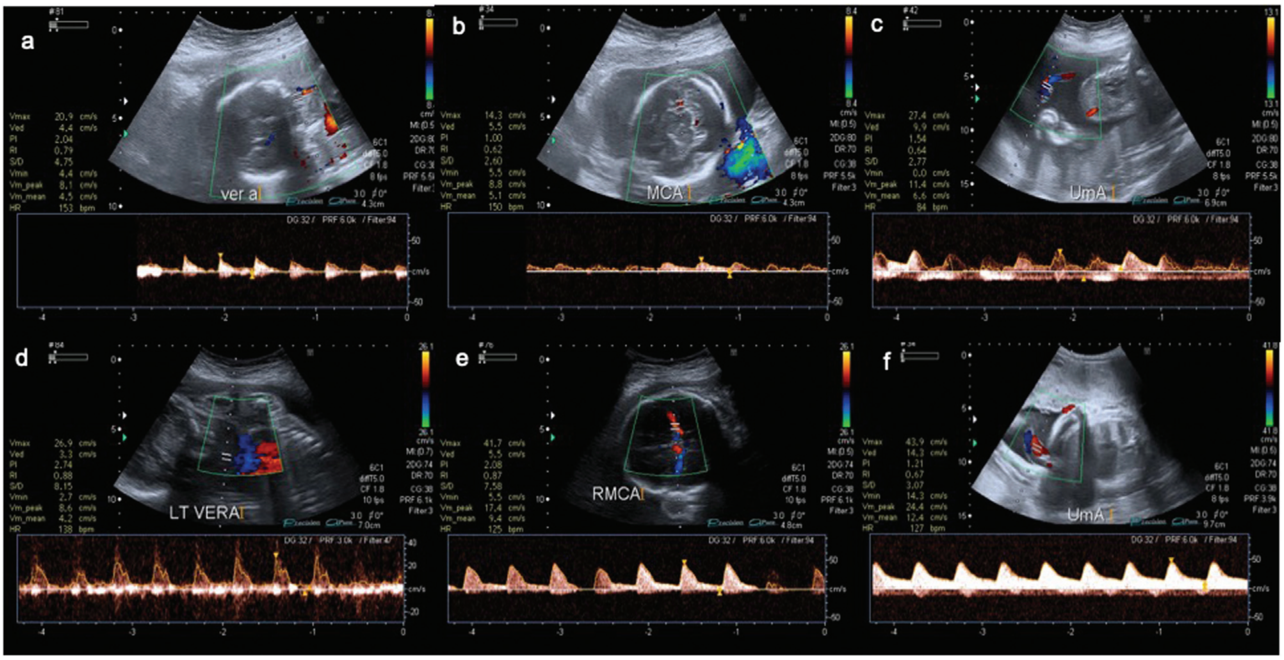
In this study, there was one case of MCA CPR of less than 1 (=0.65) in the middle of the second trimester, denoting hypoxia, and during follow-up, we found that the MCA CPR returned back to normal (>1.1) at the beginning of the third trimester (Fig. 6), and the EFW and the biophysical profile of the fetus at both times were within the normal ranges. DeVore [12] stated that CPR is an efficient predictor of adverse outcome than the conventional BPS and can also be part of a BPS. However, Arabin *et al.* [13] stated that it is true for chronic placental perfusion diseases. However, CPR may stay normal with low resistance in the UA with

Figure 5



Fetus with EFW more than 90th percentile at time A (24 weeks) and time B (34 weeks) gestation macrosomia. Doppler waveforms of vertebral artery indices at time A (a), and time B (b) were within normal ranges according to reference values, middle cerebral artery (MCA) indices at time A (c), and time B (d) ranges according to reference values, and umbilical artery (Umb A) indices at time A (e) and time B (f) were within normal ranges according to reference values. EFW, estimated fetal weight.

Figure 6



Doppler waveforms of the vertebral artery (VA) (a), middle cerebral artery (MCA) (b), and umbilical artery (Umb A) (c) in fetus at 25 weeks' gestation indicated PSV, RI, PI, and CPR within normal ranges, except for low MCA CPR of 0.65. Doppler waveforms of VA (d), MCA (e), and Umb A (f) in the same fetus at 31 weeks' gestation indicated PSV, RI, PI, and CPR within normal ranges according to reference values. CPR, cerebroplacental ratio; PI, pulsatility index; PSV, peak systolic velocity; RI, resistivity index.

associated decrease in resistance in both the MCA and UA, resulting in a normal CPR in spite of a high risk for fetal death in patients with acute or subacute disturbances of oxygen diffusion; therefore, CPR should not be interpreted in isolation. In addition, Gibbonsa *et al.* [14] concluded that a low CPR was associated with poorer neonatal outcomes, regardless of the type of DM.

The VA Doppler is an easy procedure that could be performed by an inexperienced examiner, and VA could be easily detected in all patients [15]. In our study, the percentage of failure in obtaining the VA Doppler measurement was less than 1%. This happened in one case owing to obesity (BMI, >30 kg/m^2), which agrees with Morales-Roselló *et al.* [16], who reported failure in obtaining VA, especially in obese women with the fetal head in an occipito-posterior position.

Morales-Roselló and Peralta-Llorens [15] stated that the VA Doppler waveforms were similar to those of the MCA. With lower velocities, the VA Doppler might be an alternative to the MCA Doppler, especially in cases in which the MCA is difficult to find because the fetal head is located deep within the mother's pelvis or the sonographer has access only to the fetal occipital bone. Hence, measurement of VA instead of MCA could be useful in assessing fetal well-being. Our findings revealed no noticeable differences in the fetal cerebral hemodynamic indices in the presence or absence of PDM. In normal pregnancies, Doppler findings were similar to the reference values because the VA and MCA PI at the end of the second trimester reached their maximum values (1.88 and 2.10 at 29 weeks of gestation) and subsequently decreased in the third trimester owing to an increase in the diastolic flow. Conversely, a study by Morales-Roselló and Peralta-Llorens [15] revealed that the VA and MCA PSV increased progressively until the end of the gestation (44 and 57 cm/s at 41 weeks of gestation). Regarding the VA and MCA CPR, the values were higher in the middle of the third trimester (1.82 and 2.04 at 32 weeks of gestation) and decreased slightly afterward.

With the evolution of Doppler studies in high-risk fetuses, all Doppler parameters should be evaluated to determine the global fetal well-being [13]. Morales-Roselló and Peralta-Llorens [15] proposed that the VA could also be used as an alternative measurement in the evaluation of growth-restricted fetuses as the reduction of impedance in the VA was comparable with that of the MCA.

Few studies compared the fetal brain hemodynamic indices between PDM and non-PDM pregnancies using the Doppler US technique. However, a limitation of this study was that we did not have access to the follow-up of some pregnant women and the outcome of their pregnancies. In addition, the rather small sample size could be the reason why hemodynamic indices failed to indicate significant results. Therefore, further researches should focus on the assessment of fetal cerebral circulation in mothers with PDM in relation to their glycemic control and presence of complications.

Conclusion

PDM was associated with VA and MCA Doppler changes. No correlation was observed in PDM cases between Doppler indices and fetal weight. VA Doppler could be a predictor for hemodynamic brain changes in diabetes and is recommended along with MCA Doppler, even once at any time of pregnancy.

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Author's contributions: S.T.H.: suggesting and developing the research idea, reviewing the literature, data collection and analysis, performing the examinations, organizing the results, and revising the manuscript. H.A.N.M.A.A.: performing the examinations, data collection and analysis, and performing statistical analysis. A.M.H.: recruiting the cases and performing the examinations. M.A.F.H.: data analysis, reviewing literature, organizing results, writing and revising the manuscript, and manuscript editing. All authors have read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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