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A Comparative Study of Middle Cerebral and Umbilical Arteries Doppler Indices in Controlled Versus Uncontrolled Insulin-Dependent Pregestational Diabetic Pregnancies

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Abstract

Objectives: *To evaluate the effect of glycemic control on umbilical and fetal middle cerebral arteries Doppler indices in pregestational diabetic pregnant women.*

Methods: *60 insulin-dependent pregestational diabetic pregnant women were included and equally divided into two groups according to HbA1C levels namely; controlled diabetics (HbA1C < 6.5 %) and uncontrolled diabetics (HbA1C ≥ 6.5 %). UA, MCA Doppler indices (resistance index and pulsatility index) and Cerebroplacental Doppler ratio were measured for every patient.*

Results: *There was no statistically significant differences in umbilical artery, middle cerebral artery Doppler indices and cerebroplacental ratio between the controlled & uncontrolled pregestational diabetic pregnant women.*

Conclusion: *Doppler indices of placental or fetal circulation are unaffected by maternal glycemic control in pregestational diabetic pregnant women.*

Keywords: *Diabetes mellitus, Glycemic control, Umbilical artery, Middle cerebral artery Doppler ultrasound .*

- **Introduction:**

Diabetes mellitus(DM) is a chronic multisystemic disease resulting from carbohydrate intolerance. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs **(1).**

Women with preexisting diabetes mellitus face a higher risk of pregnancy complications such as preeclampsia, fetal overgrowth, genital trauma and cesarean delivery **(2).** In addition, the incidence of major malformations is at least doubled and approximately 11 percent**(3)**. The high prevalence of these complications is strongly associated with poor glycemic control**(4).**

The goal of antenatal management in diabetic pregnant women is to control blood glucose levels, treat chronic complications and to monitor the fetus. HbA1c levels are useful for determining glucose control in individuals when used in a repeated fashion and for measuring progress of glycemic control across periods of time**(5).**

Several antepartum fetal surveillance techniques (tests) are in clinical use. This include maternal perception of fetal movements, non-stress test (NST), biophysical profile (BPP), modified BPP, and Doppler blood flow velocimetry**(6).**

Doppler ultrasound examination measures the blood flow through arteries and veins, such as umbilical and middle cerebral arteries. Doppler assessment of placental and fetal circulations is a well-established method that has been used for management of intra-uterine growth restriction**(7).** However, the utility of Doppler indices in the evaluation of oxygenation status in appropriately grown fetuses has revealed conflicting results. In fact, despite the widespread use of these techniques, few studies have investigated their effectiveness in improving perinatal outcomes in diabetic women **(8).**

Pietryga and his colleagues**(9)** evaluated the impact of maternal glucose level on placental vascular impendence in pregnancy complicated by gestational diabetes mellitus (GDM) and claimed that there was no significant correlation between maternal HBA1C levels and Doppler parameters. On the other hand, Shabani Zanjani and his colleagues **(10)** studied the Doppler indices of fetal brain hemodynamics among pregnant women with gestational diabetes mellitus compared to healthy ones and reported that higher pulsatility index (PI) of the middle cerebral artery (MCA) among diabetic group.

Therefore, we performed this study to evaluate the effect of glycemic control on umbilical and fetal middle cerebral arteries Doppler indices in pregestational diabetic pregnant women.

- **Methodology**

The current study is a cross-sectional one conducted in the department of Obstetrics & Gynecology (Faculty of Medicine - Cairo University) in the duration between June 2019 to the end of July 2020. Sixty insulin-depended pregestational diabetic pregnant women (aged from 21 - to 40 years old) with singleton healthy living fetus between 34-37 weeks gestation (confirmed by the 1st day of the LMP or 1st trimesteric ultrasound scan) were recruited from the department and they were equally divided into two groups according to HbA1C levels namely; controlled diabetics (HbA1C less than 6.5%) and uncontrolled diabetics (HbA1C equal to or more than 6.5%).

Diabetic women with either complicated diabetes or any other chronic diseases (e.g., hypertension or renal disease) were excluded. Moreover, any other well-known condition affecting fetal blood flow velocity such as multiple pregnancy, fetal anomalous or growth-restricted (EFW below the 10th percentile for gestational age) fetuses were excluded. Patients experienced any pregnancy induced medical disorders, rupture of membranes or oligohydramnios (AFI less than the fifth percentile) in the current pregnancy were also excluded.

Informed consent was obtained from all participants (after explaining the aim of the study) then all participants were subjected to the following: full history taking, thorough clinical and obstetric examination (including the 1st day of the LMP and maternal body weight) followed by obstetric ultrasound to confirm the eligibility of the current pregnancy to participate in the study (by confirming gestational age& excluding fetal anomalies or oligohydramnios) and to assess the fetal weight and amniotic fluid index (to detect presence of macrosomia defined as EFW above 90th percentile for gestational age and polyhydramnios diagnosed as AFI more than 95th percentile, respectively). Laboratory investigations (complete blood picture, liver & kidney functions, fasting and post prandial blood sugar and HbA1C estimation) were also done.

Doppler ultrasonography assessment was done using Samsung SonoAce R3 abdominal probe convex linear transducer 3.5 MHZ equipped with color and pulsed Doppler capabilities(SonoAce R3, SAMSUNG MEDISON CO., Gangnam-gu, Seoul, Korea). Using color flow imaging, the middle cerebral artery was seen as a major lateral branch of the circle of Willis. The pulsed Doppler sample gate was then placed on the middle portion of this vessel to obtain flow velocity waveforms. When the screen showed at least 3 consecutive waveforms , the image was frozen and middle cerebral artery Doppler

parameters (MCA RI&MCA PI) were estimated. Minimum of 3 separate readings were averaged before the final values were obtained**(11).**

As regard umbilical artery (UA) doppler, all patients were placed in a semi-recumbent position with a left lateral tilt. Then using a pulsed wave Doppler on a free loop of cord, the characteristic sound and shape of the umbilical artery were identified. When the screen showed at least 3 consecutive waveforms, the image was frozen and umbilical artery Doppler parameters [Resistance index (RI) and pulsatility index (PI)] were estimated. A minimum of 3 separate readings were averaged before the final values were obtained**(12).** All obstetric ultrasounds and Doppler assessments were done by single investigator.

The following data was recorded; gestational age at Doppler study , presence of macrosomia or polyhydramnios and Doppler indices for UA & MCA .

Data were coded and entered using the statistical package SPSS version 25. Data was summarized using mean, standard deviation, median, minimum and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t test in normally distributed quantitative variables while non-parametric Mann-Whitney test was used for non-normally distributed quantitative variables**(13).** For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 **(14).** P-values less than 0.05 were considered as statistically significant.

- **Results**

This prospective study included sixty pregnant women that met the inclusion criteria. Demographic characteristics of the participants were summerized in **table (1)**

As shown in **table(2)** ,the fasting blood sugar (**FBS),** postprandial blood sugar **(PPBS)** and **HbA1C** were significantly higher in uncontrolled diabetic group (119.5 versus 96.83mg/dl for FBS - 179.3 versus 151mg/dl for PPBS -7.67 versus 5. 9% for HbA1C).

There was no statistically significant difference between the mean RI &PI of **umbilical artery** in the controlled group (RI = 0.61& PI = 0.96) and the uncontrolled group (RI = 0.6 & PI= 0.93; P value =0.496 & 0.489, respectively). Similarly, there was no statistically significant difference between the mean RI & PI of the **middle cerebral artery** between the controlled group (RI= 0.82 & PI = 1.79) and the uncontrolled group (RI = 0.83& PI = 1.82 ;P value =0.627& 0.802 respectively).Consequencely, the difference between the mean **Cerebroplacental Doppler ratio** (MCA/UA PI) in both groups was not statistically significant (1.89 in the controlled diabetic group versus 1.94 in the uncontrolled diabetic group; P value =0.481)**(table 3).**

- **Discussion**

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. To reduce the risk of long-term complications**,** multidisciplinary clinic including an endocrinologist, maternal-fetal medicine specialist, dietitian and diabetes educator, when available, should ideally be considered in management of diabetic pregnant women **(15).**

Fetal surveillance is necessary for the management of pregnancies, complicated with diabetes. Doppler velocimetry is one of the most important methods of gestational management which depends on the oxygen metabolism in the maternal–placental–fetal balance**(16).**

Our results demonstrated that there was no statistically significant differences in umbilical artery, middle cerebral artery Doppler indices and cerebroplacental ratio between the controlled & uncontrolled pregestational diabetic pregnant women.

This finding was in harmony with the results reported in a study by **Pietryga and his colleagues(9)**. They investigated whether maternal glucose level and growth of the fetus were related to placental vascular impendence in pregnancy complicated by gestational diabetes. 146 gestational diabetic women of which 117 needed insulin therapy were included. Glycosylated hemoglobin (HbA1c) was evaluated as well as umbilical and uterine artery Doppler velocimetry. The results were related to adverse outcome of pregnancy including newborn birthweight. They reported that uterine and umbilical artery vascular impedance was significantly lower in macrosomic newborns. There was a poor correlation between HbA1c, vascular impedance and birthweight.. Consequencely, they concluded that uterine and umbilical artery vascular impedance in pregnancies complicated by gestational diabetes is related to birthweight and placental weight, but not to maternal HbA1c levels. Placental Doppler ultrasound does not seem to be of clinical value for fetal surveillance in these pregnancies unless the pregnancy is complicated by preeclampsia and/or intrauterine fetal growth restriction.

Likewise, **Maulik and his colleagues(17)** evaluated umbilical arterial Doppler sonography for fetal surveillance in pregnancies complicated by pregestational diabetes mellitus. Their results showed significant diagnostic efficacy of the Doppler method in diabetic pregnancies complicated by vasculopathy, and in the presence of fetal growth restriction or hypertension. However, the relationship between abnormal umbilical arterial Doppler indices and the quality of glycemic control remains unproved. Although there are no randomized trials specifically addressing this issue, existing evidence suggests that Doppler velocimetry of the umbilical artery may be beneficial for antepartum fetal surveillance in diabetic pregnancies complicated by vasculopathy, fetal growth restriction or hypertension.

Grunewald and his colleagues(18) studied the pulsatility index of the flow velocity waveform of the uterine and umbilical arteries and the fetal aorta in last trimester pregnancy complicated by insulin-dependent diabetes mellitus. 24 well-controlled insulin-dependent pregestational diabetics and 25 healthy pregnant women were studied with Doppler ultrasound on two occasions separated by a one month interval in the third trimester. In the study group, a random blood glucose was sampled at the time of the Doppler examination. They reported that there was no correlation between glycosylated hemoglobin or random blood glucose and pulsatility index values and concluded that the pulsatility index was not influenced by blood glucose regulation.

Moreover, **Zimmermann and his colleagues(19)** investigated vascular resistance by Doppler ultrasound in the umbilical artery of insulin-dependent diabetics longitudinally over the course of pregnancy and their results showed no significant correlation between vascular resistance and mean blood glucose level or concentration of HBA1C.

On the contrary, Shabani Zanjani and his colleagues (10) studied the effects of gestational diabetes mellitus (GDM) on Doppler parameters (fetal MCA and UA) and compared it with normal pregnancies. The study was performed on 66 pregnant women, including 33 women with GDM and the others without it. Peak systolic and diastolic velocities, PI, RI and systolic diastolic ratio (SD) were recorded in UA as well as both right and left fetal MCAs for every recruited pregnant woman by means of Doppler ultrasonography. The mean gestational age at the time of examination was 34.45 weeks in GDM group. Although, all the measured Doppler parameters had higher values in GDM pregnancies, the differences were not significant between two groups of study; except for the left fetal MCA-PI, which was significantly higher in GDM group. They concluded that gestational diabetes may contribute to an

elevated PI in the fetal MCA. However, this study suffered from some limitations. This study included only 33 cases with GDM and they did not give any information regarding insulin use and dose .

Our results evaluate the impact of glycemic control on the Doppler indices and show that there is no significant association between maternal HbA1c levels and Doppler parameters of placental or fetal circulation in pregestational diabetic women. We also excluded patients suffered other medical disorders to avoid any bias in Doppler indices might present in such cases.

Our study suffers from some limitations. We did not have access to the follow-up data of the pregnant women and the outcome of their pregnancies The second one was the limited sample size that led to low statistical power in between-group comparisons.

In conclusion, Doppler indices of placental or fetal circulation are unaffected by maternal glycemic control evaluated by HBA1c test in pregestational diabetic pregnancies.

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Table (1): Demographic features and pregnancy characteristics in controlled and uncontrolled diabetics groups.

Variable	Controlled DM	Uncontrolled DM	P value
Maternal Age (Y, mean ± SD)	30.33 ± 6.2	30.8 ± 6.27	0.773
BMI (kg/m^2, mean ± SD)	32.5 ± 5.32	32.3 ± 5.05	0.882
Primigravidas (No., %)	4 (13.3 %)	3 (10 %)	0.68
GA at Doppler study (wks, mean ± SD)	35.13 ±0.97	35.33±1.03	0.442
Macrosomia (No., %)	9 (30%)	10 (33.3%)	0.781
Polyhydramnios (No., %)	8 (26.7%)	11 (36.7%)	0.405

Table (2): Laboratory parameters in controlled and uncontrolled diabetics groups.

Variable	Controlled DM	Uncontrolled DM	P value
Hb (g/dl - mean ± SD)	10.93 ± 1.13	10.64 ±1.23	0.388
PLT (x10^3/ul - mean ± SD)	207.20 ± 59.11	199.03 ± 45.69	0.552

Creatine (mg/dl – mean ± SD)	0.75 ± 0.30	0.72 ± 0.10	0.547
ALT (U/L – mean ± SD)	18.80 ±14.14	28.90 ±12.01	0.004
AST (U/L – mean ± SD)	25.70 ± 13.94	29.07 ±14.28	0.359
INR (mean ± SD)	0.99 ± 0.05	1 ± 0.02	0.522
FBS (mg/dl – mean ± SD)	96.83 ± 11.99	119. 5 ±18.3	< 0.001
PPBS (mg/dl – mean ± SD)	151± 22.79	179.3 ±18.74	< 0.001
HBA1C (% - mean ± SD)	5.9 ± 0.403	7.67 ±1.24	< 0.001

Table (3): Doppler indices in controlled and Uncontrolled diabetics groups.

Variable	**Controlled DM**	**Uncontrolled DM**	**P value**
UA RI (mean ± SD)	0.61 ± 0.05	0.6 ± 0.04	0.496
UA PI (mean ± SD)	0.96 ± 0.14	0.93 ± 0.12	0.489
MCA RI (mean ± SD)	0.82 ± 0.06	0.83 ± 0.05	0.627
MCA PI (mean ± SD)	1.79 ± 0.37	1.82 ± 0.36	0.802
MCA/UA PI(mean ± SD)	1.89 ± 0.33	1.94 ± 0.25	0.481