

Comparison of Umbilical Arterial Doppler and Middle Cerebral Arterial Doppler Assessments of Fetal Well-being in Mothers with Diabetes Mellitus: A Prospective Study

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Abstract

Background: Diabetes mellitus may accompany and complicate a pregnancy, resulting in poor neonatal outcomes.

Objectives: The aim of this study was to compare middle cerebral arterial (MCA) and umbilical arterial (UA) Doppler assessments for the evaluation of fetal well-being in mothers with pre-gestational or gestational diabetes mellitus.

Methods: This cohort study was performed on 103 pregnant diabetic women, admitted for prenatal care to the department of gynecology and obstetrics of Jame Zanan hospital (Tehran, Iran) in 2015. Sampling was performed, using the convenience method. All women underwent one or more Doppler ultrasound examinations in the third trimester of pregnancy, which included blood flow measurement through umbilical and middle cerebral arteries. Women with abnormal UA or MCA Doppler test results were subjected to labor induction or cesarean section, according to different parameters. The outcomes included neonatal acidosis, one- and five-min Apgar scores, hypoglycemia, hypocalcaemia, neonatal intensive care unit (NICU) admission, gestational age at delivery, and neonatal death. Chi-square test, t-test or Fisher's exact test, and logistic regression analysis were performed to analyze the data.

Results: Based on the findings, poor outcomes were detected in 48 women. Nearly 17.5% and 9.7% of women had abnormal UA and MCA Doppler test results, respectively. In total, 62% of women gave birth via cesarean section. The UA Doppler test results were significantly related with hypoglycemia, respiratory distress syndrome (RDS), one-min Apgar score < 7, five-min Apgar score < 7, and NICU admission, while the MCA Doppler results were significantly associated with RDS and neonatal death ($P < 0.05$). The sensitivity of both tests ranged between 20% and 60%. Logistic regression analysis revealed that UA Doppler test could predict poor outcomes after fasting blood sugar control ($P = 0.028$, OR = 3.6, CI: 1.15 - 11.13).

Conclusions: Both UA and MCA Doppler tests were associated with some neonatal outcomes. However, sensitivity of both UA and MCA assessments was low in the prediction of adverse neonatal outcomes. By the comparison of these two methods, we found that UA Doppler assessment is a better predictor of neonatal outcomes.

Keywords: Diabetes Mellitus, Umbilical Arteries, Doppler, Middle Cerebral Artery, Ultrasonography, Pregnant Women, Newborn

1. Background

Diabetes mellitus (DM) in pregnancy, which is divided into two categories of pre-gestational DM (PGDM) and gestational DM (GDM), complicates approximately 6-7% of pregnancies in the United States. The results of a study in Canada showed that the rate of both GDM and PGDM had doubled from 1996 to 2010 (1). Although no previous research has estimated the rate of PGDM in Iran, the prevalence of GDM was reported to be 3.41% (2).

DM is related to increased rates of perinatal morbidity and mortality. Pregnancies affected by DM are more likely to be associated with complications, such as increased

rate of cesarean section, macrosomia, hyperbilirubinaemia, shoulder dystocia, congenital anomalies, and birth trauma (1). Appropriate management of DM in pregnancy requires planned fetal surveillance to determine whether a pregnancy must be continued or terminated.

Although diagnostic tests such as fetal scalp blood sampling or umbilical cord blood sampling are available for the assessment of fetal well-being, they are all invasive methods with a high sampling failure rate, requiring membrane puncture or rupture. Instead, screening of fetal distress is applied to detect a fetus at risk (3). Different tests have been used to assess fetal well-being, such as fetal movement analysis, non-stress test, and biophysical pro-

file (BPP) (4). Although BPP is a relatively precise method in the detection of high-risk infants, it is not highly applicable in pregnant diabetic women due to the presence of adequate amniotic fluid, which satisfies the amniotic volume criterion, while other conditions are not met.

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 non-invasive method for the evaluation of fetal well-being in high-risk pregnancies (e.g., preeclampsia and intrauterine growth retardation) (5-7). However, application of Doppler ultrasound examination in diabetic pregnancies has revealed conflicting results (8-11). In fact, despite the widespread use of these techniques, few studies have investigated their effectiveness in improving perinatal outcomes in diabetic women (1).

2. Objectives

With this background in mind, in this research, we compared middle cerebral arterial (MCA) and umbilical arterial (UA) Doppler tests to evaluate their predictive validity and to determine which method is more advantageous for the prediction of adverse neonatal outcomes. The present study is the first research in Iran, evaluating two groups of women with GDM and PGDM.

3. Methods

3.1. Study Design and Subjects

This cohort study was performed on 103 pregnant diabetic women, admitted for prenatal care at the department of gynecology and obstetrics of Jame Zanan hospital, affiliated to Tehran University of Medical Sciences (Tehran, Iran) from the autumn of 2014 through the summer of 2015. Jame Zanan Referral hospital is a specialized governmental hospital where all obstetric conditions are treated and pregnant and postpartum women receive specialized care. Overall, there are four sections and 118 beds in this hospital.

In this study, convenience sampling method was applied. All eligible diabetic women, referred to the specialized obstetrics and gynecology clinic of Jame Zanan Hospital, were included in the study. The inclusion criteria were as follows: 1) pregnant women with PGDM or GDM, and 2) singleton pregnancy.

Women with GDM or PGDM had been detected through laboratory tests in the second and first trimesters of pregnancy, respectively. The exclusion criterion was a prior history of other chronic diseases in mothers or fetal anomalies, as they could affect fetal circulation in UA and MCA Doppler tests. The participants underwent sonography at

the time of recruitment in the study to assess fetal anomalies and gestational age. Finally, 103 women were recruited and no participant was excluded from the study. The researcher was a fellowship student of perinatology, responsible for the management of pregnant diabetic women during pregnancy.

3.2. Sample Collection

The sample size was determined to be 100 cases, based on a study by Shabani, in which the mean MCA in gestational diabetes was 2.1 ± 0.4 (with a significance level of 95%, precision of 0.08 from standard deviation, and power of 80%), and the formula used for estimating the mean value in a target population (12).

All women were admitted to the clinic in the first or second trimester of pregnancy. The participants underwent one or more Doppler ultrasound examinations in the third trimester. Women with abnormal UA or MCA Doppler test results were subjected to labor induction or cesarean section, according to different parameters. Accordingly, subjects with PGDM underwent insulin treatment. Abnormal perinatal outcomes included one-min and five-min Apgar scores < 7 , neonatal acidosis ($\text{pH} < 7.2$), hypoglycemia [blood sugar (BS) < 45 mg/dL], hypocalcaemia (calcium level < 8 mg/dl), neonatal intensive care unit (NICU) hospitalization > 24 hours, and neonatal death. Women with at least one poor outcome were categorized in the abnormal neonatal outcome group.

3.3. Measurements

In the first visit, mothers' obstetrics and medical history was taken. Gestational age was precisely calculated, based on both last menstrual period (LMP) assessment and sonography through crown-rump length measurement at 11 - 13 weeks of gestation or fetal head circumference measurement at 19 - 24 weeks of gestation. Obstetric examinations and laboratory tests, including complete blood cell count, urine analysis, and evaluation of fasting blood sugar (FBS) and 2-hour postprandial BS had been performed in the first trimester and were recorded in the patients' medical files.

The UA and MCA Doppler assessments were repeated whenever delivery was indicated. In addition, abnormal UA or MCA Doppler results in late pregnancy were an indication of pregnancy termination. A physician estimated the Apgar scores after birth. The Apgar score included five indicators: muscle tone, heart rate, respiratory effort, reflexes, and color. Newborns with a one-min Apgar score of < 7 were resuscitated. The umbilical blood cord sample was taken after birth to determine the blood pH.

3.4. Data Collection Tools

A questionnaire, including socio-demographic and obstetric history of the patient, was completed during the first visit; laboratory test results were also included in the following visits. All data and test results were precisely recorded in the patients' medical records at the obstetric clinic.

The ultrasound equipment was an Acuson Antares 500 probe (3.5 - 5 MHz, Siemens AG, 2011) with pulsed wave and color Doppler modes (high resolution). All sonography measurements were recorded in triplicate in three consecutive waveforms when the fetus was not moving or breathing. The equipment was a digital system, calibrated every week by an engineer.

3.5. Statistical Analysis

SPSS version 18 was used for the statistical analysis. The results are expressed as mean \pm SD and percentages. As Kolmogorov-Smirnov test results indicated, the data were not normally distributed. Mann-Whitney U test was used to compare the medians of maternal age, gestational age, and birth weight. Chi-square or Fisher's exact test was used to analyze the independence between two variables (neonatal outcomes and other variables).

The sensitivity and specificity of both Doppler tests for the prediction of poor outcomes were examined. We used Youden index to summarize the performance of UA and MCA Doppler tests. Overall, the index value ranges from -1 to 1 and has a zero value when the test is ineffective; on the other hand, a value of 1 indicates that the test is ideal. Also, multivariate logistic regression analysis was performed to investigate which Doppler test could predict poor neonatal outcomes. The significance level was set at 95%.

3.6. Ethical Considerations

The gynecology and obstetrics department of Tehran University of Medical Sciences approved the study proposal. Also, the regional ethics committee of Tehran University of Medical Sciences approved the study proposal. All the recruited mothers were verbally informed about the project and signed a written consent form. All women received proper treatment, based on the stage of the disease. Diabetes management was performed using the newest available equipments.

4. Results

In this prospective study, 103 women with gestational diabetes were assessed. Table 1 shows the subjects' characteristics in groups with normal and abnormal neonatal

outcomes. Based on the findings, poor outcomes were detected in 48 women. The mean (range) age, gestational age and birth weight were 32.9 years (20 - 44 years), 38.3 weeks (30 - 40 weeks), and 3,539 g (1700 - 4400 g), respectively.

Nearly 62% of women gave birth through cesarean section, and 21.3% had a history of spontaneous abortion. In total, 35.9% and 62.1% of women had an FBS level of ≥ 95 and BS level of ≥ 120 mg/dL, respectively. As the findings revealed, about 17.5% and 9.7% of women had abnormal UA and MCA Doppler test results, respectively. Table 2 presents the sensitivity, specificity, and Youden index value of UA and MCA Doppler tests in the prediction of neonatal outcomes. As the findings indicated, the sensitivity of both UA and MCA tests in the prediction of all outcomes was low.

UA and MCA Doppler assessments showed the highest sensitivity in detecting one-min Apgar scores < 7 and neonatal death. The results of multiple logistic regression analysis of MCA and UA Doppler tests regarding neonatal outcomes indicated that UA Doppler test could predict poor outcomes following FBS control ($P = 0.028$, OR = 3.6, CI: 1.15 - 11.13). However, MCA assessment could not predict poor outcomes after FBS management ($P = 0.172$).

5. Discussion

Fetal surveillance is necessary for the management of pregnancies, complicated with PGDM or GDM. Doppler methods have been claimed to have significant efficacy in the diagnosis of neonatal outcomes (13). In the present study, we examined whether UA and MCA Doppler assessments could help detect a fetus at risk of DM. The results of this study indicated that both UA and MCA Doppler tests had low sensitivity for neonatal outcomes, even though they were significantly associated with some neonatal outcomes. By the comparison of these two methods, we found that UA Doppler assessment was a better predictor of poor neonatal outcomes.

The present results indicated that maternal DM was associated with abnormalities in Doppler indices. This finding was not in harmony with the results reported in a study by Salvesen (9), which showed that maternal DM is not associated with abnormalities in Doppler indices of placental or fetal circulation. Nevertheless, the current results were in accordance with a previous study which showed higher values in women with GDM, compared to their normal counterparts (12).

We found that the results of both UA and MCA Doppler tests were significantly related with some neonatal outcomes. The results of some previous studies have also confirmed the association between abnormal UA Doppler test results and adverse perinatal outcomes (14-17). However, in the present study, we found that the sensitivity of both UA

Table 1. Sample Characteristics in groups of Normal and Abnormal Neonatal Outcomes^a

Variables	Median (IQR) ^b	Normal, (n = 48)	Abnormal, (n = 55)	P Value
Age, y	34 (10)	33 (10)	35 (9.5)	0.200
Gestational age, week	38.5 (1.0)	39 (0.9)	38.4 (1.0)	0.002
Birth weight	3500 (400)	3500 (500)	3600 (400)	0.332
Primigravidity	25 (24.3)	11 (10.7)	14 (13.6)	0.279
Nulliparity	47 (45.6)	20 (19.4)	27 (26.2)	0.043
PGDM ^c	53 (51.5)	18 (17.5)	35 (34.0)	< 0.001
Cesarean section	64 (62.1)	25 (24.3)	39 (37.9)	< 0.001
Fasting blood sugar (FBS) \geq 95	37 (35.9)	15 (14.6)	22 (21.4)	0.050
Blood sugar (BS) \geq 120	64 (62.1)	27 (26.2)	37 (35.9)	0.003
One-min Apgar score < 7	16 (100)	0	16 (100)	< 0.001
Five-min Apgar score < 7	11 (100)	0	11 (100)	< 0.001
Abnormal MCA ^d Doppler test	10 (9.7)	3 (2.9)	7 (6.8)	0.119
Abnormal UA ^e Doppler test	18 (17.5)	5 (4.9)	13 (12.6)	0.016
UA high resistance	12 (11.7)	5 (4.9)	7 (6.8)	0.036
UA absence	2 (1.9)	0	2 (1.9)	
UA reserved	4 (3.9)	0	4 (3.9)	

^aValues are expressed as No. (%).

^bInterquartile range.

^cPre-gestational diabetes mellitus.

^dMiddle cerebral artery.

^eUmbilical artery.

and MCA Doppler assessments was low. The present results were in line with the findings reported by Wong and colleagues. In a cohort study, they performed UA Doppler assessment on 104 women with type I and type II PGDM. They found that the sensitivity and specificity of UA Doppler assessment in the prediction of adverse perinatal outcomes were 35% and 94%, respectively (18).

The current results showed that UA Doppler test was a better predictor of poor neonatal outcomes. These findings were not in consistence with a previous study conducted on 50 pregnant diabetic women, which showed that MCA Doppler test had a significant effect on the prediction of adverse perinatal outcomes (19). In addition, the present study showed that the mean BS level was higher in women who had abnormal MCA Doppler test results, compared to women who showed normal results.

Overall, glycemic control in DM is very important and effective in decreasing perinatal morbidity and mortality (20). In this study, 35.9% and 62.1% of women had an FBS level of \geq 95 or a BS level of \geq 120 mg/dL, respectively. We recommend that future studies assess the predictive validity of both tests in larger sample sizes with low glycemic control. Although the rate of poor neonatal outcomes in

our sample was about 54%, the outcomes were not associated with abnormal Doppler test results of fetal circulation. This may be due to the fact that the outcomes were not severe enough to affect fetal circulation.

5.1. Strengths and Limitations

The first shortcoming of this study was the limited sample size, which obliged us to apply poor tests. Although glucose control is an important factor influencing pregnancy outcomes, we did not evaluate glycemic control in the patients by A1C test, which provides information about glycemic control over the last two months of pregnancy and can help categorize women into groups of good and poor glycemic control; this is in fact the second shortcoming of this study. The third limitation of this study was that the sample was not homogenous, consisting of patients with both good and poor glycemic control. On the other hand, the strength of this study was that the sample consisted of both GDM and PGDM women. Also, Doppler examinations were performed by one perinatologist, and women were supervised by the main researcher during pregnancy.

Table 2. Comparison of the Sensitivity and Specificity of Umbilical Arterial (UA) and Middle Cerebral Arterial (MCA) Doppler Tests in the Prediction of Neonatal Outcomes

Groups		Normal UA Doppler Test Results	Abnormal UA Doppler Test Results	P Value	Sensitivity of UA	Specificity of UA	Youden Index
Acidemia	5 (4.9)	3	2	0.209	40	84	0.24
RDS ^b	16 (15.5)	10	6	0.033 ^a	37	86	0.26
Neonatal death	4 (3.9)	2	2	0.140	50	84	0.34
Hypocalcaemia	5 (4.9)	17	1	0.624	20	83	0.03
Hypoglycemia	37 (35.9)	26	11	0.016 ^a	30	89	0.19
NICU [‡] admission	17 (16.5)	11	6	0.045 ^a	35	86	0.21
One-min Apgar score < 7	16 (15.5)	6	10	< 0.001 ^c	55	93	0.48
Five-min Apgar score < 7	11 (10.7)	5	6	0.003 ^d	33	94	0.27
Fetal distress	15 (14.6)	10	5	0.089	33	85	0.18
Poor outcomes ^c		31	13	0.005 ^d	30	92	0.22
Groups		Normal MCA Doppler Test Results	Abnormal MCA Doppler Test Results	P Value	Sensitivity	Specificity	
Acidemia	5 (4.9)	3	2	0.073	40	92	0.32
RDS ^b	16 (15.5)	12	4	0.047 ^a	25	93	0.18
Neonatal death	4 (3.9)	2	2	0.046 ^a	50	92	0.42
Hypocalcaemia	5 (4.9)	5	0	0.590	00	90	-0.10
Hypoglycemia	37 (35.9)	31	6	0.095	16	94	0.10
NICU ^c admission	17 (16.5)	13	4	0.058	24	93	0.17
One-min Apgar score < 7	16 (15.5)	10	6	0.001 ^d	60	95	0.55
Five-min Apgar score < 7	11 (10.7)	7	4	0.011 ^a	36	93	0.29
Fetal distress	15 (14.6)	12	3	0.159	20	92	0.12
Poor outcomes		37	7	0.068	16	95	0.11

^aP < 0.05.

^bRespiratory distress syndrome.

^cP < 0.001.

^dP < 0.01.

[‡]Neonatal intensive care unit.

5.2. Conclusion

In the present study, we found a relationship between both UA and MCA Doppler tests and some neonatal outcomes. However, the sensitivity of both UA and MCA Doppler assessments in the prediction of adverse neonatal outcomes was low. By the comparison of these two methods, we found that UA Doppler test was a better predictor of neonatal outcomes. Considering the small sample size of performed studies, we recommend that further systematic research and meta-analyses be designed to include all studies in this context and reach a more comprehensive conclusion.

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Footnote

Authors' Contribution: Mitra Eftekhariyazdi was the main researcher who wrote the first draft of the manuscript, performed sonography assessments, and collected the data. Shirin Niromanesh and Mahboobeh

Shirazi contributed to the study design. Mamak Shariat analyzed the data. Maryam Rabiei contributed to data collection. Forough Mortazavi revised the second draft of the manuscript, contributed to data interpretation, and performed critical revision of the text.

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