Original Article

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The Value of Fetal Cerebro-umbilical Doppler Indices in Predicting Umbilical Blood Gas Abnormalities and Apgar Score in Diabetic Pregnant Women

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Abstract

Aim: There is conflicting data regarding the utility of Doppler indices in patients with diabetes. Our objective was to investigate the value of fetal Doppler parameters on umbilical blood gas abnormalities and Apgar scores in term diabetic pregnancies treated with insulin.

Methods: A total of 120 pregnant women with pregestational or gestational diabetes underwent Doppler screening between 37 and 38 weeks of gestation. The main outcome was to compare the diagnostic performance of the umbilical artery-pulsatility index (UA-PI), middle cerebral artery-PI (MCA-PI), cerebroplacental ratio (CPR), and umbilicocerebral ratio (UCR) in detecting the presence of intrauterine hypoxemia.

Results: From the sample, 18 (15%) had type 1 diabetes mellitus (DM), 40 (33.3%) had type 2 DM, and 62 (51.7%) had GDM A2. The median gestational age at the time of Doppler screening was 37 weeks and 3 days (range 37 weeks to 38 weeks 2 days) and the mean ± standard deviation gestational age at delivery was 38 weeks 4 days ± 3 days. No significant correlations were observed for MCA-PI, UA-PI, CPR, or UCR with any of the measured outcomes. Analysis of Doppler parameters of normal neonates and those with abnormal composite tests showed that Doppler parameters were non-significant in predicting abnormal composite outcomes.

Conclusion: The data obtained from this study show that the low predictive ability of Doppler velocimetry in abnormal neonatal tests results in pregnancies complicated by diabetes.

Keywords: Diabetes mellitus, fetal Doppler, fetal hypoxia, pregnancy, pulsatility index

Introduction

Diabetes mellitus (DM) is a chronic metabolic disease that affects more than 21 million births globally every year. Gestational DM is the most common metabolic disorder in pregnancy (1). The worldwide prevalence of all types of DM during pregnancy is estimated at 17% (2). While only a minority of the cases of carbohydrate intolerance during pregnancy represent women with pre-existing diabetes, most cases (~85%) develop or are first recognized during pregnancy (3,4). Diabetes during gestation is associated with an increase in adverse outcomes for the maternal-fetal dyad (5-8). In addition, maternal hyperglycemia can cause fetal hypoxia, which can ultimately lead to fetal respiratory distress syndrome, stillbirth, and neonatal death (9).

Fetal chronic hypoxia leads to persistent modifications in fetal circulation; this hemodynamic adaptation ensures the delivery of oxygen and nutrients to the brain (10). This compensatory phenomenon, the so-called "brain sparing effect", leads to vasodilatation and reduced resistance in the cerebral vessels, and reflects Doppler assessment with a decreased middle cerebral artery-pulsatility index (MCA-PI) and an increased umbilical artery-PI (UA-PI). This results in a change in the cerebroplacental ratio (CPR), i.e., MCA-PI/UA-PI, and the reversal of this ratio, termed the umbilicocerebral ratio (UCR). In recent years, fetal

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Doppler evaluation has become an important screening and surveillance tool in high-risk pregnancies (11). The use of abnormal Doppler indices in pregnancies complicated by placental insufficiency led to improvements in fetal surveillance and adverse perinatal outcomes (12). Moreover, maternal diabetes is also associated with widespread pathologic structural changes, including utero-placental circulation. This pathologic remodeling is associated with increased vascular resistance and tissue hypoperfusion. However, there is conflicting data regarding the utility of Doppler indices in a diabetic cohort. The main purpose of this study was to investigate the role of fetal Doppler parameters on umbilical blood gas abnormalities and Apgar score in term pregestational and gestational diabetic pregnancies treated with insulin.

Materials and Methods

Compliance with Ethical Standards

This study was conducted according to the principles stated in the Declaration of Helsinki. The Clinical Research Ethics Committee of the Medical Faculty of Erciyes University approved the study (KAEK-2016/170). Informed consent forms were obtained from all patients.

Study Design and Participants

This cross-sectional study was designed using the medical data of patients followed up in Erciyes University Faculty of Medicine, Department of Gynecology and Obstetrics with the diagnoses of pregestational diabetes (type 1 DM and type 2 DM) and insulin-treated gestational diabetes (GDM A2) between 2015 and 2016. The enrollment criteria were as follows: maternal age older than 18 years, singleton pregnancy, and morphologically normal fetus. Pregnancies complicated by fetal or severe maternal infections, maternal hypertensive disorders, active smokers, or maternal major medical diseases were excluded from the analyses.

After providing verbal informed consent, low-risk pregnant women routinely underwent blood glucose measurement according to the institutional guidelines at 24-28 weeks of gestation with a 50 g glucose challenge test (GCT). If 50 g of GCT was positive with a 135 mg/dL cutoff point, then a 100 g oral glucose tolerance test (OGTT) was performed according to the diagnostic criteria of Carpenter and Coustan (13). Patients with a spot blood glucose level exceeding 190 mg/dL or two or more values above the threshold levels in the OGTT were regarded as having diabetes. All diabetic pregnant women were assessed with a 1-hour postprandial blood glucose profile, followed by diet counseling (30 kcal/kg) every 2 weeks. Patients were hospitalized at 37 weeks of gestation and monitored by the nonstress test and fetal movement count. In addition, they were evaluated by ultrasound examination in terms of amniotic fluid index, estimated fetal weight, placental localization, and Doppler parameters. All deliveries were performed at 38-39 gestational weeks if the blood glucose levels were regulated and there were no additional risk factors.

Data collected included patient demographics, type of diabetes, body mass index (BMI), total daily dose of insulin, glycosylated hemoglobin (HgbA1c) levels, gestational age at the time of sonographic scan and delivery, Doppler parameters of the umbilical and MCAs, neonatal birth weight, umbilical arterial acid-base status, and Apgar score. Gestational age was based on the last menstrual period, unless the first trimester sonogram (crown-rump length measurement) and the maternal report of the last menstrual period showed an inequality exceeding 7 days.

All Doppler examinations were performed by the same experienced high-risk pregnancy specialists (M.S.K.) with a Voluson 730 Pro scanner equipped with a 5-8 MHz convex transabdominal transducer (GE Healthcare, Wauwatosa, WI) in accordance with the International Society of Ultrasound in Obstetrics and Gynecology practice guidelines: the use of Doppler ultrasonography in obstetrics (14). The UA Doppler flow velocity waveforms were obtained from a free-floating cord loop, and MCA Doppler velocimetry was performed in an axial section of the fetal head, at its origin in the circle of Willis. CPR and UCR were computed as the ratios between MCI-PI and UA-PI and, conversely, the ratios between UA-PI and MCA-PI, respectively. Since all of the measurements were performed within the same gestational week (37-38 weeks), we used absolute CPR and UCR values rather than the multiple of the median or Z score, as previously described (15,16).

The main outcome was to compare the diagnostic performance of fetal Doppler parameters (UA-PI, MCA-PI, CPR, and UCR) in detecting the presence of intrauterine hypoxemia. Intrauterine hypoxemia was measured by umbilical arterial gas analysis and Apgar score (pH, base excess, 1 min, and 5 min Apgar score). Abnormal neonatal test results were defined as follows: pH <7.23, base excess more than 6 (mEq/L), 1-min Apgar score <5, 5-min Apgar score 7 (17,18).

Statistical Analysis

The Kolmogorov-Smirnov test and histograms were used to assess the distribution of the data. Categorical variables were expressed as numbers and percentages (%). Normally distributed data were compared with the Student t-test; asymmetrically distributed data were compared with the Mann-Whitney U. A linear regression analysis was implemented to assess the association between UA-PI, MCA-PI, CPR, and UCR and each neonatal

outcome measure. The receiver-operator characteristic curve (ROC) was suggested to investigate applicability for predicting the neonatal composite outcome. SPSS version 23 (SPSS Inc., Chicago, IL) was used for analysis, and a p-value <0.05 was deemed statistically significant.

Results

A total of 120 women with DM met the inclusion criteria and were recruited for the study. Of these, 15% (18/120) had type 1 DM, 33.3% (40/120) had type 2 DM, and 51.7% (62/120) had GDM A2. The mean maternal age and BMI of our sample were 33.25±6.48 years and 33.82±6.26 kg/m^2, respectively. The majority of patients, 107 (89.2%), were multiparous, and the rest, 13 (10.8%), were primigravida. The median (Q1-Q3) gestational age at the time of Doppler screening was 37 weeks and 3 days (range 37 weeks to 38 weeks 2 days), and the mean ± standard deviation (SD) gestational age at delivery was 38 weeks 4 days ± 3 days. The interval between Doppler screening and delivery (mean ± SD) was 6.2±2.1 days. Patient baseline demographic and clinical data are described in Table 1.

Table 2 shows the results of the linear regressions of fetal Doppler parameters for predicting abnormal neonatal test results. According to our results, no significant correlations were observed for MCA-PI, UA-PI, CPR, or UCR with any of the measured outcomes.

Table 3 shows a comparison of Doppler parameters between normal neonates and those with abnormal composite tests. Abnormal composite tests were defined as the combination of pH <7.23, base excess <-6.3, and 5th Apgar score <5. According to the analysis results, Doppler parameters were not significant predictors of abnormal composite outcomes, with the ROC curves of Doppler parameters showing a poor predictive value for each Doppler parameter (Figure 1).

Table 1. The baseline demographic and clinical parameters

Maternal age (years)	33.25±6.48
Body mass index (kg/m^2)	33.82±6.26
Nulliparous	13 (10.8%)
Multiparous	107 (89.2%)
Total daily insulin dose (units)	25 (10-48)
HgbA1c levels	5.67±1.01
The type of diabetes	
Gestationel A2 Type 1 Type 2	62 (51.7%) 18 (15%) 40 (33.3%)
Gestational age at the time of Doppler screening (weeks)	37+3 (37-38+2)
Gestational age at the time of delivery (weeks)	38+4±3
Mode of delivery	
Vaginal delivery Cesarean section	16 (13%) 104 (87%)
UA-PI	0.93±0.29
MCA-PI	1.64±0.43
CPR	1.9±0.7
UCR	0.6±0.23
Newborn weight (g)	3569±543
Apgar score 1st minute	8 (2-8)
Apgar score 5th minute	10 (0-10)
Neonatal pH	7.31±0.7
Neonatal base excess	-4.1±3.8

Values are expressed as n (%), mean ± SD or median (1st-3rd quartiles).
UA: Umbilical artery, PI: Pulsatility index, MCA: Middle cerebral artery, CPR: Cerebroplacental ratio, UCR: Umbilicocerebral ratio

Table 2. Results of linear regressions of fetal Doppler parameters on predicting abnormal neonatal test results. P-values

	pH	Base excess	1st min Apgar	5th min Apgar
UI-PI	0.853	0.481	0.455	0.642
MCA-PI	0.484	0.155	0.661	0.778
CPR	0.976	0.787	0.426	0.632
UCR	0.99	0.452	0.265	0.468

UA: Umbilical artery, PI: Pulsatility index, MCA: Middle cerebral artery, CPR: Cerebroplacental ratio, UCR: Umbilicocerebral ratio

Discussion

Our study, where we investigated the role of fetal Doppler parameters on umbilical blood gas abnormalities and Apgar score, showed that Doppler ultrasonographic scans of MCA-PI, UA-PI, CPR, and UCR were not correlated with neonatal Apgar score or umbilical cord acid-base status in otherwise healthy diabetic patients. In addition,

Table 3. Comparison of Doppler parameters between normal neonates and neonates having abnormal composite tests

Doppler parameters	Normal neonatal tests (n=93)	Composite abnormal neonatal tests (n=27)	p-value
UA-PI	0.85 (0.44-2.22)	0.93 (0.65-1.77)	0.116**
MCA-PI	1.59 (0.65-2.89)	1.70 (0.74-2.54)	0.481**
CPR	1.92±0.68	1.82±0.74	0.501*
UPR	0.54 (0.26-1.35)	0.58 (0.28-1.14)	0.468**

*Student's t-test, Mean ± standard deviation was given for descriptives. **Mann-Whitney U test, Median (minimum-maximum) was given for descriptives.
Combined abnormal neonatal tests included pH pH<7.23, Base excess <-6.3, 5th Apgar score <5, p<0.05, statistically significant difference.
UA: Umbilical artery, PI: Pulsatility index, MCA: Middle cerebral artery, CPR: Cerebroplacental ratio, UCR: Umbilicocerebral ratio

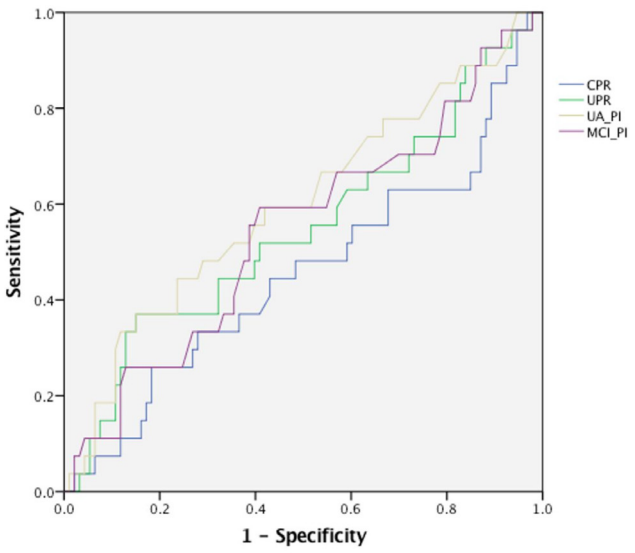

Figure 1. Receiver operating characteristic analyses for predicting abnormal composite outcomes using Doppler parameters

fetal Doppler parameters did not offer a diagnostic tool for predicting abnormal composite neonatal results among patients with diabetes.

The applicability of fetoplacental Doppler sonography in diabetic pregnancies for fetal monitoring is still disputed because previous studies showed incompatible results (15,16,19-23). In the study by To and Mok (20) the PI of UA, the diameter of UV, and the mean maximum velocity of umbilical venous flow were measured. They concluded that umbilical velocimetry at near term was unable to predict abnormal pregnancy outcomes. In parallel with this, Pietryga et al. (19) reported that placental Doppler sonography does not appear to have clinical value for fetal surveillance unless there is an absence of fetal growth restriction and/or preeclampsia. In the prospective single-center cohort study of Ganor Paz et al. (21) in pregnancies affected by GDM, they found that CPR below the 10th percentile was not associated with adverse perinatal outcomes. In a previous study that compared transcranial Doppler indices of fetal brain hemodynamics in diabetic versus normal pregnancies, a higher PI of the MCA was found among the diabetic group; however, they did not provide any information about insulin use or daily insulin dose (22). The importance of UCR is still a subject of debate in estimating fetal hypoxia, and it is currently unclear whether UCR should be preferred over other Doppler indices. In a recent study, Familiari et al. (16) found that MCA-PI and UCR were significantly correlated with a low neonatal pH; however, they only included gestational diabetic patients in their cohort, and most of these pregnancies were regulated by diet. Fetuses of women with insulin-controlled diabetes had poorer neonatal outcomes than those of women treated with dietary control alone (23). Therefore, our cohort reflects the strong metabolic and hemodynamic effects of diabetes on umbilical cord blood gas analysis.

Transcranial Doppler findings have provided valuable predictive models for assessing high-risk pregnancies. in uteroplacental insufficiency, the PI of MCA tends to reduce to increase cerebral perfusion, which is called the brain sparing effect. However, according to our results, there was no correlation between MCA-PI, CPR, and umbilical cord acid-base status, and no cerebroplacental compensation was observed, which is contrary to the situation observed in uteroplacenta insufficiency. There are some possible explanations for this. Although DM is an intrauterine hypoxic condition, the response of the ductus venosus to hypoxia is blunted and the umbilical venous/ductus venosus shunt ratio is lower compared to healthy control (24). Therefore, it may be speculated that the brain sparing effect at the ductus venosus level is less operative in fetus of DM mothers, and this disregulation may propagate to the MCAs with resultant higher MCA-PI in the acidotic fetus of DM mothers. On the other hand, UA-PI is largely dependent on placental vascular surface area and in DM pregnancies, this is known to enlarge due to increased local vascular growth factors with resultant normal UA-PI values (25,26). Therefore, it seems that hemodynamic pathologies and adaptations are not operative in the fetus of diabetic mothers (FODM). Thus, the inefficiency of the cerebral protective mechanism is partly responsible for sudden third trimester fetal distress and loss in FODM (27). Moreover, increased red blood cell mass and viscosity and altered perfusion of fetal liver may further affect cerebral regulation in these cases (28).

The clinical importance of Doppler measurement in fetal growth restriction is well known (29). However, data gathered from this study showed no predictive value for Doppler indices as a screening test for fetal well-being in pregnancies complicated with diabetes. In practice, the non-stress test is still the main clinical tool for the surveillance of diabetic pregnancies. The combination of strict glycemic control and the non-stress test may improve perinatal outcomes.

Study Limitations

The main limitation of the current study is its retrospective design and the inherent bias associated with observational data. A second limitation is the lack of a prestudy power analysis. However, this study also presents some strength. To the best of our knowledge, this study provides the first data for pre- and gestational diabetes cohorts with which the doppler parameters were investigated at term for cases treated with insulin. This stricter study population enabled us to objectively

investigate the metabolic and hemodynamic effects of diabetes on umbilical blood gas abnormalities and Apgar scores. Another important point is that all cases are managed with a single institutional protocol, and all sonographic exams are performed by the same experienced high-risk pregnancy specialists. In addition, we set pH value <7.23 as the threshold to define fetal acidosis, which was related to a 1% false-negativity for neonatal asphyxia (17). Another advantage of the present study is that it includes 85% rate of cesarean section, most of which are operated on an elective basis. This factor largely excludes intrapartum hypoxic events associated with vaginal delivery that affect fetal acid-base status in a fetus with otherwise normal doppler findings at 37 weeks (30).

Conclusion

The data obtained from the present study show that doppler velocimetry is not predictive of abnormal neonatal test results in pregnancies complicated with diabetes. Further prospective studies are needed to confirm the current findings.

Ethics

Ethics Committee Approval: The Clinical Research Ethics Committee of the Medical Faculty of Erciyes University approved the study (KAEK-2016/170).

Informed Consent: Informed consent forms were obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S.K, M.D Concept: C.C, M.S.K., M.D., Design: M.S.K., T.T., C.C Data Collection or Processing: M.S.K., M.D., Analysis or Interpretation: C.C., M.S.K., T.T., Literature Search: C.C., M.D., T.T., Writing: C.C., M.S.K., T.T.

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