The relationship between cardiac adaptation to uteroplacental Doppler flow and perinatal outcome in pregnant women with diabetes

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Summary

Diabetes is a metabolic disorder that complicates pregnancy. Early detection of patients at risk of developing complications is particularly important. Failure of normal cardiovascular adaptation that takes place in pregnancy has been associated with poor perinatal outcome in preeclamptic patients. The aim of this study was to investigate if complications were higher in diabetic patients with cardiac maladaptation. Fetal, uteroplacental Doppler and echocardiographic examinations were performed once in the second and third trimesters in diabetic and healthy pregnant patients. Physiological cardiac hypertrophy was apparent in healthy patients. This, although within normal limits, was less prominent in patients with diabetes. The majority of patients were found to have normal Doppler waveforms. The abnormal uteroplacental flow group consisted almost entirely of patients with pregestational diabetes, especially type I diabetes. Neonatal complications were most common in this group. No relationship was found between echocardiographic findings, Doppler waveforms and poor perinatal outcome.

Key words: Doppler; Echocardiography; Diabetes; Pregnancy.

Introduction

The incidence of diabetes, the most common metabolic disorder in pregnancy, is 1-4% [1]. Gestational diabetes constitutes 90% of diabetes cases [2]. Diabetes during pregnancy complicates pregnancy. Even if the glucose intolerance resolves after pregnancy, these women and their offspring are at risk of developing diabetes later on [3, 4]. Therefore, pregnancy can be considered as an opportunity to identify these women and treat them before any vascular damage occurs. Early identification of diabetic pregnancies reduces maternal and fetal mortality and morbidity. The incidence of the resultant congenital anomalies, macrosomia and birth trauma decrease with good glycemic control [5].

Diabetes affects the placenta and the fetus as well as the eye, heart and kidney. Intrauterine growth restriction (IUGR) as a result of uteroplacental insufficiency and preeclampsia is more common in diabetic pregnancies [6]. With the use of Doppler flow in fetal surveillance, fetal morbidity can be reduced.

With advancing gestational age, trophoblasts invade the spiral arteries in the decidua and myometrium, and uteroplacental resistance decreases to oxygenize and nourish the baby [7]. If the trophoblastic invasion is not complete such as in preeclampsia and IUGR, uteroplacental flow decreases and is associated with poor perinatal outcome [2, 7]. In diabetic patients, particularly in those with vascular involvement, preeclampsia and IUGR are more common [8]. Assessment of diastolic function by echocardiography has proven useful in identification of patients who show cardiac adaptation and in understanding the underlying mechanism in patients with abnormal uterine artery waveforms [9]. A study revealed that patients with abnormal uterine waveforms and cardiac maladaptation more frequently had pregnancy-related complications [10]. Another study using echocardiography in pregnant patients with type I diabetes detected cardiac maladaptation in these patients [11]. In this study we aimed to investigate the effect of cardiovascular adaptation in diabetic patients on uteroplacental flow and fetal outcome.

Material and Methods

In this prospective controlled study, patients with diabetes, including gestational and pre-gestational diabetes, and healthy pregnant women whose 50 g glucose tolerance test at 24 weeks was found to be normal were recruited over a one and a half year period. The study was carried out at Hacettepe University Medical Faculty Obstetrics and Gynecology Department. Patients who smoked, had chronic diseases other than diabetes, were on medications other than insulin and vitamins, had multiple pregnancies, fetuses with known or suspected chromosomal and structural anomalies and intrauterine infection were excluded from the study. Written informed consent was obtained from all the patients and the study was approved by the local ethics committee.

In all cases gestational age was verified in the first trimester by crown-rump-length (CRL) measurements. Diabetic and healthy patients had two scans and echocardiography in the second and third trimesters. During the scan, the bilateral uterine artery, umbilical, and middle cerebral artery, and ductus venous flow were assessed. All scans were performed by one trained operator using GE Diasonics 2. The Doppler flows were obtained when the fetus was not active and did not breathe. Every fetal vessel was sampled three times; the insonation angle was below 30° and five successive waveforms were obtained from each vessel. The patient had echocardiography on the

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Table 1. — *Demographic characteristics of the patients*.

	Diabetes (n = 20)	Control (n = 25)	*p* value
Maternal age	33.2 ± 4.18	34 ± 4.24	NS
Maternal weight (kg)	71.6 ± 7.4	69.4 ± 6.9	NS
Maternal height (cm)	163 ± 7.8	161 ± 6.4	NS
Delivery week	37.2 ± 2.25	38.6 ± 1.52	NS
Birth weight	3141 ± 617	3307 ± 74	NS

NS: not significant.

Table 2. — *Hemodynamic variables in the two groups*.

	Diabetes (n = 20)	Control (n = 25)	*p* value
Pulse	91 ±11	89 ±13	NS
MAP (mmHg)	92.4 ± 11.7	89.9 ± 8.6	NS
CO (lt)	5.33 ± 1.42	6.31 ± 1.10	NS
SV (ml)	62.2 ± 15.9	77.4 ± 13.4	0.01
TVR (Dyn/sn/cm^5)	1488 ± 669	1218 ± 326	NS

same day after a period of 20 min to avoid any possible influence of the gravid uterus on circulation. Echocardiography was done by one skilled operator with Flex Scan T57S GEVİNGMED, USA. Left ventricle end-diastolic diameter, left ventricle end-systolic diameter, left ventricle end-diastolic wall thickness, end-diastolic septum thickness, fractional shortening, ejection fraction, left atrial diameter and transmitral flow pattern (E/A ratio) were assessed according to the American Society of Echocardiography criteria. Blood pressure and pulse were recorded. After delivery, cord blood was examined and birth weight and Apgar score were recorded. The babies were followed-up until discharge from the hospital. Intensive care requirement, respiratory distress syndrome, intraventricular hemorrhage and necrotizing enterocolitis cases were recorded.

Statistical analysis

The Student's *t*-test was used to determine distribution of the patients by age. The independent two-sample *t*-test was used to determine differences between the groups, and the dependent *t*-test for paired samples was used to evaluate the differences in variables within a group. End-diastolic wall thickness did not show any parametric distribution. The Mann-Whitney U test was used to assess intragroup differences and Wilcoxon's signed rank test was used to assess intergroup differences.

Results

There were 20 patients in the study group and 25 patients in the control group. In the study group, 16 patients (80%) had gestational diabetes, two (10%) had type I diabetes and two (10%) had type II diabetes. Demographic characteristics were similar in both groups (Table 1).

Pulse, mean arterial pressure (MAP) and total peripheral vascular resistance (TVR) were higher in the diabetic group. Cardiac output (CO) and stroke volume (SV) were higher in the control group; however, only the difference in stroke volume was statistically significant (Table 2). Left ventricle end-diastolic (LV-EDD) and end-systolic (LV-ESD) and left atrial diameter (LAD), ejection fraction (EF), fractional shortening (FS), end-diastolic wall thickness (EDWT) and E/A ratio means are shown in Table 3.

LV-EDD, LV-ESD and EDWT increased from the second to third trimesters in both groups. Intragroup differences in LV-EDD and LV-ESD were statistically significant in both groups ($p < 0.001$). There was no significant difference in LV-EDD and LV-ESD between groups. The change in EDWT was only statistically significant in the control group ($p < 0.05$). EF, FS and E/A ratio decreased in the third trimester when compared to the second trimester in both groups ($p < 0.001$). LAD increased in both groups. When differences in the variables between two trimesters were evaluated, only the differences in LAD ($p < 0.001$) and E/A ratio ($p < 0.005$) were statistically significant (Table 3). The difference in EDWT was analyzed with Wilcoxon's signed rank test and there was a significant difference between the two groups ($p < 0.05$). When diastolic functions were analyzed, the E/A ratio was similar in both groups. In the subset of patients whose fetuses developed fetal distress, the E/A ratio in the second trimester was lower than the mean E/A ratio of both groups. The increased TVR decreased the E wave in these patients. However, this finding was less striking in the third trimester.

In the study group, two patients (10%) had early diastolic notch, and three had increased S/D ratios. In the control group, none of the patients had early diastolic notch and one (4%) had an increased S/D ratios in late pregnancy. Of the two patients who had early diastolic notch, one had type I diabetes and the other type II diabetes. The fetus of the type I diabetes patient developed IUGR later on. The other patient's fetus did well. Umbilical artery S/D ratios in the third trimester were 15% and 4% in the study and control groups, respectively. In the third trimester four patients had an increased S/D ratio. Three of these patients were diabetic and one was not. Two of the diabetic patients were type I diabetics. Both of the babies of the type I diabetics had IUGR, and cesarean section was required in both of them because of fetal distress. One of these fetuses had early diastolic notch as well. The cesarean rate was higher in the diabetic group. When the patients who requested elective surgery were excluded, this difference was more prominent. The main indications for cesarean in the diabetic group were fetal distress and macrosomia.

In the study group the 10 min Apgar scores for three babies were below 8. Two of these were delivered preterm and belonged to type I diabetic mothers. The preterm delivery rate was higher in the diabetic group. The indication was fetal distress in these babies and both had IUGR. They needed surfactant treatment for respiratory distress, one developed necrotizing enterocolitis and they both required long-term intensive care. One patient in the diabetic group had operative delivery because of a long second stage and maternal exhaustion. This baby was not macrosomic. In the study group two babies were macrosomic and they belonged to the mothers with gestational diabetes.

In the study group two LGA and two SGA babies had hypoglycemia. The incidence of hyperbilirubinemia was higher among the babies of the study group (Table 4).

Table 3. — *The means of the study and control groups in second and third trimester (TM) and the change (Δ) between the two trimesters*.

	Study Group (n = 20)			Control group (n = 25)		
	2nd TM	3rd TM	Δ	2nd TM	3rd TM	Δ
LV-EDD (cm)	4.870 ± 0.48	4.875 ± 0.42	-0.005 ± 0.185	4.92 ± 0.32	4.95 ± 0.34	-0.03 ± 0.102
LV-ESD (cm)	2.940 ± 0.42	2.985 ± 0.40	-0.045 ± 0.278	3.05 ± 0.34	3.09 ± 0.31	-0.040 ± 0.173
EF (%)	69.2 ± 5.7	69.1 ± 5.4	0.10 ± 1.50	69.5 ± 3.5	69.4 ± 3.6	0.12 ± 1.78
FS (%)	39.8 ± 5.2	39.3 ± 5.5	0.50 ± 2.72	39.6 ± 3.0	39.4 ± 2.8	0.2 ± 1.64
EDWT (cm)	0.89 ± 0.13	0.85 ± 0.89	0.05 ± 0.16	0.88 ± 0.10	0.89 ± 0.10	-0.01 ± 1.64
E/Aratio	1.35 ± 0.29	1.34 ± 0.28	0.01 ± 0.10*	1.40 ± 0.24	1.31 ± 0.19	0.09 ± 0.20*
LA(cm)	3.26 ± 0.30	3.37 ± 0.28	-0.11 ± 0.35*	3.25 ± 0.22	3.45 ± 0.25	-0.20 ± 0.24*

*Statistically significant when the study and control group are compared.

Table 4. — *Pregnancy complications and neonatal outcomes*.

	Diabetes (n = 20)	Control (n = 25)
Pregnancy complications		
Delivery		
Cesarean section	10 (50%)	10 (40%)
10 minute Apgar ≤ 7	3 (15%)	1 (4%)
Fetal distress	4 (20%)	2 (8%)
Pretem delivery	4 (20%)	1 (4%)
Operative delivery	1(5%)	0 (0%)
Neonatal outcome		
LGA	2 (10%)	0 (0%)
SGA	2 (10%)	1 (4%)
RDS	2 (10%)	0 (0%)
IVH	0 (0%)	0 (0%)
NEC	1(5%)	0 (0%)
Hypoglycemia	4 (20%)	1 (4%)
Hyperbilirubinemia	7 (35%)	4 (16%)
Perinatal mortality	0 (%0)	0 (0%)

Discussion

Pregnancy is a burden on the cardiovascular system. In a healthy pregnant woman plasma volume increases starting from the first weeks of pregnancy [11]. The cardiac muscle is stretched as a result of increased preload, it hypertrophies and ventricular and atrial diameters are increased. Because of low resistance in the placental vascular bed, the TVR and afterload decrease and CO and SV increase.

Echocardiography was performed in patients whose pregnancies were complicated by IUGR and preeclampsia. It was shown that CO and intravascular space were not as large as they should have been [12]. The mechanism is not very well known yet, but inadequate intravascular volume expansion is associated with defective cardiovascular adaptation. Taegtmeyer *et al*. reported that the cardiac muscle of diabetic patients shows functional, biochemical and morphologic alterations [13]. Therefore, examination of the cardiovascular system early in pregnancy helps in understanding maternal-fetal homeostasis and may prove useful in predicting complications.

In this study, with advancing gestational age, cardiac mass increased in both groups. This finding confirms other studies which found an increase in cardiac mass in pregnancy.

When the group that had developed fetal distress during labor was analyzed, the mean values of LV-EDD, LV-ESD and LAD were lower than those of both the study and control groups. However, because this sample was very small, statistical significance could not be determined, which is consistent with other studies [14]. Valensis *et al*. reported that in patients with defective placentation, left ventricular hypertrophy does not develop because of increased peripheral vascular resistance [9]. Bosio *et al*. stated that it is possible to diagnose cardiac maladaptation by echocardiography at the 12th week of pregnancy in patients with preeclampsia [15].

The sensitivity of the second trimester uterine artery Doppler assessment to detect preeclampsia and IUGR in the presence of diastolic notch and increased resistance index is reported to be 85%. Olofson *et al*. found the umbilical artery PI higher in type I diabetic patients [16]. In the fetuses with high umbilical artery PI, fetal death, IUGR, preeclampsia and chronic hypertension are more frequently seen. In this study fetal distress was 2.5 times higher in the study group. After birth, these babies develop hypoglycemia and hyperbilurinemia and more frequently require prolonged intensive care stay. Grunewald *et al*. stated that if the expected decrease in uterine artery PI does not occur, then pregnancy-related complications increase [17].

Conclusion

In this study the systolic and diastolic functions were similar in both groups. This can be explained in two ways. Either the groups were too small to detect any difference or most of the study group constituted gestational diabetics who had no vascular disease. Although high umbilical artery S/D ratio, notch in the uterine artery and fetal distress were more common in diabetic patients, it is hard to draw any conclusions because of the small size of the groups.

Fetuses of the diabetic patients are at risk of developing complications. Doppler examination is useful in these patients in fetal surveillance. If the expected physiologic cardiac hypertrophy does not appear, then it can be associated with poor perinatal outcome. Maternal echocardiography can identify cardiac maladaptation as early as the first trimester. Echocardiography may be used in combination with Doppler ultrasound in patients who have ele-

vated vascular resistance to increase the sensitivity. This study should be regarded as a preliminary study. New randomized controlled studies with larger sample sizes are required to reach definitive conclusions.

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