UTEROPLACENTAL DOPPLER FLOW VELOCITY WAVEFORM ANALYSIS CORRELATES POORLY WITH GLYCEMIC CONTROL IN DIABETIC PREGNANT WOMEN

Alexander D. Kofinas, M.D., Mary Penry, R.N., R.D.M.S., and Melissa Swain, R.N.

ABSTRACT

We examined 65 pregnant women with gestational (n = 31) and insulin dependent (n = 34) diabetes mellitus in order to evaluate the clinical usefulness of Doppler flow velocity waveform analysis in these pregnancies. Umbilical and uterine artery flow velocity waveforms were obtained during the third trimester with a continuous wave Doppler device. Quality of maternal glycemic control was evaluated by hemoglobin (Hb) A_1 measurements at the time of delivery in 61 patients and by mean capillary blood sugars during the third trimester of pregnancy in four patients. There was no difference in various clinical and Doppler parameters between patients with good glycemic control and those with poor control. In contrast, the same clinical and Doppler parameters were significantly different in patients with preeclampsia than in those without preeclampsia, regardless of glycemic control. There was a poor positive linear correlation ($r = 0.30$, $p < 0.02$) between maternal HbA_1 and umbilical artery flow velocity waveforms (systolic/diastolic ratio). Proteinuria correlated better with umbilical artery systolic/diastolic ratio ($r = 0.49$, $p < 0.001$). We conclude that Doppler flow velocity waveform analysis may be clinically useful only in diabetic pregnancies complicated by preeclampsia.

In the recent years the outcome of pregnancies complicated by diabetes has improved significantly and it has approached that of normal pregnancies. This has been achieved in part through better understanding of maternal metabolism during pregnancy and improved fetal surveillance and neonatal care. Despite all the improvements, however, diabetes mellitus remains an important cause of maternal morbidity and perinatal morbidity and mortality.[1,2] Although euglycemia is instrumental in the reduction of perinatal morbidity and mortality, it remains illusive in a number of patients.[3] It is in these patients that evaluation of fetal well-being becomes imperative in order to prevent fetal compromise and fetal death.

Various tests have been introduced over the years for the evaluation of fetal well-being. Although nonstress test remains the cornerstone of fetal surveillance in the majority of perinatal centers, it is not perfect.[4–6] Doppler flow velocity waveform (FVW) analysis has been shown to correlate with perinatal outcome in high-risk pregnancies, including some pregnancies complicated by diabetes.[7–9] Unlike in other clinical conditions, published experience with the use of Doppler in the evaluation of fetal well-being in diabetic pregnancies is limited to one investigation and a few isolated case reports.[10–12] The present study was designed in a prospective manner to further investigate the clinical significance of Doppler FVW analysis and its association with perinatal outcome in pregnancies complicated by diabetes mellitus.

MATERIAL AND METHODS

Sixty-five pregnant diabetic women were studied. The study participants were recruited from the high-risk clinics of the Wake Forest University Medical Center (Reynolds Health Center and the Depart-

Section on Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, York Hospital, York, Pennsylvania

Reprint requests: Dr. Kofinas, Chief, Maternal-Fetal Medicine, York Hospital, York, PA 17405

ment of Clinics of North Carolina Baptist Hospital, Winston-Salem, NC). Approximately half of the patients were indigent and the other half were cared for by private obstetricians. The majority of the patients (61 of 65) were managed directly by, or under the supervision of, a group of five perinatologists, who were unaware of the results of the Doppler examinations. Thirty-one patients were white class A and 34 were insulin-dependent diabetics (18 class B, 7 class C, 2 class D, 6 class F, and 1 class R). All of the class A diabetics were controlled with diet only. Sixteen of 65 patients also had hypertensive disorders (five with chronic hypertension and 11 with preeclampsia). The study was approved by the Clinical Research Practices Committee and all the patients gave written informed consent.

All patients were examined during the third trimester of pregnancy. Doppler FVW analysis was performed by the usage of a continuous wave Doppler device with a 4 MHz transducer (MedaSonics, Mountain View, CA). All examinations were obtained at the antenatal testing laboratory of the Forsyth Memorial Hospital. During fetal apnea umbilical artery (UA) FVWs were obtained from four different abdominal sites to assure representation of the entire cord length. The mean of four measurements was obtained in order to minimize the effect of the fetal heart variability.[13] The methodology for the uterine artery (UtA) FVWs was described previously.[14] The intraobserver coefficient of variation is 8% for the UtA FVWs and 7% for the UA. The systolic/diastolic (S/D) ratio was used as an expression of resistance. The UA and UtA S/D ratios were considered to be abnormal when they exceed the 95th percentile for our normal population (more than 3 after 30 weeks' gestation and more than 2.8 after 24 weeks' gestation, respectively).

Quality of glycemic control was determined by the value of HbA_1 obtained at the time of delivery. HbA_1 was determined by an affinity column method (Helena Glyco-Tek, Helena Laboratories, Beaumont, TX). In four patients HbA_1 was not available and glycemic control was determined from the patient's record of the daily capillary blood glucose levels. In our laboratory the upper normal limit for HbA_1 is 8.5%. A HbA_1 value greater than 8.5% was considered indicative of poor diabetic control as well as a mean capillary blood sugar of higher than 110 mg/dl during the third trimester of pregnancy.[15,16] Neonatal hypoglycemia was diagnosed when capillary blood sugar was less than 40 mg/dl in newborns delivered after 37 weeks' gestation and less than 25 mg/dl in premature newborns. Hypocalcemia was defined as a calcium serum level less than 7 mg/dl and hyperbilirubinemia a serum bilirubin level greater than 15 mg/dl.

All studies were performed in the third trimester. The mean time interval between the last Doppler evaluation and delivery was 10 days. Statistical analysis of the difference of various clinical parameters was performed by Student's *t* test for independent groups and chi-square test was used for comparison of frequencies. Mann-Whitney test was used for comparisons of the UA and UtA S/D ratios, since S/D ratios are not distributed normally. Simple regression analysis was used to explore the relationship between UA S/D ratio and various clinical and laboratory parameters. When p was <0.05, it was considered statistically significant.

RESULTS

Of the 65 patients, 12 (18%) delivered infants large for gestational age (LGA), 3 (5%) small for gestational age (SGA), and 50 (77%) delivered infants appropriate for gestational age (AGA). Four (6%) infants were found to have congenital anomalies. One infant with multiple congenital anomalies died from congestive heart failure 4 days after birth. One infant had mild hypospadias, another had malformation of the right hand, and a fourth was diagnosed as having Turner's mosaicism and an extra digit in the left arm. All fetuses with congenital anomalies had normal UA S/D ratios. Twelve (18%) of the infants developed some form of morbidity (one or more of the following conditions: hypoglycemia, hypocalcemia, and hyperbilirubinemia). Only 5 of the 12 infants had associated abnormal UA S/D ratios. From a total of nine patients with abnormal UA S/D ratios, six (67%) were well controlled and only three (33%) poorly controlled. Within the same group of patients, five (55%) had associated hypertension and four (45%) were normotensive (Table 1).

Of the 65 patients, 13 (20%) were poorly con-

Table 1. Clinical and Laboratory Parameters in Patients with Abnormal Flow Velocity Waveforms

Case	Umbilical Doppler S/D	White Class	Parity	Mean Arterial Pressure	Gestational Age at Delivery	Birthweight	Proteinuria (mg/24 hours)
BG	3.48	A	0	83	38	2385	120
LE	3.32	B	1	83	38	2700	110
WC	3.21	A	1	76	40	3742	170
GS	4.04	D	0	107	36	1690	1000
BK	4.40	B	1	82	35	2240	185
HM	3.12	F	0	117	39	2928	1200
JM	3.55	R	0	117	36	2280	5000
JR	3.38	B	2	105	33	1960	90
HL	5.18	F	0	115	34	1460	3050

trolled and 52 (80%) well controlled. Comparisons of various clinical and laboratory parameters between the two groups of patients (good versus poor control) did not disclose any differences (Table 2). There was no difference also in the number of patients with abnormal UA S/D ratio between patients with good control and those with poor control (chi-square, $p > 0.6$). However, when the patients were classified according to the presence or absence of preeclampsia, significant differences were found (Table 3). The mean UA and UtA S/D ratios were similar in patients with good and poor control. In contrast, patients with preeclampsia had significantly higher Doppler values than patients without preeclampsia regardless of diabetic control (Table 4).

Regression analysis of UA S/D ratio on the HbA_1, proteinuria, and maternal mean arterial pressure (MAP) revealed a poor correlation between UA S/D ratio and HbA_1 as well as MAP. In contrast, proteinuria correlated better with the UA S/D ratio, particularly in patients with hypertension or preeclampsia (Table 5). The relationship between the UA S/D ratio and HbA_1 is primarily produced by the group of patients without hypertension, since there was no correlation between the two parameters in the group of patients with hypertension.

Table 2. Comparisons of Clinical and Laboratory Parameters Between Patients with Good and Poor Diabetic Control

Parameter	*Poor Control (n = 13) (Mean ± SD)*	*Good Control (n = 52) (Mean ± SD)*	*p Value*
Maternal age (years)	26.1 ± 5.5	28.1 ± 5.7	NS
Parity	0.6 ± 0.6	0.9 ± 0.8	NS
Gestational age at delivery	37.8 ± 2.5	38.3 ± 2.0	NS
Birthweight (gm)	3101 ± 731	3400 ± 648	NS
5 minute Apgar score	9.0 ± 0.4	8.9 ± 0.5	NS
Proteinuria (mg/24 hour)	510 ± 791	283 ± 893	NS
MAP (mmHg)	95 ± 11	94 ± 12	NS

COMMENT

Abnormal FVWs were strongly associated with poor perinatal outcomes in pregnancies complicated by intrauterine growth retardation,[17,18] preeclampsia,[19] twin gestations,[20,21] and other high-risk conditions.[22,23] A significant correlation was found between poor diabetic control and abnormal UA S/D ratios in a group of 43 gestational and insulin-dependent diabetics.[10] Bradley et al.[11] reported on a case of chronic fetal hypoxia in an insulin-dependent diabetic associated with persistent abnormal UA FVWs. In this case conventional fetal surveillance failed to diagnose hypoxia, but Doppler did. When the fetus became acidotic, however, tococardiography became abnormal, too. It was not clear in that report whether hypertension or preeclampsia was present and its conclusion was challenged by Tyrrell[12] on the basis of evidence from the literature, as well as from his own study population. This evidence shows that, in some instances, Doppler failed to predict "unexplained" fetal death, and it should not be considered the ultimate test for fetal well-being in diabetic pregnancies until further studies are completed.

The present study certainly adds to the controversy regarding the clinical significance of Doppler FVW analysis in the evaluation of fetal well-being in diabetic pregnancies. Our data indicate the existence of a rather weak positive linear correlation between

Table 3. Comparisons of Clinical and Laboratory Parameters Between Patients with and without Preeclampsia Regardless of Diabetic Control

Parameter	*Preeclampsia (n = 11) (Mean ± SD)*	*No Preeclampsia (n = 54) (Mean ± SD)*	*p Value*
Maternal age (year)	24.8 ± 4.6	28.3 ± 5.7	<0.05
Parity	0.3 ± 0.4	2.6 ± 1.2	<0.001
Gestational age at delivery	37.0 ± 1.8	38.4 ± 2.0	<0.05
Birthweight (gm)	2831 ± 738	3443 ± 613	<0.03
5 minute Apgar score	8.9 ± 0.3	8.9 ± 0.5	NS
MAP (mmHg)	110.7 ± 7.5	90.8 ± 9.5	<0.001
Hemoglobin A_1	8.4 ± 1.4	6.8 ± 2.4	<0.01

Table 4. Comparisons of Doppler Parameters According to Diabetic Control and the Presence of Preeclampsia

Doppler Parameter (Mean ± SD)	*According to Diabetic Control*			*According to Presence of Preeclampsia*		
	Poor (n = 13)	*Good (n = 52)*	*p Value*	*Yes (n = 11)*	*No (n = 54)*	*p Value*
UA S/D ratio	2.7 ± 0.8	2.5 ± 0.6	NS	3.1 ± 0.9	2.4 ± 0.5	<0.002
UtA S/D ratio	2.5 ± 1.7	2.6 ± 1.5	NS	3.5 ± 2.2	2.4 ± 1.3	<0.05

Table 5. Correlations Between UA S/D Ratio and HbA_1, Proteinuria, and Maternal; Mean Arterial Pressure (MAP) in the Entire Group of Patients and According to the Presence or Absence of Hypertension

	*All Patients (n = 65)**		*Patients with Hypertension (n = 16)*		*Patients without Hypertension (n = 49)*	
Parameters	*r Value*	*p Value*	*r Value*	*p Value*	*r Value*	*p Value*
Hemoglobin A_1	0.30	<0.02	0.13	>0.60	0.30	<0.04
Proteinuria	0.49	<0.001	0.57	<0.02	0.00	1.00
MAP	0.25	<0.05	0.47	0.06	0.13	0.36

*Only 61 patients had hemoglobin A_1 values available.

HbA_1 and UA S/D ratio. From a clinical point of view, one can only explain 9% [$r^2 = (0.30)^2 = 0.09$] of the variability in UA S/D ratio based on the value of HbA_1. This correlation was totally attributed to the subgroup of patients without hypertension, since the hypertensive subgroup demonstrated no correlation between glycosylated hemoglobin and UA S/D ratio. The difference in the degree of correlation between the two studies is possibly due to the different methodology used for the evaluation of glycemic control or the different populations involved or both. We elected to use HbA_1 measurements done at the time of delivery for two reasons. First, all the Doppler evaluations were performed a few days prior to delivery and since HbA_1 levels reflect glycemic control for the previous 8 to 12 weeks, this timing appears to be the most appropriate. Second, with the exception of congenital anomalies, most of the conditions that may complicate a diabetic pregnancy take place during the third trimester when the diabetogenic effect of the pregnancy is at its maximum. In addition, this study examines the total effect of poor glycemic control and not the effect of day to day variation in blood sugar.

The presence of preeclampsia rather than the presence of poor diabetic control was more frequently associated with abnormal FVWs. Proteinuria demonstrated the strongest correlation with UA S/D ratio. UA and UtA resistance did not seem to be influenced by diabetic control. In contrast, patients with hypertension demonstrated significantly higher UA and UtA resistance, and the mean S/D ratio fell above the 95th% for both vessels. In a recent report, Landon et al[24] examined 35 insulin-dependent diabetic women longitudinally and found no correlation between glycemic control and Doppler values. These findings are in agreement with ours. Longitudinal studies are most valuable in the study of trends and the evolution of the clinical condition or pathologic state in relation to time. One should be cautioned, however, that S/D ratio declines constantly throughout pregnancy and averaging values obtained at different time intervals may have an unpredictable impact on the analysis of the data and subsequent conclusions. Since the effect of diabetes on the vascular wall is chronic, the last examination close to the time of delivery would reflect the total insult that was inflicted during the previous several weeks. The two studies are in agreement also on the fact that most of the patients who developed abnormal Doppler values had preeclampsia.

Placental vascular resistance in diabetic pregnancies can be affected either by physiologic or structural changes of the placental vessels. Mild hypoxemia has no effect on placental vascular resistance, whereas severe hypoxemia with tissue hypoxia leads to metabolic acidosis and increased placental resistance.[25] Fetuses of diabetic mothers are believed to sustain mild to moderate hypoxemia due to the increased oxygen affinity of glycosylated fetal hemoglobin.[26] This mild chronic hypoxemia does not affect the placental vascular resistance.[27] Acute hyperglycemia on the grounds of preexisting mild hypoxemia can lead to severe tissue hypoxia and lactic acidosis.[28] In such a case, the increase of the placental vascular resistance is likely to be missed, due to its short duration prior to fetal death. Therefore it should not be surprising if Doppler FVW analysis fails to diagnose fetuses with mild chronic hypoxia, as well as fetuses at risk for "unexplained" intrauterine death.

The existence of structural changes in placentas of diabetic women has been controversial.[29,30] It has been suggested that diabetic vasculopathy is to a great extent the result of advanced glycosylation of tissue proteins.[31] The formation of advanced glycosylation end products that can lead to vascular wall stiffness and increased vascular resistance is a slow process that may last from a few months to a few years, and it is unlikely to have any effect on the fetal vascular system. From this, it would seem reasonable to assume that in the absence of preeclampsia, diabetes can only alter placental vascular resistance in an acute setting of severe hypoxia. Therefore the lack of any clinically significant correlation between UA S/D ratios and glycemic control should not be surprising.

We conclude that Doppler FVW analysis does not correlate well with glycemic control in diabetic pregnancies. In addition, this study indicates that abnormal Doppler FVWs are associated with increased morbidity mostly in diabetic pregnancies complicated by hypertension or preeclampsia. We suggest that Doppler FVW analysis should not be used for fetal surveillance in diabetic pregnancies until more studies resolve the controversy. However, when diabetic pregnancies are complicated by other high-risk conditions, Doppler FVW analysis should

be used as indicated by the particular obstetric condition.

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