Abnormal Uterine Doppler Is Related to Vasculopathy in Pregestational Diabetes Mellitus

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Background—The aim of the study was to evaluate the relation between maternal placental Doppler velocimetry, levels of maternal glucose, and clinical signs of vasculopathy in pregnancy complicated by pregestational diabetes mellitus.

Methods and Results—A retrospective study of 155 pregestational diabetic women between the 22nd and 40th weeks of pregnancy, categorized in White classification as B, 49; C, 40; D, 22; R, 20; F, 5; and R/F, 19. Cases in classes R, F, and R/F were defined as having vasculopathy. Doppler velocimetry of umbilical and uterine arteries was evaluated for vascular impedance, both in terms of pulsatility index (PI) for both arteries and a notch in early diastole in the uterine arteries. The last examination before delivery was used for analysis. Increased umbilical artery PI was seen in 19 and a uterine artery abnormality in 45 cases. There was a correlation between levels of HbA1c and increased vascular impedance in the uterine and umbilical arteries. Signs of increased uterine artery vascular impedances were significantly related to pregestational vasculopathy. In cases of small-for–gestational-age newborn infants, PI was significantly increased in uterine and umbilical arteries. Furthermore, PI in macrosomic fetuses was significantly lower than in normal infants. Abnormal uterine artery Doppler was also strongly related to adverse outcome.

Conclusions—Abnormal uterine artery Doppler is related to pregestational vasculopathy and adverse outcome of pregnancy. The results suggest that the uterine arteries are affected in women with clinical signs of pregestational vasculopathy. This may influence placental perfusion and fetal well-being. (Circulation. 2005;112:2496-2500.)

Key Words: diabetes mellitus ■ perfusion ■ pregnancy ■ vessels ■ vasculopathy

Diabetes mellitus, especially of the pregestational type, is frequently related to adverse outcome of pregnancy, including perinatal death. The main objective in reducing the likelihood of complications is adequate serum-glucose control both before conception and during pregnancy. Hyperglycemia may cause changes in maternal-placental blood flow during the pregnancy that may lead to fetal distress, pre-eclampsia, and intrauterine growth restriction (IUGR).1-3 Ketoadicosis can also be lethal for the fetus. Changes in maternal placental blood vessels during the course of pregnancy under the influence of hyperglycemia may be considered as characteristic for microangiopathic diabetes.2 Thickening of basement membranes, proliferation of endothelial cells, and disarrangement in perivascular space with increase of collagen, proteoglycans, and glycosaminoglycans are characteristic vessel changes as a consequence of hyperglycemia.4 Changes in placental terminal villi in patients with nephropathy and retinopathy (class R/F) have also been reported.2,4 The likelihood of adverse perinatal outcome is reduced in well-controlled diabetic pregnancies.

Perinatal care of pregnant women with diabetes mellitus lies in correct metabolic management, stringent surveillance, and monitoring of serum glucose levels. One of the instruments of modern perinatal surveillance is Doppler velocimetry, which may estimate vascular impedance in placental circulation. The utero-placental circulation is important for fetal development and growth. Information about correlations between glycemic control and changes in utero-placental circulation are conflicting, and the value of Doppler examination for surveillance of diabetic pregnancies is still not widely accepted.7-13

The aim of the present study was to evaluate the relation between maternal placental Doppler velocimetry and levels of maternal glucose and signs of vasculopathy in pregnancy complicated by pregestational diabetes mellitus (PGDM).

Methods
A multicenter, retrospective study was carried out in 155 insulin-dependent women with PGDM delivered between 1994 and 2002 at the University of Medical Sciences, Poznan, Poland, and the University Hospital MAS, Malmö, Sweden. The study group comprised 80 cases delivered in Poznan and 75 cases in Malmö between the 22nd and 40th weeks of pregnancy. All pregnancies were singleton. All the women were evaluated at the beginning of pregnancy.
according to White classification. There were 49 women in class B (duration of diabetes, 0 to 10 years); 40 in class C (duration of diabetes, 10 to 20 years); 22 in class D (duration of diabetes, more than 20 years); 20 in class R (retinopathy); 5 in class F (nephropathy); and 19 in class R/F (retinopathy and nephropathy). Women in classes R, F, and R/F were defined as having vasculopathy. Both clinics adopted a strict program for surveillance of these pregnancies.

The main uterine arteries were located by color Doppler ultrasound and Doppler velocimetry, using the Aloka 2000, 5500, and Acuson-Sequoia machines with an abdominal transducer. The uterine artery flow signals were obtained from the vessels cranial to the anatomic crossover with the external iliac arteries. Umbilical artery Doppler spectrum was, at the same examination, obtained from a free-floating loop of the umbilical cord. The Doppler spectrum was evaluated for vascular impedance by pulsatility index (PI) according to Gosling et al. The angle of insonation was always less than 30 degrees. Apart from PI, uterine artery blood flow spectrum was evaluated for a notch in early diastole according to Campbell et al (Figure 1) and the uterine artery score (UAS) according to Gudmundsson et al (Table 1). UAS is based on the PI value and presence or absence of notching in both uterine arteries. Both arteries were evaluated for high PI (PI >1.20), or the presence of a notch was reported as 1 for each abnormality. The values of the UAS ranged from 0 to 4, depending on the number of abnormal parameters, a UAS of 4 having a bilateral notch and a bilateral PI >1.20 (Table 1). Umbilical artery blood velocities were also graded according to blood flow class according to Gudmundsson et al (Table 1). The last examination before delivery was used for analysis. Gestational age estimation was always based on an ultrasound examination performed in the first trimester.

Maternal serum glycosylated hemoglobin (HbA1c) measurements were performed in all the women with affinity chromatography. HbA1c measurements in the two clinics were performed with the Bio-Rad affinity chromatography method, but using differences analyzers Bio-Rad Hitachi Analyzer 912, normally defined as <6.4% (Polish group), and the Abbott Imx (Abbott Laboratories), normally defined as <6.0% (Swedish group). The HbA1c determinations were part of the routine workup for diabetic patients. Repeated measurements were performed for each woman throughout the course of pregnancy, and the mean was used for analysis.

Adverse perinatal outcome was defined as operative delivery for fetal distress, including cesarean section and vacuum or forceps extraction because of abnormal cardiotocograph and/or scalp pH, preterm delivery (<37 weeks of gestation), 5’ Apgar score <7, and umbilical vein pH <7.20. Macrosomia was defined as birth weight >4000 g. A small-for–gestational-age newborn infant was defined

**Figure 1.** Ultrasound Doppler spectrum of uterine artery blood velocity. Upper panel: Normal blood velocity. Lower panel: Decreased blood velocity with a characteristic notch in early diastole as a sign of increased placental vascular impedance.

**TABLE 1. Definitions of the Uterine Artery Score System and Umbilical Artery Flow Classes**

<table>
<thead>
<tr>
<th>Uterine artery score</th>
<th>Umbilical artery flow class</th>
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<tr>
<td>0=Normal blood flow velocity waveforms in both uterine arteries</td>
<td>0=Normal umbilical artery blood flow velocity waveforms</td>
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<tr>
<td>1=One abnormal parameter present (ie, high PI (&gt;1.2) or diastolic notch)</td>
<td>1=PI between +2 and +3 SD above the mean</td>
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<tr>
<td>2=Two abnormal parameters present</td>
<td>2=PI &gt; +3 SD and forward flow in diastole</td>
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<tr>
<td>3=Three abnormal parameters present</td>
<td>3=Absent or reversed end-diastolic flow</td>
</tr>
<tr>
<td>4=Four abnormal parameters present (ie, high PI and diastolic notching)</td>
<td>PI indicates pulsatility index.</td>
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as birth weight below the 5th percentile. Values of measurements were reported as means and standard deviations. No conflicts of interest were involved in the study.

**Statistical Analysis**

The Student t test was used for comparison of means and the χ² test for comparison of proportions. Regression analysis was used to test for trends in means and the χ² test for trends in numeric values across levels of uterine artery scores. Fisher’s exact test was also used to compare the group with normal uterine artery Doppler (UAS 0) and abnormal uterine blood velocity (UAS 1 to 4). Spearman correlation and linear regression models were used for analysis of the relation between HbA1c and Doppler results. Statistical analyses were performed with the use of MedCalc 6.00.014 and SPSS 12.0 for Windows software. Probability values of <0.05 were chosen as statistically significant.

**Results**

Increased umbilical artery PI was seen in 19 (12%) cases and a uterine artery spectral waveform abnormality in 45 (29%) cases. The average HbA1c concentrations in the White classes were in class B, 6.4±1.0%; C, 6.6±1.1%; D, 6.7±1.0%; F, 6.4±1.2%; R, 6.1±1.1%; and R/F, 6.9±1.0%. Levels of glycosylated hemoglobin in the two centers were different: in the Poznan group was 7.2±0.5% (normal range <6.4) and in the Malmö group, 5.8±0.9% (normal range <6.0). Mean values of HbA1c in PGDM with and without vascular complications were similar (6.5±1.1% and 6.4±1.2%).

There was a correlation between levels of HbA1c and uterine and umbilical PI values. An increase of mean PI value in the uterine and umbilical arteries was significantly related to an increase of glycosylated hemoglobin (P<0.0001, R for umbilical artery was 0.27; for uterine artery, 0.54; Figure 2). A significant relation still existed after values of uterine artery PI 1.2 were excluded. Furthermore, a higher uterine artery score was significantly related to pregestational signs of vasculopathy (Table 2). A more severe increase in uterine artery vascular impedance (UAS >2 points) was seen in 11 cases with signs of vasculopathy (9 cases in R/F class), in comparison to only 2 cases without vascular complications (Table 2). Vasculopathy was not related to umbilical artery blood flow class.

An increase of uterine artery score was also related to adverse outcome of pregnancy, including preterm birth and small-for-gestational-age newborn infants (Table 2). Adverse perinatal outcome was significantly different between a uterine artery score of 0 (21/105) and >0 (26/43) P<0.0001 (Table 2).

Vascular impedance in the uterine and umbilical arteries was significantly different between macrosomia and the small-for-gestational-age fetus. Pulsatility index for the small-for-gestational-age cases was 1.26±0.4 in uterine artery and 1.22±0.3 in umbilical artery. The corresponding figures for macrosomia were 0.65±0.1 and 0.87±0.3 (P<0.001). No statistical differences in maternal or fetal placental Doppler velocimetry were seen in fetuses with a birth weight between 4000 and 5000 g and >5000 g.

There were 49 cases in White class B, 40 in class C, 22 in class D, 5 in class F, 20 in class R, and 19 in class R/F. Duration of diabetes and appearance of vascular complications were directly related to the frequency of adverse perinatal outcome: in class B, 40%; C, 65%; D, 67%; F, 80%; R, 65%; and R/F, 80%. There was a significant difference between class R/F and other classes in relation to parameters of perinatal outcome. Small-for-gestational-age newborn infants were found in 10 cases, of which 8 were in class R/F. In the present study, there were 34 cases of macrosomia.

<table>
<thead>
<tr>
<th>TABLE 2. Uterine Artery Score and Perinatal Outcome</th>
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<tr>
<td>Uterine Artery Score</td>
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<tr>
<td>0  (n=106)       1  (n=22)       2  (n=14)       3  (n=9)       4  (n=4)       P</td>
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<tr>
<td>Gestational age at delivery, wk</td>
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<tr>
<td>38.1±1       37.1±1.4       37.0±2.3       36.2±2.5       33.2±4.7       P&lt;0.0001</td>
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<tr>
<td>Birth weight, g</td>
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<tr>
<td>3681±810      3630±790       3125±757       2561±530       1845±737       P&lt;0.0001</td>
</tr>
<tr>
<td>Small for gestational age, n (%)</td>
</tr>
<tr>
<td>1 (1)                     0            2 (14)*       4 (44)*       3 (75)*       P&lt;0.0001</td>
</tr>
<tr>
<td>Placental weight, g</td>
</tr>
<tr>
<td>714±218       692±216       601±154       523±179       400±48       P&lt;0.001</td>
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<tr>
<td>Adverse perinatal outcome, n (%)</td>
</tr>
<tr>
<td>21 (20)       9 (41)*        8 (57)*       5 (56)*        4 (100)       P&lt;0.0001</td>
</tr>
<tr>
<td>PGDM with vasculopathy, n (%)</td>
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<tr>
<td>20 (19)       7 (32)        6 (43)         8 (89)*        3 (75)*        P&lt;0.0001</td>
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Uterine artery score (UAS) 0 is defined as normal blood velocity. No. (%) or mean values ± SD are given.
Adverse perinatal outcome was defined as operative delivery for fetal distress, preterm delivery before 37 weeks of gestation; 5-minute Apgar score <7; pH umbilical vein <7.20; macrosomia, birth weight >4000 g; small for gestational age, birth weight between 4000 and 5000 g; small for gestational age, birth weight below 5th percentile. PGDM indicates pregestational diabetes mellitus.

Significance between numeric values in UAS 0 and UAS 1 through 4 are given as *P<0.05, †P<0.01, and ‡P<0.0001.
without vascular complications (16 in class B, 8 in class C, 10 in class D) but in only 8 cases with vascular complications, all having only retinopathy (class R). The risk of macrosomia was greatest in White class D and R. A comparison of cases with and without vasculopathy is given in Table 3.

Operative delivery for fetal distress was most frequent in class R/F (80%) and lowest in class B (46%). Abnormal blood flow velocity was observed in 69% of cases with pregnancy-induced hypertension, preeclampsia, or IUGR (23/33). Abnormal umbilical flow velocity was reported in only 36% (12/33) of pregnancies with these complications. Preeclampsia and IUGR were observed in 21 cases (64%) with vascular complications and in 12 cases (36%) without vasculopathy.

The results from the units in Poznan and Malmö were compared, and significant differences were found in mean HbA1c values: 7.28 ± 0.09 versus 7.23 ± 0.06, respectively. Significant differences were also found in newborn birth weight (3543 ± 740 and 3903 ± 861), umbilical venous pH at birth (7.23 ± 0.09 and 7.28 ± 0.06), and Apgar score at 5 minutes (7.9 ± 2.1 and 9.7 ± 1.2). Umbilical artery PI was higher in the Poznan population (1.09 ± 0.31 versus 0.90 ± 0.22), but no difference was found in mean uterine artery PI between the units (0.92 ± 0.3 and 0.90 ± 0.22).

**Discussion**

The findings of the present study indicate a significant relation between duration of diabetes, appearance of maternal vascular complications, and perinatal outcome. The strongest correlation between abnormal uterine artery Doppler and adverse outcome was seen in diabetic women with retinopathy and nephropathy (class R/F). We can speculate that one reason for more frequent adverse outcome in pregnancies with vasculopathy might be pregestational vascular complications. Furthermore, in cases without vasculopathy, macrosomia was related to duration of diabetes (most frequent in class D). Macrosomia in cases of vasculopathy was only seen in cases presenting with retinopathy as the only sign of vasculopathy, which might be explained by retinopathy being one of the first signs of vasculopathy in type I diabetes mellitus. The lack of a relation between retinopathy and small-for-gestational-age newborn infants might be due to the disease not yet affected the utero-placental vessels. Despite well-controlled diabetes, a slight correlation was seen between levels of long-term metabolic control (HbA1c) and blood flow velocity in the uterine and umbilical artery. Thus, hyperglycemia might influence uterine and placental vessel endothelial function, even in cases without pregestational vasculopathy.

In the present study, abnormal uterine artery Doppler velocimetry was mainly seen in class R/F-severe vasculopathy. In contrast to our results, others authors found no correlation between abnormal uterine artery Doppler and White classification, which might be due to small numbers of women with vasculopathy. Zimmermann et al reported that changes in uterine flow were more significant in women with hyperglycemia. Salvesen et al described no changes in maternal or fetal placental Doppler velocimetry and fetal circulation in diabetic pregnancy. In their group there were only 6 cases with vasculopathy. Abnormal blood flow in the uterine artery in pregnancies complicated by diabetes with vasculopathy were reported by Johnstone et al. In contrast to our findings, the changes in blood flow velocity in the uterine artery were independent of the vasculopathy in maternal vessels. These results may indicate that pregnancy induced de novo constituted vessels of the utero-placental circulation, independent of the actual balance of diabetes. Bracero et al and Kofinas et al show a weak correlation between Doppler and HbA1c. Bracero et al recorded that umbilical artery Doppler velocimetry improves the predictive value for adverse perinatal outcome in diabetic pregnancy. In the present study, the numbers of abnormal umbilical artery Doppler velocimetry were much smaller than for the uterine arteries and were not related to pregestation.
vascularopathy. This is logical, as pregestational vascularopathy might have affected the utero-placental vessels before gestation, but changes in the umbilical artery might be secondary to reduced utero-placental perfusion.

The present study shows that women with well-controlled diabetic pregnancies without vascularopathy and without abnormalities in either maternal or fetal placental blood flow velocimetry have a good possibility of giving birth to a healthy newborn infant. The present results also show the usefulness of maternal placental Doppler in the surveillance of diabetic pregnancies, especially those with vascularopathy, where subsequent adverse perinatal outcome might be expected, such as IUGR and preeclampsia. Apart from routine surveillance of diabetic pregnant women, searching for signs of fetal macrosomia and polyhydramnios are also considered a part of routine surveillance of these pregnancies. Abnormal maternal placental Doppler also may select the high-risk group of diabetic women who need more intensive care during pregnancy and labor.

One of the pathophysiology theories behind preeclampsia and intrauterine fetal growth restriction is lack or absence of normal subplacental vessel transformation, which may influence placental development, fetal growth, and adverse perinatal outcome. The vessels in these complicated pregnancies are known to maintain vessel wall structure and smaller caliber. This may result in decreased perfusion and increased risk of thrombosis and placental infarction. Pregestational vascularopathy in pregnancies with type I diabetes mellitus may also influence placental perfusion as the result of lack of vessel wall transformation or altered endothelial function.

In conclusion, abnormal maternal placental Doppler was related to long-term metabolic control, vascularopathy, and adverse perinatal outcome in pregnancy complicated by pregestational diabetes mellitus. These findings might be of value in future planning for clinical surveillance of these high-risk pregnancies.

Acknowledgments
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References


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