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Doppler velocimetry and fetal heart rate studies in nephropathic diabetics

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OBJECTIVES: Our objectives were to determine in pregnancies complicated by diabetic nephropathy (1) if impedance to flow in the uterine and umbilical arteries is normal and (2) if these fetuses are hypoxemic and acidemic and if they have decreased fetal heart rate variation and Doppler blood flow redistribution.
STUDY DESIGN: In a cross-sectional study at the Harris Birthright Research Centre for Fetal Medicine, London, serial assessment of fetal heart rate variation and Doppler velocimetry of the placental and fetal circulations was undertaken in six pregnancies complicated by diabetic nephropathy. In all cases cordocentesis was performed within 24 hours before delivery for the measurement of umbilical venous blood gases.
RESULTS: Cordocentesis demonstrated these fetuses to be hypoxemic and acidemic. The fetal heart rate variation was decreased; however, impedance to flow in the uterine artery was normal, and increased impedance to flow in the umbilical artery with evidence of blood flow redistribution was observed in only one case.
CONCLUSIONS: Fetal hypoxemia and acidemia in pregnancies complicated by diabetic nephropathy is not a consequence of impaired placental perfusion, and the degree of metabolic derangement may be obscured by the apparent normal growth and failure of these fetuses to demonstrate blood flow redistribution. (AM J OBSTET GYNECOL 1992;167:1297-303.)

Key words: Diabetic nephropathy, cordocentesis, fetal Doppler studies, blood gases, fetal heart rate patterns

In pregnancies complicated by preeclampsia or intrauterine growth retardation (IUGR) there is histologic evidence of abnormal trophoblastic invasion of the maternal spiral arteries.[1-3] Doppler studies in such cases have documented increased impedance to flow in the uterine arteries, which may precede the development of growth retardation or pregnancy-induced hypertension.[4-6] Furthermore, hypoxemic IUGR is associated with pathologic fetal heart rate (FHR) patterns and Doppler evidence of redistribution of the fetal circulation in favor of the brain and at the expense of the viscera.[7-10]

In women with diabetic nephropathy the incidence of both proteinuric hypertension and IUGR is increased.[11, 12] Previous Doppler studies in pregnancies complicated by maternal diabetes are limited to investigation of the umbilical artery; these studies have provided conflicting results.[13-15] The aim of the current study was to determine (1) if impedance to flow in the uterine artery and or umbilical artery of pregnant diabetics with nephropathy is increased and (2) if these fetuses are hypoxemic and acidemic and have appropriate changes in FHR variation and Doppler evidence of redistribution in their circulation.

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Patients and methods

During an 18-month period, September 1990 through February 1992, six pregnant, insulin-dependent diabetic women with nephropathy attended our antenatal clinic for pregnancies complicated by maternal diabetes mellitus. The patients gave written informed consent to the study, which was approved by our hospital ethics committee.

All patients had been diabetic between 10 and 27 years, all had retinopathy (two background and four proliferative), and none had any historic or clinical evidence of other renal disease. All six patients had regular menstrual cycles and were certain of the date of their last periods. Gestation was confirmed by an ultrasonographic scan at 12 to 17 weeks amenorrhea. A further scan at 20 weeks' gestation did not reveal any fetal abnormality. All six cases were managed by a combined team of obstetricians and diabetologists, and regular observations were made of maternal weight, blood pressure, insulin requirements, venous blood glycosylated hemoglobin percentage (Corning scanner, Corning, Halstead, England), serum creatinine concentration, 24-hour urinary protein excretion and creatinine clearance; ultrasonographic scanning for fetal biometry, Doppler velocimetry of the uteroplacental and fetal circulations, and FHR monitoring were undertaken.

Doppler examinations were performed with the patient in the supine position with left lateral tilt. Color flow mapping, to identify the vessels, and pulsed wave velocimetry (color Doppler Aloka echocamera SSD-680 with 3.5 MHz curvilinear transducer, Aloka Co., Tokyo) were used to obtain flow velocity waveforms from (1) both uterine arteries, at the level where they cross the corresponding external iliac artery; (2) one umbilical artery, from a free loop of the cord; (3) the descending thoracic aorta, at a position just above the diaphragm; and (4) one of the middle cerebral arteries, from a portion of these vessels near the circle of Willis. In all Doppler studies the angle of insonation of the vessels was <45 degrees, and the high-pass filter was set at 100 Hz. Care was taken not to exert undue pressure on the fetal head, because this alters the flow velocity waveforms from the middle cerebral artery.[16] Examinations of the fetal vessels were performed in the absence of fetal body and respiratory movements.[17] Measurements were obtained from four consecutive flow velocity waveforms and averaged. Impedance to flow in the umbilical artery, middle cerebral artery, and descending thoracic aorta was expressed by the pulsatility index and for the uterine artery by the resistance index; for the latter vessel measurements were taken from both uterine arteries and the higher of the values was used for further analysis. The resistance index and pulsatility index were measured with the built-in spectrum analyzer.

FHR monitoring was performed for 60 minutes with the patient in the left semirecumbent position. Computer-assisted analysis was used to reduce interobserver and intraobserver variation (Sonicaid 8000, Oxford Sonicaid, Oxford, England). The overall FHR variation was expressed as the mean minute range in milliseconds. The method of computer analysis was as previously described.[18]

Doppler studies and FHR monitoring were carried out in all cases on the day of delivery and were immediately followed by cordocentesis. Cordocentesis was carried out without fetal paralysis or maternal sedation, and all procedures were uncomplicated.[19] Fetal blood was collected into heparinized syringes (350 μl) for measurement of pH, P_{CO_2}, and P_{O_2} (Radiometer ABL330, Copenhagen) and for the measurement of whole blood glucose (YSI 23A, Yellow Springs Instruments, Yellow Springs, Col.). Fetal blood was also collected in tubes containing ethylenediaminetetraacetic acid (300 μl) for measurement of hemoglobin concentration (Coulter "S-plus, Porter Electronics, Luton, England). Kleihauer testing confirmed that all samples contained only fetal blood. Blood films were stained with Jenner's Giemsa on an automatic processing machine, and the number of erythroblasts per 100 white blood cells was calculated. At the time of cordocentesis a maternal blood sample was taken from the antecubital fossa for the measurement of whole-blood glucose concentration and glycosylated hemoglobin percentage.

The data from FHR monitoring, Doppler blood flow, and fetal abdominal circumference measurements, together with the results of cordocentesis and the fetal birth weight, were compared with published reference ranges and are plotted on the appropriate normal range with gestation in Figs. 1 through 6.[9, 10, 18, 20-22]

Results

Maternal characteristics and pregnancy outcome are shown in Table I. Fetal abdominal circumference measurements and fetal birth weight at delivery were >5th percentile for gestation in four cases (Fig. 1). Immediately after delivery all six neonates were admitted to our neonatal intensive care unit. All of the neonates had hypoglycemia and jaundice requiring phototherapy. In five cases (A, C, D, E, F) the neonatal period was further complicated by respiratory distress syndrome of sufficient severity to require ventilation in cases D, E, and F. Permanent sequelae were confined to baby D, whose course was complicated by the development of bronchopulmonary dysplasia.

The data obtained at cordocentesis are demonstrated in Table II and Figs. 2 and 3. In all cases the umbilical venous blood pH or P_{O_2} were <5th percentile, and the hemoglobin concentration and erythroblast count were >50th percentile for gestational age. All measurements

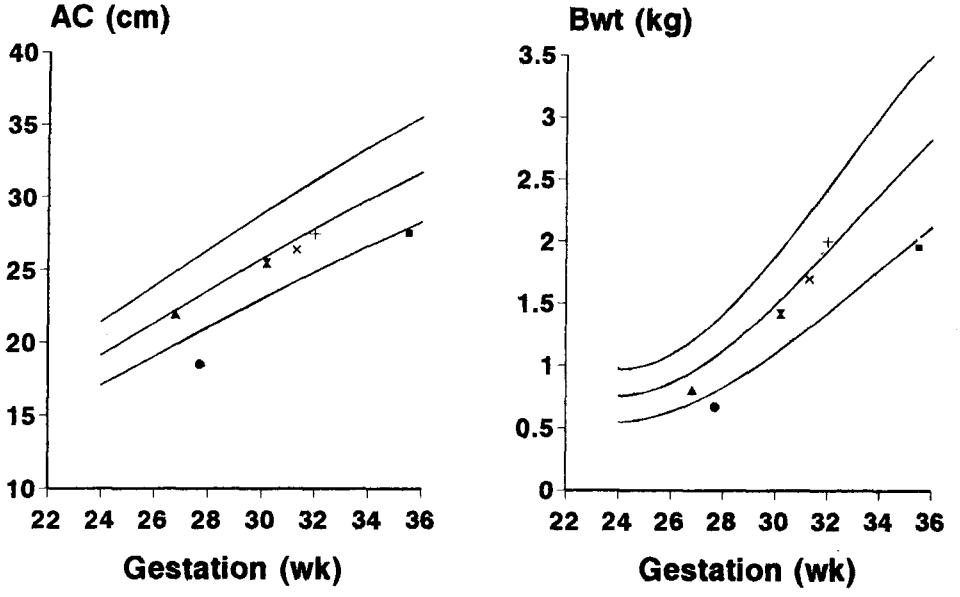

Fig. 1. Fetal abdominal circumference *(AC)* on day of delivery and birth weight *(Bwt)* plotted on appropriate reference range (mean, 5th and 95th percentiles) for case A (+), B (■), C (×), D (▲), E (⧗), and F (●).

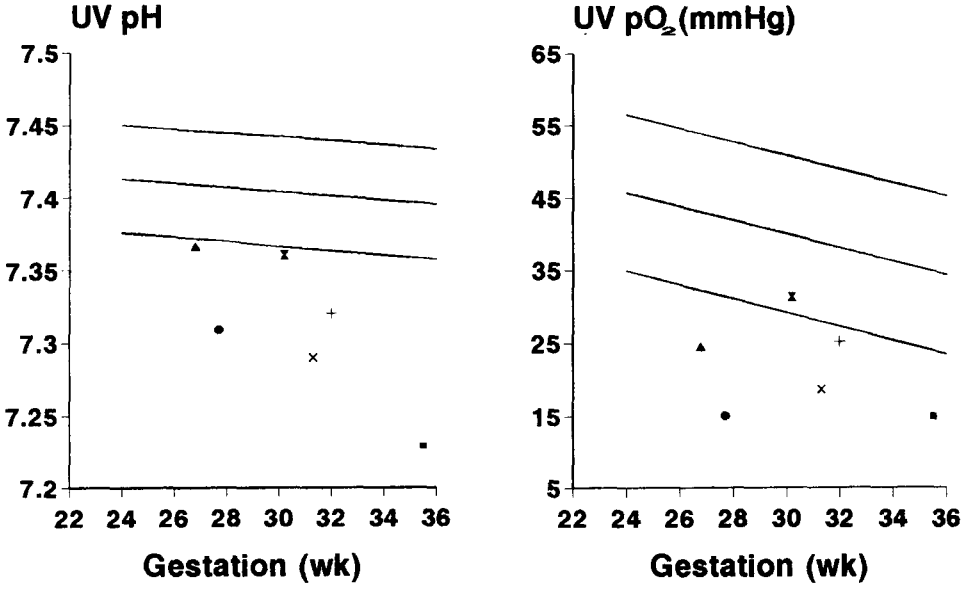

Fig. 2. Umbilical venous *(UV)* blood pH, and Po_2 at cordocentesis plotted on appropriate reference range (mean, 5th and 95th percentiles) for case A (+), B (■), C (×), D (▲), E (⧗), and F (●).

of impedance to flow in the uterine arteries were between the 5th and 95th percentiles of the reference range for gestation (Fig. 4). Increased impedance to flow in the umbilical artery and evidence of redistribution in the fetal circulation, with increased impedance in the descending thoracic aorta and decreased impedance in the middle cerebral artery was observed in only one case just before delivery (Figs. 4 and 5).

The FHR variation was within the normal range but below the mean for gestation in the majority of measurements. However, in three cases there was a progressive decrease in variation, and in four of the six cases the last measurement before delivery was <5th percentile (Fig. 6).

Comment

These data demonstrate that in pregnancies complicated by diabetic nephropathy, some fetuses are acidemic and hypoxemic. Furthermore, the fetuses have hematologic changes and alterations in FHR patterns

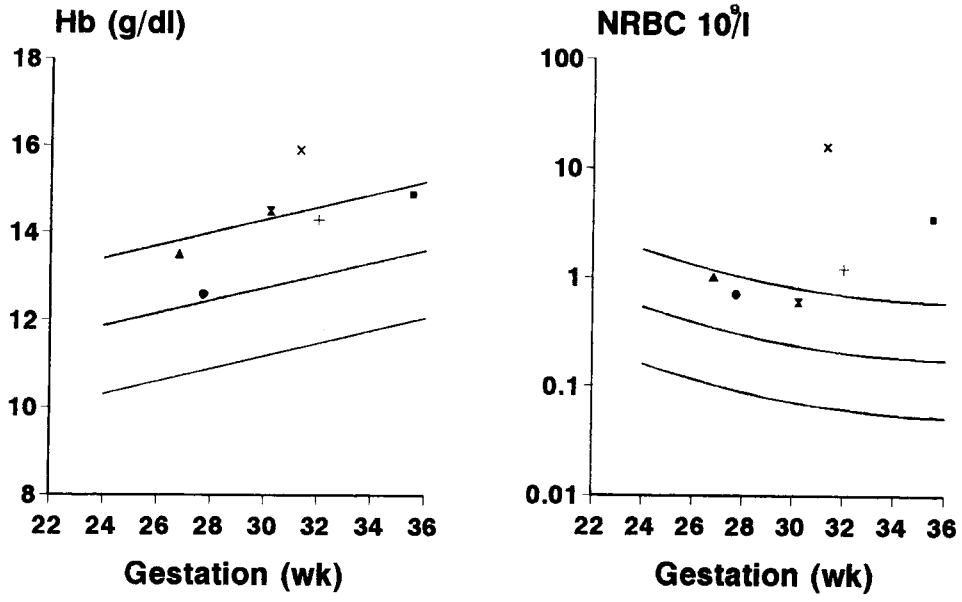

Fig. 3. Fetal hemoglobin concentration *(Hb)* and erythroblast count *(NRBC)* at cordocentesis plotted on appropriate reference range (mean, 5th and 95th percentiles) for case A (+), B (■), C (×), D (▲), E (⧗), and F (●).

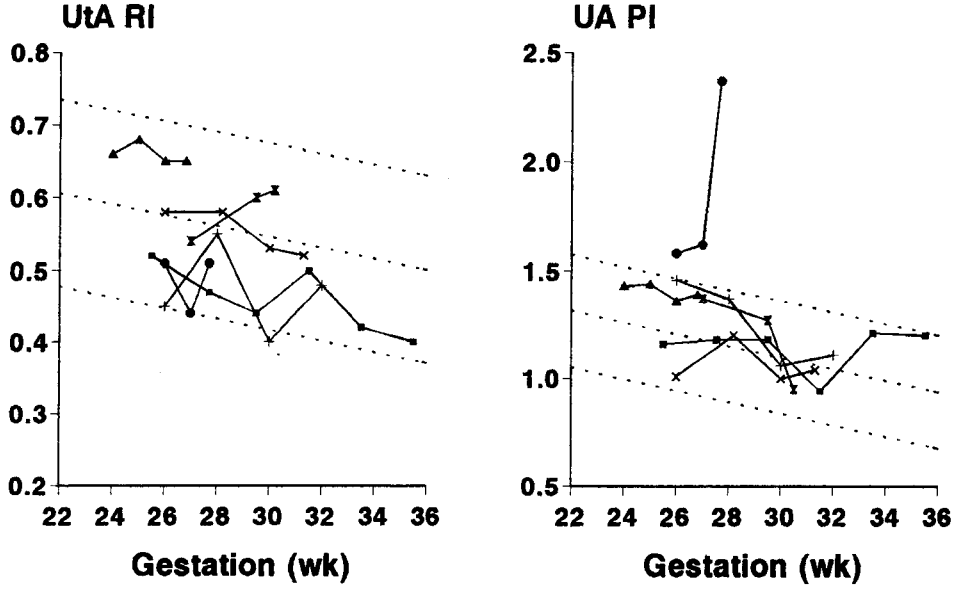

Fig. 4. Serial measurements of uterine artery resistance index *(UtA RI)* and umbilical artery pulsitility index *(UA PI)* plotted on appropriate reference range (mean, 5th and 95th percentiles) for case A (+), B (■), C (×), D (▲), E (⧗), and F (●).

similar to those observed in IUGR as a result of impaired placental perfusion.[7,8,23] However, in contrast to findings in growth retardation, there is no evidence of increased impedance to flow in the uterine arteries. Furthermore, evidence of hypoxia-induced redistribution in the fetal circulation in favor of the brain and at the expense of the viscera was observed in only one of the six cases.[9,10]

The implications of these findings in pregnant diabetic patients with nephropathy are as follows: (1) Worsening proteinuric hypertension and fluid retention may be a consequence of pregnancy-associated impairment in renal function rather than evidence for the onset of superimposed preeclampsia; (2) fetal hypoxemia or acidemia is unlikely to be the consequence of impaired placental perfusion; (3) the noninvasive diagnosis of

Table I. Individual patient details

Gestational age (wk)	*Weight (kg)*	*Blood pressure (mm Hg)*	*Insulin requirements (units/day)*	*Maternal glycosylated hemoglobin*	*Serum albumin (gm/L)*	*Urinary protein (mg/24 hr)*	*Serum creatinine (mg/L)*	*Creatinine clearance (ml/min)*
*Case A: age 25 yr, White class F**								
26	58.9	134/72	78	10.5	40	640	223	26
32	59.9	162/85	82	7.2	31	1333	249	24
Case B: age 25 yr, White class F/R†								
26	77.2	126/86	46	9.5	39	1039	79	122
35	77.8	140/95	52	7.6	36	1352	104	130
Case C: age 28 yr, White class F/R‡								
26	70.2	150/90	56	8.6	26	16300	101	127
31	80.4	150/100	58	8.7	26	11900	137	48
Case D: age 38 yr, White class F/R§								
24	70.9	155/90	36	10.2	27	3291	100	64
27	73.1	165/100	28	11.3	24	10500	174	39
Case E: age 26 yr, White class F‖								
26	96	130/90	54	9.6	27	5838	324	35
30	110	120/90	56	11.2	24	8650	437	21
Case F: age 28 yr, White class F/R¶								
25	74	150/90	32	7.1	33	2020	177	18
27	75	170/110	38	7.4	29	4290	187	21

In case E the patient was in her second pregnancy, after a cesarean delivery at 28 weeks' gestation because of proteinuric hypertension. All other patients were in their first pregnancies. In cases B, C, D, and F there was proliferative retinopathy, and in cases A, D, E, and F there was renal impairment before the current pregnancy.

*Delivery indication—worsening hypertension and proteinuria in the presence of poor renal function; gestation 32 weeks; birth weight 2080 gm.

†Delivery indication—hypertension, proteinuria, and abnormal FHR pattern; gestation 35.3 weeks; birth weight, 1980 gm.

‡Delivery indication—worsening hypertension, heavy proteinuria, and deteriorating renal function; gestation 31.4 weeks; birth weight 1800 gm.

§Delivery indication—worsening hypertension and proteinuria with deteriorating renal function; gestation 27 weeks; birth weight 840 gm.

‖Delivery indication—hypertension and increasing proteinuria with deteriorating renal function, necessitating dialysis and renal transplantation 3 months after delivery; gestation 30.2 weeks; birth weight 1480 gm.

¶Delivery indication—worsening hypertension, proteinuria with poor renal function, and abnormal Doppler and FHR studies; gestation 27.7 weeks; birth weight 670 gm.

Table II. Cordocentesis results

		Umbilical venous blood					*Maternal venous blood*	
Case	*Gestational age (wk)*	*pH*	*Po_2 (mm Hg)*	*Pco_2 (mm Hg)*	*Hemoglobin (gm/dl)*	*Glucose (mmol/L)*	*Glucose (mmol/L)*	*Glycosylated hemoglobin (%)*
A	32.0	7.320	25.3	40.1	14.3	2.8	4.1	7.2
B	35.3	7.228	15.0	55	14.9	10.3	13.6	7.4
C	31.4	7.298	18.7	57.7	15.9	10.1	11.2	8.7
D	27.0	7.370	24.5	42.5	13.5	9.5	11.2	11.3
E	30.2	7.362	31.4	39.9	14.5	1.7	2.0	11.2
F	27.7	7.309	15.1	48.0	12.6	8.8	9.9	7.4

fetal hypoxemia or acidemia may be obscured by apparent normal growth and failure of the fetuses to have blood flow redistribution.

Proteinuric hypertension is a common feature of pregnancies complicated by diabetic nephropathy.[11, 12] It may be clinically difficult to distinguish between superimposed preeclampsia and proteinuric hypertension of renal origin. In preeclampsia histologic studies of placentas have demonstrated impaired trophoblastic invasion of maternal spiral arteries.[1-3] Impedance to flow in the uterine artery is determined by the degree of dilatation of the maternal spiral arteries caused by trophoblastic invasion of these vessels. Our finding of normal impedance to flow in the uterine artery suggests that in pregnancies complicated by diabetic nephropathy the observed worsening in the triad of hypertension, proteinuria, and edema may not be caused by superimposed preeclampsia.

Because impedance to flow in the uterine and umbilical arteries was normal in all but one case, the cause

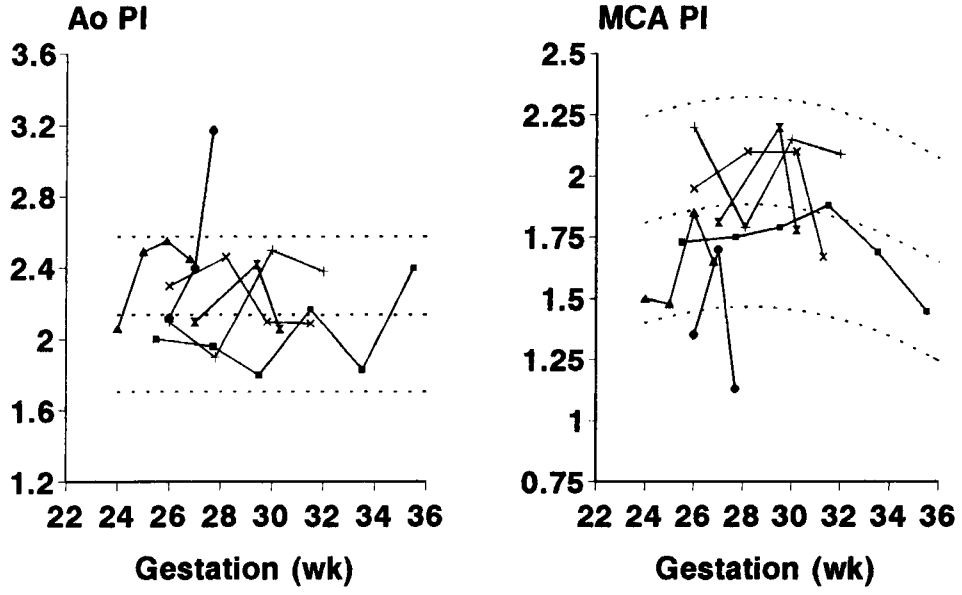

Fig. 5. Serial measurements of pulsatility index of descending thoracic aorta *(Ao PI)* and middle cerebral artery *(MCA PI)* plotted on appropriate reference range (mean, 5th and 95th percentiles) for case A (+), B (■), C (×), D (▲), E (⧗), and F (●).

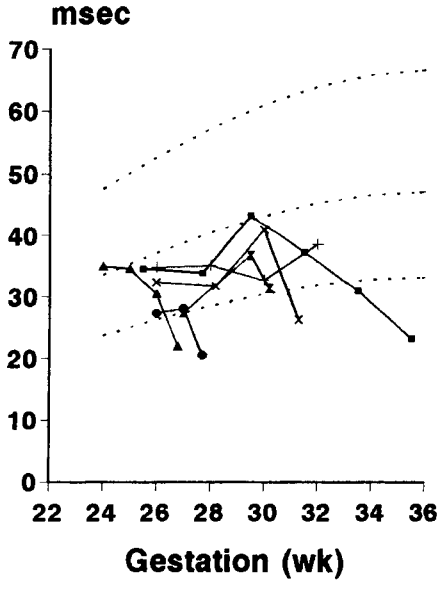

Fig. 6. Serial measurements of FHR variation (milliseconds), plotted on appropriate reference range (mean, 5th and 95th percentiles) for case A (+), B (■), C (×), D (▲), E (⧗), and F (●).

of the observed hypoxemia and acidemia is unlikely to be impaired uteroplacental or fetoplacental perfusion. It is possible that the fetal hypoxemia and acidemia is a consequence of poor glycemic control. Previous studies in pregnancies complicated by maternal diabetes mellitus have demonstrated fetal acidemia, and it was suggested that the acidemia was metabolic in origin and related to the degree of glycemic control.[24, 25] Furthermore, animal studies have shown that mild hyperglycemia is associated with acidemia alone, whereas higher degrees of hyperglycemia are associated with both acidemia and hypoxemia.[26-28] An alternative explanation for the fetal hypoxemia is that in maternal nephropathy the hypoproteinemia and fluid retention are accompanied by intervillous edema and consequent impaired placental transport in the presence of normal perfusion.

Although IUGR is more common in nephropathic than nonnephropathic diabetics, the data from this study demonstrate that in spite of hypoxemia and acidemia antenatal fetal growth was normal and the birth weight was appropriate for gestation in four of the six cases, providing further support for normal placental perfusion.[11, 12]

Unlike the findings of the current study, in IUGR caused by uteroplacental insufficiency there are significant associations between the degree of fetal hypoxemia and acidemia and alterations in fetal Doppler results.[9] However, in IUGR the metabolic disturbance extends beyond hypoxemia and acidemia, and the fetus may have deranged carbohydrate, lipid, amino acid, and endocrine function.[29] Therefore the lack of blood flow redistribution in this study may indicate that metabolic derangements other than blood pH and Po_2 are

important in the pathogenesis of this hemodynamic alteration.

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