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Fetal pancreatic β-cell function in pregnancies complicated by maternal diabetes mellitus: Relationship to fetal acidemia and macrosomia

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OBJECTIVE: Our purpose was to investigate the relationship between fetal pancreatic β-cell function and fetal acidemia and macrosomia in pregnancies complicated by maternal diabetes mellitus.
STUDY DESIGN: A cross-sectional study at the Harris Birthright Research Centre for Fetal Medicine, London, was performed. In 32 pregnancies complicated by maternal diabetes mellitus cordocentesis was performed at 36 to 39 weeks' gestation for the measurement of umbilical venous blood pH, Po_2, Pco_2, lactate, and glucose concentration; plasma insulin immunoreactivity; and insulin/glucose ratio. A reference range for plasma insulin and insulin/glucose ratio was constructed by studying fetal blood samples from 80 women who did not have diabetes mellitus.
RESULTS: Mean umbilical venous blood pH was significantly lower and plasma insulin immunoreactivity and insulin/glucose ratio were significantly higher than the appropriate normal mean for gestation. There were significant associations between (1) maternal and fetal blood glucose concentrations ($r = 0.95$, $p < 0.0001$), (2) fetal blood glucose and plasma insulin immunoreactivity ($r = 0.57$, $p < 0.01$), (3) fetal plasma insulin immunoreactivity and blood pH ($r = -0.39$, $p < 0.05$), and (4) fetal insulin/glucose ratio and degree of macrosomia ($r = 0.76$, $p < 0.0001$).
CONCLUSION: Fetal pancreatic β-cell hyperplasia is implicated in the pathogenesis of both fetal acidemia and macrosomia. (Am J Obstet Gynecol 1993;168:1363-9.)

Key words: Diabetes mellitus, cordocentesis, fetal insulin, macrosomia

Pregnancies complicated by maternal diabetes mellitus are associated with an increased incidence of fetal macrosomia and unexplained late intrauterine death.[1-3] Pedersen[4] proposed that maternal hyperglycemia causes fetal hyperglycemia and hyperinsulinemia with a consequent increase in fetal growth. Although the cause of late intrauterine death remains uncertain, it may be the result of fetal hyperinsulinemia causing an increased metabolic rate and tissue hypoxia.[5, 6] Studies of fetal blood obtained by cordocentesis from pregnancies complicated by maternal diabetes mellitus have demonstrated high correlations between maternal and fetal blood glucose concentrations and between fetal glucose and blood pH.[5, 6] However, there was no significant association between the degree of acidemia and macrosomia.[5, 6]

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Supported by a grant from John and Carol Wates (D.R.S.).
Received for publication July 18, 1992; revised November 30, 1992; accepted December 16, 1992.
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0002-9378/93 $1.00 + .20 6/1/44963

We hypothesize that fetal acidemia is the consequence of acute episodes of maternal hyperglycemia with consequent fetal hyperglycemia and hyperinsulinemia. In contrast, macrosomia is the result of poor long-term glycemic control and fetal pancreatic β-cell hyperplasia. The aim of the current study was to investigate this hypothesis by examining the interrelationships of short- and long-term maternal glycemic control with fetal pancreatic β-cell function, oxygenation, and growth.

Patients and methods

In 32 women with established (n = 22) or gestational (n = 10) diabetes mellitus umbilical venous blood was obtained by cordocentesis up to 24 hours before elective delivery at 36 to 39 weeks' gestation (mean 38 weeks). The patients were recruited between August 1990 and February 1992 from our antenatal clinic for pregnancies complicated by maternal diabetes mellitus, and all were treated with insulin. In the group with established diabetes, according to the White classification,[7] seven belonged to group B, 14 to group C, and one to group D. Gestational age was established from the maternal menstrual history and was confirmed by ultrasonography (n = 27) or by an early ultrasonographic scan in those with uncertain dates (n = 5). In all cases the fetal anatomy, both by antenatal ultrasonography and postnatal examination, was normal.

Before giving their written consent, all patients were counseled that the procedure was experimental and that the results would not give any direct benefit to their current pregnancy. The study was approved by our hospital ethics committee. During the same period (August 1990 through February 1992), there were an additional 32 diabetic patients (White class B, n = 5; class C, n = 9; class D, n = 3; gestational diabetes, n = 15) who were delivered at 37 to 39 weeks' gestation and were not included in this study; in 15 cases the patient refused to have cordocentesis, in 16 cases the patient went into spontaneous labor before the date of planned delivery, and in one patient who had cordocentesis there was insufficient fetal plasma to perform the insulin assay.

In two cases elective delivery was undertaken at 36 weeks' gestation because the patients had previous unexplained intrauterine deaths at 37 weeks. In the remaining cases the antenatal course was uncomplicated, and, according to our current policy, elective delivery was undertaken at 37 to 39 weeks' gestation. Induction of labor was undertaken in 13 patients; eight had vaginal deliveries and five were delivered by emergency cesarean section for fetal distress (n = 4) and one for suspected cephalopelvic disproportion. In 19 patients elective cesarean section was performed because of previous cesarean delivery (n = 15), macrosomia (n = 1), congenital abnormality of the maternal pelvis (n = 1), and breech presentation (n = 2). All infants survived.

Reference ranges for umbilical venous plasma insulin immunoreactivity and insulin/glucose ratio were constructed from the study of 80 appropriate-for-gestational-age fetuses undergoing prenatal diagnosis at 18 to 36 weeks' gestation. The indications for cordocentesis in these cases were (1) fetal karyotyping for advanced maternal age (n = 20) or for fetal malformations such as choroid plexus cysts or hydronephrosis (n = 49) or (2) prenatal diagnosis of an inherited blood disorder or a congenital infection (n = 11). In all cases the fetal karyotype was normal and the fetuses did not have the blood disorder or infection for which they were tested.

Cordocentesis was performed without fetal paralysis or maternal fasting or sedation, and all procedures were uncomplicated.[8] Fetal blood was collected into heparinized syringes (500 μl) for measurement of blood pH, Po_2, and Pco_2 (Radiometer ABL330, Copenhagen, Denmark); blood glucose and lactate concentrations (YSI 23A, Yellow Springs Instruments, Ohio); and plasma insulin immunoreactivity. Fetal blood (180 μl) was also collected into 20 μl of isotonic edetic acid solution (0.5 mmol/L in 0.15 mmol/L sodium chloride), and contamination with maternal blood was excluded by the Kleihauer-Betke method.

The blood samples for insulin assay were centrifuged for 10 minutes at 5000 revolutions/min, and the plasma was separated and frozen at −20° C. Plasma insulin immunoreactivity was measured by double antibody radioimmunoassay (Guildhay, Guildford, England), and the samples were analyzed in two runs. The intraassay and interassay coefficients of variation were 4% and 6.7%, respectively, for the assay range 13 to 100 μU/ml. The assay detection limit was 1.5 μU/ml, and the upper assay limit requiring sample dilution was 155 μU/ml.

At cordocentesis a maternal venous blood sample was taken from the antecubital fossa for the measurement of blood glucose concentration. The maternal-fetal blood glucose gradient was calculated by subtracting the fetal from the maternal blood glucose concentration.

The maternal glycosylated hemoglobin percentage was measured at 12 to 14, 26 to 28, and 36 to 38 weeks by immunoelectrophoresis (Corning Scanner, Corning, Halstead, England). For patients with established diabetes (n = 22) all three measurements were available, whereas in those with gestational diabetes (n = 10), only the 36 to 38 week measurement was examined because the diagnosis was made at 28 weeks' gestation, when our routine screening for this condition is undertaken.

For each infant the expected birth weight was calculated from nomograms that adjust for gestational age and sex and for maternal ethnic background, parity, height, and weight in the first trimester of pregnancy.[9]

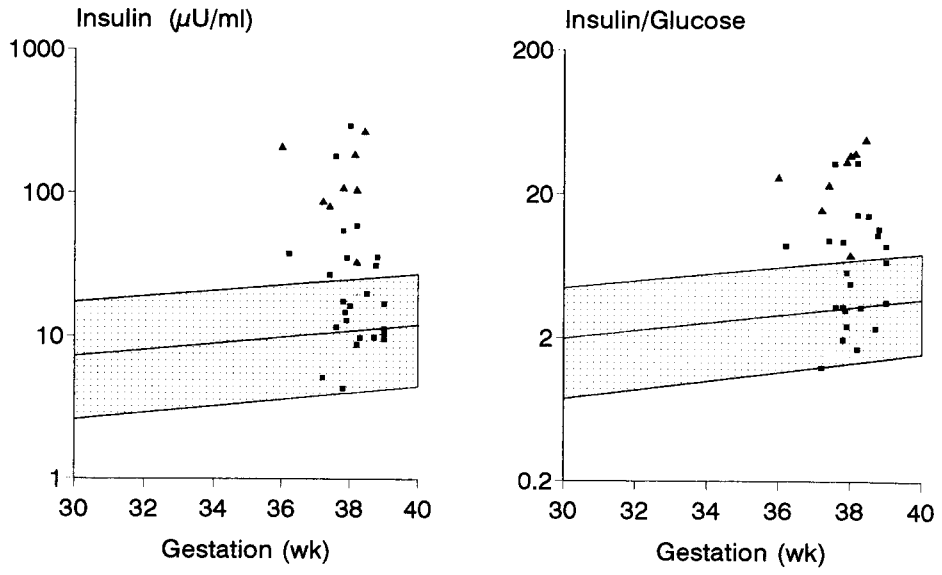

Fig. 1. Umbilical venous plasma insulin immunoreactivity (microunits per milliliter) and insulin/glucose ratio at cordocentesis plotted on appropriate reference range (mean, 95th and 5th percentiles) with gestation. ▲, Eight cases that were complicated by neonatal hypoglycemia.

The percentage of the actual to the expected birth weight was calculated. In all cases early feeding of the neonate was instituted, and the capillary blood glucose concentration was monitored with reagent sticks (BM-Test, Boehringer Mannheim, Mannheim, Germany). If hypoglycemia was suspected (BM-Test ≤2 mmol/L), a formal venous blood glucose measurement was performed (YSI 23A, Yellow Springs Instruments). The diagnosis of neonatal hypoglycemia was made if the blood glucose concentration was ≤2.2 mmol/L.[10]

Statistical analysis. Because in normal pregnancy insulin immunoreactivity and insulin/glucose ratio are distributed in a nonparametric manner, for both variables the logarithm of actual values was used. The two-tailed Student *t* test was applied to determine whether the measurements in the fetuses of diabetic mothers differed significantly from the appropriate normal mean for gestation.[8, 11-13] When the means of two measured variables were compared, the unpaired Student *t* test (two-tailed) was used.

Furthermore, linear regression analysis was used to determine the significance of associations between the measured parameters. Although in normal pregnancy many of the parameters studied change with gestational age, within the narrow gestational range of the current study group none of the parameters were significantly associated with gestation.

Results

In the 80 nondiabetic pregnancies both the fetal plasma insulin immunoreactivity and the insulin/glucose ratio increased significantly with gestation (Table I, Fig. 1; $\log_{10}$ (insulin + 3) = 0.437 × 0.019 weeks, SD = 0.177, $r = 0.479$, $p < 0.0001$ and $\log_{10}$ insulin/glucose = −0.06 × 0.018 weeks, SD = 0.155, $r = 0.503$, $p < 0.0001$).

In the 32 pregnancies complicated by maternal diabetes mellitus, compared with the appropriate normal mean for gestation, the mean umbilical venous blood pH was significantly lower and the mean plasma insulin immunoreactivity, insulin/glucose ratio, umbilical venous blood P_{CO_2}, blood lactate concentration, and birth weight were significantly higher; the mean blood P_{O_2} was not significantly different (Table II, Fig. 1). The mean percentage of expected birth weight was 113% (range 84% to 159%). The mean maternal glycosylated hemoglobin percentage was significantly higher than the normal mean for each trimester (Table II), and the mean maternal and fetal glucose concentrations at cordocentesis were 5.26 mmol/L (range 1.8 to 12.4, SD = 2.32) and 4.20 mmol/L (range 1.2 to 8.8, SD = 1.69), respectively (Fig. 2).

The interrelationships between the various parameters are shown in Table III. Although there were significant associations between maternal blood glucose concentration and fetal blood pH, birth weight was not associated significantly with either maternal blood glucose concentration or glycosylated hemoglobin percentage. However, there were significant associations between maternal blood glucose concentration and fetal plasma insulin immunoreactivity and maternal-fetal blood glucose gradient, between fetal plasma insulin immunoreactivity and fetal blood pH, and between fetal insulin/glucose ratio and percentage expected birth weight (Figs. 2 and 3).

Eight of the 32 neonates developed hypoglycemia

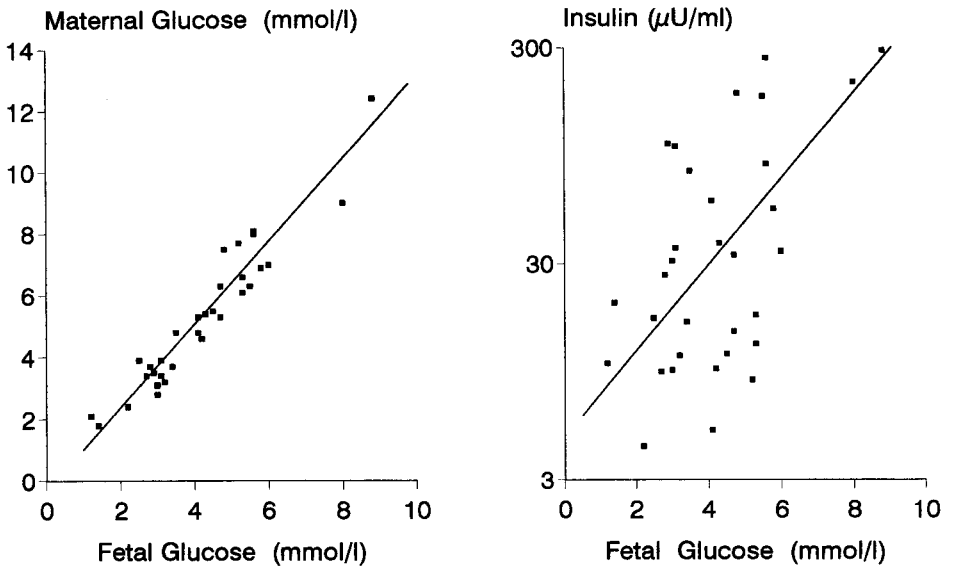

Fig. 2. Relationship between maternal and fetal blood glucose concentration (millimoles per liter) and between fetal plasma insulin immunoreactivity (microunits per milliliter) and fetal blood glucose concentration (millimoles per liter).

Table I. Reference ranges for fetal insulin immunoreactivity and insulin/glucose ratio

		Insulin immunoreactivity (μU/ml)			*Insulin/glucose ratio*		
			Percentile			*Percentile*	
Gestation (wk)	*No.*	*Mean*	*5th*	*95th*	*Mean*	*5th*	*95th*
18	7	3.032	0.030	9.008	0.823	0.010	2.332
20	19	3.587	0.321	10.062	0.978	0.086	2.605
22	16	4.192	0.636	11.227	1.147	0.181	2.905
24	13	4.854	0.975	12.517	1.331	0.283	3.234
26	4	5.576	1.339	13.948	1.530	0.393	3.597
28	5	6.364	1.731	15.536	1.747	0.510	3.997
30	4	7.225	2.151	17.300	1.981	0.634	4.438
32	3	8.166	2.600	19.262	2.236	0.768	4.925
34	4	9.192	3.081	21.445	2.513	0.909	5.464
36	5	10.313	3.594	23.878	2.813	1.060	6.059
38	–	11.537	4.142	26.589	3.139	1.220	6.717
40	–	12.874	4.727	29.613	3.493	1.390	7.445

and were treated by intravenous infusion of 10% dextrose (n = 7) or nasogastric feeding (n = 1). All eight patients had fetal insulin immunoreactivity and an insulin/glucose ratio >95th percentile (Fig. 1). The mean fetal insulin immunoreactivity and insulin/glucose ratio in the hypoglycemic neonates were significantly higher than in the nonhypoglycemic group (mean difference 0.746, SE 0.166, t = 4.48, $p < 0.001$ and mean difference 0.647, SE 0.145, t = 4.45, $p < 0.001$, respectively).

Comment

The findings that in normal pregnancy the umbilical venous plasma insulin immunoreactivity and insulin/glucose ratio increase with gestation presumably reflect fetal pancreatic maturation with gestation.

In pregnancies complicated by maternal diabetes mellitus fetal plasma insulin immunoreactivity is higher than in nondiabetic pregnancies, and the magnitude of increase is greater than would be expected from the degree of hyperglycemia. The most likely explanation for the high insulin/glucose ratio is pancreatic β-cell hyperplasia, which is a well recognized feature of these pregnancies.[14] Supportive evidence for this is provided by the association between the fetal insulin/glucose ratio and both neonatal hypoglycemia and macrosomia. The contribution of proinsulin to the observed increased insulin immunoreactivity remains uncertain and requires further study.

The findings of decreased fetal blood pH and the significant associations between maternal and fetal blood glucose concentrations, insulin immunoreactivity,

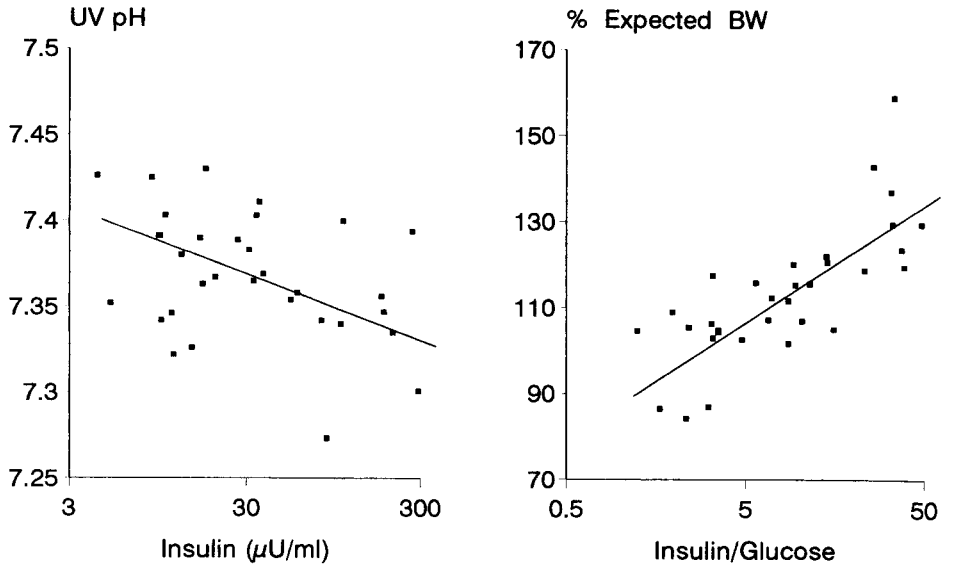

Fig. 3. Relationship between umbilical venous *(UV)* blood pH and fetal plasma insulin immunoreactivity (microunits per milliliter) and between percentage expected birth weight *(BW)* and insulin/glucose ratio.

Table II. Comparison of mean values in the 32 pregnancies complicated by maternal diabetes mellitus with appropriate normal mean

	Diabetes		*Normal mean*	*Mean difference*	*Correlation coefficient*	*Significance*
	Mean	*Range*				
Blood pH	7.368	7.273-7.430	7.392	−0.024	−3.74	$p < 0.001$
Blood Po_2 (mm Hg)	32.92	21.6-42.2	32.53	0.39	0.45	NS
Blood Pco_2 (mm Hg)	41.02	34.2-48.0	37.05	3.97	6.45	$p < 0.0001$
Blood lactate (mmol/L)	1.00	0.50-1.60	0.76	0.24	5.46	$p < 0.0001$
Maternal-fetal glucose gradient	1.05	−0.2-3.6	0.68	0.37	2.49	$p < 0.05$
Log_{10} plasma insulin (μU/ml)	1.495	0.633-2.465	1.062	0.433	4.72	$p < 0.0001$
Log_{10} insulin/glucose ratio	0.913	0.095-1.682	0.497	0.416	5.21	$p < 0.0001$
Birth weight (kg)	3.581	2.65-5.32	3.199	0.382	4.33	$p < 0.001$
Maternal glycosylated hemoglobin (%)						
First trimester (n = 22)	9.47	6.5-14.3	6.5	2.97	6.33	$p < 0.0001$
Second trimester (n = 22)	8.39	6.9-10.8	6.2	2.19	8.83	$p < 0.0001$
Third trimester (n = 32)	8.76	5.5-11.9	7.0	1.76	7.0	$p < 0.0001$

NS, Not significant.

lactate concentration, and pH are consistent with the hypothesis that in pregnancies complicated by maternal diabetes mellitus fetal acidemia is metabolic in origin.[5, 6] Furthermore, the lack of significant association between maternal glycosylated hemoglobin percentage and fetal blood pH suggests that the latter is liable to acute fluctuations dependent on short-term maternal glycemic control.[5, 6] Animal studies have demonstrated that in pregnant sheep hyperglycemia and hyperinsulinemia results in increased fetal glucose metabolism and oxygen consumption.[15, 16] Furthermore, minor degrees of fetal hyperglycemia are associated with an accumulation of lactate and a fall in pH in the absence of hypoxemia.[17]

The significant association between maternal-fetal glucose gradient and maternal blood glucose concentration presumably reflects saturation of facilitative transport across the placenta.[18] However, previous studies in labor have suggested that saturation of facilitative transport occurs only when the maternal glucose concentration exceeds 11 mmol/L, and only one of our cases had such a high glucose level.[19] The most likely explanation for our finding of increased maternal-fetal glucose gradient and the association with fetal insulin immunoreactivity is increased fetal glucose use caused by the hyperinsulinaemia.

We hypothesize that (1) the hyperglycemia or the other metabolic derangements associated with maternal diabetes mellitus act on the fetal pancreas to cause β-cell hyperplasia and (2) the critical stage for develop-

Table III. Interrelationship between maternal glucose concentration; fetal glucose concentration; maternal-fetal glucose gradient; $\log_{10}$ fetal insulin; $\log_{10}$ fetal insulin/glucose; umbilical venous blood pH, Po_2, Pco_2, and lactate; percentage expected birth weight; maternal glycosylated hemoglobin percentage in the first, second, and third trimester expressed as r values

	Fetal glucose concentration	*Maternal-fetal glucose gradient*	*Log_{10} fetal insulin*	*Log_{10} fetal insulin/glucose*	*pH*	*Po_2*
Maternal glucose concentration	0.95*	0.82	0.62†	0.34	−0.44‡	−0.10
Fetal glucose concentration		0.60†	0.57§	0.26	−0.38‡	0.01
Maternal-fetal glucose gradient			0.54§	0.41‡	−0.37‡	−0.23
Log_{10} fetal insulin				0.93*	−0.39*	−0.02
Log_{10} fetal insulin/glucose					−0.27	−0.01
pH						0.44‡
Po_2						
Pco_2						
Lactate						
Percentage expected birth weight						

*$p < 0.0001$.
†$p < 0.001$.
‡$p < 0.05$.
§$p < 0.01$.

ment of pancreatic β-cell hyperplasia is before the third trimester. Animal studies have demonstrated that β-cell hyperplasia and precocious pancreatic maturation can be induced by hyperglycemia and various amino acids.[20] Furthermore, in pregnancies complicated by diabetes mellitus there are high concentrations of insulin in the amniotic fluid from at least 28 weeks' gestation.[21] In our study the association between the fetal insulin/glucose ratio and the maternal glycosylated hemoglobin percentage was higher in the first and second than in the third trimester of pregnancy; however, we acknowledge that these associations did not reach statistical significance.

Although good diabetic control in the third trimester of pregnancy reduces the incidence of macrosomia,[22] the macrosomia is not always preventable.[23] In pregnant women with diabetes mellitus, in spite of stringent maternal glycemic control, the fluctuation in maternal glucose concentration is greater than in nondiabetics.[24] During short-lived episodes of hyperglycemia an already hyperplastic fetal pancreas will respond with a disproportionately high release of insulin, which causes macrosomia either directly through its anabolic effect on nutrient uptake and use or indirectly through related peptides such as insulin-like growth factors.[25]

This study has provided further evidence for the interrelationship between maternal hyperglycemia and fetal hyperinsulinemia and acidemia. Furthermore, the data suggest that the fetal insulin/glucose ratio provides an index of pancreatic β-cell hyperplasia, which is the likely cause of fetal macrosomia. We hypothesize that fetal pancreatic β-cell hyperplasia is determined by maternal glycemic control before the third trimester of pregnancy.

We thank Dr. P. Watkins, Dr. P. Drury, and Dr. M. Doddridge for their support in the clinical management of these patients and Dr. J. Gardosi for his assistance in calculating the expected birth weight.

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			Glycosylated hemoglobin		
Pco_2	*Lactate*	*Percentage expected birth weight*	*First trimester*	*Second trimester*	*Third trimester*
0.24	0.46§	0.24	0.15	−0.10	0.06
0.15	0.38‡	0.26	0.18	−0.15	−0.04
0.31	0.47§	0.14	0.05	0.03	0.08
0.11	0.23	0.71*	0.20	0.26	0.00
0.07	0.12	0.76*	0.21	0.37	0.02
−0.54§	−0.46§	−0.11	−0.21	−0.30	−0.02
−0.71*	−0.24	0.31	−0.13	−0.31	0.17
	0.33	−0.09	0.11	0.14	−0.06
		−0.04	0.31	0.21	−0.13
			0.02	0.08	0.07

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