Increased Macrosomia and Perinatal Morbidity Independent of Maternal Obesity and Advanced Age in Korean Women With GDM

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OBJECTIVE — To examine the impact of gestational diabetes mellitus (GDM) on perinatal outcome in a setting where influences of maternal age and obesity would be minimal.

RESEARCH DESIGN AND METHODS — A case-control study was done to compare the outcome of pregnancy in 65 women with GDM and 153 women with normal carbohydrate metabolism matched for age, height, and prepregnancy weight.

RESULTS — The frequencies of preeclampsia and primary cesarean sections were higher and delivery was earlier in pregnancies complicated by GDM. Birth weight, symmetry index, and chest circumference were greater, and macrosomia and need for phototherapy were more common in offspring of mothers with GDM. Cord-serum C-peptide and insulin concentrations were higher in the infants of mothers with GDM and were strongly correlated with birth weight and symmetry index. However, maternal age, prepregnancy weight, and prepregnancy BMI were not correlated with birth weight. Postprandial glucose levels during the first 2 weeks after diagnosis of GDM had associations with the infant's birth weight, symmetry index, and cord insulin concentration in the diet-treated patients with GDM.

CONCLUSIONS — Antepartum maternal glucose metabolism was significantly associated with fetal hyperinsulinemia and excessive fetal growth in relatively nonobese Korean women. These findings support a direct role for metabolic factors in the adverse outcomes in pregnancies complicated by GDM.

The Pederson hypothesis (1) is widely accepted as the principal mediator of excess fetal growth and perinatal morbidity in diabetic pregnancies. It states that an increase in maternal nutrients is rapidly translated into an increased nutrient milieu for the fetus. The fetal pancreas responds to glucose and amino acid stimuli, and fetal hyperinsulinemia results. The fetal hyperinsulinemia has a significant effect on adverse fetal outcomes such as macrosomia, neonatal hypoglycemia, and other perinatal morbidities.

Perinatal morbidities, especially macrosomia, are observed more often than expected in infants of mothers with gestational diabetes mellitus (GDM), even though widespread screening for and intensive management of GDM reduce overall morbidity (2). GDM may also have long-term implications for offspring. The offspring of mothers with pregestational diabetes and gestational diabetes have higher frequencies of childhood obesity, impaired glucose tolerance, and type 2 diabetes in adolescence or later (3–5) and may be at risk for impairment of intellectual and motor development (6).

Although macrosomia and perinatal morbidities are seen with increased frequency in offspring of gestational diabetic mothers, some studies have suggested that maternal obesity and advanced age, rather than concurrent mild hyperglycemia, are primarily implicated (7–10).

There have been limited studies of GDM in native Asian women. We reported that the prevalence of GDM in Korean women was similar to that in U.S. Caucasians, even though the frequency of obesity was much lower in Korean women (11). However, studies on pregnancy outcome in Korean women with GDM have not been reported previously.

The purpose of this study was to investigate the implications of GDM for perinatal morbidities in a population with a low prevalence of maternal obesity. We tried to identify the effect of maternal hyperglycemia on pregnancy outcomes without influence of maternal obesity and age. We compared the perinatal outcomes of women with GDM and control subjects with normal glucose tolerance matched in age, height, and prepregnancy weight. The data were collected prospectively in a large-scale program of universal screening for GDM in Seoul, Korea.

RESEARCH DESIGN AND METHODS

Screening and diagnosis

From January 1991 to December 1992, all pregnant women receiving antenatal care at the Samsung Cheil Hospital in Seoul were screened for glucose intolerance at 24–28 weeks' gestation. The screen consisted of a venous plasma glucose measurement 1 h after a 50-g oral glucose load administered without regard to time or amount of last meal, as recommended by the Third Inter-

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Abbreviations: FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; IBW, ideal body weight; LGA, large for gestational age; OGTT, oral glucose tolerance test; SGA, small for gestational age.

national Workshop-Conference on Gestational Diabetes Mellitus, with minor modifications (12). Women with plasma glucose levels ≥7.2 mmol/l (130 mg/dl) were recalled for a 3-h 100-g oral glucose tolerance test (OGTT) performed after an overnight fast of at least 8 h but no more than 14 h. The tests were carried out in the outpatient department after 3 days of 150 g of carbohydrate in the diet and unrestricted physical activities. Patients were considered to have GDM if at least two values reached or exceeded the following: 5.8 mmol/l (105 mg/dl) at fasting, 10.6 mmol/l (190 mg/dl) at 1 h, 9.2 mmol/l (165 mg/dl) at 2 h, and 8.1 mmol/l (145 mg/dl) at 3 h (13).

Subjects

Perinatal outcomes were studied in pregnancies in which a singleton infant was delivered at the Samsung Cheil Hospital during the study period. Pregnancies complicated by conditions that might affect the outcomes of pregnancy (chronic hypertension, thyroid disease, renal disease, asthma, chronic infectious disease, and smoking) were excluded from the study before data collection. The study protocol was approved by the Samsung Cheil Hospital research and ethics committee, and informed consent was obtained from all subjects. Our objective was to select three control subjects for each subject with GDM, specifically using those matching by age ± 3 years, prepregnancy weight ± 2 kg, and height ± 3 cm with screening dates closest to the patients with GDM. However, subjects with GDM were older and heavier than the population average. Thus, the final matching of all control subjects of eligible weights and ages yielded a ratio of 2.4:1 rather than 3:1. The control group was selected from those with normal glucose tolerance; however, to assure a representative sample, it was not mandated that the glucose value from the screening test should be <7.2 mmol/l. Thus, in the control group of 153 women, 128 had a negative screen (84%) and 25 had a positive screen but a normal glucose tolerance test (16%).

Clinical management protocol

A team approach was used in the management of GDM. The team, including physicians, nurse educators, and dietitians, provided individualized diabetes care. Diet was composed of 50–60% carbohydrate, 20% fat, and 20–30% protein, divided into three meals and two or three snacks per day. Nonobese patients were put on a diet of 35 kcal/kg ideal body weight (IBW) per day, and obese patients were put on a diet with mild caloric restriction of 30 kcal/kg IBW per day. Patients with a prepregnancy BMI of ≥27.3 kg/m^2 were classified as obese. It was recommended that patients walk for 15–20 min twice daily after meals. Total calorie intake and calorie distribution were evaluated by 24-h diet recall. Glycemic control was monitored by fasting and 2-h postprandial venous blood glucose measurements at weekly outpatient visits in patients managed with diet and exercise. Patients requiring insulin therapy monitored their fasting, 2-h postprandial (three times a day), and bedtime capillary blood glucose levels at home, and their 2-h postprandial venous blood glucose values were measured at each outpatient visit.

The goals for glycemic control were fasting blood glucose levels of 3.4–5.6 mmol/l and 2-h postprandial levels of ≤6.7 mmol/l. Insulin therapy was added (twice daily mixed regular and NPH insulin) when a patient had a fasting blood glucose level ≥5.8 mmol/l or a 2-h postprandial blood glucose level >6.7 mmol/l on two consecutive weekly visits. If a patient's diagnostic OGTT fasting plasma glucose (FPG) level was ≥6.1 mmol/l, insulin therapy was started immediately. The insulin dosage was adjusted to the results of blood glucose tests at weekly follow-up visits, and total calories in the diet and duration of exercise were also adjusted to the patient's blood glucose levels and rate of weight gain.

Obstetric surveillance

Subjects were certain of the date of their last menstrual period, or they had obstetric dating from an ultrasound examination. Clinical estimates of gestational age were used if they were within the range of the ultrasound estimates. If there were inconsistencies between the ultrasound and clinical estimates of gestational age, the ultrasound estimate was used if it had been obtained before 20 weeks' gestation.

Antepartum surveillance in pregnant women with GDM included serial ultrasounds and biophysical profiles every 2–4 weeks after diagnosis of GDM and nonstress tests and amniotic fluid index measurements weekly after 34 weeks' gestation. Labor was induced after 40 weeks' gestation if spontaneous labor had not occurred. If the fetus was estimated by ultrasound to weigh >4,000 g at 38 weeks' gestation, delivery by primary cesarean section was recommended unless the patients were multigravida. In accord with Korean Medical Practice Guidelines, the primigravidas who were >35 years of age were delivered by primary cesarean section. Preeclampsia was defined as persistently elevated blood pressure (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on more than two measurements ≥6 h apart) and proteinuria (≥1+ in a urine protein test) in the 2nd or 3rd trimester. The diagnosis of polyhydramnios was made by ultrasound.

At the beginning of labor, an intravenous infusion of normal saline was started unless the blood glucose level fell to <3.9 mmol/l (70 mg/dl). The goal of glycemic control during labor was a blood glucose level of 3.9–5.0 mmol/l (70–90 mg/dl). If the blood glucose level was <3.9 mmol/l, normal saline was changed to 5% dextrose. Blood glucose concentration was monitored hourly.

Neonatal assessment

All newborns were examined immediately after delivery. Any abnormal physical findings were noted on the detailed physical examination standardized with a code sheet, and anthropometric measurements were done by trained residents within 24 h. Each newborn's weight and length were measured with the infant in a supine position, and head circumference was measured with a disposable tape at the largest diameter across the forehead. Chest circumference was measured at the diameter across the nipple and axilla. Infants small for gestational age (SGA) at birth weighed below the 10th percentile for age, and infants large for gestational age (LGA) weighed above the 90th percentile according to Lubchenco and colleagues (14,15). Relative obesity was assessed on the basis of the symmetry index (16). Relative weight was measured as weight divided by the Lubchenco median weight for age. Relative height was measured as height divided by the Lubchenco median height for age. The relative weight divided by the relative height yields the symmetry index. At delivery, cord-blood serum was sampled for later measurements of C-peptide and insulin and stored frozen at −70°C.

Analytical methods

Plasma and whole-blood glucose concentrations were measured by a glucose oxidase method (YSI 2300 STAT, Yellow Springs Instruments), and capillary blood glucose concentrations were measured by

Table 1—*Characteristics of the study subjects*

	GDM group	Normal control group	*P*
n	65	153	
Maternal age (years)	31.3 ± 4.1	30.3 ± 4.1	NS
Height (cm)	157.9 ± 5.0	158.7 ± 4.1	NS
Prepregnancy weight (kg)	57.2 ± 9.8	55.5 ± 7.9	NS
Prepregnancy BMI (kg/m²)	22.9 ± 3.5	22.0 ± 2.8	NS
Obese subjects (≥27.3 kg/m²) (%)	12.3	9.2	NS
Weight gain during gestation (kg)	12.2 ± 4.6	13.5 ± 4.0	<0.05
Parity			
0	38 (58.5)	82 (53.6)	NS
1	21 (32.3)	63 (41.2)	NS
2	6 (9.3)	8 (5.2)	NS
Gestational age at screening test (weeks)	27.7 ± 3.8	26.9 ± 3.1	NS

Data are means ± SD or *n* (%). The normal control group consisted of 128 women who had a negative screen and 25 women who had a positive screen but a normal glucose tolerance test.

glucose meter (One Touch II, Lifescan). Concentrations of insulin and C-peptide in cord serum were measured in duplicate at the Endocrine Laboratory of Samsung Cheil Hospital using commercially available kits (insulin, Dainabot, Japan; C-peptide, Daichii, Japan). The intra- and interassay coefficients of variation for insulin were 4.5 and 8.8%, and the intra- and interassay coefficients of variation for C-peptide were 7.1 and 9.7%, respectively.

Statistical analysis

Data are expressed as means ± SD and percentages unless otherwise stated. Comparison of obstetric and neonatal outcome was computed by unpaired *t* test, Mann-Whitney *U* test, χ^2 test, or Fisher's exact test where appropriate. The changes in maternal glycemia were tested by paired *t* test. The relationships among the infants' birth weight, anthropometric measurements, and cord-blood C-peptide and insulin concentrations, and the maternal metabolic parameters were examined by Pearson correlation, Spearman correlation, partial correlation, and multiple linear regression analysis. Log transformation of insulin and C-peptide concentration was applied to correct for nonnormal distributions. Statistical significance was defined as $P < 0.05$.

RESULTS — The control and gestational diabetic groups were matched carefully, and as expected, there were no significant differences in age, prepregnancy weight, height, BMI, and parity (Table 1). The frequency of obesity (BMI ≥27.3 kg/m²) was not different between the two groups (1.4% in the general obstetrical population at Samsung Cheil Hospital). However, weight gain during pregnancy was significantly lower in the women with GDM than in the control subjects.

Gestational age at the time of the screening test was similar in both groups. A diagnostic OGTT was performed at 29.0 ± 2.7 weeks' gestation in the women with GDM. Among the 65 patients with GDM, 42 were GDM class A_1 (FPG <5.8 mmol/l), 15 were GDM class A_2 (FPG ≥5.8, <7.2 mmol/l), and 8 were GDM class B_1 (FPG ≥7.2 mmol/l) at the time of diagnostic OGTT. Of these 65 patients, 20 (30.8%) received insulin therapy for glycemic control.

Figure 1 shows mean values for fasting and 2-h postprandial glucose concentrations after the initiation of treatment of GDM. Of the patients with GDM, 45 were managed by diet and exercise (Fig. 1*A*) and 20 required insulin treatment (Fig. 1*B*). Five women with GDM were initially treated with diet and exercise, but required insulin therapy for glycemic control. In the diet-treated patients, fasting glucose decreased from 4.9 ± 0.4 to 4.6 ± 0.4 mmol/l ($P < 0.005$) at the 2nd week and was maintained at 4.5 mmol/l. Postprandial glucose decreased from 6.6 ± 0.9 to 6.2 ± 0.8 mmol/l ($P < 0.005$) at the 2nd week and 5.6 ± 0.8 mmol/l ($P < 0.05$) at the 3rd week and was maintained at 5.5–5.8 mmol/l. The overall averages of fasting and 2-h postprandial venous glucose levels in the diet-treated group were 4.6 ± 0.4 and 5.9 ± 0.8 mmol/l. In the insulin-treated group, fasting glucose decreased from 5.9 ± 0.8 to 5.0 ± 0.7 mmol/l ($P < 0.005$) at the 2nd week and 4.7 ± 0.7 mmol/l ($P < 0.05$) at the 3rd week and was maintained at 4.3–4.7 mmol/l. The mean postprandial glucose decreased from 7.8 ± 0.7 to 7.2 ±

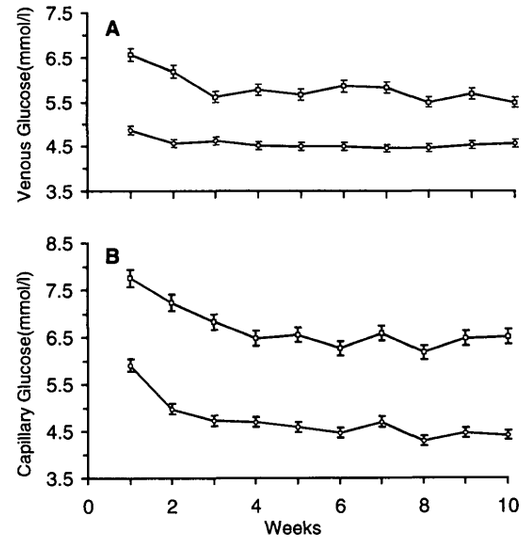

Figure 1—*Mean ± SE fasting (○) and 2-h postprandial (□) glucose concentrations in women with GDM after initiation of treatment.* A: *venous blood glucose concentrations in the diet-treated group.* B: *capillary blood glucose concentrations in the insulin-treated group. The values cannot be compared directly. There is ~15% difference between venous and capillary blood glucose measurement when compared by the same analytical method. The same may not be the case when laboratory measurements of venous plasma glucose are compared with capillary whole-blood measurements performed with reagent strips and glucose meters.*

Table 2—*Obstetric outcome in the study subjects*

	GDM group	Normal control group	*P*
n	65	153	
Gestational age at delivery (weeks)	38.8 ± 1.2	39.6 ± 1.2	<0.001
Preterm delivery (<37 weeks)	4 (6.2)	4 (2.6)	NS
Preeclampsia	7 (10.8)	2 (1.3)	<0.01
Polyhydramnios	3 (4.6)	2 (1.3)	NS
Total cesarean section	36 (55.4)	69 (45.1)	NS
Primary cesarean section	26 (40.0)	35 (22.9)	<0.05
Perineal laceration (3° and 4°)	2 (3.1)	7 (4.6)	NS

Data are means ± SD or *n* (%).

0.6 mmol/l ($P < 0.005$) at the 2nd week, 6.8 ± 0.4 mmol/l ($P < 0.005$) at the 3rd week, and 6.5 ± 0.7 mmol/l ($P < 0.05$) at the 4th week and was maintained at 6.2–6.6 mmol/l. The overall averages of capillary glucose levels were 4.7 ± 0.4 mmol/l (fasting) and 6.9 ± 0.5 mmol/l (mean postprandial).

The obstetric outcomes are summarized in Table 2. Although gestational age at delivery was significantly younger in patients with GDM, the percentage of prematurity, defined as birth before 37 weeks' gestation, was not statistically different between the gestational diabetic and control groups. The younger gestational age at delivery in the GDM group may be due, at least in part, to induction of labor at 40 weeks' gestation when spontaneous labor had not occurred. The frequency of preeclampsia was significantly higher in the patients with GDM, but the frequency of polyhydramnios was not different between the two groups. The overall rate of cesarean section was not different between the groups; however, the rate of primary cesarean section was significantly higher in those with GDM. The higher rate of primary cesarean section in those with GDM was related to higher frequencies of fetal distress (30.8% [8 of 26] vs. 8.6% [3 of 35], $P < 0.05$) and of fetal weight estimated to be >4,000 g (15.4% [4 of 26] vs. 0% [0 of 35], $P < 0.05$). The fetal weight estimated by ultrasound performed within 7 days of delivery and the actual birth weight were 4,187 ± 245 and 4,115 ± 361 g in four patients who delivered by cesarean section because of macrosomia. The frequencies of other indications for primary cesarean section did not differ in the two groups: cephalopelvic disproportion (19.2% [5 of 26] vs. 34.3% [12 of 35], $P = 0.16$), elderly primigravida (19.2% [5 of 26] vs. 37.1% [13 of 35], $P = 0.11$), abnormal presentation (7.7% [2 of 26] vs. 11.4% [4 of 35], $P = 0.49$), and failure to progress (7.7% [2 of 26] vs. 8.6% [3 of 35], $P = 0.64$). The frequency of perineal lacerations (3° and 4°) at delivery was also similar in the gestational diabetic and control groups.

The neonatal outcomes and anthropometric measurements of the offspring at birth are summarized in Table 3. Mean birth weight was 138 g heavier in the infants of mothers with GDM than that in the infants of control mothers, even though delivery was almost 1 week earlier. The frequency of an LGA infant was three times higher in the mothers with GDM. Macrosomia (birth weight >4,000 g) was four times more frequent in the pregnancies complicated by GDM, even though delivery was 1 week earlier. Although lengths and head circumferences of infants were not different between the two groups, chest circumferences and symmetry indexes were significantly higher in the infants of mothers with GDM. The proportion of infants with symmetry indexes >1.2 (a value often equated with fetal obesity) in mothers with GDM (23.1%) was much higher than that in control mothers (1.3%; $P < 0.001$). The diet-treated and insulin-treated subgroups with GDM did not differ in gestational age at delivery (38.9 ± 1.1 vs. 38.4 ± 1.3 weeks, $P = 0.14$), birth weight (3,559 ± 468 vs. 3,406 ± 628 g, $P = 0.28$), frequency of an LGA (42.2 vs. 35.0%, $P = 0.39$) or macrosomic (11.1 vs. 20.0%, $P = 0.28$) infant, or in offspring's chest circumference (33.3 ± 1.7 vs. 32.7 ± 1.9 cm, $P = 0.22$) and symmetry index (1.11 ± 0.12 vs. 1.10 ± 0.15, $P = 0.67$). Infants of mothers with GDM were at four times higher risk of requiring phototherapy (infants with a serum bilirubin concentration ≥205 μmol/l were referred for phototherapy), even after controlling for gestational age at delivery. In infants of mothers with GDM, the frequency of neonatal hypoglycemia (plasma glucose 2 h after birth <1.7 mmol/l) was 7.7%, hypocalcemia (serum calcium <2.0 mmol/l) 9.2%, and polycythemia (hematocrit >65%) 12.3%. We were not able to compare these neonatal complications between the two groups because infants of control mothers were not routinely checked for hypoglycemia, hypocalcemia, and polycythemia.

We examined the relationships between neonatal anthropometric measurements and some maternal characteristics that may influence fetal growth (Table 4). In the control group, gestational age at delivery correlated with birth weight and parity correlated with both birth weight and symmetry index. In univariate analyses, only maternal age was correlated with birth weight or symmetry index in the GDM group. A significant relationship between gestational age and birth weight was not seen in the GDM group in univariate analyses; however, as expected, a significant correlation

Table 3—*Neonatal outcomes and anthropometric measurements in offspring of the study subjects*

	GDM group	Normal control group	*P*
n	65	153	
Birth weight (g)	3,514 ± 519	3,376 ± 358	<0.05
LGA infant	26 (40.4)	20 (13.1)	<0.001
Birth weight >4,000 g	9 (13.8)	5 (3.3)	<0.01
Phototherapy	15 (23.1)	6 (3.9)	<0.001*
Length (cm)	50.1 ± 2.1	50.1 ± 1.9	NS
Head circumference (cm)	34.3 ± 1.5	34.4 ± 1.2	NS
Chest circumference (cm)	33.2 ± 1.8	32.6 ± 1.3	<0.01
Symmetry index	1.11 ± 0.13	1.05 ± 0.06	<0.001

Data are means ± SD or *n* (%). *Ajusted for effect of gestational weeks at delivery.

Table 4—*Coefficients of correlation between birth weight and symmetry index of infants and characteristics of mothers*

	Birth weight		Neonatal symmetry index	
	GDM group	Normal control group	GDM group	Normal control group
n	65	153	65	153
Maternal				
Age	−0.33† (−0.31*)	−0.11	−0.26* (−0.31*)	−0.01
Prepregnancy weight	0.09	0.07	0.13	0.11
Prepregnancy BMI	0.09	0.08	0.14	0.11
Height	0.01	0.02	−0.01	0.04
Gestational age at delivery	0.19	0.32‡	−0.13	−0.09
Parity	0.03	0.17* (0.23†)	0.01	0.28‡ (0.26†)

Data are correlation coefficients (coefficient after adjusting for gestational age at delivery). *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

between gestational age and birth weight existed in the GDM group in multivariate analyses. There was no significant correlation between maternal prepregnancy weight, prepregnancy BMI, or height and newborn birth weight or symmetry index in the control or GDM group.

We compared β-cell function in the infants of mothers with GDM and normal control subjects by measuring concentrations of C-peptide and insulin in cord-blood serum (Fig. 2). The level of cord-blood C-peptide was significantly higher in infants of mothers with GDM. The mean concentration of insulin in the infants of mothers with GDM was more than twice that in the infants of normal control mothers.

β-cell function in the offspring of mothers with GDM was also correlated with their anthropometric development. Birth weight and concentration of cord-blood C-peptide or insulin correlated strongly in the offspring of mothers with GDM ($r = 0.51$, $P < 0.001$; $r = 0.38$, $P < 0.01$, respectively) but weakly in the offspring of normal control subjects ($r = 0.21$, $P < 0.01$; $r = 0.14$, $P < 0.05$, respectively). However, the correlation between birth weight and concentration of cord C-peptide or insulin in the offspring of normal control subjects was no longer significant after controlling for gestational age at delivery ($r = 0.11$, $P > 0.05$; $r = 0.07$, $P > 0.05$, respectively). Furthermore the slope of regression between birth weight and C-peptide or insulin in offspring of mothers with GDM was greater than that in offspring of normal control mothers (C-peptide, $P < 0.001$; insulin, $P < 0.01$). The relationship between indexes of fetal β-cell function and anthropometric indexes of fetal adiposity was examined. Figure 3 illustrates a significant positive correlation between cord-blood C-peptide concentration and infant chest circumference and symmetry index in the offspring of mothers with GDM. Similar correlations were obtained between cord insulin concentration and both anthropometric measures (chest circumference, $r = 0.29$, $P < 0.05$; symmetry index, $r = 0.40$, $P < 0.01$). In contrast, we found no significant correlation between C-peptide or insulin in cord-blood serum and these anthropometric measures in the offspring of control mothers.

We examined the relationships between metabolic control and fetal β-cell function and birth weight. In the diet-treated group with GDM, infant birth weight was correlated with maternal 2-h postprandial glucose in the 2nd week (31 weeks' gestation; $r = 0.45$, $P < 0.05$) and in the 1st week (30 weeks' gestation; $r = 0.29$) after initiation of treatment with borderline significance ($P = 0.07$), but not with glycemia in subsequent weeks. Similar relationships were found between maternal postprandial glucose early after the start of dietary treatment and infant symmetry index and cord insulin in the 2nd week ($r = 0.51$, $P < 0.01$; $r = 0.44$, $P < 0.05$) and in the 1st week ($r = 0.27$, $P = 0.08$; $r = 0.34$, $P = 0.06$, respectively). We did not find correlations between maternal glycemia and birth weight, symmetry index, or cord insulin in the insulin-treated subjects. There were no significant correlations between fasting glucose levels during the 3rd trimester or plasma glucose concentrations during the diagnostic OGTT (fasting, 1 h, 2 h, and 3 h) and birth weight, symmetry index, or cord C-peptide or insulin in either group with GDM.

Maternal characteristics (age, prepregnancy weight, BMI, height, gestational age at delivery, and parity) and indexes of fetal β-cell function (cord C-peptide and insulin) were examined by stepwise multiple linear regression analysis to identify those variables independently associated with infant birth weight in the GDM group. Cord C-peptide ($P < 0.001$) and gestational age at delivery ($P < 0.005$) were significant and independent predictors of birth weight. Cord insulin was not significant; however, C-peptide and insulin were strongly correlated, with a correlation coefficient of 0.79 ($P < 0.001$).

CONCLUSIONS — From an obstetric view, the potential significance of GDM is related to the magnitude of risk for adverse outcomes of pregnancy, rather than the risk for subsequent overt diabetes in women. In

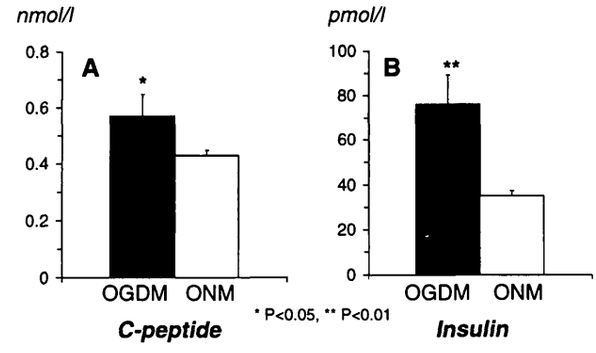

Figure 2—*β-cell function in offspring of mothers with GDM (OGDM, ■) and normal control mothers (ONM, □). A: mean ± SE concentrations of cord serum C-peptide. B: mean ± SE concentrations of cord serum insulin.*

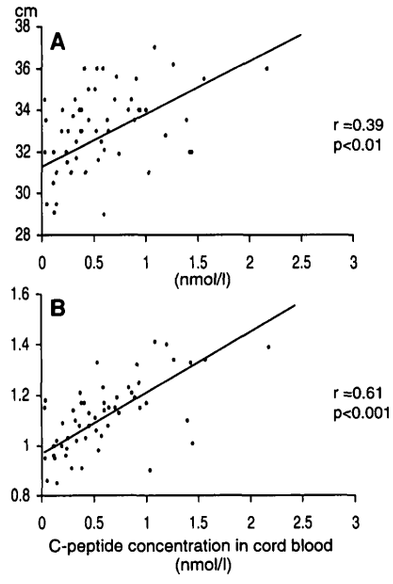

Figure 3—*Relationship between C-peptide concentration in cord blood and anthropometric measurements in 56 offspring of mothers with GDM.* A: *correlation between infant's chest circumference and cord serum C-peptide concentration.* B: *correlation between infant's symmetry index and cord serum C-peptide concentration.*

two early studies in which there was no intervention to correct hyperglycemia, O'Sullivan et al. (17) found a perinatal mortality rate of 6.4% among 187 pregnancies in women with GDM compared with 1.5% among 259 concurrent randomly selected pregnancies in women without GDM, and Pettitt et al. (18) demonstrated that the perinatal mortality rate in Pima Indians increased with an increase in 3rd trimester 2-h plasma glucose concentration during 75-g OGTT. In addition, the perinatal morbidity rate and the frequency of obstetric complications increased with increasing 2-h glucose levels (18).

Increased perinatal morbidities have subsequently been reported in pregnancy complicated by GDM. Excess perinatal mortality has not been observed. However, there has been controversy regarding the specificity of adverse outcomes associated with GDM. Some have attributed the observed risk to confounding characteristics such as maternal obesity and advanced age of subjects with GDM rather than to glucose intolerance. Lucas et al. (7) reported that there were no significant differences in perinatal morbidities and obstetric outcomes between GDM class A_1 patients and control subjects with normal glucose tolerance tests, and that maternal obesity was an independent and more potent risk factor for large infants than was glucose intolerance. However, maternal obesity was defined as last antepartum weight ≥90 kg instead of using prepregnancy BMI or relative weight. Jacobson and Cousins (19) reported that patients with GDM had a higher rate of LGA infants than did normal subjects, even though acceptable glucose control was achieved, and that only maternal weight at delivery was a significant predictor of LGA infants, but prepregnancy BMI and weight were not associated with infant birth weight percentile in their report. Leikin et al. (20) reported that severely obese (>150% IBW) patients with GDM with fasting hyperglycemia had a four times higher frequency of macrosomia than did normal subjects, but nonobese patients with fasting hyperglycemia had a frequency of macrosomia similar to that in normal subjects. However, the frequency of macrosomia in the fasting euglycemic obese patients with GDM was not different from that in fasting euglycemic nonobese patients with GDM or normal subjects.

In our study, prepregnancy weight and BMI, and weight at delivery in the patients with GDM were quite different from those in the above reports from North America. Obesity is relatively uncommon in Korean women. Furthermore, our control subjects were of similar age and weight as those with GDM to minimize the influences of maternal age and obesity. We also excluded patients with other medical conditions that might affect pregnancy outcome. In our subjects, who were matched for age, prepregnancy weight, and height, we found that the frequencies of preeclampsia and primary cesarean section were higher in pregnancies complicated by GDM. The higher frequency of primary cesarean section was attributed to higher frequencies of fetal distress and estimated macrosomia in women with GDM. However, women with GDM were treated by a high-risk obstetrical service. In women with GDM, frequent fetal surveillance by ultrasound and nonstress tests and the knowledge of GDM might contribute to an increased frequency of primary cesarean section. As pointed out by Naylor et al. (21), the diagnosis of GDM may influence obstetrical practice and increase the probability of cesarean delivery. The rates of cesarean section found in this study cannot be compared directly to many other reports because current indications for cesarean section in Korea are somewhat different from those in North America and Europe. Birth weight, frequency of macrosomia, and indexes of fetal adiposity (symmetry index and chest circumference) were greater and infants requiring phototherapy were also more common in offspring of mothers with GDM. We found no correlations between birth weight and maternal height, prepregnancy weight, or BMI in women with GDM or in control subjects. Maternal age in women with GDM was negatively correlated with birth weight, but it was confounded by the relationship between maternal age and cord C-peptide or insulin concentration.

Fetal hyperinsulinemia has been reported in women with GDM (22,23). In this study, we also found that cord C-peptide and insulin concentrations in infants of Korean mothers with GDM were higher than those in infants of control mothers, despite close supervision of diet and exercise and addition of insulin when treatment goals were not met. There were no differences in birth weight, frequencies of LGA and macrosomic infants, and infant adiposity between the diet-treated and insulin-treated subgroups with GDM. These results suggested that insulin therapy was effective in achieving the treatment goal.

Infant birth weight was significantly and independently correlated with cord C-peptide or insulin concentration in the women with GDM, but not in the control subjects. We also found significant positive correlations between cord-blood C-peptide and two indexes of relative adiposity (symmetry index and chest circumference) in the offspring of mothers with GDM. Chest circumference increases as subcutaneous soft tissues and insulin-sensitive organs (e.g., liver, heart) grow (24), and symmetry index relates to relative weight in a manner somewhat like BMI (16). Thus, a large chest circumference and a high symmetry index reflect disproportionate growth of the fetus. Maternal 2-h postprandial glucose level, but not fasting plasma glucose, was positively correlated with birth weight, symmetry index, and cord insulin in the diet-treated women with GDM. Jovanovic-Peterson et al. (25) previously demonstrated a stronger positive correlation between 1-h postprandial glucose level and birth weight than between fasting level and birth weight in women with type 1 diabetes. Fetal islet function was not measured (25). The associations we found were significant only in the first 2 weeks. These findings support the hypothesis that there is a critical period for

maternal glucose stimulation of fetal insulin secretion that may occur even before the diagnosis and treatment of GDM (26). It is also likely that alterations of other insulin-sensitive maternal nutrients (lipids and amino acids) contribute to the development of fetal hyperinsulinemia and macrosomia in the offspring of mothers with GDM (26). The loss of correlation between metabolic control later in gestation and outcome measures of fetal growth and β-cell function may also reflect the fact that these parameters did not fully return to normal even though metabolic control improved for the remaining weeks of gestation.

In summary, in Korean women, we observed more adverse outcomes of pregnancies in patients with GDM than in control subjects. Obesity is infrequent, and measures were taken to eliminate the confounding effects of maternal age and weight. Increased perinatal morbidities and macrosomia, and the infants' anthropometric measurements were related to the magnitude of perturbation of the maternal metabolic environment. These findings support a direct role for metabolic factors in adverse outcomes in pregnancies complicated by GDM.

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References

1. Pederson J, Moller B, Poulson A: Blood sugar in newborn infants of diabetic mothers. *Acta Endocrinol* 15:33–36, 1954
2. Hod M, Merlob P, Friedman S, Schoenfeld A, Ovadia J: Gestational diabetes mellitus: a survey of perinatal complications in the 1980s. *Diabetes* 40 (Suppl. 2):74–78, 1991
3. Pettitt DJ, Bennett PH, Saad MF, Charles MA, Nelson RG, Knowler WC: Abnormal glucose tolerance during pregnancy in Pima Indian women: long-term effects on offspring. *Diabetes* 40 (Suppl. 2):126–130, 1991
4. Silverman BL, Rizzo T, Green OC, Cho NH, Winter RJ, Ogata ES, Richards GE, Metzger BE: Long-term prospective evaluation of offspring of diabetic mothers. *Diabetes* 40 (Suppl. 2):121–125, 1991
5. Silverman BL, Cho NH, Metzger BE, Loeb CA: Impaired glucose tolerance in adolescent offspring of diabetic mothers: relationship to fetal hyperinsulinism. *Diabetes Care* 18:611–617, 1995
6. Rizzo T, Metzger BE, Burns WJ, Burns K: Correlations between antepartum maternal metabolism and intelligence of offspring. *N Engl J Med* 325:911–916, 1991
7. Lucas MJ, Lowe TW, Bowe L, McIntire DD: Class A1 gestational diabetes: a meaningful diagnosis? *Obstet Gynecol* 82:260–265, 1993
8. Green JR, Schumacher LB, Pawson IG, Partridge JC, Kretchmer N: Influence of maternal body habitus and glucose tolerance on birth weight. *Obstet Gynecol* 78:235–239, 1991
9. Willman SP, Leveno KJ, Guzick DS, Williams ML, Whalley PJ: Glucose threshold for macrosomia in pregnancy complicated by diabetes. *Am J Obstet Gynecol* 154:470–475, 1986
10. Cundy T, Gamble G, Manuel A, Townend K, Roberts A: Determinants of birth-weight in women with established and gestational diabetes. *Aust NZ J Obstet Gynaecol* 33:249–254, 1993
11. Jang HC, Cho NH, Jung KB, Oh KS, Dooley SL, Metzger BE: Screening for gestational diabetes mellitus in Korea. *Int J Gynecol Obstet* 51:115–122, 1995
12. Metzger BE: Summary and recommendations of the Third International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes* 40 (Suppl. 2):197–201, 1991
13. National Diabetes Data Group: Classification and diagnosis of diabetes and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
14. Lubchenco LO, Hansman C, Dressler M, Boyd E: Intrauterine growth as estimated from liveborn birthweight data at 24–42 weeks of gestation. *Pediatrics* 32:793–800, 1963
15. Lubchenco LO, Hansman C, Boyd E: Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 24–42 weeks. *Pediatrics* 37:403–408, 1966
16. Farquhar JW: Prognosis for babies born to diabetic mothers in Edinburgh. *Arch Dis Child* 44:36–47, 1969
17. O'Sullivan JB, Charles D, Mahan CM, Dandrow RV: Gestational diabetes and perinatal mortality rate. *Am J Obstet Gynecol* 116:901–904, 1973
18. Pettitt DJ, Knowler WC, Baird RH, Bennett PH: Gestational diabetes; infant and maternal complications of pregnancy in relation to third-trimester glucose tolerance in the Pima Indians. *Diabetes Care* 3:458–464, 1980
19. Jacobson JD, Cousins L: A population-based study of maternal and perinatal outcome in patients with gestational diabetes. *Am J Obstet Gynecol* 161:981–986, 1989
20. Leikin E, Jenkins JH, Graves WL: Prophylactic insulin in gestational diabetes. *Obstet Gynecol* 70:587–592, 1987
21. Naylor CD, Sermer M, Chen E, Sykora K, the Toronto Trihospital Gestational Diabetes Investigators: Cesarean delivery in relation to birth weight and gestational glucose tolerance: pathophysiology or practice style? *JAMA* 275:1165–1170, 1996
22. Ogata ES, Freinkel N, Metzger BE, Phelps RL, Depp R, Boehm JJ, Dooley SL: Perinatal islet function in gestational diabetes: assessment by cord plasma C-peptide and amniotic fluid insulin. *Diabetes Care* 3:425–429, 1980
23. Weiss PAM, Hofmann HM, Winter RR Lichtenegger W, Pürstner P, Haas J: Diagnosis and treatment of gestational diabetes according to amniotic fluid insulin levels. *Arch Gynecol* 239:81–91, 1986
24. Susa JB, Neave C, Sehgal P, Singer DB, Zeller WP, Schwartz R: Chronic hyperinsulinemia in the fetal rhesus monkey: effects of physiologic hyperinsulinemia on fetal growth and composition. *Diabetes* 33:656–660, 1984.
25. Jovanovic-Peterson L, Peterson CM, Reed GF, Metzger BE, Mills JL, Knopp RH, Aarons JH, the NICHD-DIEP: Maternal postprandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. *Am J Obstet Gynecol* 164:103–111, 1991
26. Metzger BE: Biphasic effects of maternal metabolism on fetal growth: quintessential expression of fuel-mediated teratogenesis. *Diabetes* 40 (Suppl. 2):99–105, 1991