Relationship of Fetal Macrosomia to Maternal Postprandial Glucose Control During Pregnancy

C. ANDREW COMBS, MD, PHD
ERICA GUNDERSON, MD, MPH, RD
JOHN L. KITZMILLER, MD
LAURENCE A. GAVIN, MD
ELLIOT K. MAIN, MD

OBJECTIVE — To determine the gestational ages at which maternal hyperglycemia is most closely related to fetal macrosomia; to determine whether macrosomia is related to elevations of fasting glucose, postprandial glucose, or both; and to assess the relationship of macrosomia to maternal insulin dose and caloric intake.

RESEARCH DESIGN AND METHODS — One hundred eleven consecutive pregnant women with Class B through RF diabetes were studied longitudinally from 13 to 36 wk gestation. Macrosomia was defined by birthweight >90th percentile for gestational age based on California norms. Women who delivered macrosomic infants were compared with those without macrosomic infants on pre- and postprandial blood glucose, GHb, insulin dose, macronutrient intake, and several other maternal variables.

RESULTS — Macrosomia occurred in 32 (29%) cases, although several measures indicated reasonable glycemic control throughout pregnancy. Women delivering macrosomic infants did not differ from those without macrosomic infants in maternal age, prepregnant weight, duration of diabetes, White class, macronutrient intake, GHb, or fasting glucose. Macrosomia was associated with higher postprandial glucose levels up to 32 wk gestation and lower insulin doses from 29 to 36 wk gestation. In multiple logistic regression, macrosomia was significantly associated with postprandial glucose only between 29 and 32 wk gestation. Postprandial glucose values <7.3 mM (<130 mg/dl) were associated with a higher risk of small-for-gestational-age infants (18%) compared with values above this level (1%).

CONCLUSIONS — Because macrosomia was related to postprandial glucose but not fasting glucose, we conclude that postprandial glucose measurement should be a part of routine care for diabetes in pregnancy. A target 1-h postprandial glucose value of 7.3 mM (130 mg/dl) may be the level that optimally reduces the incidence of macrosomia without increasing the incidence of small-for-gestational-age infants.

FROM THE DEPARTMENTS OF OBSTETRICS, GYNECOLOGY AND REPRODUCTIVE SCIENCES, AND MEDICINE, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO; THE CHILDREN'S HOSPITAL, SAN FRANCISCO, CALIFORNIA; AND THE DIVISION OF MATERNAL-FETAL MEDICINE, DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, UNIVERSITY OF CINCINNATI COLLEGE OF MEDICINE, CINCINNATI, OHIO.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO C. ANDREW COMBS, MD, PHD, DIVISION OF MATERNAL-FETAL MEDICINE, DEPARTMENT OF OBSTETRICS AND GYNECOLOGY (ML-526), UNIVERSITY OF CINCINNATI COLLEGE OF MEDICINE, CINCINNATI, OH 45267–0526.

RECEIVED FOR PUBLICATION 29 JANUARY 1992 AND ACCEPTED IN REVISED FORM 21 MAY 1992.

OR, ODDS RATIO; CI, CONFIDENCE INTERVAL.

Fetal macrosomia is a serious complication of diabetes in pregnancy. The mother of a macrosomic fetus is at increased risk for labor abnormalities (1), severe perineal lacerations (2), and cesarean section (1). The fetus is at risk for intracranial hemorrhage and shoulder dystocia with resultant Erb's palsy and asphyxia (1). The neonate is at risk for hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia, hyperbilirubinemia (3), neonatal cardiomyopathy (4), and obesity in later life (3).

According to Pedersen's (5) widely accepted hypothesis, fetal macrosomia is produced by fetal hyperinsulinemia that occurs as a physiological response to maternal hyperglycemia. Several researchers have confirmed that diabetic mothers with poor glycemic control during pregnancy are more likely to deliver macrosomic infants than are diabetic mothers in good glycemic control (6–15). Macrosomic infants of diabetic mothers have higher C-peptide levels in cord blood (15,16) and amniotic fluid (17), consistent with the presence of fetal hyperinsulinemia. However, some authors have noted that macrosomia occurs with increased frequency among diabetic mothers, even when normoglycemia is maintained, and have suggested that fuels other than maternal glucose may be contributors to fetal macrosomia (18,19). Amino acids and other nonglucose fuels may play an important role (20).

This study was undertaken to evaluate in detail the factors that contribute to macrosomia in infants of diabetic mothers. Our specific objectives were *1*) to determine the gestational ages at which maternal hyperglycemia is most closely related to fetal macrosomia; 2) to determine whether macrosomia is related to elevations of fasting glucose, postprandial glucose, or both; and 3) to assess the relationship of macrosomia to maternal insulin dose and caloric intake.

RESEARCH DESIGN AND METHODS— We studied women followed in the Diabetes and Pregnancy Program of the University of California, San Francisco, and Children's Hospital of San Francisco from November 1981 to August 1989. During this 8-yr period, the program maintained a computer data base containing demographic, obstetric, and neonatal data and detailed data concerning blood glucose measurements, insulin dose, and macronutrient intake. Inclusion criteria for this study were *1*) a diagnosis of diabetes mellitus established before pregnancy, 2) enrollment in the program before 12 wk of gestation, and 3) delivery after 36 wk gestation. These criteria were met in 111 cases. Women with gestational diabetes were not studied.

All women were seen weekly or biweekly in the outpatient clinic. All were trained in the use of a portable reflectance meter for daily measurement of capillary blood glucose at home. All were instructed to measure at least four blood glucose values daily—one in the fasting state and one after each meal. Each value was recorded in a logbook. In most cases, the postprandial values were obtained 1 h after the start of the meal; however, a few women measured 90-min or 2-h postprandial values because a standardized meal tolerance test showed that their peak glycemic response occurred at these later times, as described previously (21). Maternal plasma GHb values were measured monthly and referenced to an upper-limit normal of 7.6% of total Hb. Some patients used glucose meters with a memory chip after these became available; however, most did not. In the occasional case where a significant discrepancy was noted between the level of glycemic control recorded in the logbook and the level indicated by the monthly GHb value, patients were instructed to bring their actual glucose test-strips to each clinic visit for verification.

The goals of glycemic control were to maintain all fasting values <5.9 mM (105 mg/dl) and all postprandial values <7.8 mM (140 mg/dl). Most patients were managed with a split-dosage regimen of regular and NPH insulins. Ten were managed with a programmable insulin pump. Since 1985, all patients were treated with synthetic or semisynthetic human insulin. Hospitalization was rarely needed to achieve adequate glycemic control.

A specific diet plan was developed for each woman according to individual energy needs, insulin therapy, and nutrients needs for pregnancy (22). The initial diet prescription provided 25 kcal/kg desirable body wt in the first trimester and 25–35 kcal/kg desirable body wt in the second and third trimesters. The composition of macronutrients was 40–45% kcals as carbohydrate, 20–25% kcals as protein, and the remainder as fat. Women received intensive education on how to use the American Diabetes and American Dietetic Associations' Exchange Lists for Meal Planning (23). Each month, a registered dietitian conducted interviews with the women and reviewed daily food diaries to evaluate average intakes. The dietitian formulated the exchange pattern based on the types and quantities of foods recorded. The approximate macronutrient intake was then calculated from the exchange pattern with standard methods (23). The meal plan was modified as needed to achieve the desired weight gain and to prevent hypoglycemia, hyperglycemia, and morning ketonuria.

For analysis, women were divided into two groups based on birthweight: those with fetal macrosomia and those without. Fetal macrosomia was defined as a birthweight >90th percentile for sex and gestational age based on California norms (24). Birthweight ratio was defined as the ratio of birthweight to the median normal birthweight for gestational age. Gestational age was based on menstrual dates if confirmed by the earliest sonogram; if any discrepancy was apparent, dating was based on the earliest sonogram.

To compare between-group differences in glycemic control, insulin dosage, and nutrient intake, each pregnancy was divided into six 4-wk blocks (i.e., 13–16, 17–20, 21–24, 25–28, 29–32, and 33–36 wk gestation). Several measures of glycemic control were studied in each 4-wk block—mean fasting blood glucose, mean postprandial blood glucose, percentage of values >11.2 mM (200 mg/dl), percentage of values <3.36 mM (60 mg/dl), and GHb concentration. Two measures of within-day glucose variability were also calculated, the coefficient of variability (25) and the mean amplitude glycemic excursion, defined as the difference between the fasting value and the highest postprandial value on each day. For each variable in a given patient, the mean of all values during a given 4-wk block was taken as that patient's value for the block.

In the initial univariate analyses, between-group comparisons of continuous variables were made with the Student's *t* test (two-tailed), and comparisons of categorical variables were made with the χ^2 test. $P < 0.05$ was significant. Multiple logistic regression was performed because of the strong covariance of glucose values between each time period and the others. Stepwise regression models were fit with macrosomia as the dependent variable and several combinations of predictor variables, including fasting and postprandial glucose measurements in each 4-wk block, parity, prepregnant weight, and the presence or absence of microvascular disease (White's class R, F, or RF diabetes). Univariate analyses were performed with SPSS/PC+ (SPSS, Chicago, IL). Logistic regressions were performed with BMDP (BMDP Statistical Software, Los Angeles, CA).

RESULTS— Of 111 women enrolled before 12 wk gestation, fetal macrosomia occurred in 32 (29%). Data on fetal weight, gestational age, and maternal characteristics are summarized in Table 1. On average, the macrosomic infants

Table 1—*Patient characteristics*

	MACROSOMIA	NO MACROSOMIA	P
N	32 (29)	79 (71)	
BIRTH WEIGHT (G)	4244 ± 395	3284 ± 386	<0.001
BIRTH-WEIGHT RATIO	1.34 ± 0.1	1.02 ± 0.1	<0.001
GESTATIONAL AGE (WK)	37.9 ± 1.1	38.0 ± 1.2	NS
MATERNAL AGE (YR)	30.1 ± 4.8	31.0 ± 5.2	NS
AGE AT ONSET OF DIABETES (YR)	18.4 ± 8.3	19.3 ± 9.5	NS
PREPREGNANT WEIGHT (KG)	67.3 ± 15.5	69.2 ± 18.7	NS
WEIGHT GAIN (KG)	15.0 ± 4.9	13.3 ± 5.1	NS
HEIGHT (M)	1.63 ± 0.08	1.63 ± 0.07	NS
BODY MASS INDEX (KG/M^2)	25.2 ± 5.6	26.2 ± 7.2	NS
PARITY (*N*)			NS
NULLIPAROUS	13 (42)	47 (61)	
PAROUS	18 (58)	30 (39)	
PREPREGNANCY CARE (*N*)	17 (55)	37 (47)	NS
INSULIN PUMP	4 (13)	6 (8)	NS
PREECLAMPSIA (*N*)	7 (23)	12 (15)	NS
MALE FETUS (*N*)	16 (52)	38 (48)	NS
WHITE CLASS (*N*)			NS
B	11 (35)	38 (48)	
C	12 (39)	17 (22)	
D	6 (19)	11 (14)	
RF	3 (10)	13 (16)	

Values are means ± SD with percentages in parentheses.

weighed nearly 1 kg more than infants without macrosomia, although both groups were delivered at the same mean gestational age.

No significant difference was observed between the two groups in maternal age, age at onset of diabetes, prepregnant weight, or White class (Table 1). Approximately half of each group had enrolled in the program before conception. Although the trend was toward greater maternal weight gain during pregnancy in the group with fetal macrosomia (mean difference 1.7 kg, $0.05 < P < 0.10$), most of this difference was because of the greater fetal weight in that group.

Table 2 shows several measures of glycemic control throughout gestation. The total possible number of blood glucose measurements was 75,592 (111 patients × 168 days × 4 measurements/day). A total of 64,316 (86.2%) blood glucose measurements were recorded, indicating a high degree of compliance among these patients. The mean number of glucose values recorded was not different between women who delivered macrosomic infants and those who did not (565 ± 139 vs. 561 ± 100).

Most women had reasonable glycemic control throughout pregnancy, as evidenced by the normal mean GHb concentration, the relatively low mean fasting and postprandial glucose values, and the infrequency of hypoglycemic or hyperglycemic episodes. At almost every gestational age, postprandial blood glucose was significantly higher among mothers who delivered a macrosomic infant than among those who did not. After 32 wk gestation, however, no difference occurred in postprandial glucose. No significant difference was noted in fasting blood glucose or in GHb concentration at any gestational age. Insulin dosage was significantly lower after 28 wk gestation among mothers who delivered macrosomic infants. Before 25 wk gestation, insulin dose tended to be higher in this group, but these differences were not significant.

Measures of blood glucose variability also are summarized in Table 2. No between-group difference existed in either the coefficient of variability or the mean amplitude glycemic excursion at any gestational age. Macronutrient intakes are shown in Table 3. We found no significant between-group difference in total caloric intake or in intake of any of the major nutrient groups at any gestational age.

Multiple logistic regression was performed because there was a high covariance of postprandial blood glucose values between each of the 4-wk time periods. That is, a patient who had a high value in one period was also likely to have had high values during the other periods. In stepwise regression, the only variable that was associated significantly with macrosomia was the postprandial glucose at 29–32 wk gestation ($\beta = 1.76 \pm 0.82$, $P < 0.05$). Controlling for postprandial glucose during this time period, macrosomia was not associated significantly with higher glucose values at any other gestational age or with maternal weight, maternal weight gain, or the presence of microvascular disease. A marginally significant association existed between macrosomia and parity ($\beta = 0.43 \pm 0.23$, OR 1.54 for parous vs. nulliparous women, 95% CI 0.99–2.39, $P = 0.06$). However, the association between macrosomia and postprandial glucose remained significant even after controlling for parity.

The relationship of postprandial glucose at 29–32 wk to macrosomia is summarized in Table 4. The incidence of macrosomia rose progressively with increasing postprandial glucose. This might be interpreted to imply that macrosomia could be reduced by keeping postprandial glucose <7.28 mM (130 mg/dl) or eliminated by keeping it <6.7 mM (120 mg/dl). However, lower values of glucose during this time period

also were associated with increasing numbers of small-for-gestational-age infants. Among women with mean postprandial glucose <7.28 mM (130 mg/dl), 6 of 34 infants were small for gestational age (18%) compared with 1 of 77 with glucoses above this level (1%, $P < 0.005$). Among these 6, the only risk factor for growth retardation was diabetic nephropathy in 1 mother; none of these mothers had hypertension or preeclampsia. Three of the 6 small-for-gestational-age infants were delivered by cesarean section because of repetitive late decelerations.

The women with small-for-gestational-age infants tended to have lower postprandial glucose values throughout pregnancy than women with appropriate-for-gestational-age infants, averaging 6.9 ± 0.2, 7.5 ± 1.1, 7.4 ± 1.1, 7.2 ± 0.3, 7.0 ± 0.7, and 6.8 ± 0.5 mM, respectively, during the six time periods from 12 to 36 wk gestation. However, the number of such patients was too small to support a multiple regression analysis to determine whether one time period was more important than the others.

CONCLUSIONS— Most previous studies relating fetal macrosomia to poor maternal glycemic control have used combined measures of preprandial and postprandial glucose (6–9) or indirect measures of glycemic control such as GHb concentration (10,12) or fructosamine (13). With data from the Diabetes in Early Pregnancy Study sponsored by the National Institutes of Health, Jovanovic-Peterson et al. (14) recently reported that macrosomia is related to 1-h postprandial glucose levels in the third trimester and not to fasting glucose levels. Our results provide an independent confirmation of this finding. Indeed, the observed incidence of macrosomia for each level of postprandial glucose in this study was almost identical to the incidence predicted from the Diabetes in Early Pregnancy Study data (Table 4). In our study, higher lev-

Table 2—*Measures of glycemic control*

	Macrosomia	No macrosomia	*P*
Fasting blood glucose (mM)			
wk			
13–16	6.2 ± 1.2	5.9 ± 1.3	NS
17–20	6.0 ± 1.2	6.0 ± 1.3	NS
21–24	6.4 ± 1.1	6.2 ± 1.3	NS
25–28	6.2 ± 1.1	5.9 ± 1.2	NS
29–32	6.0 ± 0.9	5.9 ± 1.2	NS
33–36	5.5 ± 1.0	5.4 ± 0.9	NS
Postprandial blood glucose (mM)			
wk			
13–16	8.2 ± 1.1	7.7 ± 1.2	<0.02
17–20	7.9 ± 1.1	7.7 ± 1.3	NS
21–24	8.2 ± 0.9	7.8 ± 1.2	<0.05
25–28	8.1 ± 1.0	7.7 ± 1.0	<0.05
29–32	8.1 ± 0.8	7.6 ± 0.9	<0.005
33–36	7.4 ± 0.8	7.3 ± 0.8	NS
GHb (%)*			
wk			
13–16	7.8 ± 1.3	7.8 ± 1.8	NS
17–20	7.3 ± 1.1	7.0 ± 0.9	NS
21–24	7.1 ± 1.0	7.0 ± 1.0	NS
25–28	7.3 ± 1.1	7.0 ± 0.9	NS
29–32	7.3 ± 1.1	6.9 ± 0.9	NS
33–36	7.2 ± 1.0	6.9 ± 0.9	NS
Insulin (U/day)			
wk			
13–16	52 ± 34	45 ± 22	NS
17–20	46 ± 34	42 ± 19	NS
21–24	63 ± 46	56 ± 27	NS
25–28	66 ± 59	67 ± 45	NS
29–32	57 ± 35	77 ± 54	<0.05
33–36	62 ± 50	87 ± 60	<0.05
Hyperglycemic episodes (% of values)			
>11.2 mM			
wk			
13–16	10.5 ± 10.3	8.8 ± 9.5	NS
17–20	8.5 ± 8.6	8.7 ± 9.2	NS
21–24	9.4 ± 9.5	8.8 ± 9.1	NS
25–28	7.7 ± 7.7	7.2 ± 8.8	NS
29–32	6.3 ± 5.7	5.3 ± 6.7	NS
33–36	3.2 ± 3.8	3.2 ± 4.1	NS
<3.4 mM			
wk			
13–16	4.4 ± 4.6	5.6 ± 6.6	NS
17–20	4.0 ± 5.2	4.5 ± 6.2	NS
21–24	2.5 ± 3.0	3.4 ± 4.9	NS
25–28	2.6 ± 2.9	3.5 ± 4.0	NS
29–32	1.9 ± 2.4	2.6 ± 4.4	NS
33–36	2.3 ± 2.9	3.2 ± 4.4	NS
Coefficient of variability			
wk			
13–16			
17–20	26.0 ± 7.5	26.4 ± 8.8	NS
21–24	24.4 ± 6.6	23.6 ± 7.2	NS
25–28	23.7 ± 5.6	23.6 ± 7.8	NS
29–32	22.0 ± 6.6	22.4 ± 8.1	NS
33–36	23.7 ± 6.2	22.4 ± 7.5	NS
Mean amplitude glycemic excursion (mM)			
wk			
13–16	4.3 ± 1.3	4.1 ± 1.4	NS
17–20	4.0 ± 1.3	4.0 ± 1.5	NS
21–24	3.8 ± 1.1	3.8 ± 1.3	NS
25–28	3.8 ± 1.0	3.7 ± 1.2	NS
29–32	3.8 ± 1.2	3.5 ± 1.3	NS
33–36	3.6 ± 0.9	3.5 ± 1.2	NS

Values are means ± SD.
*Referenced to upper-limit normal = 7.6%

Table 3—*Macronutrient intake*

	MACROSOMIA	NO MACROSOMIA
TOTAL CALORIC INTAKE (KCAL/DAY)		
WK		
13–16	1811 ± 235 (26)	1762 ± 336 (67)
17–20	1825 ± 321 (13)	1798 ± 327 (41)
21–24	1888 ± 346 (25)	1805 ± 310 (63)
25–28	1840 ± 254 (12)	1788 ± 271 (46)
29–32	1789 ± 359 (18)	1800 ± 342 (41)
33–36	1889 ± 299 (22)	1828 ± 364 (63)
CARBOHYDRATE (G/DAY)		
WK		
13–16	187 ± 34 (26)	183 ± 37 (67)
17–20	186 ± 38 (13)	180 ± 37 (41)
21–24	188 ± 41 (25)	184 ± 36 (63)
25–28	180 ± 27 (12)	181 ± 34 (46)
29–32	184 ± 40 (18)	182 ± 41 (41)
33–36	195 ± 49 (22)	181 ± 40 (63)
PROTEIN (G/DAY)		
WK		
13–16	100 ± 16 (26)	98 ± 18 (67)
17–20	97 ± 14 (13)	101 ± 20 (41)
21–24	105 ± 20 (25)	100 ± 17 (63)
25–28	105 ± 18 (12)	102 ± 19 (46)
29–32	98 ± 19 (18)	98 ± 19 (41)
33–36	104 ± 14 (22)	102 ± 22 (63)
FAT (G/DAY)		
WK		
13–16	74 ± 17 (26)	71 ± 19 (67)
17–20	77 ± 19 (13)	75 ± 19 (41)
21–24	80 ± 20 (25)	75 ± 19 (63)
25–28	78 ± 18 (12)	73 ± 16 (46)
29–32	74 ± 21 (18)	76 ± 19 (41)
33–36	77 ± 18 (22)	77 ± 21 (63)

Values are means ± SD with *n* given in parentheses. Not all patients had dietary assessment during each 4-wk time period. All comparisons were nonsignificant.

Table 4—*Relationship of postprandial glucose to fetal growth*

		MACROSOMIA		SMALL FOR
POSTPRANDIAL GLUCOSE (MM)	*N*	OBSERVED	PREDICTED*	GESTATIONAL AGE
<6.7 (120 MG/DL)	9	0	<2 (<22)	1 (11)
6.7–7.27 (120–129 MG/DL)	25	5 (20)	6 (25)	5 (20)
7.28–7.83 (130–139 MG/DL)	32	9 (28)	9 (28)	0
7.84–8.39 (140–149 MG/DL)	19	6 (32)	6 (31)	0
≥8.39 (150 MG/DL)	26	12 (46)	>9 (>35)	1 (4)

Values in parentheses are percentages. Postprandial glucose, mean of all measurements from 29–32 wk gestation.
*Based on ref. 14.

els of blood glucose were related to lower doses of insulin in the third trimester rather than to higher caloric intake. We do not know why women with macrosomic infants seemed to require less insulin at 33–36 wk gestation to maintain glucose levels comparable with those of women with nonmacrosomic infants.

It is not known whether there is a critical time during pregnancy when maternal hyperglycemia begins to contribute to fetal macrosomia. Although the fetal pancreas is capable of secreting insulin as early as 11–15 wk gestation (26), the fetal insulin response to hyperglycemia increases dramatically after 20 wk gestation (26). Like Jovanovic-Peterson et al. (14), we found that women with macrosomic fetuses had higher glucose levels throughout pregnancy than did women without macrosomic fetuses. Like them, we also found that when multiple regression was used to control for third-trimester glucose values, the association of early pregnancy hyperglycemia with macrosomia was no longer statistically significant. However, neither study permits us to conclude that early pregnancy glycemic control is unimportant with respect to macrosomia because, in general, women who were relatively hyperglycemic in the first trimester also tended to be hyperglycemic in the third trimester.

A previous study by Lin et al. (8) found that the risk of macrosomia was reduced if intensive glycemic control was begun before 32 wk gestation but not if glycemic control was begun after 32 wk. In this study, after 32 wk gestation, we found no relationship between fasting or postprandial glucose and macrosomia. Therefore, we agree with Lin et al. that good glycemic control must be instituted before 32 wk to prevent macrosomia. Because several weeks of education and insulin-dose adjustment often are required to achieve acceptable glucose levels, we believe that strict control should be instituted as early in pregnancy as possible or, preferably, before pregnancy. The benefits of starting strict con-

trol before conception extend beyond the prevention of macrosomia and include the prevention of congenital malformations (18,27) and spontaneous abortion (27).

Although most of our women had fair glycemic control, macrosomia occurred in 29% of pregnancies. It is possible that amino acids (20) or other nonglucose fuels contributed to the high incidence of macrosomia. Although we found no differences in the dietary intakes of protein or fat, the estimation method based on food diaries may not be sensitive to small differences in intakes. Measurement of blood levels of amino acids and lipids would be needed to evaluate their role in producing macrosomia. Maternal obesity (6,7,10) and increasing parity (7) have been associated with increased birthweight; microvascular disease (6,9) has been associated with decreased birthweight. Although we were unable to confirm these associations in this study, our study population was relatively small, and the statistical power was thus relatively low. One report suggested that antibody-bound exogenous animal insulin may cross the placenta and contribute to macrosomia (28); however, a larger study from the same institution failed to confirm any relation between birthweight and type of insulin used (29).

Because macrosomia was related to elevated postprandial glucose but not fasting glucose, we conclude that postprandial glucose measurement should be part of the routine care of pregnant women with diabetes. The risk of macrosomia may be reduced through aggressive efforts to maintain a low postprandial glucose level. However, very low glucose levels also may be associated with an increased risk for fetal growth retardation. An association between low maternal glucose levels and small-for-gestational-age infants has been observed in pregnant women without diabetes (30) and in women with gestational diabetes (31). Our results show a similar association in women with diabetes preceding pregnancy. However, it is not known whether fetal growth retardation associated with lower maternal glucose levels has the same adverse prognostic significance as growth retardation that is attributable to other causes such as maternal vascular disease. Until long-term follow-up data are available on such infants, the most prudent course is probably to select a target glucose level that will strike a balance between the risk of macrosomia and the risk of growth retardation. Based on our results, a reasonable target for 1-h postprandial glucose seems to be 7.3 mM (130 mg/dl).

Acknowledgments— We thank Jane Khoury, MS, for help in performing multivariate analyses.

This work was presented in abstract form at the Diabetes and Pregnancy Satellite Symposium, International Diabetes Federation, Newport, RI, June 1991.

References

1. Susa JB: Effects of diabetes on fetal growth. In *Diabetes Mellitus in Pregnancy, Principles and Practice*. Reece EA, Coustan DR, Eds. New York, Churchill Livingstone, 1988, p. 105–22
2. Green JR, Soohoo SL: Factors associated with rectal injury in spontaneous deliveries. *Obstet Gynecol* 73:732–38, 1989
3. Pettit DJ, Bennet PH: Long-term outcome of infants of diabetic mothers. In *Diabetes Mellitus in Pregnancy, Principles and Practice*. Reece EA, Coustan DR, Eds. New York, Churchill Livingstone, 1988, p. 559–71
4. Kleinman CS: Diabetes and the fetal heart: application of fetal echocardiography. In *Diabetes Mellitus in Pregnancy, Principles and Practice*. Reece EA, Coustan DR, Eds. New York, Churchill Livingstone, 1988, p. 363–74
5. Pedersen J: Weight and length at birth of infants of diabetic mothers. *Acta Endocrinol* 16:330–42, 1954
6. Kitzmiller JL, Cloherty JP, Younger MD, Tabatabaii A, Rothchild SB, Sosenko I, Epstein MF, Singh S, Neff RK: Diabetic pregnancy and perinatal morbidity. *Am J Obstet Gynecol* 131:560–80, 1978
7. Willman SP, Leveno KJ, Guzick DS, Williams ML, Whalley PJ: Glucose threshold for macrosomia in pregnancy complicated by diabetes. *Am J Obstet Gynecol* 154:470–75, 1986
8. Lin C-C, River J, River P, Blix PM, Moawad AH: Good diabetic control early in pregnancy and favorable fetal outcome. *Obstet Gynecol* 67:51–56, 1986
9. Reece EA, Smikle C, O'Connor TZ, Holford T, Nelson-Robinson L, Degennaro N, Hobbins JC: A longitudinal study comparing growth in diabetic pregnancies with growth in normal gestations. I. The fetal weight. *Obstet Gynecol Survey* 45:160–64, 1990
10. Small M, Cameron A, Lunan CB, MacCuish AC: Macrosomia in pregnancy complicated by insulin-dependent diabetes mellitus. *Diabetes Care* 10:594–99, 1987
11. Berk MA, Mimouni F, Miodovnik M, Hertzberg V, Valuck J: Macrosomia in infants of insulin-dependent diabetic mothers. *Pediatrics* 83:1029–34, 1989
12. Hans M, Ditzel J: The influence of maternal weight, smoking, vascular complications and glucose regulation on the birth weight of infants of type 1 diabetic women. *Eur J Obstet Gynecol Rep Biol* 39:175–79, 1991
13. Roberts AB, Baker JR: Relationship between fetal growth and maternal fructosamine in diabetic pregnancy. *Obstet Gynecol* 70:242–46, 1987
14. Jovanovic-Peterson L, Peterson CM, Reed GF, Metzger BE, Mills JL, Knopp RH, Aarons JH: Maternal postprandial glucose levels and infant birthweight: the diabetes in early pregnancy study. *Am J Obstet Gynecol* 164:103–11, 1991
15. Sosenko JM, Kitzmiller JL, Fluckiger R, Loo SWH, Younger DM, Gabbay KH: Umbilical cord glycosylated hemoglobin in infants of diabetic mothers: relationships to neonatal hypoglycemia, macrosomia, and cord serum C-peptide. *Diabetes Care* 5:566–70, 1982
16. Cano A, Barcelo F, Fuente T, Martinez P, Parrilla JJ, Abad L: Relationship of maternal glycosylated hemoglobin and fetal beta-cell activity with birth weight. *Gynecol Obstet Invest* 22:91–96, 1986

17. Lin CC, River P, Moawad AH, Lowensohn RI, Blix PM, Abraham M, Rubenstein AH: Prenatal assessment of fetal outcome by amniotic fluid C-peptide levels in pregnant diabetic women. *Am J Obstet Gynecol* 141:671–76, 1981
18. Russell G, Farmer G, Lloyd DJ, Pearson DWM, Ross IS, Stowers JM, Sutherland HW, Visser GHA, van Ballegooie E, Sluiter WJ, Verhaaren HA, Craen M, De Gomme P, Rubens R, Parewijck W, Derom R: Macrosomy despite well-controlled diabetic pregnancy. *Lancet* 1:283–85, 1984
19. Dandona P, Besterman HS, Freedman DB, Boag F, Taylor AM, Beckett AG: Macrosomia despite well-controlled diabetic pregnancy. *Lancet* 1:737, 1984
20. Kalkhoff RK, Kandaraki E, Morrow PG, Mitchell TH, Kelber S, Borkowf HI: Relationship between neonatal birth weight and maternal plasma amino acid profiles in lean and obese nondiabetic women and in type I diabetic pregnant women. *Metabolism* 37:234–39, 1988
21. Kitzmiller JL, Gavin LA, Gin GD, Jovanovic-Peterson L, Main EK, Zigrang WD: Preconception care of diabetes: glycemic control prevents congenital anomalies. *JAMA* 265:731–36, 1991
22. Sweet Success, California's Diabetes and Pregnancy Program: *Guidelines for Care*. Sacramento, CA, Dept. of Health Services, 1988 (Maternal and Child Health Branch)
23. American Diabetes Association, American Dietetic Association: *Exchange Lists for Meal Planning*. Washington, DC, Am. Diabetes Assoc., 1986
24. Williams RL, Creasy RK, Cunningham GC, Hawes WE, Norris FD, Tashiro M: Fetal growth and perinatal viability in California. *Obstet Gynecol* 59:624–32, 1982
25. Artal R, Golde SH, Dorey F, McClellan SN, Gratacos J, Lirette T, Montoro M, Wu PYK, Anderson B, Mestman J: The effect of plasma glucose variability on neonatal outcome in the pregnant diabetic patient. *Am J Obstet Gynecol* 147: 537–41, 1983
26. Reiher H, Fuhrmann K, Noack S, Woltanski KP, Jutzi E, Dorsche HHV, Hahn H-J: Age-dependent insulin secretion of the endocrine pancreas in vitro from fetuses of diabetic and nondiabetic patients. *Diabetes Care* 6:446–51, 1983
27. Combs CA, Kitzmiller JL: Spontaneous abortion and congenital anomalies in diabetes. *Clin Obstet Gynaecol* 5:315–32, 1991
28. Menon RK, Cohen RM, Sperling MA, Cutfield WS, Mimouni F, Khoury JC: Transplacental passage of insulin in pregnant women with insulin-dependent diabetes mellitus. *N Engl J Med* 323: 309–15, 1990
29. Rosenn B, Miodovnik M, Combs CA, Siddiqi TA, Khoury J, Wittekind C, Tsang RC: Human versus animal insulin in the management of insulin-dependent diabetes in pregnancy: lack of effect on fetal growth. *Obstet Gynecol* 78:590–93, 1991
30. Abell DA: The significance of abnormal glucose tolerance (hyperglycaemia and hypoglycaemia) in pregnancy. *Br J Obstet Gynaecol* 86:214–21, 1979
31. Langer O, Levy J, Brustman L, Anyaegbunam A, Merkatz R, Divon M: Glycemic control in gestational diabetes mellitus—how tight is tight enough: small for gestational age versus large for gestational age? *Am J Obstet Gynecol* 161:646–53, 1989