

The New England Journal of Medicine

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Volume 333

NOVEMBER 9, 1995

Number 19

POSTPRANDIAL VERSUS PREPRANDIAL BLOOD GLUCOSE MONITORING IN WOMEN WITH GESTATIONAL DIABETES MELLITUS REQUIRING INSULIN THERAPY

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Abstract Background. The fetuses of women with gestational diabetes mellitus are at risk for macrosomia and its attendant complications. The best method of achieving euglycemia in these women and reducing morbidity in their infants is not known. We compared the efficacy of postprandial and preprandial monitoring in achieving glycemic control in women with gestational diabetes.

Methods. We studied 66 women with gestational diabetes mellitus who required insulin therapy at 30 weeks of gestation or earlier. The women were randomly assigned to have their diabetes managed according to the results of preprandial monitoring or postprandial monitoring (one hour after meals) of blood glucose concentrations. Both groups were also monitored with fasting blood glucose measurements. The goal of insulin therapy was a preprandial value of 60 to 105 mg per deciliter (3.3 to 5.9 mmol per liter) or a postprandial value of less than 140 mg per deciliter (7.8 mmol per liter). Obstetrical data and information on neonatal outcomes were collected.

Results. The prepregnancy weight, weight gain during pregnancy, gestational age at the diagnosis of diabe-

tes and at delivery, degree of compliance with therapy, and degree of achievement of target blood glucose concentrations were similar in the two groups. The mean (\pm SD) change in the glycosylated hemoglobin value was greater in the group in which postprandial measurements were used (-3.0 ± 2.2 percent vs. -0.6 ± 1.6 percent, $P<0.001$) and the infants' birth weight was lower (3469 ± 668 vs. 3848 ± 434 g, $P=0.01$). Similarly, the infants born to the women in the postprandial-monitoring group had a lower rate of neonatal hypoglycemia (3 percent vs. 21 percent, $P=0.05$), were less often large for gestational age (12 percent vs. 42 percent, $P=0.01$) and were less often delivered by cesarean section because of cephalopelvic disproportion (12 percent vs. 36 percent, $P=0.04$) than those in the preprandial-monitoring group.

Conclusions. Adjustment of insulin therapy in women with gestational diabetes according to the results of postprandial, rather than preprandial, blood glucose values improves glycemic control and decreases the risk of neonatal hypoglycemia, macrosomia, and cesarean delivery. (N Engl J Med 1995;333:1237-41.)

APPROXIMATELY 5 percent of all pregnancies are complicated by gestational diabetes mellitus, which increases both maternal and perinatal morbidity.¹ In treating women with this condition, many have advocated minimizing fluctuations in blood glucose concentrations to avert maternal hyperglycemia and thus decrease the risk of fetal hyperglycemia and its consequences, fetal hyperinsulinemia and excess fetal growth.²⁻⁵ However, despite early diagnosis and aggressive dietary and insulin therapy, perinatal morbidity among the infants born to women with gestational diabetes remains excessive, a fact that may or may not be attributed to suboptimal glycemic control.⁶⁻⁸

In the management of gestational diabetes, various methods of glucose monitoring have been proposed, including the measurement of fasting, preprandial, post-

prandial, and mean 24-hour blood glucose concentrations.⁹⁻¹¹ In a retrospective pilot study comparing the outcomes of pregnancy among women with gestational diabetes who were followed with preprandial or postprandial glucose measurements, we found that the women's glycosylated hemoglobin values were lower and that there was less macrosomia (defined as a birth weight greater than 4000 g) among their infants when treatment was based on the results of postprandial measurements.¹²

We conducted this prospective, randomized clinical trial to test the hypothesis that blood glucose monitoring at home with use of fasting and postprandial glucose values leads to better glycemic control in women with gestational diabetes who require insulin therapy than the combination of fasting and preprandial monitoring and improves perinatal outcomes by reducing the incidence of neonatal macrosomia and its attendant complications.

METHODS

Study Subjects

At their initial prenatal visits, we screened pregnant women who had risk factors for gestational diabetes including obesity (body

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weight, >120 percent of ideal value), advanced age (≥ 35 years), glycosuria on dipstick urinalysis ($\geq 2+$), a history of diabetes in first-degree relatives, and a previous unexplained stillbirth or miscarriage. These women were also screened at 24 to 28 weeks of gestation if the results of the initial screening were normal. All women without such risk factors were initially screened at 24 to 28 weeks. The initial screening consisted of the measurement of plasma glucose one hour after the oral administration of 50 g of glucose.

If the plasma glucose value on the initial test was 140 mg per deciliter (7.8 mmol per liter) or higher but below 190 mg per deciliter (10.6 mmol per liter), a three-hour oral glucose-tolerance test (with 100 g of glucose) was performed. Gestational diabetes was diagnosed and dietary therapy was initiated if the women had any two of the following plasma glucose values: fasting, >105 mg per deciliter (5.9 mmol per liter); one hour after the administration of glucose, >190 mg per deciliter (10.6 mmol per liter); two hours, >165 mg per deciliter (9.2 mmol per liter); and three hours, >145 mg per deciliter (8.1 mmol per liter).¹³ Women with elevated fasting values at the time of the three-hour oral glucose-tolerance test were immediately started on insulin therapy. All others in this group were initially treated with diet and monitored with weekly fasting and postprandial (one hour after breakfast) measurements of plasma glucose; insulin therapy was initiated if the values exceeded 105 mg per deciliter or 140 mg per deciliter, respectively.

If the glucose value in the initial screening test was 190 mg per deciliter or higher, a three-hour glucose-tolerance test was not performed. Women with such high concentrations were classified as having gestational diabetes, and fasting and postprandial plasma glucose concentrations were measured in order to determine the need for insulin therapy. Women with fasting values above 105 mg per deciliter or postprandial values above 140 mg per deciliter began to receive insulin therapy.

Women with gestational diabetes were eligible for the study if they required insulin according to the criteria listed above at or before 30 weeks of gestation and were pregnant with a singleton fetus. Women with a history of diabetes before pregnancy or with preexisting hypertension, renal disease, or autoimmune disorders were excluded. The gestational age was estimated from the date of the last menstrual period or early ultrasound dating (at 10 to 20 weeks). Sixty-six women who met these criteria agreed to participate in the study, which was approved by the institutional review boards of the University of California at Irvine and Long Beach Memorial Medical Center.

Study Protocol

The women were assigned to one of two blood-glucose-monitoring protocols for the duration of their pregnancies; permuted-block randomization was used to ensure that equal numbers of women were assigned to each study group throughout its duration. The preprandial-monitoring plan required daily monitoring of fasting, preprandial, and bedtime capillary-blood glucose concentrations. The postprandial-monitoring plan required daily monitoring of blood glucose concentrations before breakfast (fasting) and one hour after each meal.

All the women were evaluated weekly by the perinatal-diabetes team (consisting of an obstetrician, a dietitian, a nurse educator, and a counselor) unless complications of pregnancy, including poor glycemic control (usually indicated by hyperglycemia with persistently elevated blood glucose values after two weeks of outpatient therapy), preterm labor, or hypertension made hospitalization necessary. During any hospitalizations, the women were monitored according to their group assignment.

A diet was prescribed with a daily allotment of 30 to 35 kcal per kilogram of ideal body weight, divided into three meals and one to three snacks; 40 to 45 percent of the energy was provided by carbohydrate. Calorie intake and food choices were adjusted at the weekly visits according to weight gain and the blood glucose values measured at home by the women. All the women received split-dose therapy combining short-acting (regular) and intermediate-acting (NPH) human insulin; the doses were adjusted to achieve fasting blood glucose values of 60 to 90 mg per deciliter (3.3 to 5.0 mmol per liter) and preprandial values of 60 to 105 mg per deciliter (3.3 to 5.9 mmol per liter) or postprandial values below 140 mg per deciliter. The initial daily total insulin dose was 0.7 unit per kilogram of body weight for women in the first trimester of pregnancy, 0.8 unit per kilogram for those in the second trimester, and 0.9 unit per kilogram for those in

the third trimester. Of the total insulin dose, two thirds was administered in the morning and one third in the evening, with the morning dose (given at about 8 a.m.) split into two thirds intermediate-acting and one third regular insulin and the evening dose given as one half regular insulin at dinner (approximately 6 p.m.) and one half intermediate-acting with dinner or at bedtime (approximately 9 p.m.).

The women measured their blood glucose concentrations using memory-based reflectance glucometers; all the values, as well as insulin doses and dietary intake, were recorded. Adjustments in the insulin doses were made if any of the values were consistently higher than the target blood glucose concentrations; efforts were made to normalize fasting blood glucose first. The insulin doses were usually changed by 2 to 4 units at a time. Total glycosylated hemoglobin was measured at the beginning of the study and in the month before delivery by the method described by Gould et al.¹⁴; a value of 8.0 percent or lower was considered normal in pregnancy.

Variables

The descriptive variables we analyzed were age, gravidity, race or ethnic group, body-mass index (calculated as the reported prepregnancy weight in kilograms divided by the square of the height in meters), gestational age at the time of diagnosis of gestational diabetes and at the time of the initiation of insulin therapy, and the results of the glucose-challenge tests. The obstetrical variables were maternal weight gain, glycosylated hemoglobin values at the time of diagnosis of gestational diabetes and before delivery, mode of delivery, number of hospitalizations for problems with glycemic control, and other complications (e.g., preterm labor or preeclampsia) during pregnancy. A random sample of blood glucose values from the last four weeks of pregnancy in half the women in each study group was evaluated to assess compliance with the prescribed blood-glucose-monitoring schedules, the success in attaining target glucose values, and the mean total daily insulin doses in the groups. Neonatal outcome variables included sex, birth weight, Apgar scores, incidence of shoulder dystocia, neonatal birth trauma, and the following neonatal complications: hypoglycemia (blood glucose concentration, ≤ 30 mg per deciliter [1.7 mmol per liter]), hyperbilirubinemia (serum bilirubin concentration, >10 mg per deciliter [171 μ mol per liter] if delivered at term or >15 mg per deciliter [256 μ mol per liter] if delivered before 37 weeks of gestation), and respiratory complications. Shoulder dystocia was defined as present when one or more maneuvers were required to facilitate vaginal delivery of the neonate's shoulders. Infants were assigned birth-weight percentiles according to gestational age and sex with use of the population-specific standards published for California.¹⁵

Statistical Analysis

We used the Mann-Whitney U test for data that were not normally distributed, Student's t-test for other continuous data, and the two-tailed Fisher's exact test for categorical data. Relative risks and 95 percent confidence intervals were calculated with Epi Info software (version 5; Stone Mountain, Ga.).

RESULTS

The two study groups were similar in age, race or ethnic group, and physical characteristics (Table 1). The results of the one-hour 50-g glucose tests and the fasting plasma glucose values at the time of the three-hour glucose-tolerance tests, the duration of pregnancy at the time of the diagnosis of gestational diabetes requiring insulin treatment, and the week of gestation at the time of the initiation of insulin therapy were also similar (Table 1). Weight gain in both groups of women was similar (Table 2).

A review of the patients' records of home blood glucose monitoring during the last four weeks of pregnancy (112 glucose samplings) revealed similar degrees of compliance (≥ 95 percent) and achievement of target blood glucose values in the two groups (Table 2). However, the women in the postprandial-monitoring group

Table 1. Characteristics of Pregnant Women with Gestational Diabetes, According to Study Group.*

CHARACTERISTIC	PREPRANDIAL MONITORING (N = 33)	POSTPRANDIAL MONITORING (N = 33)
Age (yr)	31±6	29±5
Gravidity	4.3±3.0	3.6±2.2
Race or ethnic group (no.)		
Hispanic	27	29
White	4	3
Black or Asian	2	1
Prepregnancy weight (kg)	79±13	77±13
Body-mass index†	29.0±3.2	28.4±3.8
Plasma glucose (mg/dl)‡		
At 1 hr§	216±56	214±67
Fasting¶	137±38	145±50
Week of gestation at diagnosis	22.9±7.5	21.8±6.5
Week of gestation at start of insulin	24.3±5.2	25.1±5.1

*Plus-minus values are means ±SD. There were no significant differences between the groups.

†The weight in kilograms divided by the square of the height in meters.

‡To convert plasma glucose values to millimoles per liter, multiply by 0.056.

§After the administration of 50 g of glucose.

¶At the time of the three-hour oral glucose-tolerance test.

received significantly more insulin than those in the preprandial-monitoring group (Table 2). Although the glycosylated hemoglobin values at the time insulin therapy was initiated were similar in the two groups, the values before delivery were significantly lower in the postprandial-monitoring group; thus, the decrease in glycosylated hemoglobin values during treatment was significantly greater in this group.

The number of women who required hospitalization to optimize glycemic control during pregnancy was similar in the groups (Table 2). Preeclampsia requiring preterm delivery developed in two women in each group. No women were treated with a β -adrenergic-agonist drug for preterm labor. There were no other medical complications.

There was a trend toward a higher rate of cesarean deliveries in the preprandial-monitoring group, and there was a significant difference between the groups in the frequency of cesarean sections performed for cephalopelvic disproportion during labor or for suspected fetal macrosomia (36 percent in the preprandial-monitoring group vs. 12 percent in the postprandial-monitoring group, $P=0.04$) (Table 2). More women in the preprandial-monitoring group were offered an elective cesarean section because the weight of the fetus, estimated by ultrasonography, was more than 4000 g; all these women delivered an infant with a confirmed birth weight greater than 4000 g. There was also a trend to-

ward more third- and fourth-degree perineal lacerations during vaginal deliveries in the preprandial-monitoring group (24 percent, vs. 9 percent in the postprandial-monitoring group).

Despite similar gestational ages at delivery (Table 2), the mean (\pm SD) birth weight in the preprandial-monitoring group was significantly higher than that in the postprandial-monitoring group (3848 ± 434 vs. 3469 ± 668 g, $P=0.01$) (Table 3). The proportion of infants who were large for gestational age (birth weight above the 90th percentile for gestational age and sex, according to population-specific standards for California) was significantly higher in the preprandial-monitoring group (42 percent, vs. 12 percent in the postprandial-monitoring group; $P=0.01$), as was the number of infants weighing more than 4000 g (36 percent vs. 9 percent, $P=0.01$). There were more instances of shoulder dystocia during vaginal delivery in the preprandial-monitoring group (18 percent vs. 3 percent, $P=0.10$). Although two infants in the preprandial-monitoring group and one in the postprandial-monitoring group were given a diagnosis of Erb's palsy, the palsy resolved before discharge. One infant in each group had a fracture (one of the clavicle and one of the humerus). Only one unexplained stillbirth occurred, and it was in the preprandial-monitoring group (Table 3).

More infants in the preprandial-monitoring group

Table 2. Obstetrical Data and Outcomes in Women with Gestational Diabetes, According to Study Group.*

VARIABLE	PREPRANDIAL MONITORING (N = 33)	POSTPRANDIAL MONITORING (N = 33)	RELATIVE RISK (95% CI)	P VALUE
<i>mean ±SD</i>				
Gestational age at delivery (wk)	37.6±3.8	37.9±1.4	—	0.16†
Maternal weight gain (kg)	10.7±5.4	10.5±5.4	—	0.94†
Success in glycemic control (%)‡	86±4.1	88±5.2	—	0.62§
Compliance with schedule (%)¶	98±1.9	95±2.2	—	0.76§
Insulin dose				
Units/day	76.8±21.4	100.4±29.5	—	0.003†
Units/kg	0.9±0.1	1.1±0.2	—	0.001†
Glycosylated hemoglobin (%)				
Initial	8.6±2.3	8.9±3.2	—	0.55†
Final	8.1±2.2	6.5±1.4	—	0.006†
Change	-0.6±1.6	-3.0±2.2	—	<0.001†
<i>number (percent)</i>				
Cesarean section				
Total	13 (39)	8 (24)	1.6 (0.8-3.4)	0.29**
For CPD	12 (36)	4 (12)	3.0 (1.1-8.3)	0.04**
Perineal lacerations (third- or fourth-degree)	8 (24)	3 (9)	2.7 (0.8-9.4)	0.16**
Hospitalization for glycemic control	3 (9)	4 (12)	0.7 (0.2-3.1)	1.00**
Preeclampsia	2 (6)	2 (6)	1.0 (0.1-6.7)	1.00**

*CI denotes confidence interval, and CPD cephalopelvic disproportion.

†By Student's t-test.

‡Success in achieving glucose control during the four weeks before delivery, expressed as the percentage of blood glucose values that matched the target values: fasting, 60 to 90 mg per deciliter (3.3 to 5.0 mmol per liter); preprandial, 60 to 105 mg per deciliter (3.3 to 5.9 mmol per liter); and postprandial, <140 mg per deciliter (7.8 mmol per liter).

§By the Mann-Whitney U test.

¶Compliance during the four weeks before delivery, expressed as the percentage of blood glucose values measured at the 112 prescribed times (fasting, preprandial, or postprandial).

||During the last four weeks of pregnancy, including both regular and intermediate-acting insulin.

**By Fisher's exact test (two-tailed).

had hypoglycemia (glucose concentration, ≤ 30 mg per deciliter) requiring glucagon or dextrose infusion for treatment during the first four days after birth (21 percent vs. 3 percent, $P=0.05$) (Table 3). There were no significant differences between the groups in the frequency of other neonatal complications.

DISCUSSION

The results of this study support the hypothesis that postprandial glucose monitoring, in combination with fasting blood glucose measurements, can significantly improve the outcomes of pregnancy in women with gestational diabetes who require insulin therapy. Previous studies of combined preprandial and postprandial glucose monitoring found an association between fetal macrosomia and suboptimal glycemic control.^{7,16} In one study, blood glucose monitoring before meals in women with insulin-dependent diabetes mellitus did not provide an adequate indication of metabolic control or of the risk of macrosomia; the authors therefore recommended postprandial glucose monitoring in order to optimize glycemic control.¹⁷ In another study, macrosomia was related to postprandial but not to fasting blood glucose values.¹⁸

We found that compliance among patients was similar for both blood-glucose-monitoring plans. Although the adjustment of insulin doses may be simpler when preprandial glucose monitoring is used, we found that more stringent glycemic control could be achieved with postprandial monitoring. The hypoglycemic episodes during gestation that have been described in women who have insulin-dependent diabetes mellitus before pregnancy rarely occur in women with gestational diabetes, because of their hyperinsulinemic, insulin-resistant state after meals. Women in whom preprandial monitoring is used have their blood glucose concentrations measured only at times when they are least likely to be hyperglycemic.

Measurements of glycosylated hemoglobin have

proved to be a useful index of long-term (four-to-six-week) glycemic control during pregnancy, and elevated values have been linked to fetal macrosomia.^{19,20} Our results indicate that with tighter glycemic control, a significant decrease in the frequency of neonatal macrosomia can be achieved. Moreover, postprandial glucose values may be a more sensitive indicator of carbohydrate intolerance than fasting or preprandial values, potentially allowing more aggressive insulin treatment.

Large-for-gestational-age infants are delivered in 15 to 45 percent of pregnancies complicated by diabetes.²¹ Gestational diabetes is strongly associated with maternal obesity, and considerable controversy exists as to whether macrosomia is attributable to maternal obesity, poor glycemic control, or both.²²⁻²⁵ Despite the similar body-mass indexes and weight gains during pregnancy in our study groups, significantly fewer infants who were large for gestational age or weighed more than 4000 g were born to the women in the postprandial-monitoring group. Since maternal weight was similar in the two groups, the differences are most readily attributable to differences in the degree of glycemic control. Infants with macrosomia who are born to women with diabetes have a disproportionately increased fetal trunk and shoulder size.²⁶ The decreased incidence of cesarean section for cephalopelvic disproportion, of shoulder dystocia, and of maternal perineal lacerations in the postprandial-monitoring group is thus not surprising.

Neonatal complications, including hypoglycemia, hyperbilirubinemia, and respiratory compromise, have been described in infants born to women with gestational diabetes who require insulin therapy, particularly those in whom glycemic control was poor.^{6,22} The decreased incidence of neonatal hypoglycemia in the infants born to the women in the postprandial-monitoring group is consistent with the better glycemic control documented in this group. There was also a trend toward a lower rate of hyperbilirubinemia in the infants of women in the postprandial-monitoring group.

Some limitations of this study must be considered. First, the women were predominantly Hispanic. Race or ethnic group has been reported to have an independent influence on birth weight and on the prevalence of gestational diabetes, with Hispanics at higher risk for both.²⁷ This factor may limit the extrapolation of our findings to the general population. Second, some of the women probably had previously undiagnosed non-insulin-dependent diabetes mellitus, because their diabetes was identified in early pregnancy. Third, the exclusion of women who started insulin therapy after 30 weeks of gestation increased the likelihood that we would find a difference in perinatal outcome between the groups. Earlier studies may have failed to show ben-

Table 3. Neonatal Outcomes, According to Study Group.*

VARIABLE	PREPRANDIAL MONITORING (N = 33)	POSTPRANDIAL MONITORING (N = 33)	RELATIVE RISK (95% CI)	P VALUE
	<i>mean \pmSD</i>			
Birth weight (g)	3848 \pm 434	3469 \pm 668	—	0.01†
	<i>number (percent)</i>			
Large for gestational age	14 (42)	4 (12)	3.5 (1.3–9.5)	0.01‡
Birth weight >4000 g	12 (36)	3 (9)	4.1 (1.3–13.2)	0.01‡
Small for gestational age	0	1 (3)	—	1.00‡
Shoulder dystocia	6 (18)	1 (3)	6.0 (0.8–47.1)	0.10‡
Neonatal hypoglycemia	7 (21)	1 (3)	7.0 (0.9–53.8)	0.05‡
Hyperbilirubinemia	4 (12)	3 (9)	1.3 (0.3–5.5)	1.00‡
Transient tachypnea	2 (6)	2 (6)	1.0 (0.1–6.7)	1.00‡
Apgar score at 5 min ≤ 7	3 (9)	1 (3)	3.0 (0.3–27.4)	0.61‡
Stillbirth§	1 (3)	0	—	1.00‡

*CI denotes confidence interval. Infants who were large for gestational age had birth weights above the 90th percentile for gestational age and sex according to population-specific growth curves, and those who were small for gestational age had birth weights below the 5th percentile.

†By Student's t-test.

‡By Fisher's exact test (two-tailed).

§One unexplained stillbirth at 21 weeks; the autopsy was normal.

efits of therapeutic intervention in women with gestational diabetes because glucose intolerance is often diagnosed after macrosomia is already apparent, since macrosomia may develop as early as 20 weeks of gestation. Conversely, women in whom gestational diabetes is diagnosed in early pregnancy may have more severe metabolic abnormalities that contribute to accelerated fetal growth. We excluded women with medical complications known to impair fetal growth in order to permit a more accurate assessment of our therapeutic intervention. Fourth, since this was a non-blinded study and some members of the health care team were aware of the hypothesis, bias in the clinical management and the assessment of perinatal outcomes could have been introduced. However, many of the physicians involved believed that preprandial glucose monitoring was as effective as postprandial glucose monitoring.

The fact that the demographic characteristics and details of clinical management in the two groups were similar, as was the degree of compliance with the glucose-monitoring schedules, allowed us to assess the effects of the intervention on perinatal outcomes. Although neonatal macrosomia and other complications are probably multifactorial in origin, in this predominantly Hispanic population of women with gestational diabetes requiring insulin therapy, postprandial glucose monitoring led to better glycemic control than preprandial monitoring. Better control of blood glucose concentrations, in turn, decreased both neonatal risks and perinatal complications.

We are indebted to the staffs of the University of California at Irvine and Long Beach Memorial Medical Center for their invaluable assistance in patient care and data collection.

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