

Clinical predictors for a high risk for the development of diabetes mellitus in the early puerperium in women with recent gestational diabetes mellitus

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OBJECTIVE: The purpose of this study was to identify which maternal, antepartum, or neonatal clinical parameters were predictive for a high risk of diabetes mellitus in the puerperium in women with recent gestational diabetes mellitus and to calculate the associated diabetes mellitus rates and odds ratios.

STUDY DESIGN: One thousand six hundred thirty-six women underwent an oral glucose tolerance test within 1 to 4 months of delivery. Demographic, historic, and antenatal glycemic parameters and neonatal outcome parameters were tested by univariate and multivariate logistic regression for risk of postpartum diabetes mellitus. Continuous variables were divided into quartiles that compared the upper to lower quartile adjusted odds ratio and prevalence of diabetes mellitus.

RESULTS: Postpartum diabetes mellitus was diagnosed in 230 women (14.1%) according to the American Diabetes Association criteria (1997). No maternal demographic or neonatal parameters were significantly associated with diabetes mellitus. The final model of independent predictors in decreasing significance included the highest fasting plasma glucose level during pregnancy, any fasting plasma glucose level of ≥ 105 mg/dL (class A₂), the area under the curve of pregnancy oral glucose tolerance test, gestational age at diagnosis, previous gestational diabetes mellitus history, and 50-g glucose challenge test results. The fasting plasma glucose level was the best discriminator, with a 21-fold (95% CI, 4.6-96.3) increased odds ratio comparing the 4th quartile (fasting plasma glucose level, >121 mg/dL; diabetes mellitus rate, 36.7%) to 1st quartile (fasting plasma glucose level, <95 mg/dL; diabetes mellitus rate, 0.5%). The presence of previous gestational diabetes mellitus or current class A₂ gestational diabetes mellitus approximately doubled the odds ratio for diabetes mellitus. The odds ratio increased 3- to 4-fold when the area under the curve was ≥ 33.36 min \cdot g/dL (4th quartile) or the glucose challenge test was ≥ 155 mg/dL (2nd-4th quartiles) and decreased $>50\%$ if gestational diabetes mellitus was diagnosed at >27 weeks (3rd-4th quartile).

CONCLUSION: During pregnancy, the highest fasting glucose level, followed by the severity of glucose intolerance, and earlier gestational diabetes mellitus diagnosis were the best predictors for postpartum diabetes mellitus. Diabetic education should begin during pregnancy, especially for women who are identified to be at a high risk when they are highly motivated and under medical care. (*Am J Obstet Gynecol* 2002;186:751-6.)

Key words: Gestational diabetes mellitus, postpartum diabetes mellitus, risk factors, fasting glucose

After delivery, glucose tolerance returns to normal in most women with gestational diabetes mellitus (GDM).¹ Studies have reported diabetes mellitus rates from 3% to 24% during the first year²⁻⁷ and support the recommendation that all women with GDM should undergo a

postpartum oral glucose tolerance test (oGTT) to reclassify their glucose tolerance status.^{1,8} Despite these recommendations, $<50\%$ of the women return for such testing, even in centers with established follow-up programs.^{4,7,9,10} Easily identifiable clinical risk factors to assess the individual risk for the development of postpartum diabetes mellitus would help the provider to identify those women at greatest risk before delivery. Counseling and education regarding diabetes mellitus risk and care could be initiated in these women during pregnancy. Several studies that have examined glucose tolerance during the early puerperium have concentrated largely on maternal parameters and have been limited by relatively small sample sizes.²⁻⁷ The purpose of our present study was (1) to identify which maternal,

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antepartum, or neonatal clinical parameters were predictive of a high risk of diabetes mellitus in the puerperium in a large cohort of women with recent GDM and (2) to calculate the risk and prevalence of postpartum diabetes mellitus that were associated with the identified predictors.

Methods

Study population and diagnosis and treatment of GDM.

This retrospective study was performed with data collected in a prospective database from a cohort of women who were followed for GDM at Los Angeles County and University of Southern California Women's and Children's Hospital between January 1987 and July 1995. GDM was diagnosed with a 2-step procedure and universal screening policy.¹¹ If risk factors for GDM or clinical signs of overt diabetes mellitus were present at the initial visit for prenatal care, early screening for GDM was performed with the use of a 50-g 1-hour post-glucose challenge test (GCT). Women who were found not to have diabetes mellitus were retested between 24 and 28 weeks of gestation. Otherwise, universal screening for GDM was performed between 24 and 28 weeks of gestation. Women with a plasma glucose concentration of 141 to 199 mg/dL during the 1-hour test were tested for GDM with a 100-g 3-hour oGTT. The results were interpreted according to the recommendations of the Third International Workshop Conference on GDM. Eleven women with GCT levels of ≥ 200 mg/dL or significant glycosuria (+2) underwent an initial measurement of fasting plasma glucose (FPG) levels; an oGTT was performed only if the FPG level was < 130 mg/dL. Otherwise the diagnosis of GDM was made on the basis of FPG alone.¹² Plasma glucose concentrations were measured by glucose oxidase (Beckman Glucose Analyzer II; Beckman Instruments, Brea, Calif). All women who were diagnosed with GDM were placed on a standard diabetic diet that provided 30 kcal/kg of actual pregnancy body weight if their prepregnancy weight was normal ($< 120\%$ ideal body weight). If their prepregnancy weight was obese ($\geq 120\%$ ideal body weight), a diet of 25 kcal/kg of actual pregnancy weight was prescribed. A certified laboratory measured FPG concentrations at 1- to 2-week intervals after the initiation of diet therapy. Women whose glucose levels remained ≥ 105 mg/dL were placed on a split-dose insulin therapy and self-monitoring of blood glucose 4 to 7 times per day. Insulin doses were adjusted to achieve FPG levels of < 90 mg/dL and 2-hour postprandial values of < 120 mg/dL.

Collection of maternal, antepartum, and neonatal data.

Maternal, antepartum, and postpartum data and neonatal data were collected prospectively and entered into a standardized database. Maternal and historic variables consisted of age, parity, prepregnancy and pregnancy weight indices (weight [pounds] and body mass index [BMI; kilograms per square meter]), and any previous

pregnancies complicated by GDM, macrosomia (birth weight, > 4000 g), or a malformed or stillborn infant. Antepartum glycemic variables consisted of the 50-g GCT level, the gestational age and FPG at the time of diagnosis of GDM, the hourly plasma glucose levels and glucose area under the curve (AUC) of the diagnostic oGTT, the highest FPG level recorded before insulin therapy, and the classification of GDM (A_1 , all FPG levels < 105 mg/dL; A_2 , any FPG level ≥ 105 mg/dL). Neonatal variables that were collected from chart review included birth weight, birth length, obstetric outcome (live born, stillborn, or neonatal death), and the presence of any major congenital anomalies. The neonatal BMI was calculated from the birth weight and length (kilograms per square meter).

Postpartum testing. FPG levels were measured before hospital discharge and, in patients whose condition required insulin, at the time the diagnosis of diabetes mellitus was made without further glucose tolerance testing.¹ In the remainder of subjects, a 75-g 2-hour oGTT was scheduled between 1 and 4 months after delivery. The postpartum oGTT was performed in a standard fashion after an overnight fast and 3 days of a carbohydrate-rich diet. Venous blood was collected in heparin fluoride-containing tubes. Fasting and 30-, 60-, 90-, and 120-minute postchallenge plasma glucose levels were measured by similar methods as during pregnancy. During the study period, oGTT results were classified with the use of the 1979 National Diabetes Mellitus Data Group criteria,¹ which were current during the study period. Diabetes mellitus was diagnosed when either the fasting glucose was > 140 mg/dL or when the oGTT 2-hour plasma level was > 200 mg/dL plus the 30-, 60-, or 90-minute glucose level was > 200 mg/dL.

Statistical analysis. For study purposes, diabetes mellitus was defined by the new diagnostic criteria¹³ of either an overnight FPG level of ≥ 126 mg/dL or a 120-minute oGTT glucose level of ≥ 200 mg/dL. The chi-square test for categorical or *t*-test for continuous variables was used to test for significant differences in maternal and neonatal parameters between women who did and women who did not have diabetes mellitus after delivery. Means are presented with SDs, and all probability values are 2-sided, with a probability value of $< .05$ defined as significant. Univariate regression analysis was applied to calculate the odds ratio (OR) for the risk of postpartum diabetes mellitus for each maternal, antepartum, and neonatal variable. Multivariate analysis was performed to identify the set of variables that were statistically significant predictors of postpartum diabetes mellitus, independent of other related variables. Continuous variables, which were identified as predictors, were divided into quartiles for each variable (using as cutoff points 25th, 50th, and 75th percentile). The OR of the risk of diabetes mellitus were calculated for the quartiles, comparing the highest with the lowest quartile for those predictors that were continuous

Table I. Characteristics of women with recent GDM with nondiabetic (normal or impaired) and diabetic postpartum glucose tolerance, which are significant univariate predictors of diabetes mellitus

	<i>Nondiabetic women</i> (<i>n</i> = 1406)	<i>Women with diabetes mellitus</i> (<i>n</i> = 230)	<i>OR (95% CI)</i>	<i>P value</i>
Previous pregnancy history				
GDM (%)	10.4	26.1	3.05 (2.70-4.28)	.0001
Macrosomia, >4000 g (%)	21.8	32.6	1.43 (1.05-1.93)	.02
Stillbirth (%)	3.6	8.3	2.42 (1.40-4.18)	.001
Congenital anomaly (%)	1.6	3.5	2.16 (0.95-4.88)	.059
Maternal age (y)	31.1 ± 5.8	32.2 ± 6.0	1.04 (1.01-1.17)	.006
Parity (No.)	1.9 ± 1.7	2.2 ± 1.9	1.08 (1.001-1.17)	.048
Gestational age (wk)				
50-g GCT	20.8 ± 7.9	19.3 ± 7.6	0.98 (0.96-0.996)	.019
100-g Glucose tolerance test	25.9 ± 8.2	22.5 ± 7.7	0.95 (0.93-0.97)	.0001
Glycemic variables (mg/dL)				
GCT	178 ± 36	225 ± 58	1.023 (1.019-1.027)	.0001
Fasting glucose level (oGTT)	105 ± 21	142 ± 42	1.039 (1.034-1.045)	.0001
Highest fasting glucose level	108 ± 22	147 ± 43	1.041 (1.035-1.047)	.0001
Area under glucose curve*	30.9 ± 4.3	37.0 ± 8.4	1.19 (1.15-1.23)	.0001
Class A ₂ , any FPG ≥105 mg/dL (%)	64.7	95.2	11.37 (6.14-21.03)	.0001

*Calculated by trapezoid method (g · min/dL).

and for the presence versus absence of variables that were dichotomous. All ORs given were adjusted for the effects of the other independent predictors. The adjusted ORs are presented with the 95% CI. The cumulative incidence rate of diabetes mellitus in the 2nd, 3rd and 4th quartile was compared with the rate in the 1st quartile. All analyses were performed on the SAS, version 6.12 (SAS Institute Inc, Cary, NC).

Results

Of 4041 pregnancies that were complicated by GDM and were delivered during the study period, 1861 of the mothers (46%) returned for diabetes mellitus testing within 1 to 4 months after delivery. Two hundred twenty-five patients were excluded from analysis because of incomplete antepartum data; 1636 pregnancies were analyzed. The women who returned for the postpartum testing were not statistically different from women who did not return, with regard to most of the maternal demographic and glycemic parameters or neonatal parameters that were evaluated. However, those women who returned were less likely to have had previous GDM (13% vs 19%; *P* = .02), were slightly younger (31.2 ± 0.1 years vs 31.8 ± 0.1; *P* = .04), and had slightly lower AUC during pregnancy (31.5 ± 0.1 min · g/dL vs 31.06 ± 0.1 min · g/dL; *P* = .05).

Diabetes mellitus was diagnosed in 230 of the women (14.1%), and impaired glucose tolerance or impaired fasting glucose was diagnosed in 440 of the women (21.8%). Significantly different maternal demographic and glycemic characteristics of women who did and women who did not have diabetes mellitus 1 to 4 months after delivery are summarized in Table I. Women with postpartum diabetes mellitus were significantly more likely to have had a poor obstetric history, either compli-

cated by GDM or a macrosomic, stillborn, or anomalous infant. They also were significantly older, delivered at an earlier gestational age (38.3 ± 2.6 weeks vs 39.0 ± 2.1 weeks; *P* = .0002) but were not significantly heavier either before pregnancy (30.2 ± 5.5 kg/m² vs 29.3 ± 5.7 kg/m²) or at delivery (34.2 ± 6.2 kg/m² vs 34.1 ± 5.3 kg/m²). Screening for and diagnosis of GDM occurred at a significantly earlier gestational age, and all glycemic parameters evaluated were significantly higher (Table I). Infants of mothers with diabetes mellitus after delivery did not differ significantly in birth weight, which was adjusted for gestational age (3420 ± 689 g vs 3505 ± 600 g), rates of stillbirth (0 vs 0.4%) or anomaly (3.5% vs 2.1%) compared with infants of mothers without diabetes mellitus after delivery. Of the 37 mothers whose infants had major congenital anomalies 8 women (21.6%) had postpartum diabetes mellitus, compared with 13.9% of mothers (*P* = .18) with infants without anomalies.

The ORs of all the variables significantly associated with postpartum diabetes mellitus by univariate regression analysis are shown in Table I.

Multivariate logistic regression analysis of all significant variables yielded a final model of 6 independent clinical predictors of diabetes mellitus postpartum (Table II). These were in order of greatest predictive ability: increasing levels of the highest FPG levels during pregnancy, class A₂ GDM (any FPG level of ≥105 mg/dL), increasing glucose AUC, earlier gestational age at diagnosis of GDM, a previous history of GDM, and increasing glucose levels of the GCT. The final model is shown in Table II (with ORs) after the adjustment for each of the other 5 independent predictors. The crude rates of postpartum diabetes mellitus are given for each predictor when the

Table II. The final model of independent predictors of diabetes mellitus after a pregnancy that was complicated by GDM

<i>Independent predictors for postpartum diabetes mellitus</i>	<i>Adjusted OR (95% CI)*</i>	<i>Rate of diabetes mellitus (%)</i>
Highest FPG level (mg/dL)†		
1st Quartile (≤95)		0.5 (2/390)
2nd Quartile (>95, ≤108)	7.82 (1.77, 34.52)	5.9 (26/438)
3rd Quartile (>108, ≤121)	11.13 (2.44, 50.72)	12.7 (50/394)
4th Quartile (>121)	21.01 (4.58, 96.29)	36.7 (152/414)
Class A2 (any FPG ≥105 mg/dL)	2.40 (1.22, 4.72)	19.7 (219/1114)
Area under the glucose curve of pregnancy oGTT (min · g/dL)†		
1st Quartile (≤28.45)	1.0	4.0 (14/351)
2nd Quartile (>28.45, ≤30.46)	0.93 (0.41, 2.13)	3.2 (11/346)
3rd Quartile (>30.46, ≤33.36)	1.47 (0.73, 2.99)	6.1 (22/361)
4th Quartile (>33.36)	3.64 (1.93, 6.84)	22.1 (78/353)
Gestational age at time of 100-g 3-hour glucose tolerance test (wk)†		
1st Quartile (≤19.1)	1.0	21.4 (82/383)
2nd Quartile (>19.1, ≤27.3)	1.12 (0.72, 1.74)	17.3 (68/393)
3rd Quartile (>27.3, ≤31)	0.45 (0.27, 0.76)	8.3 (32/384)
4th Quartile (>31)	0.35 (0.23, 0.54)	8.7 (34/358)
Previous history of GDM	1.63 (1.07, 2.47)	29.1 (60/206)
50-g GCT (mg/dL)†		
1st Quartile (≤155)	1.0	2.6 (9/348)
2nd Quartile (>155, ≤175)	2.86 (1.24, 6.58)	6.9 (26/376)
3rd Quartile (>175, ≤202)	3.82 (1.72, 8.48)	11.8 (42/355)
4th Quartile (>202)	3.46 (1.57, 7.64)	27.3 (101/370)

*Adjusted for each of the other independent predictors in the model.

†The continuous variables are divided into quartiles, and each quartile is compared with the lowest quartile. The crude rate of postpartum diabetes mellitus for each quartile or for each predictor is given.

individual risk factor was present or by quartile for those factors, which were continuous.

The highest FPG level during pregnancy was the best predictor of diabetes mellitus after delivery. Each successive quartile of FPG was associated with significantly increased ORs and diabetes mellitus rates (Table II). Only 0.5% of women whose highest FPG level was in the lowest quartile (≤95 mg/dL) had diabetes mellitus within 4 months after delivery; 37% of women whose highest FPG level exceeded 121 mg/dL (4th quartile) during pregnancy had a diabetic postpartum oGTT. Compared with the 1st quartile, women with FPG in the 4th quartile (>121 mg/dL) had a 21-fold increase in the risk for development of diabetes mellitus. If any FPG level reached or exceeded 105 mg/dL (class A₂), the adjusted ORs were increased by 2.4-fold compared with all FPG levels that stayed below 105 mg/dL on diet therapy (class A₁). Only the highest quartile of glucose AUC (>33.3 g · min/dL) carried a significant increase in risk for the development of diabetes mellitus (adjusted OR, 3.65) compared with the lowest quartile. A gestational age at diagnosis >27.3 weeks of gestation (ie, in the 3rd or 4th quartile) was associated with a >50% reduction in risk compared with an earlier diagnosis. Having had GDM in a previous pregnancy was associated with a 1.6-fold increase in risk compared with never having had GDM before the index pregnancy. Any GCT level above the 1st quartile (≥155 mg/dL) was associated with a 2.8- to 3.8-fold increase in postpartum diabetes mellitus risk (2nd through 4th quartiles).

Comment

Our study cohort was of sufficient size to evaluate the relative importance of multiple clinical risk factors that were related to the mother, pregnancy, and neonate for the prediction of diabetes mellitus post partum. We found 6 independent predictors that could provide useful ORs to identify women during pregnancy who were at substantial risk for diabetes mellitus in early puerperium. All predictors were either related to the degree or the duration of hyperglycemia, and all predictors were easily identifiable during pregnancy. The best discriminator was the highest FPG level during pregnancy.

The independent predictors of postpartum diabetes mellitus that we have identified in our current study are similar in part to variables that have been previously identified by our own group^{7,14} and by others.^{2,4,15} Most studies that examined early postpartum glucose tolerance in women with recent GDM have not been of sufficient size to identify clinical predictors of postpartum diabetes mellitus but rather have identified risk factors for early postpartum "abnormal" glucose tolerance, which combined both impaired and diabetic glucose tolerance.^{3,4,7,15} In contrast to other studies,^{3,16,17} we did not find an association between any measure of maternal weight, either prepregnancy or predelivery or BMI to be associated with postpartum diabetes mellitus. This finding was consistent with our previous studies in which we did not find prepregnancy or predelivery weight to be associated with the long-term development of diabetes mellitus.^{9,14,18}

The difference between our results and the results of others regarding the effect of body weight may be due to the high prevalence of obesity (mean prepregnancy BMI, 29.4 ± 5.7 kg/m²) in our cohort. Interestingly, a previous pregnancy with poor obstetric outcome (eg, stillbirth, macrosomia, or congenital anomalies) was associated with an increased diabetes mellitus risk, but current index pregnancy neonatal outcome measures were not. This may reflect the possible presence of undiagnosed glucose intolerance during the historic pregnancy, which identified these women as high risk in the subsequent index pregnancy and resulted in early GDM screening and treatment.

All 6 independent predictors of postpartum diabetes mellitus were related to the severity or duration of hyperglycemia. The highest FPG level, a classification as A₂ GDM (any FPG of ≥ 105 mg/dL), a measurement of the glucose AUC from the pregnancy oGTT, and the 1-hour postglucose challenge concentration all directly measure glucose levels during pregnancy. The diagnosis of GDM earlier in gestation suggests a more chronic or severe form of insulin resistance, present before the physiologic insulin resistance that occurs in the third trimester. Similarly, a previous history of GDM may indicate a longer duration of an underlying and chronic metabolic defect that may have antedated the current pregnancy.

The fact that so many measures of hyperglycemia remained in our final model and were each independently predictive may seem puzzling. In nonpregnant, asymptomatic individuals at least 2 episodes of elevated glucose are required to diagnosis diabetes mellitus¹³ because of the significant variance (up to 17%) in oGTTs in individuals when tested on different days.¹⁹ Similarly, if abnormalities of glucose metabolism are documented more frequently and are of greater duration or severity during pregnancy then the more likely it is that there exists true underlying glucose intolerance, which is not caused by the pregnancy. Thus, the finding of 6 independent predictors, all of which either measure the severity or duration of hyperglycemia, suggests that women with these characteristics were likely to have either undiagnosed diabetes mellitus before pregnancy or a very rapid deterioration of glucose tolerance beginning in or continuing after pregnancy. Our findings support the Fourth International Workshop-Conference on GDM recommendations that women with GDM that recurs in a subsequent pregnancy without having diabetes mellitus excluded in the interim period and women with GDM diagnosed in the first trimester or with fasting hyperglycemia should be considered to have diabetes mellitus rather than GDM.⁸

All predictive parameters that we identified are routinely obtained during the diagnosis and treatment of GDM and can be used to antenatally identify women at highest risk of postpartum diabetes mellitus and possibly

chronic glucose intolerance preceding pregnancy. A highest fasting glucose value of >121 mg/dL, insulin use in pregnancy, diagnosis of GDM before 19 weeks of gestation, a history of GDM, and a glucose value of the GCT of >202 mg/dL were parameters for the highest risk of postpartum diabetes mellitus. Using the given ORs and rates of postpartum diabetes mellitus can help in counseling patients regarding their individual risk while they are still pregnant, highly motivated, and under frequent medical care. Hopefully, introducing this concept during pregnancy, especially to those women at greatest risk, will improve medical follow-up after delivery.

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