

Metabolic and Therapeutic Assessment of Gestational Diabetes by Two-Hour and Twenty-Four-Hour Isocaloric Meal Tolerance Tests

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SUMMARY

Lean and obese women with gestational diabetes (GDM) were given two different isocaloric meal challenge tests to assess glucose and insulin responses. Forty-three pregnant women received a 400-kcal isocaloric breakfast meal tolerance test (mini-MTT). Twenty of the subjects were also given a 2000-kcal isocaloric diet with three meals and three snacks during a 24-h period (maxi-MTT). This was the first study to utilize the physiologic challenge of mixed meals to compare insulin and glucose responses of both obese and lean normal pregnant women and women with GDM around the clock.

Normal obese pregnant women had higher integrated glucose and insulin values around the 24-h clock ($P < 0.003$ and < 0.03 , respectively) than lean pregnant women. Lean and obese women with GDM also responded differently to the physiologic challenge of mixed meals. Some, but not all, obese diabetic subjects were markedly hyperinsulinemic in contrast to lean diabetic women who were relatively insulin deficient. One normoglycemic massively obese 18-yr-old pregnant woman was unexpectedly found to be severely hyperinsulinemic.

The two meal tolerance tests clearly defined a delay in the release of insulin in women with GDM (lean and obese) and markedly different quantitative insulin responses to identical meal challenges in obese diabetic subjects. Maternal hyperinsulinemia was positively correlated with prepregnancy body mass index (kg/m^2) and heavier infants, but not with plasma glucose levels.

These studies provide evidence that GDM is a heterogeneous syndrome. Because of the variety of tests for GDM, the not unusual occurrence of carbohydrate intolerance in lean pregnant women without risk factors, and the worldwide differences in diagnostic criteria for this syndrome, we recommend screening for diabetes

in all pregnant women. Finally, we have proposed that an extension of the National Diabetes Data Group classification be applied to pregnant women. In this scheme, gestational carbohydrate intolerance would be considered type III or GDM and be subdivided into non-obese and obese women. The increasing number of patients with carbohydrate intolerance secondary to renal dialysis, transplantation, cystic fibrosis, and other disorders might be called type IV or secondary diabetes. *DIABETES* 1985; 34 (Suppl. 2):81-87.

There is no unanimity of opinion concerning either the definition or diagnostic criteria for gestational diabetes mellitus (GDM).¹⁻¹⁶ We have been puzzled by the heterogeneous clinical features of women who develop carbohydrate intolerance during the course of pregnancy. Screening tests and glucose loading tests that measure only plasma glucose levels have not provided a definitive metabolic assessment of these patients.

We have previously reported evidence for metabolic heterogeneity among women with GDM demonstrated during the course of a physiologic challenge provided by an isocaloric breakfast meal.¹⁵ The present study was undertaken to extend our observations on glucose and insulin responses in obese as well as lean normal pregnant women and lean and obese subjects with GDM. Two-hour and 24-h isocaloric meal tolerance tests were administered during late third trimester when maternal metabolic alterations evoked by pregnancy are at their peak.^{17,18} Both types of meal challenges were useful in the metabolic assessment of lean versus obese women with GDM.

MATERIALS AND METHODS

Normal pregnant women and those with GDM were recruited from the obstetric clinics at the University of California, San Diego Medical Center. Lean controls were nonobese, with a mean prepregnancy body mass index (kg/m^2) of 20 ± 2 (\pm SD), $< 120\%$ ideal body wt, normal glucose tolerance, and

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TABLE 1
2000-Kcal isocaloric maxi-meal tolerance test

Meal	Pro (g)	CHO (g)	Fat (g)	Kcal	Fiber (g)
Breakfast, 8:00 a.m.					
¾ Cup cereal	2	15	—	70	3
1 Slice wheat bread	2	15	—	70	3
1 Cup fresh fruit	—	20	—	80	4
8 Oz low fat milk	10	13	5	140	—
Snack, 10:00 a.m.					
1 Slice wheat bread	2	15	—	70	3
Lunch, noon					
2 Oz meat	14	—	10	150	—
1 Cup vegetables	4	10	—	50	—
½ Cup starchy vegetables	2	15	—	70	3
½ Cup legumes	9	21	1	125	4
1 Slice wheat bread	2	15	—	70	3
½ Cup fresh fruit	—	10	—	40	2
1 Tsp margarine	—	—	5	45	—
8 Oz low fat milk	10	13	5	140	—
Snack, 3:00 p.m.					
1 Slice wheat bread	2	15	—	70	3
½ Cup fresh fruit	—	10	—	40	2
Dinner, 5:00 p.m.					
3 Oz meat	21	—	15	225	—
1 Cup vegetables	4	10	—	50	4
½ Cup starchy vegetables	2	15	—	70	3
1 Slice wheat bread	2	15	—	70	3
½ Cup fresh fruit	—	10	—	40	2
1 Tsp margarine	—	—	5	45	—
8 Oz low fat milk	10	13	5	140	—
Snack, 10:00 p.m.					
2 Slices wheat bread	4	30	—	140	6
Total caloric intake (%)	109 (22)	280 (55)	51 (23)	2010	50

no family history of diabetes. Obese normal controls met the same criteria but had a mean body mass index of 31 ± 9.

Women with GDM had no previous history of diabetes and met the criteria of O'Sullivan and Mahan¹ for the diagnosis of gestational carbohydrate intolerance. Informed consent for the study was obtained from each patient.

The 400-kcal isocaloric mini-meal tolerance test in pregnant normal and diabetic women has been described previously.^{12,14} In this study, patients with GDM were divided on the basis of prepregnant body mass index and percent ideal body wt into lean (body mass index 21 ± 2; 90–120% ideal body wt, N = 14) and obese (body mass index 32 ± 5;

TABLE 2
Characteristics of lean and obese women with normal pregnancy or gestational diabetes*

Group	Maternal age (yr)	Body mass index (kg/m ²)	Wt. gain in pregnancy (kg)	3rd Trimester HbA _{1c} (%)	Placental wt (g)	Infant birth wt (g)	Gestational age
Normal lean (7)	25 ± 5	20 ± 2	16 ± 5	5.8 ± 0.5	563 ± 83	3225 ± 566	39.6 ± 2
Normal obese (4)	25 ± 7	31 ± 9†	14 ± 5	6.1 ± 0.7	490 ± 42	3395 ± 355	39.2 ± 0.9
Gestational diabetes lean (14)	29 ± 6	21 ± 2	12 ± 5	6.9 ± 0.7‡	504 ± 87	3509 ± 637	39.2 ± 2
Gestational diabetes obese (18)	30 ± 8	32 ± 5†	13 ± 6	7.1 ± 0.6‡	626 ± 165§	4158 ± 604	39.3 ± 1

*All patients had term births and all data are presented as mean ± SD. Values in parentheses indicate subjects in each group.

†Normal lean and lean GDM versus obese normal and obese GDM, P < 0.01.

‡HbA_{1c}: normal lean versus obese GDM, P < 0.04; normal lean versus lean GDM, P < 0.01; normal obese versus obese GDM, P < 0.003.

§Placental weight of obese versus lean GDM, P < 0.003.

||Infant birth weight: normal lean versus obese GDM, P < 0.003; normal obese versus obese GDM, P < 0.02; lean GDM versus obese GDM, P < 0.003.

122–205% ideal body wt, $N = 18$) groups. Normal pregnant women ($N = 11$) followed an unrestricted diet (30–35 kcal/kg body wt) and activity program. Women with GDM were prescribed the 1979 American Diabetes Association diet^{19,20} (elimination of free sucrose, carbohydrate 55%, protein 20%, fat 25%). None of the patients were treated with insulin.

2000 Kcal 24-h isocaloric maxi-meal tolerance test. Twenty women participated in the 24-h study (lean normal: $N = 6$; obese normal: $N = 4$; lean GDM: $N = 3$; obese GDM: $N = 7$). One lean normal patient had incomplete insulin values and one obese normal was markedly hyperinsulinemic. Both were excluded from the analysis of the insulin data.

Each subject was instructed to eat a diet with 150–200 g of carbohydrate for the 3 days before the test. All patients were admitted to the Clinical Research Center on the afternoon or evening before the test and food was restricted after 2200 h. On the morning of the study, a small catheter was inserted into a hand or wrist vein. Patency was maintained with a heparin lock for hourly blood samples for 24 h for determination of plasma glucose and insulin levels. Measurements of glucagon, C-peptide, prolactin, cortisol, total cholesterol, triglycerides, lipoproteins, and binding of insulin to red blood cell receptors have been reported elsewhere.^{17,18,21} Patients were dressed and ambulatory during the daytime hours of the test. The test diet consisting of breakfast at 0800 h, lunch at 1200 h, dinner at 1700 h, and snacks at 1000, 1500, and 2200 h is described in detail in Table 1.

Laboratory studies. Plasma glucose was measured by a glucose-oxidase method and glycosylated hemoglobin by the Isolab fast hemoglobin test system.²² Determinations of immunoreactive insulin and C-peptide (not included in this report) were by the methods of Kuzuya et al.²³ Analysis of data was by group and paired *t*-tests, two-factor analysis of variance, linear regression, and Duncan's multiple range testing as appropriate.

RESULTS

PATIENTS

Table 2 shows the characteristics of the four groups of patients. Normal pregnant women were younger than those with GDM. Both obese groups were significantly heavier than their lean counterparts. Although all groups had mean HbA_{1c} concentrations within the normal range for nonpregnant women, the values for lean and obese GDM were significantly elevated ($P < 0.01$ and $P < 0.04$, respectively) for third trimester. Obese GDM had higher placental and infant birth weights, despite a lower weight gain during pregnancy.

400-KCAL ISOCALORIC BREAKFAST MINI-MEAL TOLERANCE TEST

Figure 1 (top) shows the slightly increased glucose levels in obese versus lean normal pregnant women ($P = NS$). Insulin responses to the test meal were prompt in both groups (30 min). Obese women, however, had higher levels of plasma insulin at fasting, 30, 60, and 120 min ($P < 0.01$ by paired *t*-test and < 0.05 by analysis of variance).

In contrast, Figure 1 (bottom left) shows that patients with GDM were hyperglycemic relative to controls and obese

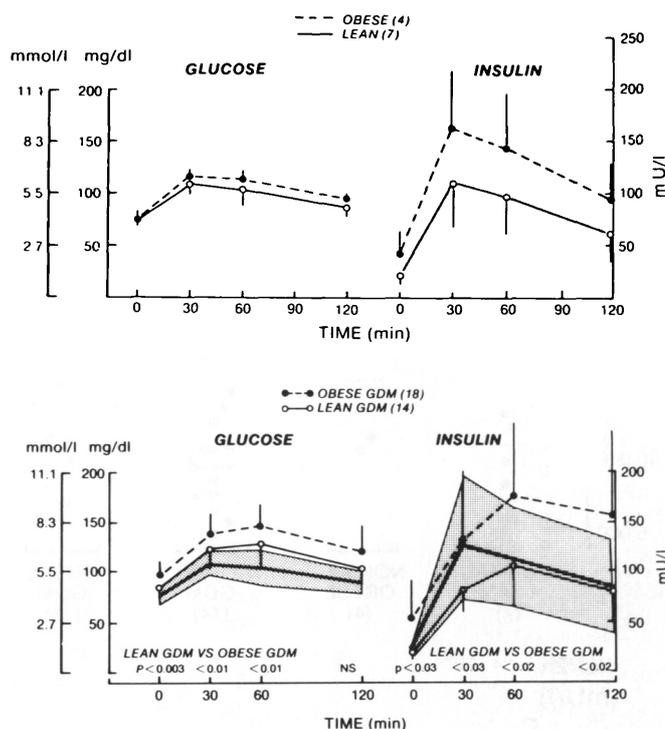


FIGURE 1. Fasting and 400-kcal breakfast meal-stimulated plasma levels of glucose and insulin in normal lean and obese pregnant women and lean and obese women with gestational diabetes. All points represent mean \pm SD. (Top panel, left) In obese women (broken lines) except when fasting, mean plasma glucose levels at each time point and the integrated area of glucose U/min under the 2-h curve were slightly but not significantly higher. (Top right) Obese normal women had higher insulin values at each time period. The differences between the two groups were significant with a paired *t*-test ($P < 0.01$) and analysis of variance ($P < 0.05$). (Bottom panel, left) Normal lean pregnant women \pm SD are shown in the heavy line and shaded area; obese GDM in broken lines and lean GDM in solid lines with open circles. In obese GDM mean glucose levels at fasting, 30, and 60 min are significantly higher than those of lean GDM and remained so at 2 h. (Bottom right) Normal pregnant women had a maximum insulin response by 30 min but there was a delay in peak response in both lean and obese GDM to 60 min. Obese GDM had higher mean insulin levels at all time periods of the test and significantly higher integrated insulin units under the 2-h curve compared with lean GDM ($P < 0.003$).

GDM had significantly higher values at fasting, 30, and 60 min than lean GDM. The bottom right panel shows the striking difference in mean insulin levels in obese versus lean GDM during the test meal. Although both groups had a delay in maximum insulin response (60 min versus 30 min in normals), the most impressive difference was clearly the remarkable hyperinsulinemia apparent in obese versus lean GDM.

Figure 2 is a plot of mean integrated insulin areas under the 2-h curve (mU/L/120 min) for patients in the four groups. Obese normal women had a higher mean value than lean normals. Of particular interest was the higher mean value in obese GDM versus lean GDM ($P < 0.003$). In this group seven women were clearly hyperinsulinemic relative to lean normals and lean GDM. Eight women, however, had values similar to those of the other three groups of patients. Figure 2 (bottom) shows the positive correlation ($r = 0.507$; $P < 0.05$) between integrated insulin units under the 2-h curve and body mass index.

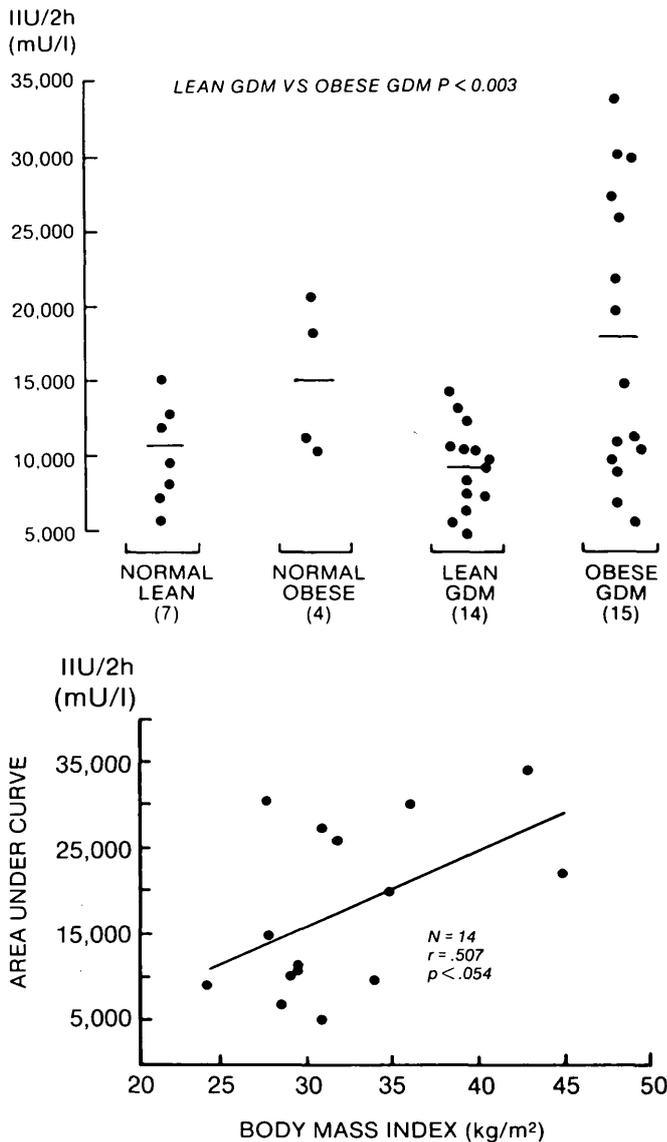


FIGURE 2. (Top) Mean integrated insulin units (IIU) under the 2-h 400-kcal mini-breakfast meal tolerance test curve in lean and obese normal and diabetic women. Obese normal subjects had higher insulin mU/L/2 h than lean normals (14,989 versus 10,151, P = NS). Obese GDM had significantly higher mean integrated insulin values versus lean GDM (P < 0.003), but wide individual variation was apparent. (Bottom) In obese GDM there was a positive correlation between BMI and integrated insulin units under the 2-h curve (r = 0.507, P < 0.05).

2000-KCAL ISOCALORIC 24-H SIX FEEDING (THREE MEALS PLUS THREE SNACKS) MAXI-MEAL TOLERANCE TEST

Normal lean and obese pregnant women. Except for identical fasting plasma glucose levels (76 mg/dl; 4.2 mmol/L), obese normal pregnant women had higher values after each meal and at night (Figure 3, top). In the obese the total integrated glucose units under the 24-h curve were significantly higher (P < 0.003).

Figure 3 (bottom) shows that normal lean and obese subjects had identical fasting levels of plasma insulin, but obese women had higher insulin responses to the three major meals and higher nocturnal values (P < 0.03).

One obese normal subject (C.M.) was plotted separately and not included in the group data. She was unique in that

she maintained 25 normal plasma glucose levels around the clock with a mean 24-h plasma glucose value of only 85 mg/dl (4.7 mmol/L). Her remarkable insulin resistance was associated with extreme hyperinsulinism in response to meals and wide excursions of plasma levels of insulin.

Lean and obese women with GDM. Figure 4 (top) shows the pattern of glucose excursions of lean and obese GDM around the 24-h clock. The 24-h mean values (lean: 109 mg/dl ± 20 [6.0 ± 1.1 mmol/L]; obese: 111 mg/dl ± 12 [6.1 ± 0.6 mmol/L]) and integrated glucose units under the 24-h curve were similar (P = NS).

Obese GDM (Figure 4, bottom) had higher mean insulin levels at each hour of the day and night. The mean peak

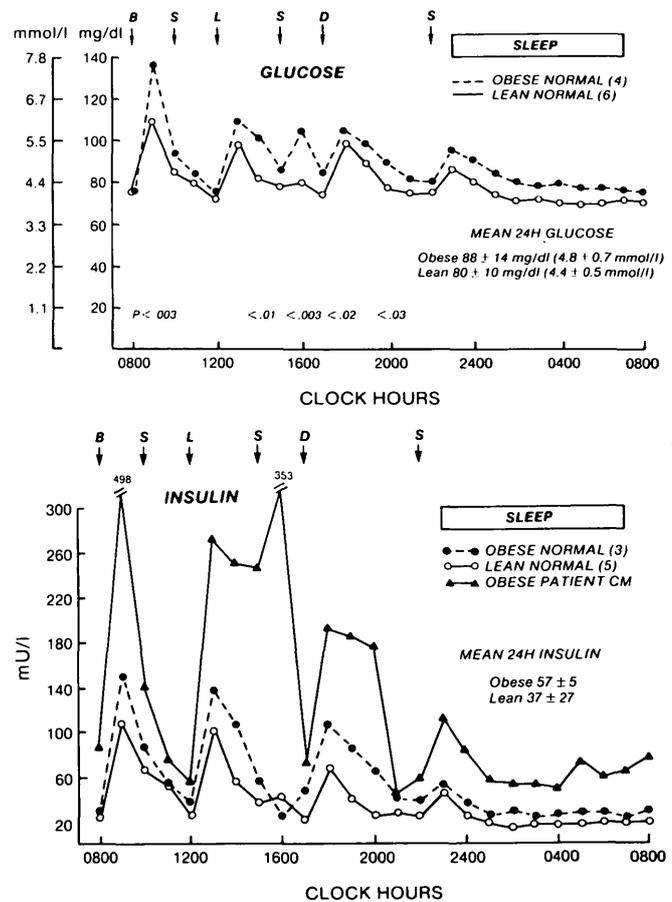


FIGURE 3. Mean hourly glucose and insulin levels in normal obese and lean pregnant women during the 2000-kcal isocaloric 24-h maxi-meal tolerance test. ↓ indicates the timing of meals and snacks. B: break fast; L: lunch; D: dinner; S: snacks. All values represent mean ± SD. (Top) Mean 24-h glucose levels in lean (80 ± 10 mg/dl; 4.4 ± 0.5 mmol/L) and obese (88 ± 14 mg/dl; 4.8 ± 0.7 mmol/L) were similar, but obese women had higher meal-stimulated values 1 h after breakfast, 2 h after lunch, 1 h and 2 h after the afternoon snack, and 3 h after dinner. The integrated glucose units (IGU) under the 24-h curve were higher in obese versus lean normal pregnant women (P < 0.003). (Bottom) Normal lean (solid line, open circles) and obese (broken line, closed circles) women had identical fasting levels of plasma insulin. However, obese normals had higher peak insulin responses to the three major meals and higher nocturnal values than lean women. Integrated insulin units (IIU) under the 24-h curve were: normal lean: 56,612; normal obese: 83,810 (P < 0.03). Obese normal subject C.M. (body mass index 44) was excluded from the analysis of mean insulin values in the normal obese group. She exhibited marked hyperinsulinemia in response to each meal during the test diet and wide excursions in plasma levels of insulin.

values of the insulin pulses induced by breakfast, lunch, and dinner were significantly different in obese versus lean GDM ($P < 0.01$), but there were large individual variations. In addition, the daytime hyperinsulinemic values of obese GDM never returned to the fasting baseline, and nocturnal levels were uniformly higher. Lean GDM exhibited much wider excursions. Integrated insulin units under the 24-h curve for all subjects who received the 2000-kcal meal tolerance test were positively correlated with body mass index ($r = 0.5$; $P < 0.02$).

DISCUSSION

Gestational diabetes has previously been considered to represent a single metabolic entity. Several earlier reports, however, have described maternal age and weight,²⁴ abnormal fasting plasma glucose levels,²⁵ or heterogeneity of insulin secretory response²⁶ to subclassify patients with GDM. In this study and our previous reports,^{15,17,24} we have provided evidence that lean and obese women who develop carbohydrate intolerance during pregnancy clearly differ from each other. They represent a complex and heterogeneous syndrome evoked by the metabolic stress of pregnancy. Moreover, this is the first report to show that obese normal pregnant women have normal glucose values but significantly higher insulin levels after a small (400-kcal) mixed breakfast meal. In 24-h studies with six mixed meal feedings, obese normal women are significantly more hyperglycemic and hyperinsulinemic than normal lean women.

Normal obese women were observed to have a prompt maximum release of insulin (30 min) in response to a 400-kcal breakfast, a finding also noted by Kuhl and Hornnes.²⁷ In contrast, both lean and obese women with GDM had a delayed and prolonged insulin response to the physiologic stimulus of mixed meals. In one massively obese 18-yr-old control with normal glucose tolerance and normal fasting plasma cholesterol and triglyceride levels we unexpectedly documented severe hyperinsulinemia and insulin resistance.

Obese women with GDM, in contrast to their lean counterparts, had heavier placentas and larger babies despite lower weight gains during pregnancy. It was of interest that maternal integrated insulin units under the 24-h curve of the 2000-kcal meal tolerance test were positively correlated with both maternal prepregnancy body mass index and infant birth weight. Neither of these variables, however, was correlated with plasma glucose levels.

Some, but not all, obese women had striking hyperinsulinemia. Although the number of patients in some subgroups was small, the number of obese GDM studied was 18. Our findings suggest further heterogeneity within this group.

Because markedly obese diabetic women have an exaggerated insulin response to the same isocaloric meals fed to lean women with GDM, this observation may have important implications for the content and timing of meals during their pregnancies. The higher insulin levels in obese GDM persisted through the night and were especially remarkable after what most nutritionists would consider hypocaloric breakfast meals. Furthermore, these observations suggest that the "glycemic index" of specific foods could be much less important than the recipient and her set point for release of insulin and other hormones.

Our studies provide the first clear evidence of metabolic

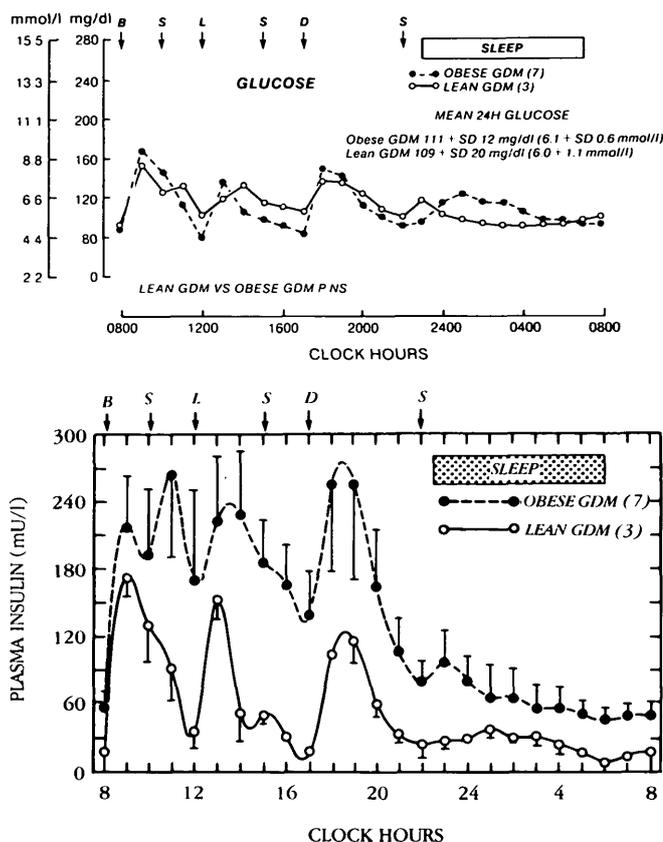


FIGURE 4. (Top) Plasma glucose values around the 24-h clock in lean versus obese women with GDM. There was no significant difference between the two groups. (Bottom) Smoothed curve of plasma insulin levels around the 24-h clock in the same subjects. Peak postprandial values at 1 h and 2 h after dinner were significantly higher in the obese group ($P < 0.01$ by two-factor analysis of variance). The mean insulin values of obese GDM were significantly higher than those of lean GDM (Duncan's multiple range test, $P < 0.01$). There was marked individual variation within groups, and these data are presented as mean \pm SEM.

heterogeneity within the large group of women who develop gestational carbohydrate intolerance. The important differences between lean and obese women with GDM are easily delineated by either a simple breakfast test or a longer 24-h study. This approach is both more physiologic and informative than oral or intravenous glucose loading tests.

Our current view is that GDM represents a failure of adaptation during the severe metabolic stress of pregnancy. It may provide the first hint of expression of diabetogenic genotypes. Over time, and in appropriate medical or environmental circumstances, ascertainment of slowly evolving insulin-dependent (type I) or non-insulin-dependent (type II) diabetes and their subtypes may occur. It is not yet possible to identify the genetic markers for diabetes.^{28,29} Our understanding of the various expressions of the disorder must rely on subclinical markers or predictors such as GDM in the absence of the full phenotype.

We agree with Beard and Hoet¹³ that the widely used World Health Organization (WHO) Expert Committee on Diabetes Mellitus 2nd Report,⁵ which states that diagnostic criteria for diabetes should be the same in all adults, pregnant or not, is not sufficiently specific. In the published WHO classification, GDM is nebulously defined as "statistical" risk

TABLE 3
Recommendation for classification of glucose intolerance in pregnant women*

Nomenclature	Old names	Clinical characteristics or condition
Type I insulin-dependent diabetes mellitus (IDDM)	Juvenile diabetes (JD) Juvenile-onset diabetes (JOD) Ketosis-prone diabetes Brittle diabetes	Ketosis-prone. Insulin deficient due to islet cell loss. Often associated with specific HLA types with predisposition to viral insulinitis or autoimmune (islet cell antibody) phenomena. Occurs at any age. Common in youth. These women are usually of normal weight but may be obese.
Type II non-insulin-dependent diabetes mellitus (NIDDM) Nonobese Obese	Adult-onset diabetes (AOD) Maturity-onset diabetes (MOD) Ketosis-resistant diabetes Stable diabetes Maturity-onset diabetes of youth (MODY)	Ketosis-resistant. More frequent in adults but occurs at any age. Majority are overweight. May be seen in family aggregates as an autosomal dominant genetic trait. Always require insulin for hyperglycemia during pregnancy. Previous history of "borderline diabetes." Impaired glucose tolerance or treatment with oral hypoglycemic agents. HbA _{1c} ≥ 9% ≤ 20 wk gestation.
Type III gestational diabetes† Nonobese Obese	Gestational diabetes	Screening tests: all pregnant women. Oral glucose load (50 g) given randomly (need not be fasting). A plasma glucose 1 h later ≥ 140 mg/dl is an indication for a 3-h OGTT with 100 g of glucose.‡
Type IV secondary diabetes	Conditions and syndromes associated with impaired glucose tolerance	Cystic fibrosis. Endocrine disorders such as acromegaly, hyperprolactinemia, Cushing's syndrome, insulin receptor abnormalities, or aberrant forms of insulin, drugs or chemical agents, renal dialysis, organ transplantations, certain genetic syndromes.

*Adapted from the NDDG and WHO criteria.

†All pregnant women at higher risk for gestational diabetes should be screened at the first prenatal visit. Risk factors are glycosuria, family history of diabetes in a first-degree relative, history of a stillbirth or spontaneous abortion, presence of fetal demise in a previous pregnancy, a previous heavy-for-date baby, obesity in the mother, a high maternal age, or parity of five or more.

‡Diagnosis of gestational diabetes is based on criteria that two or more of the following plasma glucose excursions be met or exceeded: fasting 105 mg/dl; 1 h 190 mg/dl; 2 h 165 mg/dl; 3 h 145 mg/dl.

classes (subjects with normal glucose tolerance, but statistically increased risk of developing diabetes); previous abnormality of glucose tolerance or potential abnormality of glucose tolerance.⁵ Moreover, the WHO classification ignores those normal women with no risk factors who develop GDM and would not be detected by WHO recommended screening procedures. To bridge the differences between WHO and NDDG criteria and to recognize the increasing number of women with secondary carbohydrate intolerance who become pregnant, we suggest a new definition for women with these problems (Table 3).

Our proposed terminology for this new classification expands the 1979 NDDG and 1980 WHO criteria for GDM and suggests this disorder be called type III diabetes. The patients should be categorized as nonobese or obese as is recommended by NDDG for type II diabetes.

Pregnant women with secondary carbohydrate intolerance such as occurs with renal dialysis, transplants, cystic fibrosis, and other conditions might be considered to have type IV or secondary diabetes, which would also be compatible with the numerical system selected by NDDG.

We conclude from our observations with 2-h and 24-h is-

ocaloric meal challenge tests that GDM results from the complex interaction of (1) delayed pancreatic β -cell response to feeding and (2) marked insulin resistance and hyperinsulinemia in some but not all obese women and relative insulin deficiency in lean patients. A new classification has been proposed for carbohydrate intolerance during pregnancy. Metabolic observations in pregnant women with GDM will assume increasing importance as advances in molecular biology, immunogenetics, and epidemiology permit precise definition of the many types of carbohydrate intolerance that comprise the diabetic syndrome.

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