Metabolic Effects of 1200-kcal Diet in Obese Pregnant Women With Gestational Diabetes

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Calorie restriction is widely used as a primary therapy for obese pregnant women with gestational diabetes. To better understand the metabolic consequences of marked calorie restriction, we performed a randomized prospective trial under metabolic ward conditions. Obese gestationally diabetic women were randomized to control (n = 5) and calorie-restricted (n = 7) groups. All patients consumed an ~2400-kcal/day diet during the 1st wk of the study, and at the end of the 1st wk, metabolic features of the two groups were statistically indistinguishable. During the 2nd wk, the control group continued to consume ~2400 kcal/day, whereas the calorie-restricted group consumed ~1200 kcal/day. Twenty-four-hour mean glucose levels remained unchanged in the control group (6.7 ± 0.8 mM wk 1 vs. 6.8 ± 0.8 mM wk 2), although they dropped dramatically in the calorie-restricted group (6.7 ± 1.0 mM wk 1 vs. 5.4 ± 0.5 mM wk 2, $P < 0.01$). Fasting plasma insulin also declined in the calorie-restricted group (265 ± 165 pM wk 1 vs. 145 ± 130 pM wk 2), resulting in a significant change between groups ($P < 0.02$). Surprisingly, fasting plasma glucose and glucose tolerance measured by the 3-h oral glucose tolerance test did not change within or between groups. Fasting levels of β-hydroxybutyrate rose in the calorie-restricted group (290 ± 240 μM wk 1 vs. 780 ± 30 μM wk 2) but not in the control group ($P < 0.01$). Finally, urine ketones increased significantly ($P < 0.02$) in the calorie-restricted group, whereas they remained absent in the control group. We conclude that diets in the range of ~1200 kcal/day improve glycemic status in obese pregnant women with gestational diabetes but cause significant increases in ketonemia and ketonuria. Because the impact of maternal ketonemia and ketonuria on fetal well-being remains controversial, these changes are of concern. This level of calorie restriction appears unwise for general clinical usage. Further studies are needed to characterize the metabolic consequences of 1600- to 1800-kcal/day diets that have recently been reported to improve glycemic status without causing ketonuria or profound ketonemia. *Diabetes* 39:234–40, 1990

The pioneering work of O'Sullivan and Mahan (1,2) firmly established diagnostic criteria for gestational diabetes and its association with fetal morbidity and mortality. Since their original work, the diagnostic criteria have been modified slightly, and all causes of fetal mortality have declined dramatically (3). However, gestational diabetes remains important because of associated maternal and fetal morbidity (4,5) and its strong predictive power for eventual development of non-insulin-dependent diabetes in the mother (6,7).

Proper management of women with gestational diabetes is controversial. A review of recent literature shows a confusing range of approaches and recommendations. The guidelines of the American Diabetes Association are on one (conservative) extreme in proposing a diabetic diet (generally ~2400 kcal/day) and limitation of sucrose intake (8). A more aggressive extreme is insulin administration to all women with gestational diabetes from the time of diagnosis until delivery (9,10). Occupying a middle ground are groups that propose dietary manipulation in the form of varying degrees and duration of calorie restriction as the primary therapy for this disorder (11–16). Calorie restriction is attractive in this setting for several reasons: most women with gestational diabetes have the comorbid condition of obesity (6,14), calorie restriction is a cornerstone of treatment for non-insulin-dependent diabetes in the obese nonpregnant population, and calorie restriction may be more easily instituted and associated with less anxiety than insulin injection (for both patient and health-care provider) in a primary-care setting. Counterbalancing these positive features is the un-

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resolved issue of whether calorie-restricted diets are associated with significant increases in ketonemia and ketonuria during pregnancy and, if so, whether this effect is potentially detrimental to fetal neural development and subsequent infant intellectual performance.

We performed a prospective randomized trial of marked calorie restriction in obese pregnant women with gestational diabetes. Our goals were to examine its efficacy in lowering plasma glucose levels and to better understand concurrent metabolic changes.

RESEARCH DESIGN AND METHODS

Women receiving prenatal care at the University of Washington Obstetrics Clinics were routinely screened for gestational diabetes at or by 28 wk gestation. All patients received a 50-g 1-h screening test, and those with a 1-h postchallenge plasma glucose ≥7.8 mM were recalled for a full 3-h 100-g oral glucose tolerance test (OGTT). The diagnosis of gestational diabetes was made when two or more of the following values were met or exceeded during the 3-h OGTT: fasting, 5.3 mM; 1 h, 10 mM; 2 h, 8.6 mM; and 3 h, 7.8 mM (3). Prepregnancy weight >120% of ideal body weight (as defined by the corrected 1959 Metropolitan Life Insurance tables) was used to define obesity. Obese patients diagnosed with gestational diabetes in this manner and willing to voluntarily participate in this protocol were enrolled after signed, informed consent was obtained. Subjects were randomized to the control or calorie-restricted group (Fig. 1).

All patients were hospitalized for the 2-wk duration of this protocol. Studies and diet during the 1st wk were identical for all patients. Calorie allowances were individually calculated with the Harris-Benedict formula (Table 1; 17). Meal and snack patterns were: 0800 breakfast, 25% of day's calories; 1200 lunch, 25% of day's calories; 1500 snack, 12.5% of day's calories; 1800 dinner, 25% of day's calories; and 2200 snack, 12.5% of day's calories. Thus, morning (0700) plasma measurements were obtained after a 9-h fast. Diets were 50% carbohydrate, 30% fat, and 20% protein with 11 g of total dietary fiber per 500 kcal.

During the 2nd wk, the control group continued on the same diet (~2400 kcal/day), but the calorie-restricted group was placed on an ~1200-kcal/day diet. This reduction was accomplished by decreasing portion sizes without changing other features of the diet, i.e., meal times, percent of day's calories in each meal, and overall diet proportion of carbohydrate, fat, and protein.

A morning double-voided urine sample for ketone testing and a blood draw for fasting plasma glucose (FPG) were obtained daily from all subjects. On the 6th day of each week, blood was drawn at 0700 after an overnight fast for plasma glucose, insulin, triglyceride, free fatty acids, glycerol, and β-hydroxybutyrate. A glucose profile with 25 samples drawn over 24 h was initiated at that time. On these days, patients ate their assigned diet for that portion of the study. On day 7 of each week, fasting blood work (as on day 6) was repeated, and a 3-h 100-g OGTT was performed.

Glucose analyses were performed with a glucose oxidase procedure coupled to the dye indicator 3-methyl-2-benzothiazolinone hydrazone/dimethoxyaniline (18). Insulin was measured by the University of Washington Diabetes Research Center with a previously published technique (19). Total triglycerides were measured by standard Lipid Research Clinic procedures with the colorimetric technique of the AutoAnalyzer II (20). Free fatty acids were extracted by the procedure of Dole and Meinertz (21) and washed once with lower-phase wash to minimize the effect of titratable acidity of acidic phospholipids that increase in pregnancy. β-Hydroxybutyrate was assayed with an NAD-NADH–linked enzymatic assay developed by Williamson et al. (22) coupled to measurement of glycerol and read on a Turner spectrofluorometer. Urinary ketones were measured visually with ketone dipsticks (Keto-Diastix, Miles, Elkhart, IN) and numerically scored: negative = 0, trace = 1, small = 2, moderate = 3, and large = 4.

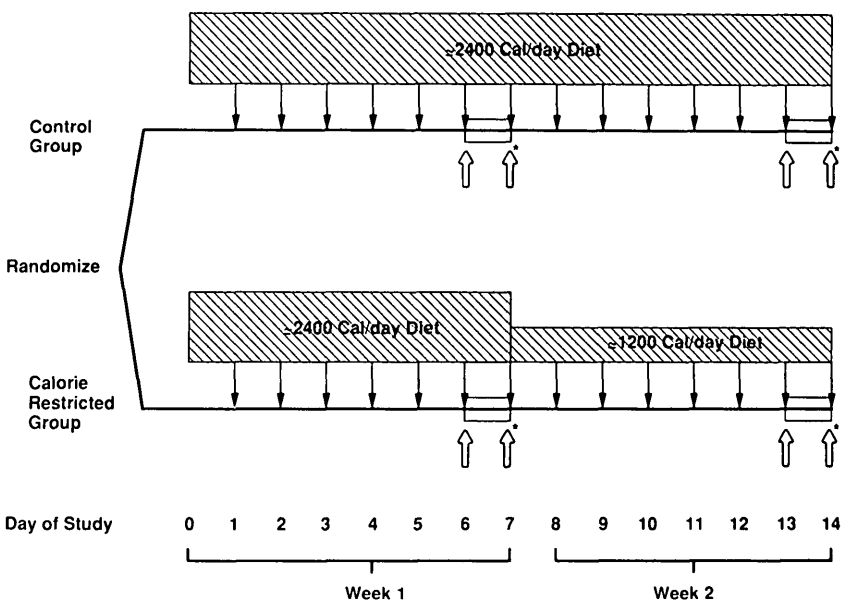

FIG. 1. Study design. Urine ketone testing was performed daily on double-voided first morning urine samples (*shaded arrow*); fasting morning blood work for plasma glucose, insulin, triglyceride, free fatty acids, glycerol, and β-hydroxybutyrate was performed on last 2 mornings of each week of study (*open arrow*); 24-h glucose profiling (⊟) followed by 3-h 100-g glucose tolerance tests (✻) were also performed on last 2 days of each week of study.

TABLE 1
Patient characteristics and study diets

	n	Age (yr)	Prepregnancy weight (kg)	Prepregnancy percent of ideal body weight	Prior pregnancies (n)	Wk of gestation*	Calorie ration (kcal/day)	
							Wk 1	Wk 2†
Control group	5	36 ± 5	88 ± 12	147 ± 13	7 ± 6	30 ± 3	2307 ± 174	2307 ± 174
Calorie-restricted group	7	30 ± 4	96 ± 17	171 ± 24	5 ± 5	31 ± 7	2476 ± 205	1238 ± 103

Values are means ± SD.
*At initiation of study on metabolic ward.
†$P < 0.01$. All other comparisons not significant.

Statistical analyses were performed with the Wilcoxon rank-sum test to determine differences between groups. Significance was reported when $P \leq 0.05$. Because of our small sample size, our power to detect significant differences may be limited. Data in all tables and figures are means ± SD. Urine ketone results are reported as the mean of the seven values collected during each week of the study. Fasting plasma measurements (glucose, insulin, free fatty acids, β-hydroxybutyrate, glycerol, and triglycerides) are reported as the mean of the values obtained on days 6 and 7 of each week of the study.

RESULTS

The two study groups (control and calorie restricted) were similar in terms of age, prepregnancy weight, prepregnancy percent of ideal body weight, number of prior pregnancies, and duration of current pregnancy at initiation of this study (Table 1). The calorie-restricted group tended to be younger and heavier than the control group, and these two features may have counterbalancing effects on glucose tolerance and insulin sensitivity. By design, the calorie ration for the calorie-restricted group during the 2nd wk was significantly reduced.

FPG and glucose tolerance (measured by area under the 3-h OGTT curve; Fig. 2) were similar at the end of wk 1 (Table 2). By the end of wk 2, these parameters had declined slightly in both groups, but these changes were statistically indistinguishable.

The means of the plasma glucose concentration obtained over a 24-h period were similar at the end of wk 1. Although there was no discernable change in the control group between wk 1 and 2, there was a marked fall in the mean glucose concentration of the calorie-restricted group (Fig. 3). The resultant change between the two groups was significant ($P < 0.01$).

Mean fasting plasma insulin concentrations tended to be higher in the calorie-restricted group at the end of the 1st wk but were associated with substantial variability and did not reach statistical significance (Table 2). The fasting insulin concentration did not change in the control group between wk 1 and 2, but it decreased in the calorie-restricted group so that the change between the groups was significant ($P < 0.02$).

There were no statistically distinguishable differences between the two groups at the end of wk 1 in levels of fasting triglycerides, free fatty acids, glycerol, β-hydroxybutyrate, and urinary ketones. At the end of wk 2, triglycerides were slightly higher in the control group and slightly lower in the calorie-restricted group, but the change between the groups was not statistically significant. Free fatty acids increased in both groups between wk 1 and 2, but the change between the groups was not significant. Glycerol showed a minimal increase in the control group and a decrease in the calorie-restricted group such that the difference of the change between the groups did reach statistical significance ($P < 0.04$) at the end of the 2nd wk. β-Hydroxybutyrate, one of the plasma ketone bodies, did not change in the control group but nearly tripled in the calorie-restricted group, making the change between the control and calorie-restricted groups significant ($P < 0.01$).

Finally, urine ketones were variably present during wk 1 in the calorie-restricted group. Because of this variability and

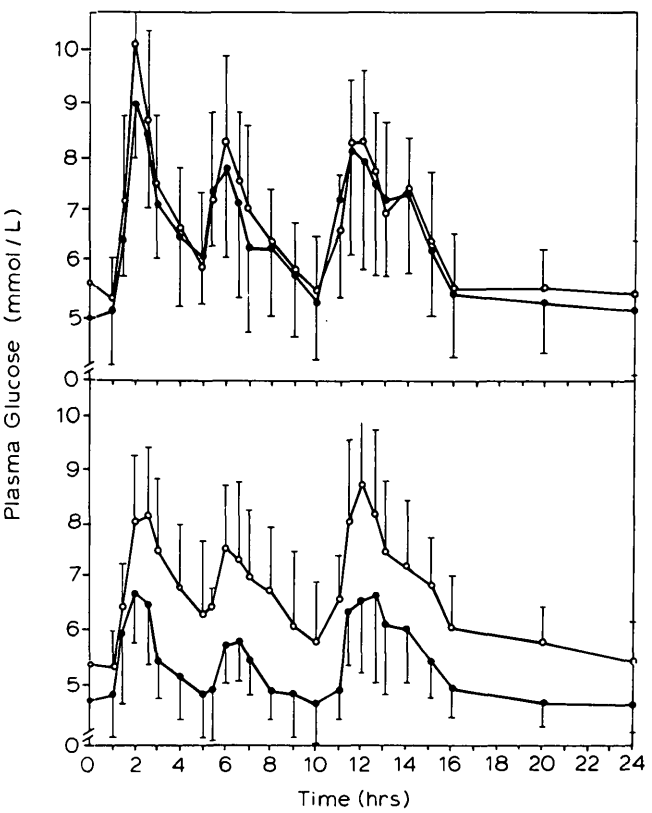

FIG. 2. Twenty-four-hour plasma glucose profiles. Although 24-h mean glucoses remained unchanged in control group (6.7 ± 0.8 mM wk 1 vs. 6.8 ± 0.8 mM wk 2; *top*), dramatic drop occurred in calorie-restricted group (6.7 ± 1.0 mM wk 1 vs. 5.4 ± 0.5 mM wk 2; *bottom*). ○, Wk 1; ●, wk 2.

TABLE 2
Metabolic indices

	Control group	Calorie-restricted group	P
Fasting plasma glucose (mM)			
Wk 1	5.4 ± 0.8	5.1 ± 0.6	
Wk 2	5.2 ± 0.9	4.9 ± 0.7	
Difference	−0.3	−0.2	NS
Area under 3-h OGTT curve			
Wk 1	51.0 ± 6.2	45.2 ± 6.7	
Wk 2	48.8 ± 6.8	42.8 ± 4.2	
Difference	−2.2	−2.4	NS
24-h mean plasma glucose (mM)			
Wk 1	6.7 ± 0.8	6.8 ± 0.8	
Wk 2	6.7 ± 1.0	5.4 ± 0.5	
Difference	−0.1	−1.3	<0.01
Fasting plasma insulin (pM)			
Wk 1	165.0 ± 35	265.0 ± 165	
Wk 2	165.0 ± 55	145.0 ± 130	
Difference	0	−120	<0.02
Plasma triglyceride (mM)			
Wk 1	3.18 ± 1.68	3.08 ± 1.74	
Wk 2	3.74 ± 1.56	2.89 ± 1.44	
Difference	0.56	−0.20	NS
Plasma free fatty acids (mg/L)			
Wk 1	330.0 ± 180	220.0 ± 30	
Wk 2	390.0 ± 200	360.0 ± 240	
Difference	60	140	NS
Glycerol (mM)			
Wk 1	0.09 ± 0.08	0.15 ± 0.10	
Wk 2	0.11 ± 0.09	0.09 ± 0.02	
Difference	0.02	−0.06	<0.04
β-Hydroxybutyrate (μM)			
Wk 1	220.0 ± 100	290.0 ± 240	
Wk 2	210.0 ± 60	780.0 ± 30	
Difference	−10	490	<0.01
Urine ketones*			
Wk 1	0.0 ± 0.0	1.0 ± 1.5	
Wk 2	0.0 ± 0.0	2.1 ± 1.2	
Difference	0	1.1	<0.02

OGTT, oral glucose tolerance test.
*Numerically scored (see text).

our small sample size, there were no statistically significant differences at this time point. Clearly, some of these women have ketonuria even when consuming ~2400 kcal/day. Women in the calorie-restricted group had no increase in ketonuria when placed on a calorie-restricted diet such that the change between the groups from wk 1 to 2 was significant ($P < 0.02$).

DISCUSSION

Diets that supply ~2400 kcal/day are recommended during pregnancy in healthy adult women (23). Unfortunately, there is no consensus regarding the appropriateness of this level of energy intake for pregnant women who are obese, gestationally diabetic, or both. Previous trials of calorie restriction during pregnancy complicated by these conditions have been limited in several ways. Most of the work has been retrospective, diagnostic criteria have varied, and patient populations have often been poorly defined. Obstetric outcome has usually been the focus of these studies, and little or no specific data have been given regarding glycemic status, other metabolic indices, or potential confounders of outcome such as tobacco or ethanol usage. To the best of our knowledge, only one previously published trial has included both pre- and postintervention data (16). Clearly, there is a need for further work in this area.

One of the most striking findings in this study was the marked improvement in 24-h mean plasma glucose values in the calorie-restricted group. This was achieved without a significant change in the FPG. We were surprised because FPG usually falls in nonpregnant obese individuals with non-insulin-dependent diabetes who are placed on hypocaloric diets (24,25). Maresh et al. (16) noted a similar improvement in 24-h mean plasma glucose values in gestationally diabetic pregnant women consumig 1500–1800 kcal/day. Also in their study, FPG did not change. It may be that hepatic glucose production, which is a close correlate and determinant of FPG, is more firmly "clamped" during pregnancy and less susceptible to exogenous factors, e.g., moderate changes in calorie intake.

Area under the 3-h OGTT curve is one index of glucose tolerance. Usually, OGTT area increases throughout pregnancy as a consequence of progressive insulin resistance (26). In both control and calorie-restricted groups, OGTT area decreased an insignificant amount during the 2-wk

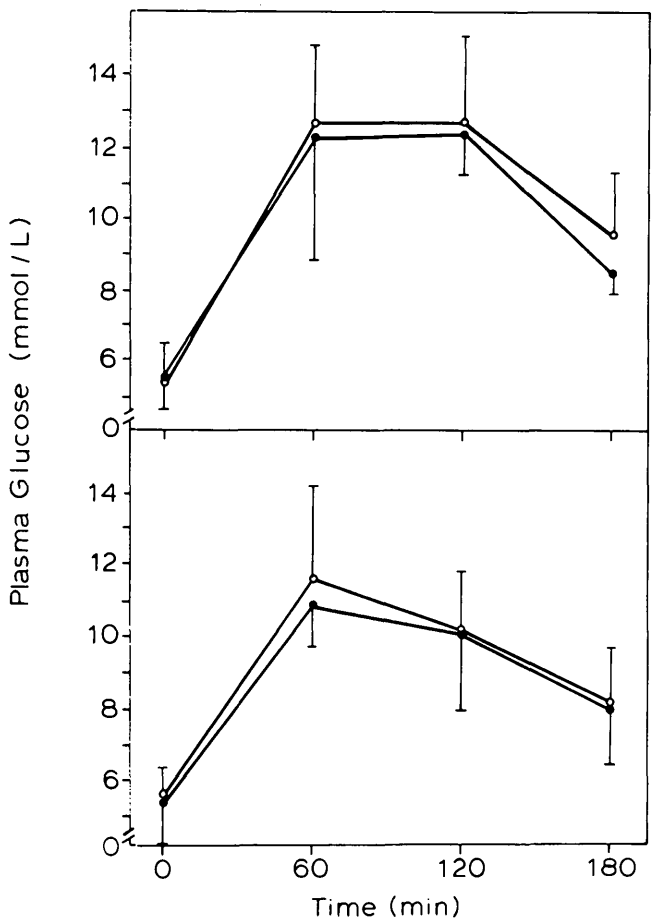

FIG. 3. Three-hour oral glucose tolerance tests (OGTTs). Despite other metabolic differences that emerged after calorie restriction (*bottom*), repeated OGTTs at end of wk 2 demonstrated no significant change in groups' degree of glucose intolerance. *Top*, control group; ○, wk 1; ●, wk 2.

study. We know of only one previous study in which the 3-h OGTT was repeated in obese gestationally diabetic women before and after calorie restriction (1000-kcal/day diet; 14). Similarly, no improvement in glucose tolerance was seen in that study. This lack of change in glucose tolerance, despite marked improvement in glycemic status, underscores the important role of diet in determining day-to-day glycemic status.

Women with the mildest and most common form of gestational diabetes (i.e., those without fasting hyperglycemia: FPG < 5.8 mM) have been characterized as "underutilizers" rather than "overproducers" of metabolic fuels, particularly glucose (27). If this characterization is correct, calorie restriction would seem to be a rational approach to moderate the dietary challenge to glycemic homeostasis. As long as prolonged intervals (≥4 h) without calorie intake are avoided, this approach should lead to an improvement in the metabolic profile (28).

The absence of improvement in glucose tolerance with calorie restriction suggests that there was no improvement in insulin sensitivity. Although insulin determinations during repeated 3-h OGTTs were not obtained, fasting insulin-glucose ratio may also be used as a crude index of insulin sensitivity (29). Although FPG values did not change significantly in either group, fasting insulin values fell dramatically in the calorie-restricted group, implying an improvement in insulin sensitivity. A similar reduction in fasting insulin values and improvement in fasting insulin-glucose ratios was seen in the study by Maresh et al. (16). This discrepancy between improved insulin sensitivity in the basal state without improved tolerance to a glucose load is unexplained and deserves further study.

Plasma triglyceride concentrations typically increase threefold during pregnancy to mean levels of ~2.04 mM (30). Increases to mean values of ~3.16 mM have been reported in women with gestational diabetes who do not have fasting hyperglycemia (31). The triglyceride levels in our patients are typical for this latter group. We are unaware of prior reports of the effect of calorie restriction on the hypertriglyceridemia of normal or gestationally diabetic pregnancies. This decline in triglycerides is an important observation, because we have shown in a population-based study that triglyceride levels are correlated with adjusted birth weights and may be a predictor of macrosomia (32).

Both tissue and plasma levels of free fatty acids and glycerol are markers of lipolysis and generally are increased in pregnancy, especially in the fasted state (33,34). On this basis, we expected that free–fatty acid and glycerol levels would increase markedly in the calorie-restricted group. Free fatty acids showed large interindividual variation, and the relative change between the groups was not significant. Plasma glycerol levels increased slightly in the control group and decreased slightly in the calorie-restricted group such that the differences of the changes between the groups was statistically significant ($P < 0.04$), an effect opposite to that expected. We cannot fully explain these findings but would point out that the fasting blood samples were collected after only a 9-h overnight fast, precluding observation of changes that might have been more pronounced and uniform after a 14- to 18-h fast (28). In contrast, circulating levels of β-hydroxybutyrate increased almost threefold in the calorie-restricted group, whereas there was no significant change in the control group. This striking difference between behaviors of glycerol, free fatty acids, and β-hydroxybutyrate suggests that the observed ketonemia may be more closely linked to the rate of hepatic ketogenesis than to lipolysis.

Not surprisingly, ketonuria was more pronounced in the calorie-restricted group. The group mean value doubled after the initiation of calorie restriction, and all individuals had some increase in ketonuria. Thus, with a diet of ~1200 kcal/day, a significant increase in ketonuria was clearly detected after a 9-h overnight fast under carefully controlled metabolic ward conditions. This observation is in strong contrast to previous studies in which either no comment was made regarding ketonuria (12,16), urine was tested but ketonuria was not detected (11,15), or only a small portion of gestational diabetic subjects on a 1000-kcal/day diet had ketonuria, and this proportion was not significantly different from the proportion that had ketonuria on a more liberal calorie intake (13,14).

The biological significance of ketonemia and ketonuria increases during pregnancy is still uncertain. In absolute terms, the ketone body concentrations are well below the level that would have measurable effects on acid-base balance. Regarding infant outcome, the initial observation by

Churchill and Berendes (35) that offspring of mothers with acetonuria late in pregnancy had lowered IQ scores has been refuted largely on methodological grounds (36) and by further studies showing that ketonuria is a sporadic occurrence during many normal pregnancies (37). However, more recent work has shown deleterious effects of ketone bodies on in vitro embryogenesis (38) and that offspring of mothers with gestational diabetes may indeed have abnormalities of psychomotor development (39).

The diet used in this trial closely resembles that used in three earlier studies that were not randomized, did not contain appropriate controls, did not give pre- and postintervention data, and were not conducted on a metabolic ward (12–14). Thus, we had somewhat different results than previous studies. Recent work has generally had better study designs, has been prospective, and has contained arguably appropriate controls. These latter studies have used diets supplying 1500–1800 kcal/day and have shown improvement of glycemic status without increased ketonuria or profound ketonemia (15,16). In the interim, until further data are available, recommendations for the management of obese patients with gestational diabetes by calorie restriction must remain guarded, because there has not been a well-conducted group of studies showing that morbidity is significantly altered by such interventions. Conversely, a few studies have now appeared showing that various insulin regimens decrease the morbidities associated with these pregnancies (9,10). Further research is required to study the relative benefits of dietary regimens versus insulin on metabolic parameters and obstetric outcome both in small well-defined populations and in epidemiological or population-based studies. Until the results of such studies are available, physician judgment must balance the relative benefits versus encumbrances of diet or insulin therapy for the management of gestational diabetes.

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