GESTATIONAL DIABETES REVERSES THE CIRCADIAN VARIATION OF PLASMA INSULIN RESPONSE TO INTRAVENOUS GLUCOSE

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Gestational diabetes reverses the circadian variation of plasma insulin response to intravenous glucose

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Both healthy third-trimester pregnant women and a group of women with gestational diabetes failed to show a difference in glucose clearance rates when given an intravenous glucose bolus at 8 AM compared with 4 PM. The plasma insulin response in the healthy pregnant women was greater at 8 AM. In the diabetic group, the peak insulin response was greater at 4 PM, but it was more prolonged after the 8 AM tests. These alterations in plasma insulin response were especially striking in the subgroup of obese women with gestational diabetes, who demonstrated metabolic differences compared with their nonobese counterparts. (AM J OBSTET GYNECOL 1988;159:607-11.)

Key Words: Gestational diabetes, intravenous glucose tolerance, circadian variation, plasma insulin responses

Human plasma insulin response to an oral or intravenous stimulus is known to exhibit a circadian variation or rhythm. Numerous studies have shown a higher plasma insulin response to a glucose challenge in tests performed in the morning compared with those done in the afternoon or evening.[1, 2] This enhanced insulin response is typically accompanied by faster clearance of the circulating plasma glucose.

Examples of this phenomenon from data previously published from our laboratory[3] are shown in Figs. 1 and 2, in which the results of 26 pairs of intravenous glucose tolerance tests performed at 8 AM and, on separate days, at 4 PM are shown. The plasma insulin response to the morning test shows an enhanced response compared with the afternoon test. This higher morning insulin response is accompanied by faster clearance of glucose from the plasma compared with the afternoon test (Fig. 2).

Because alterations of metabolism may change usual chronobiologic relationships,[1] we performed the following study to examine differences in plasma insulin response related to the time of day in a group of clinically healthy third-trimester pregnant women and in a group of women with gestational diabetes mellitus.

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Methods

Subjects. Ten pregnant volunteers were studied in the third trimester (32 to 34 weeks' gestation). All had been screened for glucose intolerance and had plasma glucose concentrations <100 mg/dl in the fasting state and <135 mg/dl 1 hour after a 50 gm oral glucose drink. No high-risk pregnancy factors were known to exist.

A second group of subjects consisted of 10 pregnant women in the third trimester (32 to 34 weeks' gestation) who demonstrated abnormal glucose tolerance based on 3-hour oral test and a 100 gm glucose drink. The criteria of the National Diabetes Data Group[4] were used to interpret the results of these tests; two abnormal values indicated an abnormal test result.

All subjects delivered healthy infants. One infant of a patient in the gestational diabetes group was delivered preterm and weighed 2070 gm; another infant in that group was large for gestational age and weighed 4657 gm.

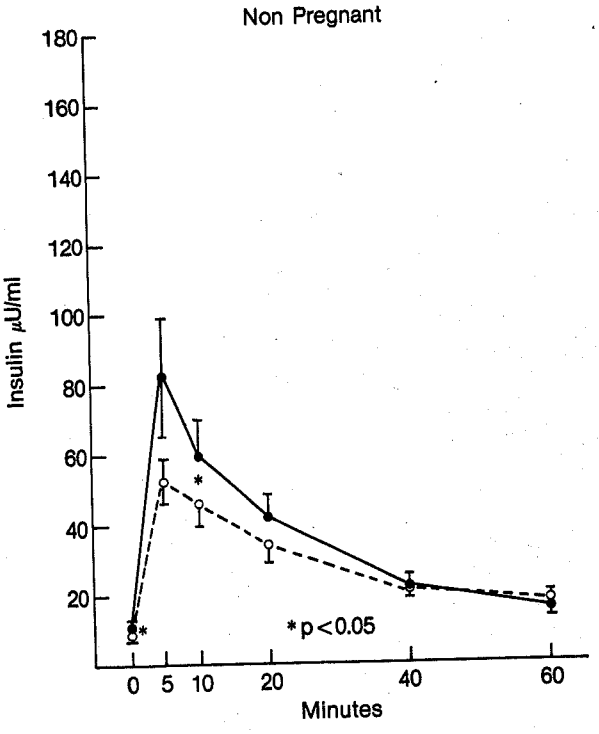

Fig. 1. Mean (±SEM) plasma insulin response to an intravenous glucose bolus given at 8 AM *(solid line)* or at 4 PM *(dashed line)* in a group of clinically healthy nonpregnant subjects.

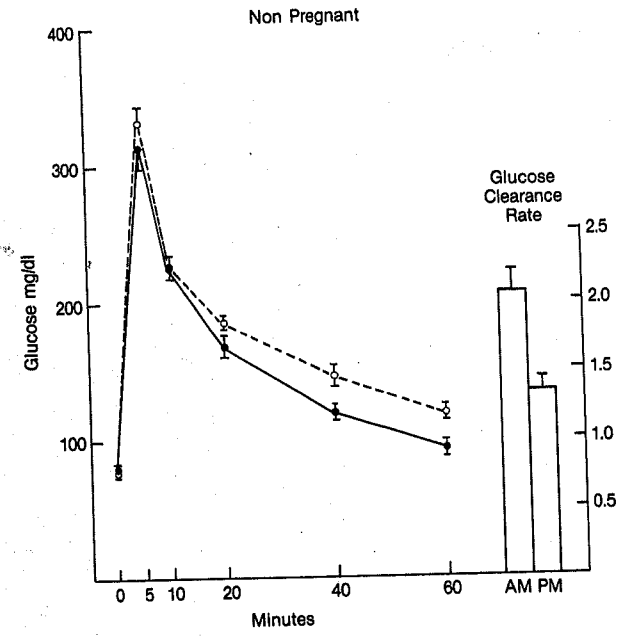

Fig. 2. Mean (±SEM) plasma glucose concentrations after an intravenous glucose bolus given at 8 AM *(solid line)* compared with 4 PM *(dashed line)* in a group of clinically healthy nonpregnant subjects. Glucose clearance rates (shown in graphs on right) were more rapid after the AM tests ($p < 0.005$).

The subjects consented to participate in the study and signed a form approved by the institution's Clinical Research Practices Committee.

Testing protocol. Intravenous glucose tolerance tests were performed at 8 AM and 4 PM on separate days 1 week apart after similar fasts of approximately 8 hours. Blood was drawn from an antecubital vein before and at 5, 10, 20, 40, and 60 minutes after the injection of 25 gm of glucose. The subjects maintained their usual times of sleeping. Activity before the test was not restricted.

Assays. Blood was centrifuged promptly and plasma aliquots were stored frozen until analyzed. Glucose was analyzed with a Beckman glucose analyzer. Plasma insulin was measured by specific radioimmunoassay[5] with commercially available reagents. Morning and afternoon samples from each individual were analyzed in the same assay.

Statistical methods. Comparisons between morning and afternoon values were made by paired *t* tests. Glucose clearance rates were calculated by linear regression analysis of log glucose values. Comparisons of the glucose clearance values between different groups were made by the Mann-Whitney test for independent groups. Comparisons between morning and afternoon total insulin response were made by the sign test.

Results

Plasma insulin responses in the clinically healthy pregnant women were enhanced compared with nonpregnant subjects (Fig. 3). The usual circadian variation was present, as plasma insulin concentrations were greater in morning tests than afternoon tests in the 40-minute samples. Furthermore, the overall insulin response as evaluated by the sign test was higher in morning than afternoon tests.

Plasma glucose values in these subjects are shown in Fig. 4. Fasting plasma glucose concentrations tended to be lower in morning than in afternoon tests ($p = 0.06$). After the intravenous glucose bolus, plasma glucose concentrations were similar in morning and afternoon tests. Glucose clearance rates (Table I) did not differ by time of day of test and were in a similar range to those seen in nonpregnant subjects.

The plasma insulin response in the group of women with gestational diabetes (Fig. 5) was in a range similar to that of the healthy pregnant women. The usual pattern of circadian variation was not seen in these subjects; in contrast, they showed higher plasma insulin concentrations after the afternoon tests compared with morning tests in the 10-minute samples. The morning insulin response was more prolonged, however, and resulted in higher morning than afternoon insulin con-

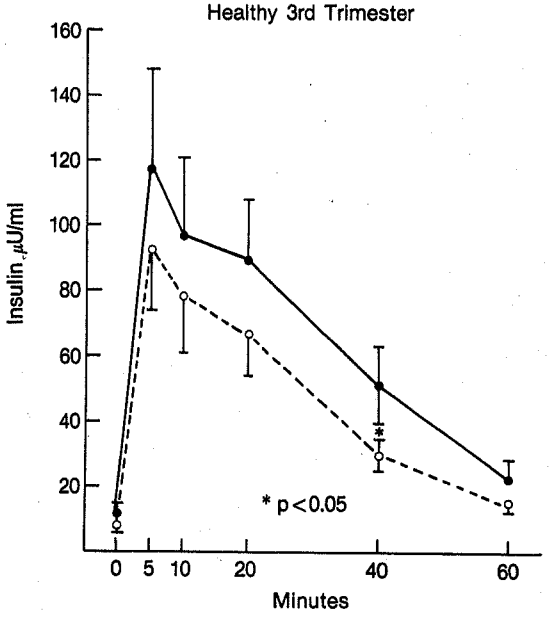

Fig. 3. Mean (±SEM) plasma insulin response to an intravenous glucose bolus given at 8 AM *(solid line)* or at 4 PM *(dashed line)* in a group of clinically healthy third-trimester pregnant women.

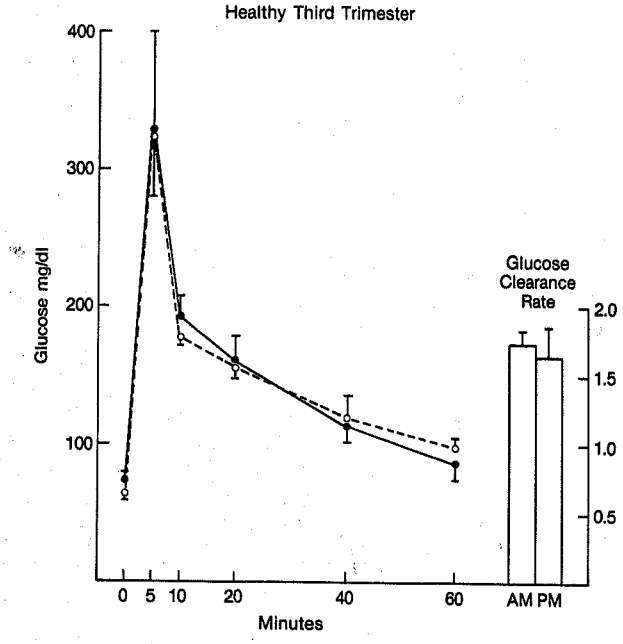

Fig. 4. Mean (±SEM) plasma glucose concentrations after an intravenous glucose bolus given at 8 AM *(solid line)* or at 4 PM *(dashed line)* in a group of clinically healthy third-trimester pregnant women.

centrations at 60 minutes. Overall insulin response did not differ by time of day of test.

The plasma glucose concentrations in these women with gestational diabetes are shown in Fig. 6 and the clearance rates are listed in Tables I and II. A trend is present for all glucose concentrations to be slightly higher in the patients with gestational diabetes than for the healthy pregnant subjects. Morning values were higher than afternoon values before and 20 minutes after the intravenous glucose bolus. No difference is seen in glucose clearance rates by time of day of test. As seen in Table II, of the 20 intravenous glucose tolerance tests in this group of subjects with abnormal oral glucose tolerance, only two tests showed grossly abnormal clearance rates <1.0, and only three tests showed rates <1.20. All three of these results were from the morning tests.

Because obesity is known to strongly influence metabolic processes, we examined the pregnant subjects for the presence or absence of obesity, based on the body mass index calculated at the first prenatal visit. All clinically healthy subjects had a body mass index ≤26, values less than those considered obese. Five of the women with gestational diabetes had body mass index values ranging from 19.3 to 22.8 (nonobese), and five had values ranging from 29.7 to 41.5 (obese).

The plasma insulin responses of the nonobese subjects are shown in Fig. 7. No difference is seen between morning and afternoon tests. In contrast, the plasma insulin responses in the obese women with gestational diabetes (Fig. 8) clearly show the differences between morning and afternoon tests seen earlier in the pooled data.

Table I. Comparisons of glucose clearance between normal and diabetic pregnant women

	Normal	*Women with diabetes*	p *value*
8 AM	1.73 ± 0.40	1.38 ± 0.43	NS
4 PM	1.65 ± 0.64	1.62 ± 0.15	NS

Data are the mean ± SD.

Comment

Although the circadian rhythmicity of glucose clearance and insulin response has been the subject of a number of studies, few studies have examined the effect of pregnancy on these relationships. Both Zulli et al.[6] and Tandon et al.[7] report an inability to detect a circadian variation in blood glucose levels in oral glucose tolerance tests in the morning compared with those in the afternoon. Zulli et al. also measured the plasma insulin response and found an enhanced insulin response in morning compared with afternoon tests, with both morning and afternoon responses greater in pregnant women than in nonpregnant controls. Our subject's responses to an intravenous glucose challenge are

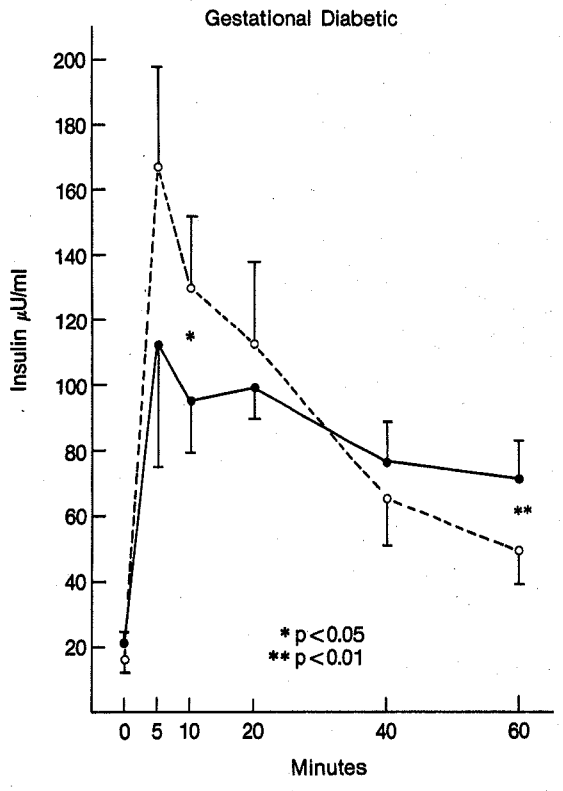

Fig. 5. Plasma insulin response to an intravenous glucose bolus given at 8 AM *(solid line)* or at 4 PM *(dashed line)* in a group of third-trimester women with gestational diabetes.

Table II. Glucose clearance rates of subjects with gestational diabetes

	8 AM	*4 PM*
Nonobese women		
1	1.48	1.73
2	1.87	1.50
3	2.11	1.44
4	0.77	1.75
5	1.20	1.69
Obese women		
1	1.57	1.57
2	1.63	1.37
3	0.88	1.62
4	1.24	1.62
5	1.05	1.88

consistent with these previous reports, with no circadian variation seen in glucose clearance but with an enhanced insulin response in the morning test.

In the group of women who had abnormal oral glucose tolerance, only three results of the battery of 20 intravenous glucose tolerance tests were clearly abnormal (glucose clearance <1.2). Thus, in these patients, the results of oral and intravenous glucose tolerance tests did not agree. A previous study by Benjamin and Casper[8] found a lack of agreement between oral and intravenous glucose tolerance data in pregnancy and

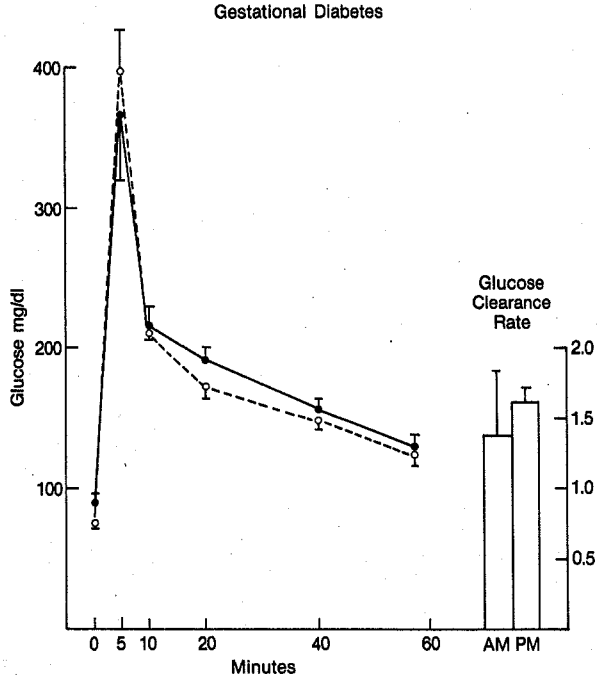

Fig. 6. Plasma glucose concentrations after an intravenous glucose bolus given at 8 AM *(solid line)* or at 4 PM *(dashed line)* in a group of third-trimester women with gestational diabetes.

suggested the intravenous glucose tolerance test is less sensitive than the oral glucose tolerance test in detecting early metabolic disturbances.

Published results do not agree concerning insulin response to a glucose challenge in patients with gestational diabetes. Some authors find a diminished plasma insulin response compared with healthy pregnant controls,[9-12] whereas others report no differences[7, 13] or even an enhanced response[14, 15] in women with gestational diabetes. The testing protocols and the selection of subjects in these studies vary widely. This lack of uniformity makes attempts at drawing conclusions difficult. Most of these studies did not compare obese versus nonobese subjects and most performed tests at an unspecified time of day (presumably in the morning). The differences observed in insulin response in our subjects depending on time of day of test and presence or absence of obesity suggest that these differences must be considered in testing protocols and may in part explain the differences described in the literature.

Recent studies by Catalano et al.[16] with the euglycemic glucose clamp technique in nonpregnant subjects who had gestational diabetes in a previous pregnancy showed enhanced insulin response and greater insulin resistance in obese subjects compared with nonobese women.

Further examination is needed of time of day–

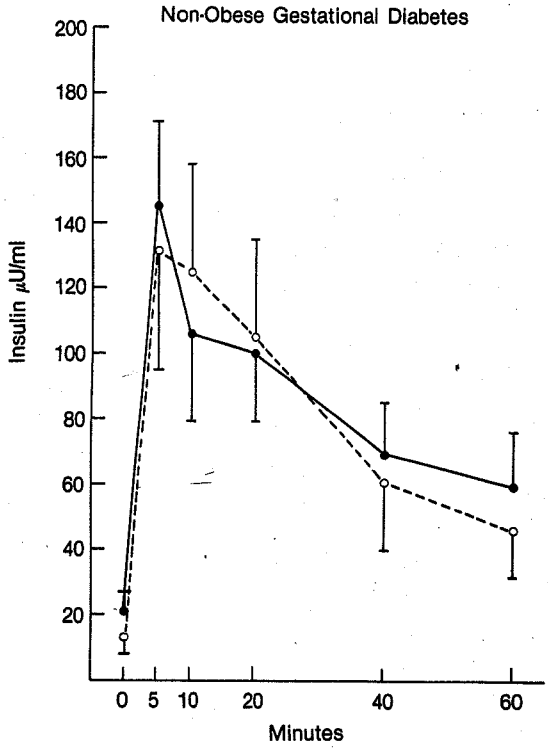

Fig. 7. Plasma insulin response to an intravenous glucose bolus given at 8 AM *(solid line)* or at 4 PM *(dashed line)* in the subgroup of women with gestational diabetes who were not obese.

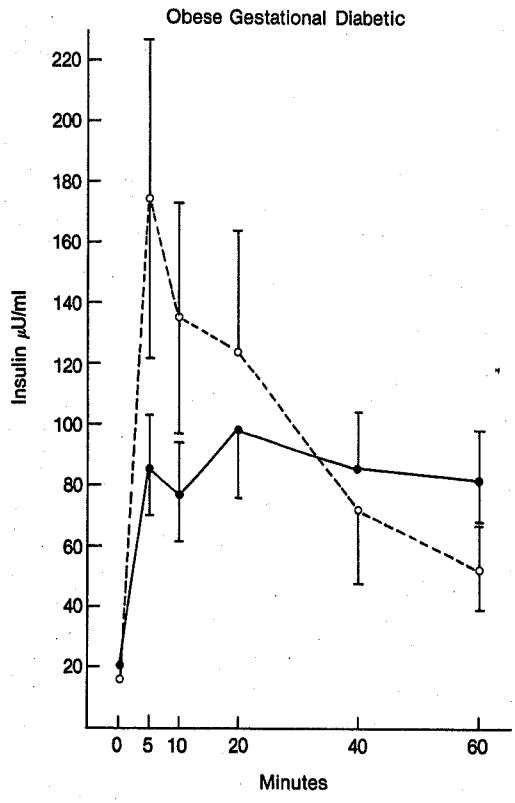

Fig. 8. Plasma insulin response to an intravenous glucose bolus given at 8 AM *(solid line)* or at 4 PM *(dashed line)* in the subgroup of women with gestational diabetes who were obese.

related metabolic differences in obese women with gestational diabetes. Confirmation of an altered response to oral feeding as well as that seen to an intravenous glucose bolus may result in clinically useful information, which may suggest alterations in meal timing or meal content to provide the optimal maternal and fetal metabolic environment for a healthy pregnancy outcome.

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