Insulin Secretion in Insulin-Resistant Women With a History of Gestational Diabetes

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Women with a history of gestational diabetes mellitus (GDM) tend to be insulin-resistant and hyperinsulinemic and are predisposed to the subsequent development of non–insulin-dependent diabetes mellitus (NIDDM). In the evolution of glucose intolerance, the first clinically detectable abnormality has not been defined and the relative importance of contributions of abnormal insulin secretion and insulin resistance is controversial. The present study was performed to evaluate the insulin secretory responses to oral and intravenous glucose and to mixed meals in women with a history of GDM, and to determine if the hyperinsulinemia present in these subjects is appropriate for the degree of insulin resistance. To address these questions, we studied the insulin secretory responses to oral glucose over a 3-hour period and to three mixed meals over a 24-hour period, and quantified the acute insulin response to glucose ($AIR_{glucose}$) and insulin sensitivity (S_I) during frequently sampled intravenous glucose tolerance tests (FSIVGTTs). Studies were performed in seven subjects with a history of GDM and in seven matched controls. Insulin secretion rates (ISRs) were derived by deconvolution of peripheral C-peptide values using a two-compartment model and standard C-peptide kinetic parameters. Subjects with a history of GDM demonstrated (1) impairment in S_I (2.15 ± 0.49 *v* $4.40 \pm 0.56 \times 10^{-5} \cdot min^{-1} \cdot [pmol/L]^{-1}$, $P < .02$); (2) an inappropriately low $AIR_{glucose}$ for the prevailing S_I (percentile rank, 15.3% ± 7.4% *v* 62.6% ± 14.3%, $P < .02$); (3) basal glucose and insulin values that were not significantly elevated; (4) increased plasma glucose during a 24-hour meal study accompanied by increased serum insulin and ISR; and (5) normal temporal profiles of meal responses including normal ultradian insulin secretory oscillations, normal insulin clearance, and normal proinsulin to insulin molar ratio.
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A SIGNIFICANT PROPORTION of women with a history of gestational diabetes mellitus (GDM) will eventually develop non–insulin-dependent diabetes mellitus (NIDDM), particularly if they are obese.[1] The relative importance of abnormal insulin secretion and insulin resistance in the pathogenesis of NIDDM is controversial.[2] The normal β cell can increase insulin secretion in response to insulin resistance and thereby maintain normal glucose tolerance. Buchanan et al[3] have demonstrated that women with GDM fail to increase insulin secretion appropriately for the degree of insulin resistance. Previous studies have reported decreased first-phase insulin secretion after intravenous glucose in subjects with a personal history of GDM, and a lower index of insulin sensitivity (S_I). Insulin response to arginine at all glucose levels has been reported to be normal.[4] Previous mixed-meal studies in subjects with NIDDM have demonstrated delayed and decreased insulin secretory responses, with profound alteration in the temporal organization of stimulated insulin secretion.[5] Subjects with functional ovarian hyperandrogenism who are at increased risk for development of NIDDM have attenuated secretory responses to mixed meals and a reduction in amplitude of the meal-related secretory pulses, resembling the pattern of NIDDM.[6] Gumbiner et al[7] demonstrated physiologic hyperinsulinemia secondary to increased insulin secretion rather than decreased insulin clearance in elderly subjects in response to mixed meals.

The present study was undertaken to evaluate β-cell function and insulin action in a group of subjects with a recent history of GDM who did not have impaired glucose tolerance or NIDDM according to National Diabetes Data Group (NDDG) criteria[8] at the time of study. Patterns of insulin secretion over 3 hours in response to oral glucose and over 24 hours in response to three mixed meals were characterized, and the response to intravenous glucose was defined by use of the frequently sampled intravenous glucose tolerance test (FSIVGTT). Insulin secretion rates (ISRs) were measured by deconvolution of peripheral C-peptide levels. These procedures facilitated assessment of pancreatic insulin production, insulin clearance, and S_I, thereby allowing us to determine the relationship between potential defects in these parameters.

SUBJECTS AND METHODS

Subjects

Studies were performed in seven women with documented histories of GDM and in seven controls matched for weight, age, sex, and race. Their clinical and laboratory characteristics are listed in Table 1. Subjects had been given 100-g oral glucose tolerance tests (OGTTs) during weeks 24 to 33 of gestation and had been diagnosed as having GDM according to NDDG criteria.[8] Five were treated with diet and two with insulin during their pregnancy. Control subjects had no history of glucosuria during pregnancy, infant macrosomia, or diabetes in siblings or parents. None of the controls had a history of GDM (all were screened with a 50-g oral glucose load, and 1-hour glucose levels were normal). All studies were performed between 2 and 6 months postpartum and during the follicular phase of the menstrual cycle. None of the subjects were breast-feeding, nor were they taking oral contraceptives or any other medications. The protocols were approved by the Institutional Review Board, and written informed consent was obtained.

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Table 1. Clinical Characteristics of GDM Subjects and Controls

	GDM Subjects	Controls	*P*
Age (yr)	29.4 ± 2.9	29.0 ± 5.9	NS
Weight (kg)	82.4 ± 10.0	86.4 ± 5.6	NS
Body mass index (kg/m²)	31.1 ± 3.2	31.7 ± 1.5	NS
Body surface area (m²)	1.86 ± 0.1	1.94 ± 0.1	NS

Experimental Protocol

Studies were performed beginning at 8 AM with subjects in the recumbent position after a 12-hour overnight fast. An intravenous catheter was placed in each forearm, one for blood sampling and one for glucose administration. In all experiments, the arm containing the sampling catheter was maintained in a heating blanket to ensure arterialization of the venous sample.

OGTT

On one occasion, after two baseline samples were obtained, each subject ingested 75 g glucose at time 0 minutes as a lemon-lime–flavored solution (Baxter, Deerfield, IL). Blood samples were then drawn at 30-minute intervals for 180 minutes for glucose, C-peptide, and insulin determinations.

24-Hour Study With Mixed Meals

On a separate occasion, after a 12-hour overnight fast, blood samples for glucose, insulin, and C-peptide were collected at 20-minute intervals from an indwelling sampling catheter for a 24-hour period beginning at 8 AM. Proinsulin samples were drawn from 8 AM to 2 PM. Meals were presented at 10 AM, 2 PM, and 7 PM and were consumed within 20 minutes. The diet consisted of 30 cal/kg/24 h with 50% carbohydrate, 15% protein, and 35% fat. Twenty percent of the total calories were eaten at breakfast and 40% at lunch and at dinner.

IVGTT

After baseline samples were drawn at −20, −15, −10, and −5 minutes, 50% intravenous dextrose at a dose of 300 mg/kg body weight was injected smoothly over 60 seconds, starting at time zero. Blood samples were obtained at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 24, 25, 27, 30, 40, 70, 90, 100, 120, 140, 160, and 180 minutes thereafter. Orinase 125 mg/m² was injected at 20 minutes. Samples were collected within 15 seconds, and great care was taken to avoid contamination with saline or blood from previous samples.

Analytical Methods

Glucose, Insulin, C-peptide, and Proinsulin Assays

Plasma glucose levels were measured by the glucose oxidase technique (semiautomatic YSI analyzer, Model 2300 STAT; Yellow Springs Instrument, Yellow Springs, OH). The coefficient of variation of this method is less than 2%. Serum insulin was assayed by a double-antibody technique[9] with a lower limit of sensitivity of 20 pmol/L and an average intraassay coefficient of variation of 6%. Plasma C-peptide level was measured as previously described.[10] The lower limit of sensitivity of the C-peptide assay is 0.02 pmol/mL, and the intraassay coefficient of variation averaged 6%. Proinsulin level was measured by a sensitive proinsulin enzyme-linked immunosorbent assay,[11,12] in which insulin and C-peptide do not cross-react. The two major proinsulin conversion products (Des 31,32 and Des 64,65 proinsulin) demonstrate 100% cross-reactivity in the assay in relation to proinsulin. Thus, proinsulin concentration measured in this assay reflects the combined concentrations of proinsulin and its conversion intermediates. Biosynthetic human proinsulin was used as the assay standard.[11] All samples were measured in duplicate.

Data Analysis

OGTT

Integrated glucose, insulin, and C-peptide responses to the OGTT were calculated as the incremental area under the curve (AUC) for 3 hours postingestion of glucose, ie, from 0 to 180 minutes.

24-Hour Study With Mixed Meals

ISRs. Standard kinetic parameters for C-peptide clearance that account for age, sex, and body surface area were used.[13] These parameters were used to derive, in each 20-minute interval between blood sampling, ISR from plasma C-peptide concentrations by deconvolution as previously described.[14,15]

Fasting, 24-hour, and postmeal insulin secretion. Fasting ISR (picomoles per meter squared per minute) was defined as the mean ISR during the period of 8 to 10 AM. Basal insulin secretion over the 24-hour period was derived by extrapolating the fasting ISR over 24 hours. Total daily insulin secretion (nanomoles per meter squared per 24 hours) was calculated as the area under the 24-hour profiles of instantaneous ISRs. The insulin secretory response to each meal was calculated as the incremental AUC above baseline for the 4 hours after each meal. To evaluate possible differences in the dynamics of insulin secretion after breakfast, lunch, and dinner, respectively, the incremental AUC above baseline was also calculated for each hour after meal ingestion.

Pulses of insulin secretion. Each individual 24-hour profile of ISR was analyzed using Ultra, a computer algorithm for pulse identification.[16] Peaks of insulin secretion in the time series were considered true secretory pulses if both the increment and decrement exceeded three times the measurement error of the C-peptide assay. Previous studies have shown that such a detection limit results in a false-positive rate of less than 1% and thus minimizes the impact of any cumulative error resulting from deconvolution.[16] The relative amplitude of these pulses was calculated by dividing the absolute amplitude of each individual pulse by the value at the preceding trough.

Metabolic clearance rate of insulin. In this study, the metabolic clearance rate (MCR) of insulin under basal conditions was defined in each subject as the ratio of the fasting ISR and the simultaneously measured peripheral insulin concentration. Under the conditions of mixed meals, insulin clearance was calculated as the ratio of the area under the 24-hour ISR curve to the area under the peripheral insulin concentration curve.[17]

Minimal Model Analysis of the FSIVGTT

Basal insulin and glucose levels were calculated as the mean of the four prestimulus levels. The acute insulin response to glucose ($AIR_{glucose}$) was calculated as the mean increment above basal of insulin values measured at 2, 3, 4, 5, 6, 8, and 10 minutes. S_I and glucose effectiveness were calculated by the minimal model technique[18] using the MINMOD program kindly provided to us by Dr Bergman.

Percentile ranking for the relationship between S_I and $AIR_{glucose}$ was calculated from the equation $Z\alpha = [\ln(S_I \times 10^{-5} \times AIR_{glucose}) + 3.802]/0.5613$ as described by Kahn et al.[19] With knowledge of S_I and $AIR_{glucose}$, the equation is used to calculate a $Z\alpha$ value and then determine the percentile ranking of that individual or group from the tables of normal distribution.[19]

Statistical Tests

Repeated-measures ANOVA and unpaired t test were used where appropriate using the Statistical Analysis System (SAS Version 6 for personal computers; SAS Institute, Cary, NC).

RESULTS

OGTT

Results of the OGTT are depicted in Fig 1. Fasting plasma glucose concentrations were similar in subjects and controls (5.35 ± 0.22 *v* 5.16 ± 0.10 mmol/L, $P > .44$). After glucose ingestion, two subjects had normal glucose tolerance and five subjects had nondiagnostic OGTTs according to NDDG criteria.[8] All the controls had normal OGTTs. The incremental AUC for glucose from 0 to 180 minutes was significantly greater in subjects with a history of GDM (462 ± 42 *v* 208 ± 35 mmol/L · min, $P < .0007$). In the basal state, plasma insulin (147 ± 28 *v* 106 ± 15 pmol/L, $P > .2$) and C-peptide (0.67 ± 0.1 *v* 0.58 ± 0.1 pmol/mL, $P > .4$) levels were not significantly different. After glucose ingestion, plasma insulin responses (incremental AUC) in subjects with a history of GDM increased to values approximately double those of controls (98,900 ± 14,300 *v* 49,400 ± 8,000 pmol/L · min, $P < .02$). Plasma C-peptide response (incremental AUC) was also elevated in subjects as compared with controls (246 ± 15 *v* 175 ± 17 pmol/mL · min, $P < .01$).

24-Hour Meal Study With Mixed Meals

Basal and 24-hour levels of glucose, insulin, proinsulin, C-peptide, and ISR. The mean profiles of plasma glucose, insulin, C-peptide, and ISR are shown in Fig 2. Under basal conditions, these parameters tended to be higher in the GDM group, but most differences were not statistically significant (Table 2). Basal insulin secretion represented 48.5% ± 2.9% of total 24-hour insulin secretion in GDM subjects and 47.7% ± 1.8% in controls ($P > .8$). Because of large within-group variability, differences in mean basal proinsulin were not significant between subjects and controls (9.4 ± 3.7 *v* 5.1 ± 1.4 pmol/L, $P > .3$). Furthermore, the mean basal proinsulin to insulin ratio did not differ between subjects and controls (7.1% ± 1.8% *v* 6.1% ± 1.3%, $P > .6$). Mean 24-hour glucose levels were significantly higher in subjects as compared with controls, and this was associated with higher 24-hour mean levels of insulin and C-peptide and with increased total secretion of insulin (Table 2). Mean proinsulin levels in the 4-hour period after breakfast tended to be higher in the subjects (37.5 ± 10.2 *v* 18.2 ± 2.9 pmol/L, $P > .1$), but this was not associated with a significant increase in proinsulin to insulin molar ratio (12.2% ± 3.3% *v* 9.0% ± 0.5%, $P > .3$) in this group.

Meal-induced insulin secretion. Insulin secretory responses to breakfast (51.6 ± 7.1 *v* 37.8 ± 4.5 nmol, $P > .12$), lunch (73.4 ± 10.3 *v* 54.8 ± 6.1, $P > .14$), and dinner (64..1 ± 10.0 *v* 52.1 ± 4.3, $P > .3$) as determined by the incremental areas under insulin secretion curves above baseline in the 4 hours after meals were not significantly different between subjects and controls. Hourly insulin secretory responses after each meal also were not significantly different between the two groups by repeated-measures ANOVA (data not shown).

Relationship between glucose and ISR during 24-hour meal study. To investigate the relationship between glucose and ISR during the 24-hour meal study, mean values of ISR were plotted against corresponding mean values of glucose for both groups (Fig 3). Although ISR generally was higher in GDM subjects (Table 2), when set in relation to the prevailing glucose concentration, the best-fit lines obtained by linear regression analysis were superimposable.

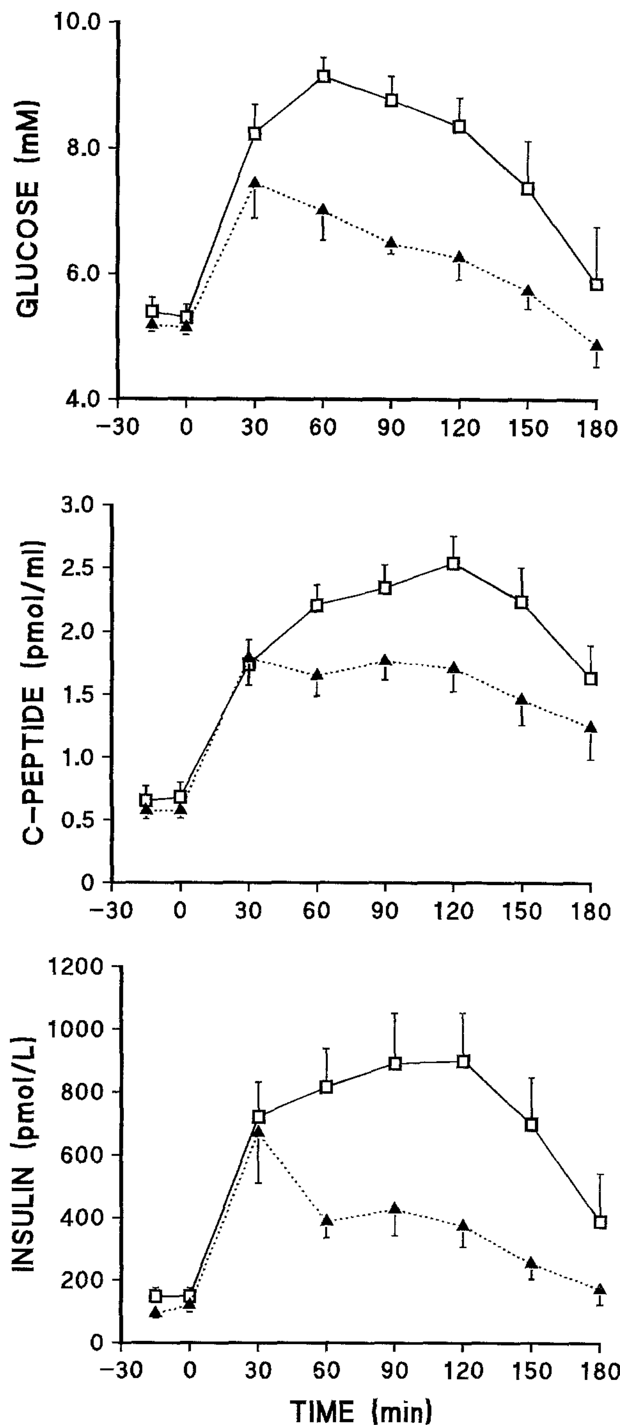

Fig 1. Glucose, C-peptide, and insulin during OGTT in controls (▲, n = 7) and subjects with a history of GDM (□, n = 7). Time zero corresponds to the time of glucose ingestion.

Pulses of insulin secretion. Each 24-hour profile of ISR was submitted to formal pulse analysis. For controls, on average, 12.1 ± 0.7 pulses of insulin secretion were identified, and this was not different from the corresponding value in GDM subjects (12.6 ± 0.7, $P > .6$). In controls,

Fig 2. Twenty-four-hour profiles of (A) glucose and C-peptide and (B) insulin and ISR on a weight-maintenance diet in controls (▲, n = 7) and subjects with a history of GDM (□, n = 7). Breakfast, lunch, and dinner were presented at 10 AM, 2 PM, 7 PM, respectively.

8.4 ± 0.5 pulses were meal-related and occurred between 10 AM and midnight; the remainder (3.7 ± 0.5) occurred between midnight and 10 AM. GDM subjects showed a similar temporal distribution of secretory pulses, with 8.9 ± 0.6 meal-related pulses ($P > .5$) and 3.7 ± 0.4 non-meal-related pulses ($P > .9$). The relative amplitudes of meal-related (2.18 ± 0.43 *v* 2.36 ± 0.31, $P > .7$) and non-meal-related (0.39 ± 0.03 *v* 0.43 ± 0.04, $P > .5$) pulses were also similar in GDM and control groups, respectively.

Table 2. 24-Hour Studies With Mixed Meals in GDM Subjects and Controls

Study period	GDM Subjects	Controls	P
Basal period (8 to 10 AM)			
Insulin (pmol/L)	130.2 ± 26.8	75.9 ± 6.8	>.09
Glucose (mmol/L)	5.43 ± 0.21	5.15 ± 0.12	>.27
C-peptide (pmol/mL)	0.64 ± 0.09	0.47 ± 0.03	>.11
ISR (pmol/m²/min)	85.0 ± 10.5	57.7 ± 4.7	<.04
24-Hour study			
Insulin (pmol/L)	356.1 ± 54.1	216.3 ± 28.7	<.05
Glucose (mmol/L)	6.06 ± 0.18	5.45 ± 0.12	<.02
C-peptide (pmol/mL)	1.35 ± 0.13	0.96 ± 0.07	<.03
ISR (nmol/m²/24 h)	252.7 ± 24.4	175.1 ± 14.0	<.02

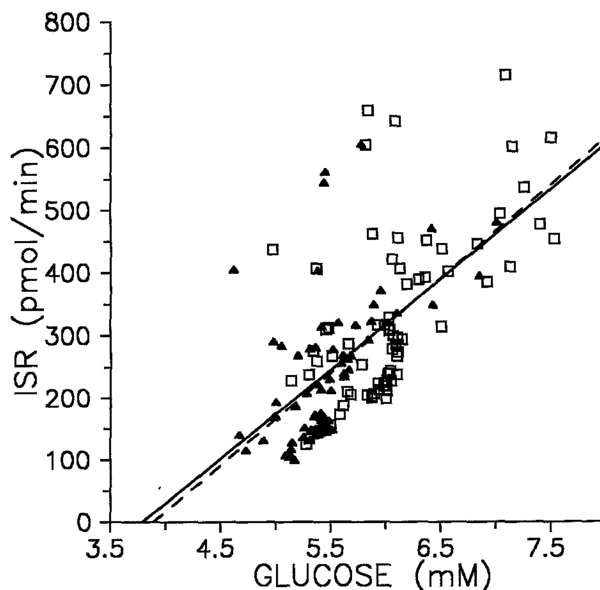

Fig 3. Mean ISR from 24-hour meal studies plotted against corresponding mean levels of glucose in controls (▲, n = 7) and subjects with a history of GDM (□, n = 7). Best-fit lines to data in controls (----) and GDM subjects (———) are also indicated.

Clearance of endogenous insulin. Endogenous insulin clearance was calculated under basal conditions and during the entire 24-hour study period. The basal endogenous MCR of insulin was 1.4 ± 0.2 L/min in the GDM group and 1.4 ± 0.2 in the control group ($P > .8$). Over the 24-hour period, MCR was also similar in the two groups (1.0 ± 0.1 *v* 1.1 ± 0.1 L/min, $P > .4$).

Responses During FSIVGTT

Mean profiles of plasma glucose, C-peptide, and insulin during the FSIVGTT are shown in Fig 4. During the FSIVGTT, the incremental AUC for glucose from 0 to 10 minutes after glucose injection was similar in subjects with GDM and controls (78 ± 5 *v* 80 ± 6 mmol/L · min, $P > .7$). $AIR_{glucose}$ tended to be lower in subjects with GDM than in controls, but these differences were not statistically significant (473 ± 100 *v* 871 ± 243 pmol/L, $P > .15$).

S_I was lower in subjects with a history of GDM as compared with controls (2.15 ± 0.49 *v* $4.40 \pm 0.56 \times 10^{-5} \cdot \text{min}^{-1} \cdot [\text{pmol/L}]^{-1}$, $P < .02$). Figure 5 shows $AIR_{glucose}$ plotted against S_I. It can be seen that even though women with a history of GDM were significantly more insulin-resistant than controls, first-phase insulin secretion was not elevated in these subjects and tended to be decreased, particularly when viewed in relation to the prevailing insulin resistance. Thus, the percentile ranking for β-cell function was lower in the GDM group (15% ± 7% *v* 63% ± 14%, $P < .02$). Glucose effectiveness was not different in subjects with a history of GDM (0.015 ± 0.003 *v* 0.019 ± 0.004 min^{-1}, $P > .5$).

DISCUSSION

Women who have had GDM are at increased risk of developing NIDDM.[20] Rates of NIDDM reported worldwide in women with prior GDM vary considerably (from 6% to 62% as reviewed by O'Sullivan[21] as a result of different diagnostic criteria, study populations, and follow-up durations. A 15-year follow-up study of women with previous GDM showed that the incidence of NIDDM was 47% in overweight women and 26% in normal-weight women.[1,21] The present study was undertaken to define alterations in insulin secretion, action, and clearance in women with a history of GDM. The lack of overt hyperglycemia in any subject obviated the impact of hyperglycemia on insulin secretion and insulin action. Insulin secretory responses to oral glucose, mixed meals, and intravenous glucose were measured. The use of a two-compartment model of insulin secretion allowed alterations in insulin clearance to be defined, and application of Bergman's minimal model allowed differences in S_I and glucose effectiveness to be identified. Our study subjects with a history of GDM included two subjects with normal glucose tolerance and five subjects who had nondiagnostic OGTTs according to NDDG criteria (impaired glucose tolerance by World Health Organization criteria[22]). In a 3- to 4-year follow-up study of GDM subjects, Persson et al[23] described an incidence of 34% for NIDDM and 22% for impaired glucose tolerance by World Health Organization criteria.

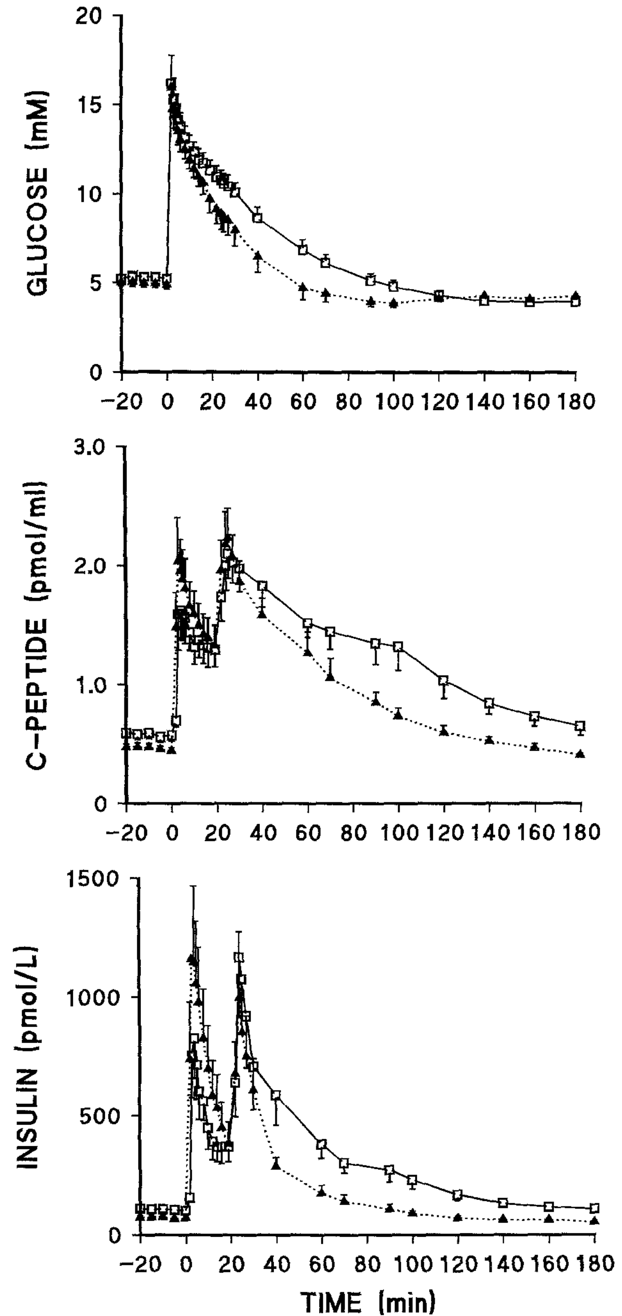

Fig 4. Glucose, C-peptide, and insulin during a FSIVGTT in controls (▲, n = 7) and subjects with a history of GDM (□, n = 7). Time zero corresponds to the time of injection of glucose.

This suggests that our subjects may have had a higher incidence of nondiagnostic OGTT postpartum, ie, 70%. Kjos et al[24] have recently proposed that AUC for glucose is highly predictive of the development of NIDDM in women with former GDM. Our group may therefore be at particularly high risk for developing NIDDM in the future.

Under basal conditions, subjects with a history of GDM had glucose, insulin, and C-peptide levels that were not significantly different from control values. However, some of these comparisons did display trends, and the relatively

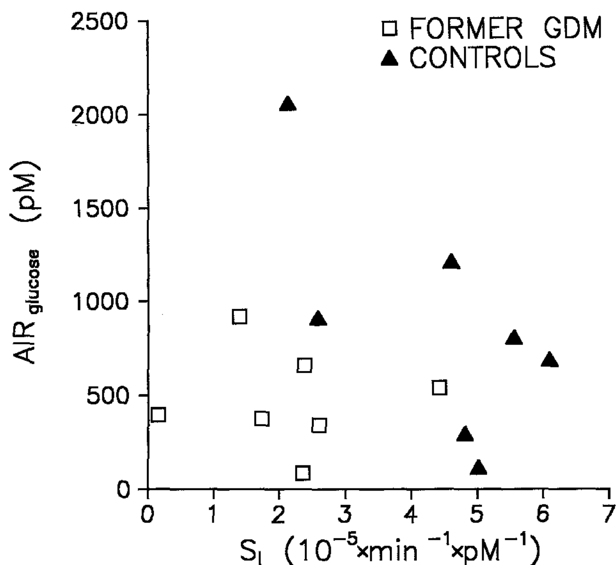

Fig 5. $AIR_{glucose}$ and S_I in controls (n = 7) and subjects with a history of GDM (n = 7).

small number of subjects perhaps concealed what would be significant differences given larger groups. However, basal ISR was elevated in GDM subjects, and after oral glucose and mixed meals they demonstrated exaggerated secretory responses with hyperinsulinemia. This was not due to alterations in insulin clearance, since these rates were not different between the two groups during the 24-hour meal study. There was also no evidence of an increased proinsulin to insulin molar ratio in the former GDM group. During the OGTT and meal study, glucose levels were higher in GDM subjects. It is known that the glucose-ISR dose-response curve is linear over the physiologic range.[25] Figure 3 demonstrates that when ISRs are related to the corresponding glucose levels, the apparent hyperinsulinemia can be fully accounted for by the slight elevation in plasma glucose. This highlights the importance of taking into account the prevailing glucose concentration when comparing ISRs or insulin levels.

After mixed-meal ingestion, temporal patterns of insulin secretory responses were characterized in detail and the nature of ultradian oscillations of insulin secretion was studied. Both of these parameters of insulin secretory function were found to be normal. These results are similar to those of Gumbiner et al[7] in elderly subjects with physiologic hyperinsulinemia, and are in contrast to the abnormalities found in subjects with NIDDM and subjects with functional ovarian hyperandrogenism.[5,6]

Analysis of glucose and insulin responses to intravenous glucose and tolbutamide using the minimal model approach demonstrated diminished tissue sensitivity to insulin in women with a history of GDM. Data were analyzed according to refinements of the minimal model approach proposed by Bergman et al[26] and modified by Kahn et al,[19] which allow determination to be made on whether the level of hyperinsulinemia present is appropriate for the degree of insulin resistance. These analyses indicated that the degree of hyperinsulinemia in women with a history of GDM was not appropriate for the degree of insulin resistance, implying that these subjects have diminished β-cell compensatory capacity. The IVGTT data demonstrate a β-cell defect in prior-GDM subjects when the glucose signal to the β cell (ie, peak glucose level after injection) is matched between groups and the effects of intergroup differences in S_I are taken into account. These results are consistent with data from previous studies that have documented insulin responses to glucose during an IVGTT that were inadequate for the degree of insulin resistance. Buchanan[27] demonstrated that women without known diabetes may develop glucose intolerance by late gestation if their pancreatic β cells are not capable of compensating for inherent insulin resistance and/or the normal insulin resistance of pregnancy. Ward et al[4] demonstrated in nonpregnant women with a recent history of GDM that β-cell function is less than expected for the degree of insulin resistance. Thus, the higher glucose levels may actually be the result of the β-cell defect in that initial insulin responses to OGTTs and meals were similar in the GDM group but should have been greater because of the relative insulin resistance in that group.

In conclusion, the present data indicate that this group of women with a history of GDM are insulin-resistant and demonstrate inappropriately low insulin responses to glucose for the degree of insulin resistance, suggesting that the predisposition of women with a history of GDM to the subsequent development of NIDDM is due to the inability of the β cell to compensate adequately for resistance to the action of insulin.

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