Pronounced Insulin Resistance and Inadequate β-cell Secretion Characterize Lean Gestational Diabetes During and After Pregnancy

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OBJECTIVE — To evaluate β-cell secretion and glucose metabolism in lean subjects with gestational diabetes mellitus (GDM) compared with that in subjects with normal pregnancy and obesity.

RESEARCH DESIGN AND METHODS — Insulin secretion, insulin sensitivity (S_I), and hepatic insulin extraction were assessed in pregnant women with GDM before and after delivery and in those with normal glucose tolerance (NGT) in comparison to healthy nonpregnant lean and obese women. Kinetic analysis of glucose, insulin, and C-peptide plasma concentrations during oral and intravenous glucose tolerance tests was performed by mathematical modeling.

RESULTS — S_I was blunted in pregnant women with GDM by 84% and in those with NGT by 66% compared with lean nonpregnant women ($P < 0.005$ vs. healthy nonpregnant lean control subjects; $P < 0.05$, GDM vs. pregnant women with NGT), whereas glucose effectiveness was decreased by 33% in both pregnant groups ($P < 0.05$ vs. healthy nonpregnant lean control subjects). Insulin secretion was 30% higher ($P < 0.05$) in subjects with GDM than in pregnant women with NGT or in nonpregnant lean women, but decreased ($P < 0.005$) when compared with obese women with a comparable degree of insulin resistance. Fractional hepatic insulin extraction was similar in both pregnant groups, being lower ($P < 0.0001$) by 30% versus nonpregnant females. β-cell sensitivity to glucose for insulin release was decreased in subjects with GDM versus pregnant women with NGT as well as nonpregnant women by 40–50% ($P < 0.01$). Twelve weeks after delivery, GDM returned to normal glucose tolerance, but S_I remained 50% lower than that in lean nonpregnant women, while β-cell sensitivity to glucose did not change ($P < 0.01$ vs. healthy nonpregnant lean control subjects).

CONCLUSIONS — Pregnancy is characterized by insulin resistance, diminished hepatic insulin extraction, and glucose effectiveness. Lean subjects with GDM are additionally characterized by having more pronounced insulin resistance and inadequate insulin secretion, which persist after delivery. Compared with other insulin-resistant prediabetic states like impaired glucose tolerance (IGT), defective insulin secretion seems to be a predominant defect in lean GDM subjects, indicating that it might represent a specific prediabetic condition.

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Abbreviations: FSIGT, frequently sampled intravenous glucose tolerance test; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; S_G, glucose effectiveness; S_I, insulin sensitivity index; WHR, waist-to-hip ratio.

Gestational diabetes mellitus (GDM) is one of the most common complications of pregnancy and frequently predictive of later maternal NIDDM (1–7). Uncomplicated pregnancy is characterized by insulin resistance and increased insulin secretion as a compensatory mechanism to maintain normal glucose tolerance (NGT) (1,8–12). An additional defect in insulin secretion is assumed to contribute to the development of GDM (1,8–10), which may be regarded as a prediabetic state (13). Studies investigating carbohydrate metabolism during pregnancy showed controversial results with regard to defects in insulin secretion or insulin action (8–12,14–17). While the insulin sensitivity index (S_I) has been shown to be reduced to the same extent in GDM and uncomplicated pregnancy (10,14), some investigators also described a more pronounced insulin resistance in GDM, which might contribute to hyperglycemia in addition to defective insulin release (12,15,16). As most studies only inferred on peripheral insulin data, prehepatic insulin secretion and the role of hepatic insulin extraction in pregnancy in humans is still unclear. In addition, only few studies tried to assess carbohydrate metabolism in the same subjects during pregnancy and after delivery to elucidate the potential reversibility of associated metabolic perturbances.

In the present study, we assessed integrated carbohydrate metabolism in lean women with uncomplicated pregnancy and with GDM by oral and intravenous glucose tolerance tests, both during pregnancy and after delivery. This approach describes the β-cell behavior under rapid and direct glucose stimulation (frequently sampled intravenous glucose tolerance test [FSIGT]) and under slower and more physiological stimulation (oral glucose tolerance test [OGTT]), which involves indirect actions of gut hormones and gastric emptying. The FSIGT minimal model (18,19) and the recently introduced OGTT model (20,21) both allow for description of prehepatic insulin secretion and hepatic insulin extrac-

Table 1—*Clinical characteristics of pregnant women with GDM and NGT at gestational weeks 26–29 compared with those of nonpregnant healthy lean control subjects*

	GDM	Pregnant women with NGT	Nonpregnant healthy lean control subjects
n	10	9	10
Age (years)	27.9 ± 1.5	27.2 ± 1.3	27.0 ± 1.3
(Preconceptual) BMI (kg/m²)	23.7 ± 0.9	23.3 ± 0.5	22.3 ± 0.8
HbA_{1c} (%)	5.4 ± 0.3*†	4.7 ± 0.1	4.5 ± 0.1
Fasting blood glucose (mmol/l)	5.21 ± 0.47*	3.97 ± 0.08‡	4.56 ± 0.23
Fasting serum insulin (pmol/l)	96.7 ± 13.0†	72.9 ± 7.2‡	50.5 ± 5.9
Fasting serum C-peptide (nmol/l)	0.86 ± 0.10*†	0.66 ± 0.06	0.64 ± 0.05

Data are means ± SE. *$P < 0.05$, GDM vs.NGT; †$P < 0.05$, GDM vs. nonpregnant healthy lean control subjects; ‡$P < 0.05$, NGT vs. nonpregnant healthy lean control subjects.

tion. The FSIGT provides a reliable measurement of S_I and glucose effectiveness (S_G) as well as first- and second-phase β-cell sensitivity to glucose (18). Analysis of data was performed by mathematical modeling already used in various metabolic disorders (21–23) and without need of administration of radioactive tracers. Comparing the magnitude, time course, and the potential reversibility of the defects in insulin secretion and insulin resistance in GDM with the data obtained in another high-risk population for NIDDM like impaired glucose tolerance (IGT) could further elucidate whether GDM may serve as a model of later NIDDM or rather represents a distinct subset of diabetes.

RESEARCH DESIGN AND METHODS

Subjects

Pregnant women were tested for IGT between the 26th and 29th gestational week at the obstetric outpatient clinic by a 50-g glucose tolerance screening test. Patients exhibiting a 1-h plasma glucose >7.8 mmol/l (140 mg/dl) were referred to the Division of Endocrinology and Metabolism for further diagnosis (OGTT, 100 g) and treatment. There were 10 pregnant women diagnosed with GDM following the criteria of O'Sullivan and of the 3rd International Workshop on Gestational Diabetes Mellitus (6) studied before institution of diet and/or insulin therapy between the 26th and 31st gestational week. In addition, nine healthy pregnant women without any risk factors, with normal screening tests (50 g), and with NGT (100 g), but matched for preconceptual BMI and age to the GDM subjects, were included in the study. All pregnant women with GDM were negative for islet cell antibodies. The data were compared with those of 10 lean and 17 obese healthy nonpregnant control subjects. The obese group consisted of eight women with NGT (obese group with NGT, age: 26.7 ± 2.1, BMI: 26.8 ± 2.8 kg/m²) and nine women with IGT (obese group with IGT, age: 28.9 ± 3.1, BMI: 27.6 ± 3.4 kg/m²). The nonpregnant lean and obese control subjects as well as the subjects with GDM after delivery were studied during the luteal phase of the menstrual cycle. Four women with GDM were still breast feeding. None of the subjects investigated reported a family history of diabetes. All subjects had normal renal and liver function, and none was taking any drug known to affect carbohydrate metabolism or oral contraceptive steroids. The study was approved by the Ethics Committee of the University of Vienna, and all volunteers gave informed consent to participate in the study. The clinical characteristics of pregnant and nonpregnant lean control women are shown in Table 1. Women with GDM were reinvestigated with oral and intravenous glucose tolerance tests for reevaluation of their metabolic state 12–16 weeks after delivery.

Tests

OGTTs and FSIGTs were performed to obtain comparable measures of the pancreatic secretory capacity and glucose metabolism under different kinds of glucose stimulation. The tests were carried out on different days in the morning after an overnight fast. Glucose, insulin, and C-peptide were measured in samples taken immediately before glucose ingestion and at 10, 20, 30, 60, 90, 120, 150, and 180 min after oral glucose administration (100 g; OGTT) and at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, 180, 210, and 240 min after glucose injection (0.3 g/kg; FSIGT). Neither tolbutamide nor exogenous insulin was administered during the FSIGT, since the insulin profile contained enough dynamics for a valid performance of the minimal model of glucose disappearance. In both tests, blood was rapidly centrifuged, and plasma glucose concentration was assessed immediately using an automated glucose analyzer (Beckman, Fullerton, CA). Insulin (Serono Diagnostics, Freiburg, Germany) and C-peptide (CIS Bio International, Cedex, France) were determined by commercially available radioimmunoassays with an interassay coefficient of variation of <5%.

Data analysis

Glucose, insulin, and C-peptide concentration data from the two tests were analyzed by means of mathematical models specifically designed for each experimental condition. In particular, the computer program MINMOD (24) provided glucose disappearance parameters by exploiting the minimal model technique on FSIGT data (18,25). FSIGT data also allowed the estimation of parameters characteristic of the β-cell secretion under a rapid and direct glucose stimulation (19). OGTT data were analyzed by a two-compartment mathematical model (20) that reconstructs the patterns per unit volume of C-peptide secretion and posthepatic insulin appearance into peripheral circulation. This model yielded figures of the β-cell function and of insulin degradation in the liver during a slow stimulation, such as that occurring after oral glucose administration. The OGTT model, implemented using PANSYM (26), has been used already in other pathological situations (21,23). A summary of all FSIGT and OGTT parameters is shown in Table 2.

Statistical methods

The measurement error, expressed as the coefficient of variation, assessed by our laboratory procedures for a single determination was ±1.5% for glucose, ±5% for insulin, and ±6% for C-peptide. Differences in mean values between the groups were tested for significance by analysis of variance and post hoc tests with Tukey's adjustment. Correlation coefficients were calculated by linear regression analysis. Differences between the pregnant and postpartum state in the patients with GDM

Table 2—*Summary of physiological parameters*

Parameter	Units	Description	Calculation
FSIGT			
S_I	$min^{-1} \cdot (\mu U/ml)^{-1}$	Insulin sensitivity index	*
S_G	min^{-1}	Glucose effectiveness	*
$CPS_{IV}(t)$	$pmol \cdot l^{-1} \cdot min^{-1}$	C-peptide secretion rate†	*
k_{CP}	min^{-1}	C-peptide fractional clearance rate	*
$IDR_{IV}(t)$	$pmol \cdot l^{-1} \cdot min^{-1}$	Posthepatic insulin appearance rate into periphery	*
Φ_1	$pmol \cdot l^{-1} \cdot min^{-1} \cdot (mg/dl)^{-1}$	Dynamic first-phase β-cell sensitivity to glucose	*
Φ_2	$pmol \cdot l^{-1} \cdot min^{-2} \cdot (mg/dl)^{-1}$	Dynamic second-phase β-cell sensitivity to glucose	*
TIS_{IV}	$nmol \cdot l^{-1}$	Total amount of insulin secreted by the β-cells in 4 h	$\int_0^{240} CPS_{IV}(t)\,dt$
H_{IV}	% of secreted hormone	Mean hepatic insulin degradation	$100 \int_0^{240} \frac{CPS_{IV}(t) - IDR}{CPS_{IV}}\,dt$
BSR_{IV}	$pmol \cdot l^{-1} \cdot min^{-1}$	Basal prehepatic insulin secretion rate	$k_{CP}\,CP_{bIV}$†
OGTT			
$CPS_{OG}(t)$	$pmol \cdot l^{-1} \cdot min^{-1}$	C-peptide secretion rate†	*
$IDR_{OG}(t)$	$pmol \cdot l^{-1} \cdot min^{-1}$	Posthepatic insulin appearance rate into periphery	*
H_{OG}	% of secreted hormone	Hepatic insulin degradation	*
TIS_{OG}	$nmol \cdot l^{-1}$	Total amount of insulin secreted by the β-cells in 3 h	$\int_0^{180} CPS_{OG}(t)\,dt$
BSR_{OG}	$pmol \cdot l^{-1} \cdot min^{-1}$	Basal prehepatic insulin secretion rate	$k_{CP}\,CP_{bOG}$†

Further details can be found in references 18 and19 for FSIGT and in references 20 and 21 for OGTT parameters. *Model parameters directly estimated from fitting experimental data; †$CPS_{IV}(t)$ and $CPS_{OG}(t)$ represent also prehepatic insulin secretion due to the equimolar release. ‡CP_{bIV} and CP_{bOG} are basal concentrations of C-peptide before FSIGT and OGTT, respectively.

studied before and after delivery were calculated by paired Student's *t* test. All data and results are given as means ± SE, unless otherwise designated. A *P* value <0.05 was considered significant.

RESULTS

During pregnancy

Neither the preconceptual BMI nor weight gain during pregnancy (13.5 ± 1.5 and 16.3 ± 2.2 kg, GDM and pregnant women with NGT) differed between both pregnant subgroups. The preconceptual BMI was almost the same in GDM, pregnant women with NGT, and lean control subjects (Table 1) and correlated with parity ($P < 0.001$, $r = 0.64$) and age ($P < 0.01$, $r = 0.46$) in the whole group of pregnant women. The HbA_{1c} levels were elevated ($P < 0.04$) in pregnant women with GDM compared with those with NGT, though still in the normal range (Table 1). Blood pressure, cholesterol, and triglycerides did not differ between both pregnant groups. However, the GDM subjects who required treatment with insulin ($n = 5$) featured significantly higher diastolic blood pressure levels (74 ± 2 vs. 66 ± 2 mmHg, $P < 0.04$) and 1-h stimulated glucose concentrations during the diagnostic OGTT (14.19 ± 0.26 vs. 11.94 ± 0.84 mmol/l, $P < 0.04$) compared with GDM treated by diet only.

In GDM, the fasting concentrations for glucose and C-peptide were higher ($P < 0.05$) than those in pregnant women with NGT, whose fasting glucose levels were even lower than those in nonpregnant lean control subjects (Table 1). Fasting insulin concentration was increased in both pregnant groups ($P < 0.05$ vs. healthy nonpregnant lean control subjects).

The concentration curves for glucose, insulin, and C-peptide in pregnant women with GDM and in those with NGT during the FSIGT are shown in Fig. 1. The model-derived parameters in each group (Table 3) revealed a markedly insulin-resistant state in GDM such that the S_I was reduced by 84% versus nonpregnant lean control subjects. Pregnant women with NGT also featured a significantly reduced S_I compared with healthy nonpregnant lean control subjects, but their insulin sensitivity was elevated by 50% versus GDM. Glucose effectiveness (S_G) was almost the same in GDM and pregnant women with NGT, but significantly reduced in both groups compared with

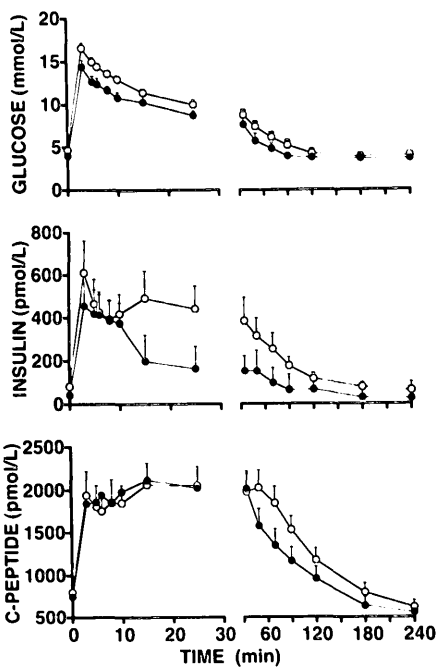

Figure 1—*FSIGT. Mean plasma concentrations of glucose, insulin, and C-peptide after an intravenous glucose load (0.3 g/kg at time zero). ○, women with GDM; ●, pregnant women with NGT. The time axis has been split to better show the patterns during the first 30 min.*

Table 3—*Parameters from the analysis of OGTT and FSIGT data for pregnant women with GDM and NGT as well as for nonpregnant lean control subjects*

	Units	Pregnant women		Nonpregnant women	
		GDM	NGT	GDM_{post}	Lean control subjects
OGTT					
BSR_{OG}	$pmol \cdot l^{-1} \cdot min^{-1}$	48.3 ± 5.3*	33.1 ± 3.4	34.9 ± 4.2§	36.1 ± 2.9†
TIS_{OG}	$nmol \cdot l^{-1} \times 3\ h$	34.8 ± 2.8	27.0 ± 2.8	21.5 ± 1.7§	26.8 ± 1.4†
H_{OG}	%	59.5 ± 1.9	49.2 ± 4.0‡	67.5 ± 3.5	78.0 ± 3.5†
FSIGT					
S_I	$10^4 \cdot min^{-1} \cdot (\mu U/ml)^{-1}$	1.49 ± 0.37*	3.11 ± 0.73‡	4.40 ± 0.9§‖	8.64 ± 1.4†
S_G	min^{-1}	0.022 ± 0.002	0.021 ± 0.003‡	0.030 ± 0.002§	0.031 ± 0.002†
BSR_{IV}	$pmol \cdot l^{-1} \cdot min^{-1}$	50.9 ± 7.5*	32.8 ± 7.4	36.7 ± 7.1§	34.6 ± 3.4†
Φ_1	$pmol \cdot l^{-1} \cdot min^{-1} \cdot (mg/dl)^{-1}$	88.9 ± 16.9*	134.5 ± 16.2	87.0 ± 19‖	140.3 ± 14.4†
Φ_2	$pmol \cdot l^{-1} \cdot min^{-2} \cdot (mg/dl)^{-1}$	0.032 ± 0.006*	0.078 ± 0.01	0.038 ± 0.008‖	0.061 ± 0.009†
TIS_{IV}	$nmol \cdot l^{-1} \times 4\ h$	25.4 ± 3.7*	15.2 ± 1.2	15.2 ± 2.7§	16.9 ± 2.2†
H_{IV}	%	69.2 ± 5.2	64.5 ± 6.1‡	76.7 ± 8	79.8 ± 3.6

Data are means ± SE. See Table 2 for parameter definitions. *$P < 0.05$, GDM vs. NGT; †$P < 0.05$, GDM vs. nonpregnant lean control subjects; ‡$P < 0.005$, NGT vs. nonpregnant lean control subjects; §$P < 0.05$, GDM vs. GDM_{post}; ‖$P < 0.05$, GDM_{post} vs. nonpregnant lean control subjects.

nonpregnant lean control subjects. The first- (Φ_1) and second-phase (Φ_2) β-cell sensitivity to glucose was reduced in GDM compared with the other groups. During both tests, the basal insulin secretion rate as well as total prehepatic insulin secretion (with exception of suprabasal-stimulated secretion during the first hour during FSIGT and 30 min after oral glucose loading during OGTT) were elevated in GDM versus pregnant women with NGT and nonpregnant lean control subjects (Table 3). The hepatic insulin extraction did not differ significantly between pregnant women with GDM or NGT but was reduced by 30–45% when compared with nonpregnant lean control subjects.

When compared with nonpregnant obese subjects with IGT with a similar degree of insulin resistance (Table 4), GDM featured increased S_G by 70% and decreased first-phase (Φ_1) β-cell sensitivity to glucose, insulin secretion, and hepatic insulin extraction by ~40%.

Total insulin secretion correlated inversely ($P < 0.05$) with the S_I in pregnant women with NGT ($r = -0.8$, $n = 25$) as well as in the nonpregnant obese patients with IGT ($r = -0.8$, $n = 9$), while no relationship was found in GDM.

After delivery

Twelve to sixteen weeks after delivery, all GDM subjects displayed NGT. They showed no change in HbA_{1c} levels (5.4 ± 0.17%) compared with their pregnant state. HbA_{1c} was still increased ($P < 0.05$) in post-GDM subjects versus lean control subjects, however within the normal range. BMI 3–4 months after delivery was 24.0 ± 1.7 kg/m² in GDM, not significantly different from that of the lean control subjects. The concentration curves in GDM after delivery and nonpregnant control subjects during the FSIGT are shown in Fig. 2. Basal glucose (4.4 ± 0.2 mmol/l) did not differ significantly, whereas basal insulin (45.4 ± 6.1 pmol/l) and C-peptide (0.55 ± 0.07 nmol/l) as well as basal ($P < 0.05$) and total insulin secretion ($P < 0.006$) decreased, while hepatic insulin extraction remained unchanged ($P = 0.09$) (Table 3).

During FSIGT, former GDM showed a significant increase in the S_I ($P < 0.05$, Table 3). However, when comparing it to BMI-matched lean control subjects, it became evident that S_I after delivery still remained decreased ($P < 0.05$). In contrast, S_G increased ($P < 0.05$) postpartum and was restored to the same value as in the lean control subjects (Table 3). First- and second-phase β-cell sensitivity to glucose remained completely unchanged after delivery and was reduced versus healthy lean control subjects. All other variables either normalized versus healthy nonpregnant lean control subjects or at least showed a tendency toward normalization in former GDM within 3–4 months after delivery.

Table 4—*Parameters from the analysis of OGTT and FSIGT data for obese women with NGT and IGT*

	Units	Obese nonpregnant women	
		NGT	IGT
OGTT			
BSR_{OG}	$pmol \cdot l^{-1} \cdot min^{-1}$	55.3 ± 5.1†	109.3 ± 27.7*
TIS_{OG}	$nmol \cdot l^{-1} \times 3\ h$	68.6 ± 9.7†	78.9 ± 8.4*
H_{OG}	%	86.2 ± 2.0	86.0 ± 1.8*
FSIGT			
S_I	$10^4 \cdot min^{-1} \cdot (\mu U/ml)^{-1}$	3.51 ± 0.65	2.10 ± 0.55
S_G	min^{-1}	0.022 ± 0.003†	0.013 ± 0.002*
BSR_{IV}	$pmol \cdot l^{-1} \cdot min^{-1}$	44.9 ± 6.7†	78.1 ± 14.8
Φ_1	$pmol \cdot l^{-1} \cdot min^{-1} \cdot (mg/dl)^{-1}$	129.9 ± 21.2†	156.8 ± 27.1*
Φ_2	$pmol \cdot l^{-1} \cdot min^{-2} \cdot (mg/dl)^{-1}$	0.060 ± 0.010†	0.042 ± 0.007
TIS_{IV}	$nmol \cdot l^{-1} \times 4\ h$	25.7 ± 4.3†	38.1 ± 5.0*
H_{IV}	%	81.5 ± 2.4	82.5 ± 1.9*

Data are means ± SE. See Table 2 for parameter definitions.*$P < 0.05$, GDM vs. obese women with IGT; †$P < 0.05$, GDM_{post} vs. obese women with NGT.

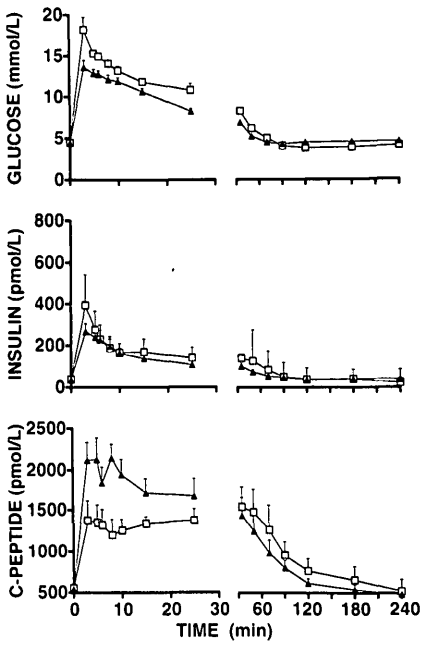

Figure 2—*FSIGT. Mean plasma concentrations of glucose, insulin, and C-peptide after an intravenous glucose load (0.3 g/kg at time zero) in women with GDM after delivery (□) and nonpregnant healthy control women (▲).*

However, again, when comparing GDM postpartum to obese women with NGT matched for insulin sensitivity, basal and total insulin secretion remained reduced by 20% ($P < 0.05$) and 42% ($P < 0.01$), respectively, and β-cell sensitivity to glucose by 33% ($P < 0.05$) for the first phase and by 37% ($P < 0.01$) for the second phase (Table 4).

CONCLUSIONS — This study was designed to comprehensively investigate the metabolic effects of pregnancy per se and to characterize gestational diabetes by oral and intravenous glucose tolerance tests. The OGTT model was chosen to account for the influence of factors involved in the physiological mode of glucose absorption. The FSIGT was additionally performed to obtain first- and second-phase responsiveness to glucose of the β-cells, S_I, and S_G. Mathematical modeling from oral as well as intravenous glucose tolerance tests yielded comparable results with regard to basal and total insulin secretion and hepatic insulin extraction among groups. This is in agreement with the results of previous studies in healthy subjects (23). Thus, it can be concluded that the route of glucose administration does not essentially affect the characteristics of insulin secretion and hepatic insulin extraction parameters during pregnancy.

After delivery, all GDM subjects reversed to NGT, as described by others (27). In women with a history of GDM, a persisting defect in first-phase insulin secretion (28,29) and variable degrees of insulin resistance (7,9,28,29) have been described. Because GDM and NIDDM are, therefore, characterized by similar metabolic abnormalities, GDM is considered as an early manifestation of NIDDM (4,13). It was, thus, of interest to reevaluate insulin secretion and sensitivity parameters in GDM subjects to elucidate their reversibility and identify markers for subsequent development of NIDDM.

S_G was impaired in both pregnant groups and might be part of and specific for the metabolic changes in pregnancy. Basal glucose levels, being in the normal range for all groups evaluated, were increased by 33% in GDM subjects versus pregnant subjects with NGT. Likewise, total glucose response (area under the curve [AUC]) was even ~1.5-fold higher in GDM subjects versus pregnant subjects with NGT during both OGTT and FSIGT. After delivery, integrated glucose response decreased significantly but remained markedly elevated compared with healthy nonpregnant lean control subjects, although still being within the normal range.

During pregnancy, insulin resistance was twofold greater in women with GDM than in nondiabetic women, which is in agreement with a previously published observation (12). After delivery, insulin sensitivity increased in GDM to the level of obese nonpregnant women with NGT; however, it remained 50% lower compared with that of lean subjects. This decrease in insulin sensitivity compares with the observation in obese NIDDM that ~60% of insulin resistance is due to the diabetic state (30) and might be attributed to increased postchallenge glycemia after delivery in GDM subjects.

Accordingly, GDM subjects exhibited a significantly higher basal (prehepatic) insulin secretion rate than pregnant women with NGT or control subjects as a potential mechanism to compensate for insulin resistance. Despite the overall increase in insulin secretion of GDM, the β-cell sensitivity to glucose for promptly releasable insulin (Φ_1) was decreased, indicating a loss of dynamic first-phase insulin response. Similarly, a decrease in dynamic sensitivity to glucose for long-term release of insulin (Φ_2) was found in GDM, suggesting inadequate β-cell secretory capacity for the prevailing glucose levels. This defect, which is characteristic of NIDDM (13), persisted after delivery as described in previous studies (4,17,28,29) despite improved glucose disposal. Hepatic insulin extraction, the other factor controlling peripheral insulinemia, was decreased both in pregnant women with GDM and NGT leading to a more marked posthepatic insulin delivery during pregnancy when compared with both nonpregnant obese and normal-weight women (Tables 3 and 4). Reduced hepatic insulin extraction in pregnancy may thus serve as an adaptive mechanism to compensate for insulin resistance in pregnancy by augmenting peripheral insulin availability. While the responsible mechanism is not known, a similar reduction in hepatic insulin extraction in nonpregnant hyperinsulinemic subjects (31) has been ascribed to the saturation of hepatic receptors or extraction sites (32). An association between an increase in the waist-to-hip ratio (WHR), as a marker for upper-body obesity, and a decrease in hepatic insulin extraction, calculated from C-peptide to insulin molar ratios, has previously been described in nonpregnant (33) and pregnant obese subjects (34). We did not measure WHR during pregnancy because of bias in evaluation of body fat distribution by this method in pregnant women. However, after delivery, WHR did not differ significantly between the women with GDM and the control subjects, although WHR tended to be slightly (+4%) increased in GDM. This is in agreement with another study reporting a subtle increase in WHR in normal-weight women with a history of GDM (29). Furthermore, we have found no differences in hepatic insulin extraction between the pregnant women with GDM and those with NGT, arguing against any potential effect of differences in body fat distribution on hepatic insulin clearance during pregnancy in our study groups.

When considering GDM as a prediabetic state, it is of interest to compare its metabolic defects with those of patients with IGT who are at high risk to develop frank NIDDM (35). Because of the hyperbolic relationship between insulin secretion and sensitivity reflecting a regulated feedback loop control system, insulin secretion is best compared between groups of comparable insulin sensitivity (18,36) despite differences in body weight.

The magnitude of the insulin secretory defect in GDM was higher than that in

obese subjects with IGT matched for degree of insulin resistance. After delivery, insulin secretion was lower than that in control subjects and thus definitely inappropriate for the persisting reduced insulin sensitivity. This is substantiated by the markedly lower insulin secretion in post-GDM subjects versus obese female subjects with NGT, matched for the degree of insulin resistance. In GDM, basal and total insulin secretion rate did not correlate inversely with insulin sensitivity, which might indicate a defective feedback between insulin sensitivity and β-cell function. Because first-phase insulin secretion is almost 50% lower in GDM subjects after delivery than in twofold more insulin-resistant subjects with IGT, we assume that the defect in insulin secretory capacity is predominant in GDM. Similar results in post-GDM subjects after a much longer follow-up period after pregnancy (28,29) strongly suggest that this is not a temporal phenomenon. The finding of an inadequate insulin secretion for a given degree of insulin sensitivity in GDM compared with other insulin-resistant states supports the contention of a major defect of insulin secretion. GDM might thus possibly represent a specific entity different from other known prediabetic states. This suggestion is further supported by the absence of preconceptual obesity in women with GDM in this study. We attempted to exclude obesity in GDM as an additional contributing factor to insulin resistance. We therefore cannot speculate whether the pathophysiology of GDM is different between obese and lean subjects. Recent studies in moderately obese GDM patients suggest no difference in the mechanism because women with a history of GDM, regardless of body weight, are consistently characterized by impaired early insulin response versus BMI-matched control subjects (10,17,28). However, it seems that among women with prior GDM, the lean subjects feature a more pronounced defect in early insulin release, while the obese women show a more marked insulin resistance (37). The observation of pronounced quantitatively impaired first-phase insulin secretion in GDM, which thereby differs from the prediabetic state of IGT, may imply specific therapeutic strategies in diabetic patients with a history of GDM, who may rather benefit from early insulin therapy. In addition, because episodes of insulin resistance contribute to the decline in β-cell function leading to NIDDM in high-risk populations (38), any reduction in insulin sensitivity induced by obesity or pharmacological means should be avoided in GDM.

In summary, pregnancy is characterized by insulin resistance, reduced S_G, and diminished hepatic insulin extraction contributing to increased peripheral insulin levels. Furthermore, lean women with GDM feature more pronounced insulin resistance during pregnancy than pregnant subjects with NGT, which does not completely abate after delivery. In addition, β-cell sensitivity for glucose is decreased in GDM and does not change postpartum. Compared with subjects with IGT matched for the degree of insulin resistance, patients with GDM exhibit a lower β-cell sensitivity to glucose and an inadequate insulin secretory capacity. This might indicate that impaired insulin secretion is the predominant defect in GDM, which thus may be regarded as a prediabetic entity distinct from IGT.

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References

1. Buchanan TA, Metzger BE: Gestational diabetes mellitus. In *Advances in Endocrinology and Metabolism*. Vol. 4. Mazzaferri EL, Bar RS, Eds. Chicago, Mosby Yearbook, 1993, p. 29–46
2. Ramus RM, Kitzmiller JL: Diagnosis and management of gestational diabetes. *Diabetes Rev* 2:43–52, 1994
3. American Diabetes Association: *Medical Management of Pregnancy Complicated by Diabetes*. Jovanovic-Peterson LE, Ed. Alexandria, VA, American Diabetes Association, 1993
4. Kjos SL, Peters RK, Xiang A, Henry OA, Motoro M, Buchanan TA: Predicting future diabetes in Latino women with gestational diabetes: utility of early postpartum glucose tolerance testing. *Diabetes* 44:586–591, 1995
5. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose tolerance. *Diabetes* 28:1039–1057, 1979
6. Metzger BE: Summary and recommendations of the Third International Workshop Conference on Gestational Diabetes Mellitus. *Diabetes* 40 (Suppl. 2):197–201, 1991
7. Oats JN, Beischer NA, Grant PT: The emergence of diabetes and impaired glucose tolerance in women who had gestational diabetes. In *Gestational Diabetes*. Weiss PA, Coustan DR, Eds. New York, Springer Verlag, 1988, p. 199–207
8. Kühl C: Insulin secretion and insulin resistance in pregnancy and GDM. *Diabetes* 40 (Suppl. 2):18–24, 1991
9. Cousins L: Insulin sensitivity in pregnancy. *Diabetes* 40 (Suppl. 2):39–43, 1991
10. Buchanan TA, Metzger BE, Freinkel N, Bergman RN: Insulin sensitivity and beta cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. *Am J Obstet Gynecol* 162:1008–1014, 1990
11. Fisher PM, Sutherland HW, Bewsher PD: The insulin response to glucose infusion in gestational diabetes. *Diabetologia* 19:10–14, 1980
12. Ryan EA, O'Sullivan MJ, Skyler JS: Insulin action during pregnancy: studies with the euglycemic clamp technique. *Diabetes* 34:380–389, 1985
13. Pendergrass M, Fazioni E, De Fronzo R: Non-insulin-dependent diabetes mellitus and gestational diabetes mellitus: same disease, another name? *Diabetes Rev* 3:566–583, 1995
14. Cousins L, Rea C, Crawford M: Longitudinal characterization of insulin sensitivity and body fat quantitation in normal and gestational diabetic pregnancies (Abstract). *Diabetes* 37 (Suppl. 1):251A, 1988
15. Dornhorst A, Beard RW: Gestational diabetes: a challenge for the future. *Diabet Med* 10:897–905, 1993
16. Garvey WT, Maianu L, Zhu JH, Hancock JA, Golichowski AM: Multiple defects in the adipocyte glucose transport system cause cellular insulin resistance in gestational diabetes: heterogeneity in the number and a novel abnormality in subcellular localization of GLUT4 glucose transporters. *Diabetes* 42:1773–1785, 1993
17. Yen SSC, Tsai CC, Vela P: Gestational diabetogenesis: quantitative analyses of glucose-insulin interrelationship between normal pregnancy and pregnancy with gestational diabetes. *Am J Obstet Gynecol* 111:792–800, 1971
18. Bergman R, Phillips LS, Cobelli C: Physiologic evaluation of factors controlling glucose tolerance in man. *J Clin Invest* 68:456–467, 1981
19. Cobelli C, Pacini G: Insulin secretion and hepatic insulin extraction in humans by minimal modeling of C-peptide and insulin kinetics. *Diabetes* 37:223–231, 1988
20. Thomaseth K, Kautzky-Willer A, Ludvik B, Prager R, Pacini G: Integrated mathematical model to assess β-cell activity during the oral glucose tolerance test. *Am J Physiol* 270:E522–E531, 1996
21. Kautzky-Willer A, Thomaseth K, Pacini G, Clodi M, Ludvik B, Streli C, Waldhäusl W, Prager R: Role of islet amyloid polypeptide

secretion in insulin-resistant humans. *Diabetologia* 37:188–194, 1994
22. Pacini G: Mathematical models of insulin secretion in physiological and clinical investigations. *Comp Meth Prog Biomed* 41:269–285, 1994
23. Kautzky-Willer A, Thomaseth K, Clodi M, Ludvik B, Waldhäusl W, Prager R, Pacini G: Beta-cell activity and hepatic insulin extraction following dexamethasone administration in healthy subjects. *Metabolism* 45:486–491, 1996
24. Pacini G, Bergman RN: MINMOD: computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intraveneous glucose tolerance test. *Comp Meth Progr Biomed* 23:113–122, 1986
25. Bergman RN, Prager R, Volund A, Olefsky J: Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. *J Clin Invest* 79:790–800, 1987
26. Thomaseth K: PANSYM: a symbolic equation generator for mathematical modeling, analysis and control of metabolic and pharmacokinetic systems. *Comput Methods Programs Biomed* 42:99-112, 1994
27. Jovanovic-Peterson L: The diagnosis and management of gestational diabetes mellitus. *Clin Diabetes* 13:32–39, 1995
28. Ward WK, Johnston CLW, Beard JC, Benedetti TJ, Halter JB, Porte D: Insulin resistance and impaired insulin secretion in subjects with histories of gestational diabetes mellitus. *Diabetes* 34:861–869, 1985
29. Ryan EA, Imes Sh, Liu D, McManus R, Finegood DT, Polonsky KS, Sturis J: Defects in insulin secretion and action in women with a history of gestational diabetes. *Diabetes* 44:506–512, 1995
30. Ludvik B, Nolan JJ, Baloga J, Sacks D, Olefsky J: Effect of obesity on insulin resistance in normal subjects and patients with NIDDM. *Diabetes* 44:1121–1124, 1995
31. Waldhäusl W, Bratusch-Marrain P, Gasic S, Korn A, Nowotny P: Insulin production rate and splanchnic carbohydrate metabolism after oral glucose ingestion in hyperinsulinemic non insulin-dependent diabetes mellitus. *Diabetologia* 23:6–15, 1982
32. Ferrannini E, Wahren J, Faber OK, Felig P, Binder C, DeFronzo RA: Splanchnic and renal metabolism of insulin in human subjects: a dose-response study *Am J Physiol* 244:E517–E527, 1983
33. Peiris AN, Müller RA, Smith GA, Struve MF, Kissebah AH: Splanchnic insulin metabolism in obesity. *J Clin Invest* 78:1648–1657, 1986
34. Landon MB, Osei K, Platt M, O'Dorisio T, Samuels P, Gabbe SG: The differential effects of body fat distribution on insulin and glucose metabolism during pregnancy. *Am J Obstet Gynecol* 171:875–884, 1994
35. Stern MP, Morales PA, Valdez RA, Monterrosa A, Haffner SM, Mitchell BD, Hazuda HP: Predicting diabetes: moving beyond impaired glucose tolerance. *Diabetes* 42:706–714, 1993
36. Kahn S, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP, Porte D Jr: Quantification of the relationship between insulin sensitivity and β-cell function in human subjects. *Diabetes* 42:1663–1672, 1993
37. Catalano BM, Bernstein IM, Wolfe RR, Srikanta S, Tyzbir E, Sims EAH: Subclinical abnormalities of glucose metabolism in subjects with previous gestational diabetes. *Am J Obstet Gynecol* 155:1255–1262, 1986
38. Peters RK, Kjos SL, Xiang A, Buchanan TA: Long-term diabetogenic effect of single pregnancy in women with previous gestational diabetes mellitus. *Lancet* 347:227–230, 1996