Normal Glucose Tolerance and Gestational Diabetes Mellitus

What is in between?

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OBJECTIVE — The aim of this article was to define the metabolic phenotype of pregnant women with one abnormal value (OAV) during an oral glucose tolerance test (OGTT) and to test whether OAV could be considered metabolically comparable to gestational diabetes mellitus (GDM) or a specific entity between GDM and normal pregnancy.

RESEARCH DESIGN AND METHODS — After 100-g 3-h OGTTs, 4,053 pregnant women were classified as having GDM, OAV, or normal glucose tolerance (NGT). Those with OAV were subdivided into three subgroups: fasting hyperglycemia (one abnormal value at fasting during an OGTT), 1-h hyperglycemia (one abnormal value at 1 h during an OGTT [1h-OAV]), or 2- or 3-h hyperglycemia (one abnormal value at 2 or 3 h during an OGTT). As derived from the OGTT, we measured insulin sensitivity (insulin sensitivity index [ISI] Matsuda) and insulin secretion (homeostasis model assessment for the estimation of β-cell secretion [HOMA-B], first- and second-phase insulin secretion). The product of the first-phase index and the ISI was calculated to obtain the insulin secretion–sensitivity index (ISSI).

RESULTS — GDM was diagnosed in 17.9% and OAV in 18.7% of pregnant women; women with GDM and OAV were older and had higher BMI and serum triglyceride levels than those with NGT (all $P < 0.05$). Women with NGT had the highest ISI followed by those with OAV (−21.7%) and GDM (−32.1%). HOMA-B results were comparable with those for OAV and GDM but significantly ($P < 0.01$) lower than those for NGT; first- and second-phase insulin secretion appeared progressively reduced from that in women with NGT to that in women with OAV and GDM ($P < 0.01$). ISSI was higher in women with NGT than in women with either OAV (−34%) or GDM (−51.7%) ($P < 0.001$). Among OAV subgroups, the 1h-OAV subgroup showed the lowest ISSI ($P < 0.05$).

CONCLUSIONS — OAV and GDM are clinically indistinguishable, and both groups are different from women with NGT. Women with GDM and OAV showed impaired insulin secretion and insulin sensitivity, although these defects are more pronounced in women with GDM. Compared with other OAV subgroups, 1h-OAV could be considered a more severe condition.

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Abbreviations: AUC_{Gluc}, incremental area under the glucose curve; AUC_{Ins}, incremental area under the insulin curve; F-OAV, one abnormal value at fasting during an oral glucose tolerance test; GCT, glucose challenge test; GDM, gestational diabetes mellitus; HOMA-B, homeostasis model assessment for the estimation of β-cell secretion; ISI, insulin sensitivity index; ISSI, insulin secretion–sensitivity index; L-OAV, one abnormal value at 2 or 3 h during an oral glucose tolerance test; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; 1h-OAV, one abnormal value at 1-h during an OGTT; OAV, one abnormal value during an OGTT.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Gestational diabetes mellitus (GDM) is the most common metabolic complication of pregnancy, occurring up to 14% of pregnant women (1). Women with GDM have a greater risk for future development of diabetes, and pregnancy outcome is more commonly complicated by perinatal morbidity and mortality (2). Therefore, early identification of women at risk of or actually developing GDM is strongly warranted (3). Greater risk for GDM is conferred by a positive family history for diabetes, ethnicity, maternal age, and prepregnancy overweight or obesity (4). Universal screening is recommended by performance of a 50-g glucose challenge test (GCT) between the 24th and 28th week of gestation (5). A plasma glucose value ≥7.7 mmol/l 1 h after glucose ingestion calls for a confirmatory 3-h 100-g oral glucose tolerance test (OGTT) with results interpreted on the basis of the criteria of Carpenter and Coustan (6).

According to these criteria, the diagnosis of GDM requires that two or more of the glucose values should be met or exceeded, whereas women with only one abnormal value for the 100-g 3-h OGTT (OAV) are considered as having the same risk as women with normal OGTT results. This, however, is a matter of discussion. Some authors have found no difference (7,8), whereas others have noticed that women with OAV have increased obstetric complications and a higher rate of macrosomia and large-for-gestational-age infants compared with women with treated GDM (9–11).

The limited but still recognizable alterations in glucose tolerance in women with OAV should indicate possible impairment of mechanisms responsible for glucose homeostasis. In women with GDM the coexistence of defects in insulin sensitivity and insulin secretion have been repeatedly demonstrated (12). On the contrary, it has not yet been fully established whether women with OAV may represent an intermediate phenotype between normal women and women with GDM, because limited data are available (13–15).

Table 1—*Clinical features of pregnant women with NGT, OAV, and GDM*

	NGT	OAV	GDM	*P* value
n	2,568 (63.3)	759 (18.7)	726 (17.9)	
Primiparous (%)	53.6	50.47	51.04	NS
Age (years)	31.4 ± 4.6	32.01 ± 4.6	32.3 ± 4.4	<0.001*
Age ≥35 years (%)	25.1	27.1	30.9	0.007*
Diabetes familiarity (%)	28.4	27.1	28.3	NS
Prepregnancy weight (kg)	64.3 ± 11	65.4 ± 12	66.6 ± 12	<0.001*
Prepregnancy BMI (kg/m^2)	24.1 ± 4.1	24.5 ± 4.3	25.1 ± 4.5	<0.001*
BMI ≥25 kg/m^2 (%)	33.7	38.8	43.2	<0.001*
Weight gain (kg)	7.63 ± 3.4	7.59 ± 3.5	7.61 ± 3.6	NS
Systolic blood pressure (mmHg)	115.7 ± 12	115.9 ± 11	116.6 ± 12.5	NS
Diastolic blood pressure (mmHg)	71.5 ± 8.7	71.3 ± 8.2	71.6 ± 8.5	NS

Data are *n* (%), means ± SD, or %. *NGT vs. OAV and GDM.

We have analyzed a large cohort of pregnant women with abnormal 50-g glucose screening test results to identify those with OAV and describe their metabolic phenotype, compared with those for women with GDM and control women, paying attention to subtle alterations in insulin secretion and action that may be already present in these individuals. This investigation should help us to define the metabolic phenotype associated with different 100-g OGTT profiles in addition to testing whether OAV could be considered metabolically comparable to GDM or a specific entity between GDM and normal pregnancy, requiring specific medical attention in the course of a pregnancy.

RESEARCH DESIGN AND METHODS

The study was performed according to the guidelines of the Third International Workshop-Conference on Gestational Diabetes Mellitus (5). A total of 4,053 pregnant women with positive glucose challenge test (GCT) results were consecutively referred to two diabetes centers in the Tuscany region in Italy (Pisa and Pistoia) from January 2001 to December 2005. All women recruited had plasma glucose values ≥7.7 mmol/l 1 h after a standard 50-g glucose load (GCT positive) administered after an overnight fast. For this reason, they then underwent a 3-h 100-g OGTT. The test was performed after a 12-h overnight fast. On the morning of the test, demographic, anthropometric, and clinical data (age, family history of diabetes, obstetric history, and BMI) were recorded. An antecubital vein was cannulated, and a basal blood sample was taken for determination of fasting plasma glucose, insulin, and lipid concentrations. Blood samples were then collected at 60-min intervals for 3 h to determine plasma glucose and insulin concentrations. Glucose tolerance was defined according to the criteria of Carpenter and Coustan (6); i.e., fasting plasma glucose ≤5.2 mmol/l, ≤10 mmol/l at 1 h, ≤8.6 mmol/l at 2 h, and ≤7.7 mmol/l at 3 h. GDM was diagnosed when two or more plasma glucose levels exceeded these cutoff values. Women with a single altered value were classified as having OAV. These women were further subdivided into three subgroups: isolated fasting hyperglycemia (one abnormal value at fasting during an OGTT [F-OAV]), 1-h hyperglycemia (one abnormal value at 1 h during an OGTT [1h-OAV]), or late (2- or 3-h) hyperglycemia (one abnormal value at 2 or 3 h during an OGTT [L-OAV]). Women who did not meet the cutoff value were considered normotolerant (NGT).

Measurements

Plasma glucose levels were determined on a Beckman Glucose Analyzer 2 (Beckman, Fullerton, CA) by the glucose oxidase method, and the plasma insulin concentration was measured by radioimmunoassay (INSI-CTK Irma; Dia Sorin). Serum concentrations of triglycerides and total, LDL, and HDL cholesterol were determined by using standard enzymatic procedures on an automatic analyzer (Modular; Roche Diagnostics, Mannheim, Germany).

The inter- and intra-assay coefficients of variation for all parameters were <5%. Incremental areas under the glucose curve (AUC_{Gluc}) and insulin curve (AUC_{Ins}) during the OGTT were calculated using the trapezoidal rule. Insulin sensitivity was estimated using the whole-body insulin sensitivity index (ISI) derived from the OGTT as proposed by Matsuda and DeFronzo (16). As a measures of insulin secretion we used the homeostasis model assessment for the estimation of β-cell secretion (HOMA-B) (17) calculated as follows: $(20 \times Ins_0)/(Gluc_0 - 3.5)$. We also estimated first- and second-phase insulin secretion using formulas by Stumvoll et al. (18) (first phase: $1{,}194 + 4.724 \times Ins_0 - 117 \times Gluc_{60} + 1{,}414 \times Ins_{60}$; second phase: $295 + 0.349 \times Ins_{60} - 25.72 \times Gluc_{60} + 1{,}107 \times Ins_0$).

The product of the ISI and the Stumvoll first-phase index of insulin secretion was calculated to obtain an insulin secretion–sensitivity index (ISSI). This index, which relates β-cell function with insulin resistance, has previously been used in pregnant women (14).

Statistical analysis

Data are given as percentages or means ± SD. ANOVA with post hoc Bonferroni analysis was used to assess univariate differences among continuous variables; the χ^2 test was used to compare observed frequency between groups for qualitative variables. All statistical comparisons were considered significant at $P < 0.05$. Statistical analyses were performed using a statistical package (StatviewSE; SAS Institute, Cary, NC) on a Macintosh computer (Apple, Cupertino, CA).

RESULTS

During the study period, a total of 4,053 Caucasian women with positive screening test results for GDM were referred to the two diabetic centers to undergo 3-h 100-g diagnostic OGTTs. The tests were performed at 27 ± 3.2 weeks of gestation; GDM was diagnosed in 726 women (17.9%), OAV in 759 (18.7%) women, and NGT in 2,568 (63.3%) women. The clinical character-

Table 2—*Metabolic parameters of pregnant women with NGT, OAV, and GDM*

	NGT	OAV	GDM	*P* value
Total cholesterol (mmol/l)	6.75 ± 0.97	7.19 ± 1.06	6.74 ± 1.09	NS
LDL cholesterol (mmol/l)	4.24 ± 0.95	4.57 ± 1.19	4.21 ± 1.07	NS
HDL cholesterol (mmol/l)	2 ± 0.36	1.94 ± 0.39	1.92 ± 0.3	NS
Triglycerides (mmol/l)	1.79 ± 0.62	2.12 ± 0.52	2.08 ± 0.56	<0.05*
Fasting plasma glucose (mmol/l)	4.41 ± 0.45	4.86 ± 0.62	4.98 ± 0.67	<0.001
1-h plasma glucose (mmol/l)	7.64 ± 1.41	9.45 ± 1.44	10.83 ± 1.31	<0.001
2-h plasma glucose (mmol/l)	6.26 ± 1.22	7.56 ± 1.35	9.36 ± 1.44	<0.001
3-h plasma glucose (mmol/l)	5.2 ± 1.22	5.92 ± 1.42	7.24 ± 1.76	<0.001
AUC_{Gluc} ($mmol \cdot l^{-1} \cdot min^{-1}$)	592.13 ± 92.38	709.99 ± 79.79	848.41 ± 90.9	<0.001
Fasting plasma insulin (pmol/l)	59.11 ± 44.96	63.53 ± 45.26	65.66 ± 46.61	0.04*
Insulin 60-min OGTT (pmol/l)	521.58 ± 302.62	555.67 ± 317.52	554.79 ± 330.90	NS
Insulin 120-min OGTT (pmol/l)	537.65 ± 341.93	622.15 ± 367.51	702.10 ± 459.32	<0.001
Insulin 180-min OGTT (pmol/l)	376.59 ± 283.53	430.63 ± 307.86	532.64 ± 440.97	<0.001
AUC_{Ins} (10^3 $pmol \cdot l^{-1} \cdot min^{-1}$)	55.553 ± 27.017	61.312 ± 28.096	65.578 ± 31.957	<0.001
ISI Matsuda	5.94 ± 3.4	4.65 ± 2.4	4.03 ± 2.2	<0.001
HOMA-B	285 ± 439.4	195 ± 222.9	200.9 ± 306.8	<0.01†
Stumvoll first-phase secretion	1,323.9 ± 553.1	1,167.9 ± 584.6	1,020.5 ± 626.3	<0.001
Stumvoll second-phase secretion	347.5 ± 134.1	314.8 ± 141.6	282.4 ± 151.7	<0.001
ISSI	6,793.4 ± 2807	4,467.9 ± 1475	3,280.5 ± 1241	<0.001

Data are means ± SD. *P* values refer to overall differences across groups as derived from ANOVA: *NGT vs. GDM. †NGT vs. GDM and OAV.

istics of the three groups are shown in Table 1.

Women with GDM and OAV were significantly older than those with NGT ($P < 0.001$). Prepregnancy body weight and BMI increased from women with NGT to women with GDM ($P < 0.01$) with a greater prevalence of overweight and obesity (BMI ≥25 kg/m^2) among women with OAV (38.8%) and GDM (43.2%) than among those with NGT (33.6%; $P < 0.001$). There were no differences in the three groups in family history of diabetes, incremental gestational body weight, and blood pressure. Regarding lipid profiles, total, LDL, and HDL cholesterol levels were similar in all groups, whereas serum triglyceride levels were higher in women with GDM and OAV than in women with NGT ($P < 0.05$) (Table 2).

Evaluation of OGTT results showed that in women with OAV mean glycemic and insulin values at each time point of the OGTT were significantly higher than those for women with NGT but lower than those for women with GDM; accordingly AUC_{Gluc} and AUC_{Ins} showed an increasing trend from women with NGT to women with GDM (all $P < 0.001$) (Table 2). Women with NGT had the highest ISI (5.94 ± 3.4), followed by those with OAV (4.65 ± 2.4) and GDM (4.03 ± 2.2) ($P < 0.001$), corresponding to a 21.7% reduction in women with OAV compared with women with NGT and a further 10.4% reduction in women with GDM (32.1% vs. NGT; $P < 0.001$) (Fig. 1).

No difference was apparent in the HOMA-B between women with OAV and GDM, although HOMA-B was significantly lower compared with that for women with NGT. When first- and second-phase insulin secretions were calculated, they both appeared to be progressively reduced going from women with NGT to those with OAV and GDM status (first phase: NGT 1,323.9 ± 553, OAV 1,167.9 ± 584.6, and GDM 1,020.5 ± 626.3 pmol/l, $P < 0.001$; second phase: NGT 347.5 ± 134.1, OAV 314.8 ± 141.6, and GDM 282.4 ± 151.7 pmol/l, $P < 0.001$).

To properly assess insulin β-cell function, insulin secretion was evaluated with respect to prevalent insulin sensitivity. Therefore, the product of the Stumvoll first-phase index and the Matsuda insulin action index was calculated to express the ISSI as previously suggested (14). This index was higher in women with NGT compared with those with either OAV and GDM (34 and 51.7% lower in the latter two groups, respectively, $P < 0.001$). Moreover, when the Stumvoll first-phase index was plotted as a function of the ISI Matsuda, a hyperbolic function was obtained, showing a progressive shift to the left moving from women with NGT

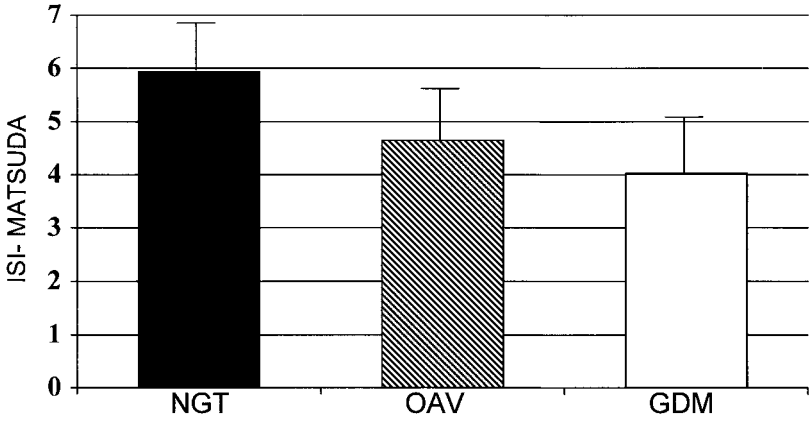

Figure 1—*ISI derived from the OGTT (ISI Matsuda) by glucose tolerance group. The ISI value moved progressively lower in women with NGT to those with OAV (−21.7%) and GDM (−32.1%). ANOVA:* P < *0.001.*

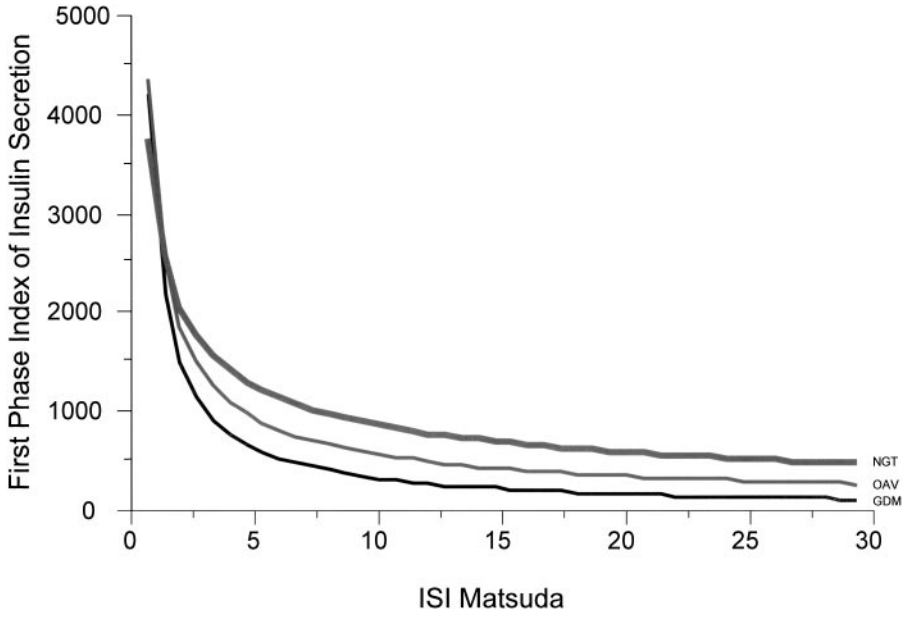

Figure 2—*ISSI (Stumvoll first-phase secretion index × ISI Matsuda) curves, according to glucose tolerance status.*

to women with OAV and to those with GDM (Fig. 2).

Women with OAV were identified irrespective of the time during the OGTT when the abnormal plasma glucose level was recorded. To gain a better definition of the clinical phenotype, women with OAV were stratified in three subgroups. Isolated fasting hyperglycemia (F-OAV) was documented in 219 women (28.8%), 316 women (41.6%) had isolated 1-h hyperglycemia (1h-OAV), and the remaining 224 (29.5%) had isolated hyperglycemia either at 2- or 3-h (L-OAV).

Although a trend was apparent for progressive reduction in the ISI Matsuda from the F-OAV subgroup (4.9 ± 2.8) to the 1h-OAV (4.67 ± 2.41) and L-OAV (4.41 ± 2.25) subgroups, this reduction did not reach statistical significance. As for insulin secretion parameters, HOMA-B was markedly lower in the F-OAV subgroup (102.3 ± 67.5 vs. 234.7 ± 201.4 [1h-OAV] and vs. 219.2 ± 157 [L-OAV], $P < 0.001$), whereas first- and second-phase insulin indexes did not appear to be statistically different. When the ISSI was calculated, however, a significant difference was found in the subgroup with 1h-OAV (4,172.5 ± 1,482). Their ISSI was significantly lower than those for either the F-OAV (4,794 ± 1,581, $P < 0.01$) and L-OAV (4,597.2 ± 1,313, $P < 0.05$) subgroups.

CONCLUSIONS — The importance of early detection and prompt intensive treatment of GDM is universally recognized (19). Based on these considerations and on the peculiar changes in glucose homeostasis during pregnancy, specific criteria have been adopted to diagnose GDM on the basis of a 3-h OGTT. Upon diagnosis, blood glucose monitoring, nutritional changes and, if necessary, insulin therapy are then initiated (20). Strict glycemic control is necessary to reduce the risk of fetal and maternal morbidity brought about by maternal hyperglycemia.

Despite all evidences on the importance of treating GDM, the current criteria lead to a dichotomous diagnosis, leaving out a large number of women with nondiagnostic isolated hyperglycemia, i.e., women with a single altered OGTT glucose value (OAV). Nevertheless, the increase in plasma glucose levels, even those below the diagnostic threshold for diabetes in the second half of pregnancy, is associated with a slight, but continuous, increase in the incidence of macrosomia and caesarean section (21). A link between mild glucose intolerance and adverse maternal-fetal outcome has been epidemiologically suggested (22).

From these considerations, it appears that a better understanding of the metabolic features and risk of women with intermediate alterations in glucose homeostasis is warranted. To date only three articles (13–15), involving a total of 97 women with OAV, have reported investigations on the metabolic phenotype of this population. We now report data obtained in a large cohort of pregnant women with OAV ($n = 759$) compared with those with GDM ($n = 726$) or normal pregnancies (NGT, $n = 2,568$). These women were referred to our diabetes clinics because they all had positive screening tests for GDM.

The first observation emerging from this survey is that OAV is not a trivial phenomenon as it occurs at a rate (18.7%) comparable to that of GDM (17.9%). Moreover, the two groups are more than alike. There were indeed no differences in age, prevalence of overweight or obesity, and weight gain during pregnancy. In agreement with previous observations, in our population too alterations of glucose homeostasis occurred in older and more obese women (23). Moreover, lipid profiles for OAV and GDM are not distinguishable. High triglyceride concentrations have been previously reported in women with GDM (24,25). The same is true for women with OAV, whose triglyceride levels were higher than those for women with NGT and similar to those for women with GDM, suggesting that similar pathogenetic mechanisms (i.e., impaired insulin action) may be at work in both conditions.

This hypothesis was directly addressed by assessing insulin sensitivity and insulin secretion in this large Caucasian population, using indexes derived from the OGTT. We now show that in going from one condition of glucose tolerance to another, both insulin sensitivity and β-cell function progressively decline. Insulin secretory capability was determined by calculation of the HOMA-B index, a surrogate of basal insulin secretion, and by the Stumvoll first- and second-phase indexes, which reflect dynamic insulin response. With both approaches, it was quite clear that insulin secretion tends to deteriorate with worsening of glucose tolerance, confirming results obtained in a smaller study (14).

Insulin secretion, however, must be assessed as a function of prevalent insulin sensitivity as originally proposed by Kahn et al. (26). The product of the Stumvoll first-phase index and the ISI Matsuda has been proposed as an ISSI during pregnancy by Retnakaran et al. (14). This index expresses the ability of the β-cell to compensate for insulin resistance. Similarly to Retnakaran et al., we observed in a much larger population that the ISSI is

progressively reduced; this reduction is due to concomitant worsening of insulin sensitivity and insulin secretion. In fact, the ISI Matsuda was reduced by 22 and 32% in women with OAV and GDM, respectively, versus that in women with NGT, whereas the Stumvoll first-phase secretion index declined by 12 and 23%, respectively.

When one parameter was plotted as a function of the other, the expected hyperbolic function became apparent (Fig. 2), showing a shift to the left when the women with NGT, OAV, and GDM were considered. Again, this result confirms and supports what was reported in smaller populations (14) and emphasizes early alterations of both insulin secretion and action in determining disturbances of glucose metabolism in pregnant women.

We recognize the limitation of a cross-sectional study in describing the development of glucose intolerance and GDM. Therefore, from our data, we cannot tell which factor may act as the precipitating one.

The definition of OAV was made irrespective of the time when the single plasma glucose alteration occurred. However, this timing may be relevant as metabolic and pathogenetic differences have been identified, for instance, when individuals with impaired fasting glucose and impaired glucose tolerance have been analyzed (27). Therefore, we have subdivided women with OAV according to isolated fasting, 1-h, or late (2- to 3-h) hyperglycemia to determine whether this may be associated with some characteristic metabolic phenotypes. This analysis revealed that women with F-OAV are characterized by an impairment in basal insulin secretory capacity as indicated by a significant reduction in the HOMA-B. On the other hand, when stimulated insulin secretion was evaluated in the context of ambient insulin sensitivity, a significant impairment occurred in 1h OAV compared with the other groups. Therefore, as previously suggested (15), 1-h OGTT hyperglycemia can be considered a more severe condition. The early impairment of insulin secretion after an oral glucose load in these women might translate to greater postprandial glucose excursions, conferring greater risk for fetal development. Consequently, strict control of early postprandial glucose excursions in GDM has been shown to be associated with better neonatal outcomes (28).

Thus, findings for the OAV group, especially the 1-h OAV subgroup, do not reflect a metabolically normal population. We could postulate that if we reevaluated women with OAV later in pregnancy, when insulin resistance increases as a result of placental activity (29), some OAV could be diagnosed as GDM. In support of such a hypothesis, there are epidemiological observations indicating an increase in the prevalence of GDM in women at high risk when an OGTT is repeated later in pregnancy (30). Nevertheless, longitudinal studies are needed to define whether this group of women may have a greater risk of advancement toward an overtly diabetic status late in pregnancy or greater risk of developing type 2 diabetes later in life.

In summary, our results indicate that the prevalence of OAV and GDM is high in pregnant women with a positive glucose challenge test; women with OAV are clinically indistinguishable from patients with GDM, and both groups are different from the women with NGT. Both GDM and OAV groups have impairment of insulin secretion and insulin sensitivity, although these defects are more pronounced in women with GDM. These results should draw attention to the need for better understanding of the risk associated with OAV, particularly 1 h post-OGTT hyperglycemia, to define whether intensive treatment should be recommended for these women as well.

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