Estimating the risk after gestational diabetes mellitus: can we improve the information from the postpartum OGTT?

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Göbl CS, Bozkurt L, Prikoszovich T, Tura A, Pacini G, Kautzky-Willer A. Estimating the risk after gestational diabetes mellitus: can we improve the information from the postpartum OGTT? Am J Physiol Endocrinol Metab 304: E524–E530, 2013. First published January 8, 2013; doi:10.1152/ajpendo.00461.2012.—Risk stratification after pregnancy with gestational diabetes mellitus (GDM) is based on screening with the 2-h oral glucose tolerance test (OGTT). Actually, prediabetes and diabetes are diagnosed by impaired fasting [fasting plasma glucose (FPG)] and 120 min-postload glucose levels (120'-PLG). We hypothesized that the clinical information could be improved by including measurements at different time points from the OGTT in the medical decision-making process. One hundred ten women with previous gestational diabetes (pGDM) and 41 controls were included 3–6 mo after delivery and underwent specific metabolic assessments: 3-h OGTT, frequently sampled intravenous glucose tolerance test (FSIGT) with markers of inflammation and endothelial function. pGDMs were annually invited for reexaminations for a maximum of 10 yr. Multiple linear regression suggested that postload glucose levels at 60 min (60'-PLG) were a better predictor for insulin sensitivity [β: −0.10, 95% confidence interval (CI) −0.14 to −0.05, P < 0.001] and disposition index (DI) (β: −0.07, 95% CI −0.12 to −0.02, P = 0.004) estimated from the FSIGT compared with other time points during the OGTT. The association between 60'-PLG and insulin secretion was of particular importance in women after GDM. We further identified associations of 60'-PLG with ultrasensitive C-reactive protein, plasminogen activator inhibitor 1, tissue plasminogen activator, endothelial-leukocyte adhesion molecule 1, and intercellular adhesion molecule (ICAM)-1. There appeared to be no interactions between females with pGDM and controls, suggesting comparable effects. We observed that 60'-PLG levels were closely related to the later onset of diabetes independent from the routinely measured FPG and 120'-PLG levels. Our data suggest that the sole interpretation of FPG and 120'-PLG of the OGTT leads to significant loss of information. Particularly 60'-PLG was shown to distinguish women at low or high metabolic and cardiovascular risk.

gestational diabetes mellitus; oral glucose tolerance test; postpartum risk stratification;

PREGNANCY REPRESENTS A UNIQUE stress situation for the female metabolism, potentially damasking latent disturbances in glucose homeostasis (21). In accordance with the escalating prevalence of obesity in reproductive age and related disorders of carbohydrate metabolism (i.e., insulin resistance or impaired β-cell function) the number of pregnant women affected by gestational diabetes mellitus (GDM) is rising (11). Because β-cell function remained attenuated after delivery (21), females affected by GDM are at high risk for developing overt type 2 diabetes in their later life (10, 14, 22, 23, 24, 27). Recently, we and others have highlighted the advantage of the postpartum oral glucose tolerance test (OGTT) performed within the first 6 mo after delivery, since 120 min-postload glucose (120'-PLG) was shown to be superior to fastig plasma glucose (FPG) measurement by identifying subjects at specific metabolic assessments: 3-h OGTT, frequently sampled intravenous glucose tolerance test (FSIGT) with markers of inflammation and endothelial function. pGDMs were annually invited for reexaminations for a maximum of 10 yr. Multiple linear regression suggested that postload glucose levels at 60 min (60'-PLG) were a better predictor for insulin sensitivity [β: −0.10, 95% confidence interval (CI) −0.14 to −0.05, P < 0.001] and disposition index (DI) (β: −0.07, 95% CI −0.12 to −0.02, P = 0.004) estimated from the FSIGT compared with other time points during the OGTT. The association between 60'-PLG and insulin secretion was of particular importance in women after GDM. We further identified associations of 60'-PLG with ultrasensitive C-reactive protein, plasminogen activator inhibitor 1, tissue plasminogen activator, endothelial-leukocyte adhesion molecule 1, and intercellular adhesion molecule (ICAM)-1. There appeared to be no interactions between females with pGDM and controls, suggesting comparable effects. We observed that 60'-PLG levels were closely related to the later onset of diabetes independent from the routinely measured FPG and 120'-PLG levels. Our data suggest that the sole interpretation of FPG and 120'-PLG of the OGTT leads to significant loss of information. Particularly 60'-PLG was shown to distinguish women at low or high metabolic and cardiovascular risk.

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To date only the fasting (≥100 mg/dl) and the 120'-PLG (≥140 mg/dl) measurements are recommended for diagnosis of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), the two major forms of prediabetic dysglycemia (6, 12, 13). However, some epidemiological studies demonstrated that a significant number of subjects developing overt diabetes during follow-up had normal glucose tolerance (NGT) at baseline and thus would be missed by conventional OGTT screening for prediabetes (5, 35). In the past only few research groups focused on investigations of the contributing information from other time points during the OGTT examination to detect pathologies in glucose regulation (39). This is surprising, particularly considering the postpartum risk stratification, since the 60 min (60'-PLG) levels are integrated in the diagnostic algorithm for GDM during the pregnant state (17). Moreover, isolated hyperglycemia at 60 min in pregnant females was recently shown to be closely associated with impaired cardiovascular risk profile after delivery (32). Some authors previously suggested that particularly 60'-PLG levels might be a better predictor for insulin resistance or impaired insulin secretion compared with FPG or 120'-PLG, and a cut-off level of 155 mg/dl has been proposed to discriminate between low- and high-risk groups (5). However, the interpretation of OGTT measurements other than fasting and at 120 min after ingestion is still far from established in the medical decision-making process, and for our knowledge there is almost no information on females with history of GDM available at that moment.

We hypothesized that the sole interpretation of FPG and 120'-PLG from the OGTT examination following pregnancy with GDM causes a significant loss of information. To clarify this topic, we aimed to assess the association of glucose measurements at multiple time points during the postpartum OGTT with the
degree of impaired insulin resistance and glucose disposition estimated independently from OGTT data as the primary objective of this report. As secondary outcomes, we investigated the specific association of 60'-PLG with subclinical inflammation, adhesion molecules, and the later development of diabetes.

MATERIALS AND METHODS

Study participants. This report was performed within the “Vienna Post-Gestational Diabetes Project.” A detailed description of the study design was reported previously (e.g., see Ref. 38). In short, we consecutively included 110 women with a recent history of GDM (pGDM), attending the diabetes outpatient clinic of the Medical University of Vienna during pregnancy with 3–6 mo after delivery. GDM was diagnosed according to the guidelines of the 4th International Workshop Conference on GDM with a 75-g OGTT (27). Women with overt type 2 diabetes were excluded. Additionally, 41 women, after gestation without GDM served as a control group (CONT).

All subjects received a complete metabolic characterization as follows: fasting blood samples of ultrasensitive C-reactive protein (usCRP); the prothrombotic factors plasminogen activator inhibitor 1 (PAI-1), tissue plasminogen activator (TPA); adhesion molecules intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule (VCAM), and endothelial-leukocyte adhesion molecule 1 (ELAM); and serum cholesterol levels. OGTT measurements were performed at the fasting state and at 10, 20, 30, 60, 90, 120, 150, and 180 min after ingestion of a 75-g glucose solution. We further performed examinations of routine laboratory body composition, including body mass index (BMI) and waist circumference (WC). One hundred two pGDMs and 39 controls received a frequently sampled intravenous glucose tolerance test (FSIGT): glucose (300 mg/kg body wt) was infused for 30 s starting at time 0. This report was performed within the “Vienna Post-Gestational Diabetes Project.” A detailed description of the study design was reported previously (e.g., see Ref. 38). In short, we consecutively included 110 women with a recent history of GDM (pGDM), attending the diabetes outpatient clinic of the Medical University of Vienna during pregnancy with 3–6 mo after delivery. GDM was diagnosed according to the guidelines of the 4th International Workshop Conference on GDM with a 75-g OGTT (27). Women with overt type 2 diabetes were excluded. Additionally, 41 women, after gestation without GDM served as a control group (CONT).

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Thereafter, pGDMs were annually invited for reexaminations (OGTT and biometric parameters) until December 2010. A manifestation of overt diabetes was diagnosed if FPG or 120'-PLG levels exceeded 126 or 200 mg/dl, respectively. As previously reported, 23 (21.3%) subjects with a history of GDM developed overt diabetes during follow-up. The median time to diagnosis was 3.0 yr (2.0–4.5 yr). Patients with no reported diabetes manifestation had a median follow-up of 5.0 yr (4.0–7.5) (14). While the association of fatty liver and parameters of the metabolic syndrome with diabetes manifestation were reported elsewhere (9, 14), data on the specific objectives of the present report (i.e., association of multiple OGTT measurements with FSIGT data or subclinical inflammation) were not reported until now.

This study was approved by the local ethics committee (Ethics Committee of the Medical University of Vienna) and performed in accordance with the Declaration of Helsinki. All subjects gave written informed consent to participate in the study.

Laboratory methods. Plasma glucose was measured using an automated glucose analyzer (Beckman, Fullerton, CA). Insulin (Serono Diagnostics) was quantified in duplicate by radioimmunoassay with interassay coefficients of variation of <5.5%. Adhesion molecules were measured in duplicate with ELISA (British Biotechnology Product). Plasma concentrations of active PAI-1 antigen were measured by an ELISA system (Technoclone) according to the manufacturer’s instructions. TPA antigen concentrations were determined using the Coali tiger TPA enzyme-linked immunosorbent assay (Chromogenix). usCRP was measured by means of particle-enhanced immunonephelometry (N High Sensitivity CRP Reagent; BN Systems).

Statistical analysis. Continuous variables were summarized by means and SD and were compared with Student’s t-test. Comparisons of metric-scaled variables in three groups (CONT, pGDM-IS, pGDM-IR) were performed with Fisher protected least-significant difference tests. Data transformations were performed in case of skewed distributed variables (PAI-1, TPA, usCRP, triglycerides, AUGC: natural logarithm (ln); SI, DI, ΔAIRG: square root (sqrt)). The time to an event was summarized by median values and interquartile ranges (IQR). Nonparametric procedures (Kruskal-Wallis and Wilcoxon test) were used to compare times of maximum glucose concentration during the OGTT.

Stepwise linear regression analyses were used to assess the association between different glucose measurements during the OGTT with SI and DI estimated from the FSIGT. The selection algorithm was performed with Akaike’s Information Criterion. Twenty-fold cross validated variable shrinkage (L1-penalized regression models) was used as sensitivity analysis. We used Pearson’s product-moment correlation for analyzing linear associations between PLG levels and outcome parameters.

Kaplan-Meier estimators and the proportional hazard model were used to assess the predictability for developing overt diabetes in the future. The effects were expressed as hazard ratios (HR).

For a better interpretation of the regression coefficients, glucose levels were converted in millimoles per liter before being included in linear and Cox regression models.

Statistical analysis was performed with R (version 2.14.2) (31). For penalized regression models we used the contributed package developed by Goeman (15). A two-sided P value ≤0.05 was considered statistically significant.

RESULTS

Glucose kinetics during the OGTT. Descriptive comparisons of pGDM and CONT subjects are given in Table 1. Figure 1, A–C, revealed that glucose kinetics during the postpartum OGTT strongly depends on status of insulin resistance. The glucose peak after ingestion was lowest in the control group (n = 41, 134 ± 20 mg/dl) but was significantly increased in the pGDM-IS subgroup (n = 63, 156 ± 27 mg/dl, pGDM-IS vs. CONT: P < 0.001) and particularly in women with impaired insulin sensitivity (n = 39, 176 ± 37 mg/dl, pGDM-IR vs. pGDM-IS: P < 0.001 and pGDM-IR vs. CONT: P < 0.001). Insulin-resistant subjects reached the maximum serum concentration at a median time of 60 min (IQR: 30–60) after ingestion. In contrast CONT (median: 30 min, IQR: 30–30) and pGDM-IS (median: 30 min, IQR: 30–60) reached the maximum serum concentration significantly earlier. IFG or IGT was observed in 18 (16%) and 21 (19%) females with pGDM, respectively. Of a total of 56 pGDMs with 60'-PLG ≥155 mg/dl, 32 subjects (57%) showed normal FPG and 120'-PLG levels.

Association of OGTT measurements with parameters of glucose disposition. As shown in Table 2 univariable correlation analyses revealed a significant inverse association between serum glucose levels during the OGTT and sqrt(SI). By using stepwise variable selection, only 60'-PLG (mmol/l) reached significance (β: −0.10, 95% confidence interval (CI) −0.15 to 0.03, P = 0.001). This was confirmed by multivariable analyses (Table 3): pGDM-IS, pGDM-IR, and 60'-PLG were independently associated with SI, DI, ΔAIRG, and AUGC. Association of OGTT measurements with parameters of glucose disposition. As shown in Table 2 univariable correlation analyses revealed a significant inverse association between serum glucose levels during the OGTT and sqrt(SI). By using stepwise variable selection, only 60'-PLG (mmol/l) reached significance (β: −0.10, 95% confidence interval (CI) −0.15 to 0.03, P = 0.001). This was confirmed by multivariable analyses (Table 3): pGDM-IS, pGDM-IR, and 60'-PLG were independently associated with SI, DI, ΔAIRG, and AUGC.
Table 1. Characteristics of the study sample

<table>
<thead>
<tr>
<th></th>
<th>n (CONT/pGDM)</th>
<th>CONT</th>
<th>pGDM</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>41/110</td>
<td>31.0 ± 5.7</td>
<td>32.7 ± 4.7</td>
<td>0.070</td>
</tr>
<tr>
<td>SI, 10−1 min−1</td>
<td>39/102</td>
<td>5.40 ± 2.6</td>
<td>3.94 ± 2.6</td>
<td>0.003</td>
</tr>
<tr>
<td>DL, 10−4 min−1</td>
<td>39/102</td>
<td>2.54 ± 1.8</td>
<td>1.45 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>36/104</td>
<td>81.2 ± 14.5</td>
<td>91.3 ± 13.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>38/109</td>
<td>25.0 ± 5.7</td>
<td>27.3 ± 5.4</td>
<td>0.024</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dl</td>
<td>41/107</td>
<td>116.0 ± 44.0</td>
<td>129.0 ± 33.5</td>
<td>0.056</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dl</td>
<td>41/110</td>
<td>61.4 ± 14.0</td>
<td>55.7 ± 14.3</td>
<td>0.032</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>41/110</td>
<td>193.3 ± 49.0</td>
<td>208.9 ± 41.8</td>
<td>0.053</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>41/110</td>
<td>89.8 ± 43.1</td>
<td>116.5 ± 99.7</td>
<td>0.107*</td>
</tr>
<tr>
<td>PAI-1, ng/ml</td>
<td>33/107</td>
<td>18.3 ± 15.7</td>
<td>28.3 ± 22.5</td>
<td>0.001*</td>
</tr>
<tr>
<td>TPA, ng/ml</td>
<td>33/107</td>
<td>3.03 ± 1.3</td>
<td>4.52 ± 2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICAM-1, ng/ml</td>
<td>39/101</td>
<td>238.0 ± 54.1</td>
<td>298.5 ± 78.6</td>
<td>0.001</td>
</tr>
<tr>
<td>VCAM, ng/ml</td>
<td>39/101</td>
<td>502.3 ± 164</td>
<td>613.6 ± 200</td>
<td>0.002</td>
</tr>
<tr>
<td>ELAM, ng/ml</td>
<td>34/102</td>
<td>45.1 ± 18.5</td>
<td>52.0 ± 24.5</td>
<td>0.139</td>
</tr>
</tbody>
</table>

Data are nos. and means ± SD. CONT, control; pGDM, previous gestational diabetes mellitus; SI, insulin sensitivity index; DL, disposition index; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; PAI-1, plasminogen activator inhibitor 1; TPA, tissue plasminogen activator; usCRP, ultrasensitive C-reactive protein; ICAM-1, intercellular adhesion molecule 1; VCAM, vascular cell adhesion molecule 1; ELAM, endothelial-leukocyte adhesion molecule 1. *P values are based on log-transformed data.

−0.05, P < 0.001]. Comparable results were observed by using 20-fold cross validated L1-penalized regression: 60’-PLG showed the strongest association with sqrt(SI), whereas FPG, 10’-PLG, 20’-PLG, 120’-PLG, and 180’-PLG were penalized exactly to zero. The association between 60’-PLG and degree of insulin resistance was comparable in pGDMS (r = −0.38, P < 0.001) and control subjects (r = −0.43, P = 0.006), and thus no interaction was found by including an interaction term in the linear model (P60’-PLG−group = 0.318).

Comparable results were observed considering sqrt(DI) (Table 2). Once again, 60’-PLG (mmol/l) was selected as the significant predictor (β: −0.07, 95% CI −0.12 to −0.02, P = 0.004) by stepwise selection in addition to 20’-PLG (P = 0.020) and 30’-PLG (P = 0.013) levels. By using L1-penalization, 60’-PLG showed the strongest association with sqrt(DI). FPG, 10’-PLG, 20’-PLG, 90’-PLG, 150’-PLG, and 180’-PLG were penalized to zero. Although there appeared no significant interaction between pGDMS and control subjects (P60’-PLG−group = 0.205), the association of 60’-PLG with sqrt(DI) was more pronounced in women with a history of GDM (r = −0.55, P < 0.001) compared with control subjects (r = −0.10, P = 0.538). However, this interaction was more pronounced when only sqrt(AIRG) as a parameter of insulin secretion was concerned as the dependent variable: pGDMS (r = −0.31, P = 0.001) vs. CONT (r = 0.17, P = 0.294, P60’-PLG−group = 0.028).

The observed associations between 60’-PLG and parameters of glucose disposition remained also significant after adjustment for BMI and WC.

Association of 60’-PLG with latent inflammation, markers of hemostasis, adhesion molecules, as well as with body composition and atherogenic lipid profile. As shown in Fig. 2, we identified positive linear associations between 60’-PLG and ln(PAI-1) (r = 0.36, P < 0.001), ln(TPA) (r = 0.40, P < 0.001), ln(usCRP) (r = 0.43, P < 0.001), ICAM-1 (r = 0.37, P < 0.001), and ELAM (r = 0.32, P < 0.001) but not with VCAM (r = 0.12, P = 0.149). Regarding parameters of body composition, 60’-PLG levels were positively correlated with BMI (r = 0.38, P < 0.001) as well as with WC (r = 0.42, P < 0.001). The results remained unchanged after additionally including FPG and 120’-PLG levels in a stepwise regression. No interactions were found between CONT and pGDMS.

Although 60’-PLG was significantly associated with atherogenic lipid profile in univariable analysis [total cholesterol: r = 0.17, P = 0.039; low-density lipoprotein cholesterol: r = 0.21, P = 0.012; high-density lipoprotein (HDL) cholesterol: r = −0.22, P = 0.007; ln(triglycerides): r = 0.27, P = 0.001], the correlations of HDL and ln(triglycerides) diminished after including FPG and 120’-PLG levels in a multivariable model.

Association of 60’-PLG with diabetes incidence. Longitudinal analyses revealed that 60’-PLG levels (mmol/l) were significantly related with the risk for overt diabetes up to 10 yr of follow-up (HR 1.63, 95% CI 1.36–1.97, P < 0.001). This effect was shown to be independent of FPG (P = 0.006) or 120’-PLG (P = 0.019) in bivariable analysis but failed significance after adjustment for both variables: FPG in addition to 120’-PLG (P = 0.245). Previously suggested cut-off levels of 60’-PLG ≥155 mg/dl (HR 7.4, 95% CI 2.2–25.0, P < 0.001; Fig. 3) as well as ≥161 mg/dl (HR 8.5, 95% CI 2.5–28.5, P < 0.001) showed a good predictability of diabetes, independent of baseline IFG and IGT status after adjustment in multivariable analyses. This observation was also approved by a second model excluding those women with IFG or IGT including 60’-PLG (mmol/l) as a covariate (HR 2.18, 95% CI 1.4–3.5, P = 0.001). Thus, we conclude that of all 23 reported cases of overt diabetes in up to 10 yr of follow-up, 16 (70%) are explained by IFG or IGT at baseline. By adding the information of 60’-PLG (with a cut-off of ≥155 or ≥161 mg/dl), the ability to predict type 2 diabetes is increased to 96%. Moreover, there remained an association of baseline 60’-PLG levels (mmol/l) with ln(AUCG) of the last follow-up visit (β: 0.037 95% CI 0.008–0.066, P = 0.012), even in a full adjusted linear regression model (corrected for baseline FPG and 120’-PLG as well as time of follow-up).

DISCUSSION

This prospective study aimed to assess the contributing information of different time points during the OGTT examination in postpartum risk stratification. The data of this study suggest that particularly glucose measurements at 60 min after ingestion are potentially predictive for impaired insulin sensitivity as well as β-cell dysfunction and thus closely associated with the later development of overt diabetes in females after pregnancy with GDM. Moreover, we observed significant associations of 60’-PLG with subclinical inflammation and adhesion molecules indicating an increased risk for atherosclerosis.

To date it is well accepted that the two conventional prediabetic conditions IFG and IGT represent different underlying deteriorations in carbohydrate metabolism. Whereas IFG and IGT are highly predictive for the later development of type 2 diabetes, it was proposed by previous investigations that subjects with isolated IFG particularly suffer from impaired first-phase insulin secretion and increased hepatic insulin resistance.
It was further proposed that subjects with IFG exhibit an excessive increase in glucose levels at 30 and 60 min during the OGTT examination (1), whereas the decline in plasma glucose levels after 30–60 min corresponds to \(\beta\)-cell dysfunction and moreover to insulin resistance in skeletal muscle (2). As a consequence, impaired muscle insulin sensitivity is rather reflected by elevated 120'-PLG levels resulting in IGT (5). Accordingly, it was hypothesized that elevated 60'-PLG levels are a good indicator of total body insulin resistance (reflecting both liver and skeletal muscle insulin resistance) and \(\beta\)-cell dysfunction (5). These observations are comparable to our findings in subjects after pregnancy with GDM, since mainly pGDMs with a higher degree of insulin resistance reached their maximum glucose concentrations significantly later (at 60 min) compared with their insulin-sensitive counterparts or healthy controls, who even showed attenuated glucose profiles with significantly lower maximum concentrations after ingestion. Therefore, our results indicate that glucose kinetics during the OGTT examination might comprise quite more prognostic information as is given by the routinely measured and interpreted FPG and 120'-PLG levels, probably mirrored by the 60'-PLG value. This is in accordance with previous studies that have proved that all of the samples of the OGTT, and not only the fasting and 2-h values, may yield relevant clinical information. Specifically, it was proved that the shape of the OGTT curves (glucose, but also insulin and C-peptide) is related to the subject’s metabolic condition (34).

With the major advantage of including the data of a standardized euglycemic-hyperinsulinemic clamp test, Manco et al. characterized the metabolic phenotype of subjects with NGT but excursed 60'-PLG levels participating in the Relationship between Insulin Sensitivity and Cardiovascular Risk study and found that 1-h plasma glucose identifies another high-risk subgroup with impaired insulin sensitivity and \(\beta\)-cell dysfunction, otherwise regarded as having NGT. Therefore, the authors recommended including the 60'-PLG measurement as an ad-

![Spaghetti plots of plasma glucose levels during the oral glucose tolerance test (OGTT) in control (n = 41) patients (A), patients with previous gestational diabetes mellitus (pGDM) who are insulin sensitive (n = 63) (B), and patients with pGDM who are insulin resistant (n = 39) (C).](attachment:image.png)

Table 2. *Univariable associations between glucose measurements during the OGTT with parameters of insulin resistance and glucose disposition*

<table>
<thead>
<tr>
<th>OGTT, min</th>
<th>SI*</th>
<th>P Value</th>
<th>DI*</th>
<th>P Value</th>
<th>(\Delta)AIRG*</th>
<th>P Value</th>
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<tbody>
<tr>
<td>0</td>
<td>-0.34</td>
<td>&lt;0.001</td>
<td>-0.32</td>
<td>&lt;0.001</td>
<td>-0.12</td>
<td>0.167</td>
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<tr>
<td>10</td>
<td>-0.19</td>
<td>0.028</td>
<td>-0.14</td>
<td>0.106</td>
<td>-0.02</td>
<td>0.807</td>
</tr>
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<td>20</td>
<td>-0.26</td>
<td>0.002</td>
<td>-0.20</td>
<td>0.017</td>
<td>-0.02</td>
<td>0.806</td>
</tr>
<tr>
<td>30</td>
<td>-0.36</td>
<td>&lt;0.001</td>
<td>-0.43</td>
<td>&lt;0.001</td>
<td>-0.22</td>
<td>0.009</td>
</tr>
<tr>
<td>60</td>
<td>-0.45</td>
<td>&lt;0.001</td>
<td>-0.52</td>
<td>&lt;0.001</td>
<td>-0.25</td>
<td>0.003</td>
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<tr>
<td>90</td>
<td>-0.46</td>
<td>&lt;0.001</td>
<td>-0.48</td>
<td>&lt;0.001</td>
<td>-0.21</td>
<td>0.011</td>
</tr>
<tr>
<td>120</td>
<td>-0.42</td>
<td>&lt;0.001</td>
<td>-0.41</td>
<td>&lt;0.001</td>
<td>-0.19</td>
<td>0.026</td>
</tr>
<tr>
<td>150</td>
<td>-0.35</td>
<td>&lt;0.001</td>
<td>-0.25</td>
<td>0.003</td>
<td>-0.03</td>
<td>0.752</td>
</tr>
<tr>
<td>180</td>
<td>-0.29</td>
<td>&lt;0.001</td>
<td>-0.22</td>
<td>0.008</td>
<td>-0.04</td>
<td>0.603</td>
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</tbody>
</table>

\(\Delta\)AIRG, acute insulin response to glucose; OGTT, oral glucose tolerance test. *A square root transformation was performed.
ditional important index for impaired glucose metabolism in clinical practice (26). Indeed, 60'-PLG levels were suggested to be superior to FPG and 120'-PLG as predictors for more severe glycemic disorders in the San Antonio Heart Study (3) and the Botnia study (4) especially when other metabolic deteriorations were present. This concept is also corroborated by the results of our study and specifically extended to females after pregnancy with GDM, since out of multiple measurements during the OGTT, 60'-PLG was selected as the most predictive parameter for insulin sensitivity and glucose DI, which describes the capacity of the β-cell to compensate for increasing insulin resistance. Moreover, we observed a strong association of 60'-PLG with the incidence of type 2 diabetes in up to 10 yr of follow-up, by using 60'-PLG as a covariate, but also after categorizing according to the previously described cut-off levels as well as after exclusion of subjects with altered FPG and 120'-PLG levels.

Our observations are of major clinical importance, particularly for females after pregnancy with GDM. It was suggested by the Diabetes Prevention Program that women with a history of GDM and presence of IGT after pregnancy showed a significantly increased incidence of overt diabetes but also received a greater effect of treatment strategies compared with females with IGT but without former GDM (30). Therefore, isolated alterations in 60'-PLG levels after pregnancy affected by GDM might represent another phenotype of altered glucose metabolism missed by conventional postpartum screening but would take benefit if referred to an early and sufficient treatment (i.e., lifestyle modification or even pharmacological agents). The higher conversion rates to overt diabetes compared with other epidemiological studies (3, 4) of mixed populations underlines the need of postpartum risk stratification in this specific study collective.

As secondary outcomes, we identified positive associations between 60'-PLG levels and markers of subclinical systemic inflammation, including usCRP, PAI-1, TPA, and soluble cell

Fig. 2. Association of OGTT 60 min (60')-postload glucose (PLG) levels with plasminogen activator inhibitor 1 (PAI-1, A), ultrasensitive C-reactive protein (usCRP, B), intercellular adhesion molecule 1 (ICAM-1, C), and endothelial-leukocyte adhesion molecule 1 (ELAM, D).

Fig. 3. Kaplan-Meier Plot for the manifestation of diabetes up to 10 yr of follow-up: for subjects with 60'-PLG levels ≥155 mg/dl, y-Axis, percent of patients under risk; x-axis, time of follow-up in days.

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adhesion molecules. The majority of these parameters was previously shown to be enclosed with metabolic deteriorations but might additionally reflect an early onset of atherosclerosis (7, 8, 18). The presence of subclinical inflammation is also a characteristic feature of females with a history of GDM, and it was postulated that transient hyperglycemia during pregnancy represents a latent form of the metabolic syndrome, indicating an increased risk for the later development of cardiovascular disease (16, 32). Therefore, our results further suggested that the additional information gained from the 60’-PLG levels is not only helpful for the prediction of type 2 diabetes but also for identifying females after GDM with high risk for cardiovascular diseases. Indeed, it was recently demonstrated by Strandberg et al. that 1-h plasma glucose levels were related to total and cardiovascular mortality in a 44-yr follow-up study in male subjects (33). However, data focused on cardiovascular events in females and, particularly, in subjects with a history of GDM are still missing.

Some strength and limitations of the study should be pointed out. As a major advantage of this study, estimators of insulin resistance and DI were performed independently of the OGTT data, which ensures consistent and reliable model estimators. The use of variable shrinkage as sensitivity analysis, the longitudinal follow-up (up to 10 yr), and the inclusion of a subgroup of women after normal pregnancy are further advantages. However, the longitudinal analyses are limited by the number of subjects who developed diabetes and thus indicate the need for larger investigations with long-term follow-up in this field particularly focused on the risk for cardiovascular disease.

We summarize that the clinical information from the OGTT examination after pregnancy with GDM could be significantly improved by including the 60’-PLG levels in the medical decision-making process. Previously proposed cut-off levels could be used to distinguish between low- and high-risk groups. Females after GDM with solely excursions of plasma glucose levels at 1 h after ingestion should be considered as having "prediabetes" and treated as if IFG or IGT is present.

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DISCLOSURES

The authors have nothing to disclose.

AUTHOR CONTRIBUTIONS


REFERENCES


