Association Between Metabolic Deteriorations and Prior Gestational Diabetes According to Weight Status

Jessica Vigneault, Simone Lemieux, Véronique Garneau, S. John Weisnagel, André Tchernof, and Julie Robitaille

Objective: The aim of the present study is to investigate the effect of prior gestational diabetes mellitus (GDM) on glucose and insulin homeostasis according to weight status.

Methods: The analysis included 299 women, 216 with [GDM(+)] and 83 without prior GDM [GDM(-)]. The mean time between pregnancy and testing was 3.9 years. Glucose values were obtained from a 2-h 75 g oral glucose tolerance test (OGTT). Body composition was measured by dual-energy X-ray.

Results: In women with normal BMI, fasting glucose, 2-h post-OGTT glucose, and HbA1c were higher for GDM(+) (P < 0.05). Normal-weight women with GDM(+) presented lower HOMA-IR, insulin secretion, and insulinogenic index (P < 0.05) compared to GDM(-). Body fat and android fat mass were higher, while fat mass was similar, and lean body mass was decreased in GDM(+) vs. GDM(-) with normal weight (P < 0.05). A greater proportion of GDM(+) with overweight/obesity had prediabetes (72.1%) or type 2 diabetes (T2D) (21.7%) vs. GDM(-) and overweight/obesity (17.1% and 2.4%) or GDM(+) and normal weight (60.5% and 14.0%).

Conclusions: A combination of GDM and overweight/obesity is associated with T2D-related metabolic deteriorations. Nevertheless, normal-weight women with GDM(+) had increased android fat and greater metabolic complications, suggesting that women with prior GDM should benefit from lifestyle intervention, regardless of their weight status.

Introduction

Gestational diabetes mellitus (GDM) is defined as any glucose intolerance with onset or first recognition during pregnancy. From 6 to 12 weeks after delivery, more than thirty percent of women with previous GDM may be diagnosed with prediabetes (1,2). Furthermore, the future risk of developing type 2 diabetes (T2D) varies from 20 to 70%, depending on insulin resistance and plasma glucose levels during pregnancy (3,4).

Prepregnancy obesity has been recognized as a critical risk factor for GDM and for T2D (5), and obesity now affects a greater proportion of women of reproductive age (2,6). Similarly, the rise in T2D prevalence coincides with the actual obesity pandemic and now concerns young adults (7,8). Recent studies provided evidence that T2D risk is higher in women with both obesity and a history of GDM (9,10). Still, previous studies did not show a clear dissociation between obesity and hyperglycaemia during pregnancy as contributors to future maternal complications. Both obesity and GDM have been positively associated with maternal and neonatal outcomes, metabolic deteriorations, and important T2D risk factors (9,11-13). Several studies point to obesity as the main factor causing metabolic deteriorations among GDM women (14,15). GDM may have distinct effects on clinical outcomes independently of obesity status (16). However, there is a lack of information in lean women with a GDM history. The aim of the present study is to investigate the effect of prior GDM on glucose and insulin homeostasis according to weight status.

Methods

Subjects and study design

This research was conducted at the Institute of Nutrition and Functional Foods (INAF) in Quebec City, Canada between 2009 and 2012. Women were recruited by access to databanks from...
TABLE 1 Participant’s characteristics by GDM and weight status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal weight</th>
<th></th>
<th>Overweight</th>
<th></th>
<th>Obese</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GDM(+) n = 86</td>
<td>GDM(−), n = 42 P 0.83</td>
<td>GDM(+) n = 69 GDM(−), n = 26 P 0.97</td>
<td>GDM(+) n = 61 GDM(−), n = 15 P 0.04</td>
<td></td>
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</tr>
<tr>
<td>Age (years)</td>
<td>36.2 ± 0.6</td>
<td>36.0 ± 0.8</td>
<td>36.0 ± 0.6</td>
<td>36.0 ± 0.9</td>
<td>37.0 ± 0.6</td>
<td>34.1 ± 1.2</td>
</tr>
<tr>
<td>Parity</td>
<td>2.14 ± 0.89</td>
<td>2.12 ± 0.13 P 0.91</td>
<td>1.93 ± 0.11</td>
<td>2.38 ± 0.17 P 0.03</td>
<td>2.20 ± 0.11</td>
<td>2.07 ± 0.22 P 0.59</td>
</tr>
<tr>
<td>Time between index pregnancy</td>
<td>3.48 ± 0.18</td>
<td>3.92 ± 0.26 P 0.16</td>
<td>3.43 ± 0.24</td>
<td>4.56 ± 0.39 P 0.02</td>
<td>3.57 ± 0.25</td>
<td>2.85 ± 0.51 P 0.21</td>
</tr>
<tr>
<td>and metabolic testing (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Caucasian (%)</td>
<td>78 (90.70)</td>
<td>39 (92.66) P 0.58</td>
<td>58 (84.06)</td>
<td>23 (88.46) P 0.77</td>
<td>54 (88.52)</td>
<td>14 (93.33) P 0.86</td>
</tr>
<tr>
<td>BMI (kg m(^{-2}))</td>
<td>22.1 ± 0.2</td>
<td>21.9 ± 0.3 P 0.45</td>
<td>27.3 ± 0.2</td>
<td>26.7 ± 0.3 P 0.17</td>
<td>36.0 ± 0.7</td>
<td>33.9 ± 1.4 P 0.11</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>79.1 ± 0.7</td>
<td>77.5 ± 0.9 P 0.15</td>
<td>91.2 ± 0.8</td>
<td>88.5 ± 1.3 P 0.09</td>
<td>107.8 ± 1.6</td>
<td>102.7 ± 3.3 P 0.16</td>
</tr>
</tbody>
</table>

Mean ± SE or n (%). P values calculated by LS means in an ANOVA model.

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the provincial health plan registry, the Régie de l’assurance maladie du Québec (RAMQ) (ICD-9 648.0;648.8 and ICD-10 O24.4;O24.9). Women living in and around the greater Quebec City area aged ≥18 years with a pregnancy between 2003 and 2010 were invited to participate. A total of 3,896 women were on the lists provided by the RAMQ and were sent an invitation letter. The GDM diagnosis was confirmed by reviewing medical records of participants. Exclusion criteria included: pregnancy at the time of the study; or type 1 diabetes. Eligibility was assessed through telephone interviews. A total of 565 participants contacted the research team of which 75 were not eligible and 254 refused to participate. The study sample consisted of 216 women with prior GDM (GDM(+)) and 83 women without prior GDM (GDM(−)). Ethical approval for the study was obtained from the Laval University research ethics committee. Informed consent was obtained from all subjects. This trial was registered at clinicaltrials.gov as NCT01340924.

Anthropometric measurements

Anthropometric measurements included weight, height, and waist circumference (17). Subjects were measured by a trained registered dietician. Body mass index (BMI) was calculated in kg m\(^{-2}\). Women were stratified into three BMI groups: normal (18.5-24.9 kg m\(^{-2}\)), overweight (25-29.9 kg m\(^{-2}\)), and obese (≥30 kg m\(^{-2}\)) (18). Body composition including body fat, regional fat, and lean body mass was measured by dual-energy X-ray absorptiometry (DEXA, GE LUNAR, Madison, WI) using automatic total body scan mode. The abdominal region of interest (android) was measured within a 5-cm-wide region across the entire abdomen, just above the iliac crest at a level of the 4th lumbar vertebra on the whole body scan (19). The hip region (gynoid) was delineated below the pelvis cut line and had 1.5 times the height of the android region (20). The coefficient of variation of whole-body measurements was below 1.0%. Because of poor image resolution caused by excess of adipose tissue and weight limitations of the DEXA table (300 pounds), data from some women were not available [n = 42(14) (36.8%) for GDM(+), n = 12(79) (15.2%) for GDM(−)]. In addition, body composition measured by DEXA became available only in 2010 when recruitment had already begun. For these reasons, results on body composition using DEXA are available only for a subsample of women with prior GDM (n = 72/216, 33.3%) and without prior GDM (n = 67/83, 81.7%). Characteristics (age, parity, time between pregnancy and metabolic testing, and waist circumference) of the subsample of women with measures of body composition were similar to those of women without measures of body composition (not shown). However, as expected, women for whom body composition measures were not available had higher BMI and fasting and 2-h post-OGTT insulin (P < 0.01 for all, data not shown).

Oral glucose tolerance test

At the time of testing, a standard 75-g OGTT was administered to all participants. Plasma glucose was measured by enzyme technology (21), and insulin levels were measured by RIA (22). HbA\(_1\) was determined using Cobas Integra 800 and standardized to the National Glycated Haemoglobin Standardization Program (Integra; Roche, Switzerland). HbA\(_1\) is shown in percentage (%) and in International Federation of Clinical Chemistry and Laboratory Medicine units (mmol mol\(^{-1}\)). Women were separated in categories according to glucose tolerance status [normal, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), prediabetes, and T2D] based on the most recent guidelines of the Canadian Diabetes Association (23). IFG was defined by a fasting glucose (IFG), impaired glucose tolerance (IGT), prediabetes, and T2D based on the most recent guidelines of the Canadian Diabetes Association (23). IFG was defined by a fasting glucose value between 6.1 and 7.0 mmol l\(^{-1}\) and IGT by a 2-h plasma glucose value between 7.0 and 11.1 mmol l\(^{-1}\). Prediabetes was defined as IFG and/or IGT and/or HbA\(_1\) between 6.0 and 6.4% (42.1 and 46.4 mmol mol\(^{-1}\)). T2D was defined as fasting plasma glucose ≥7.0 mmol l\(^{-1}\) or 2-h plasma glucose post-OGTT ≥11.1 mmol l\(^{-1}\) and HbA\(_1\) ≥6.5% (47.5 mmol mol\(^{-1}\)). Abnormal glucose metabolism was defined as the presence of one or more of these criteria.

AUC for glucose and insulin were calculated by the trapezoidal method (24). Insulin secretion was obtained by the ratio of the AUCI to the AUCg (25). The insulinoenic index for insulin secretion (insulin 30 min—fasting insulin/glucose 30 min—fasting glucose) was also calculated (12,24). HOMA-IS was calculated with the following formula: (fasting insulin concentration × fasting glucose concentration)/22.5 (26). The Matsuda index was calculated as
TABLE 2 Body fat composition and insulin and glucose profile according to GDM antecedent and weight status

| Characteristic | Normal weight |  |  |  |  |  |  |  |  |
|----------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
|                | GDM(+), n = 86 | GDM(−), n = 42 | P             | GDM(+), n = 69 | GDM(−), n = 26 | P             | GDM(+), n = 61 | GDM(−), n = 15 | P             |
| Fasting glucose (mmol L⁻¹) | 5.58 ± 0.07 | 5.18 ± 0.10 | 0.001 | 5.63 ± 0.07 | 5.32 ± 0.12 | 0.03 | 6.05 ± 0.09 | 5.38 ± 0.17 | 0.0004 |
| 2-h post-OGTT glucose (mmol L⁻¹) | 7.95 ± 0.31 | 5.51 ± 0.45 | <0.0001 | 7.85 ± 0.27 | 6.32 ± 0.44 | 0.002 | 9.34 ± 0.28 | 7.05 ± 0.58 | 0.0002 |
| Fasting insulin (pmol L⁻¹) | 59.49 ± 3.20 | 84.66 ± 4.61 | <0.0001 | 77.93 ± 3.88 | 95.23 ± 6.32 | 0.02 | 123.44 ± 7.21 | 128.07 ± 14.30 | 0.77 |
| 2-h post-OGTT insulin (pmol L⁻¹) | 466.81 ± 33.41 | 426.95 ± 48.11 | 0.50 | 608.24 ± 44.25 | 463.73 ± 71.03 | 0.09 | 825.64 ± 65.88 | 698.13 ± 130.66 | 0.39 |
| HbA₁ (%) | 5.56 ± 0.04 | 5.34 ± 0.05 | 0.0005 | 5.53 ± 0.04 | 5.34 ± 0.07 | 0.02 | 5.71 ± 0.05 | 5.34 ± 0.10 | 0.001 |
| AUC for glucose (pmol L⁻¹ per min) | 1.020 ± 30 | 766 ± 42 | <0.0001 | 1.013 ± 27 | 785 ± 45 | <0.0001 | 1176 ± 26 | 904 ± 53 | <0.0001 |
| AUC for insulin (pmol L⁻¹ per min) | 47,498 ± 2,620 | 52,303 ± 3,772 | 0.30 | 57,915 ± 2,900 | 52,458 ± 4,805 | 0.34 | 83,813 ± 52 | 81,915 ± 10,463 | 0.87 |
| HOMA-ISR | 0.67 ± 0.10 | 0.74 ± 0.34 | 0.02 | 0.85 ± 0.44 | 0.38 ± 0.05 | 0.30 | 0.25 ± 0.02 | 0.27 ± 0.03 | 0.69 |
| Matsuda index | 13.57 ± 1.08 | 14.50 ± 1.54 | 0.62 | 12.45 ± 1.69 | 10.30 ± 2.78 | 0.52 | 6.40 ± 0.38 | 7.49 ± 0.78 | 0.22 |
| Insulin secretion | 49.6 ± 3.0 | 68.3 ± 4.3 | 0.0005 | 58.5 ± 3.0 | 67.6 ± 4.9 | 0.12 | 73.9 ± 5.0 | 90.9 ± 10.2 | 0.14 |
| Insulinogenic index | 122.5 ± 67.1 | 338.3 ± 96.7 | 0.07 | 136.6 ± 25.5 | 329.8 ± 42.9 | 0.0002 | 157.2 ± 17.8 | 233.0 ± 36.1 | 0.07 |
| DEXA | n = 31 | n = 37 |  | n = 25 | n = 22 |  | n = 16 | n = 8 |  |
| Fat mass (kg) | 18.5 ± 9.4 | 17.0 ± 8.6 | 0.27 | 28.6 ± 9.3 | 26.8 ± 9.9 | 0.19 | 39.3 ± 11.7 | 40.5 ± 11.6 | 0.56 |
| Fat mass (%) | 31.4 ± 1.6 | 28.2 ± 1.3 | 0.06 | 40.0 ± 1.2 | 38.4 ± 1.2 | 0.10 | 45.6 ± 1.3 | 47.6 ± 1.1 | 0.19 |
| Fat mass android (kg) | 1.7 ± 0.1 | 1.4 ± 0.1 | 0.02 | 2.7 ± 0.1 | 2.5 ± 0.1 | 0.20 | 4.1 ± 0.2 | 3.8 ± 0.3 | 0.39 |
| Fat mass android (%) | 37.8 ± 1.8 | 31.1 ± 1.7 | 0.009 | 46.6 ± 1.2 | 44.4 ± 1.2 | 0.19 | 52.7 ± 1.1 | 54.0 ± 1.6 | 0.50 |
| Fat mass gynoid (kg) | 4.1 ± 0.2 | 4.1 ± 0.2 | 0.95 | 5.6 ± 0.2 | 5.5 ± 0.2 | 0.70 | 7.1 ± 0.2 | 7.6 ± 0.3 | 0.19 |
| Fat mass gynoid (%) | 42.6 ± 1.1 | 40.7 ± 1.0 | 0.21 | 48.0 ± 0.8 | 47.7 ± 0.9 | 0.28 | 50.5 ± 0.8 | 53.4 ± 1.2 | 0.07 |
| Lean mass (kg) | 37.4 ± 7.4 | 39.5 ± 6.8 | 0.04 | 39.4 ± 7.3 | 40.4 ± 7.8 | 0.36 | 44.3 ± 10.6 | 42.0 ± 14.9 | 0.22 |

Mean ± SE.

P values calculated by LS means in an ANOVA model.

follows: 10,000/[fasting glucose concentration × fasting insulin concentration × (mean glucose × mean insulin)] (27).

Statistical analysis

Variables are presented as the mean ± SE. Continuous variables were tested for normality and were log-10 transformed when distribution was not normal. Comparisons were performed through General Linear Model procedure using the type-III sum of squares (for unbalanced study designs). Frequency data were obtained using the Proc FREQ and $\chi^2$ test. A P value <0.05 was considered significant. All analyses were conducted with SAS version 9.2.

Results

Characteristics of study participants were compared between women with and without prior GDM according to BMI categories (normal, overweight, or obese) (Table 1). The majority (89.0%) of participants were Caucasians [88.0% of GDM(+) and 91.6% of GDM(−)]. Other groups included Blacks, Aboriginals, Asians, and
Hispanics (<2% for each group) (data not shown). Women with or without prior GDM shared the same BMI and waist circumference values within each BMI category. In normal-weight women, there was no difference in participant characteristics. Among overweight women, GDM(−) had more children (2.38 ± 0.17 vs. 1.93 ± 0.11, \( P = 0.03 \)) and a longer time between index pregnancy and testing (4.56 ± 0.39 vs. 3.43 ± 0.24 years, \( P = 0.02 \)) than GDM(+). Among obese women, GDM(+) were older compared to GDM(−) (37.0 ± 0.6 vs. 34.1 ± 1.2 years, \( P = 0.04 \)).

Body composition, insulin, and glucose profile according to GDM history and BMI status are shown in Table 2. In women with normal BMI, we observed that fasting glucose, 2-h post-OGTT glucose, HbA1c, and AUCg were higher for GDM(+) when compared to their GDM(−) counterparts. In normal-weight and overweight women, fasting insulin was lower in women with GDM(+) whereas fasting insulin was similar between obese women with and without prior GDM. Furthermore, normal-weight women with GDM(+) presented lower HOMA-IS (0.67 ± 0.10 vs. 0.74 ± 0.34, \( P = 0.02 \)), insulin secretion (49.6 ± 3.0 vs. 68.3 ± 4.3, \( P = 0.0003 \)), and insulinogenic index (122.5 ± 67.1 vs. 338.3 ± 96.7, \( P = 0.0005 \)) compared to normal-weight women with GDM(−). Body composition measures were similar between overweight or obese women with vs. without prior GDM. However, among normal-weight women, we observed that GDM(+) women had increased total and android fat mass, similar gynoid fat mass, and decreased lean body mass compared to GDM(−).

The prevalence of abnormal glucose metabolism as a function of GDM history and BMI status is shown in Figure 1. For each BMI category, the proportion of women with abnormal glucose tolerance status was higher in GDM(+) compared to their GDM(−) counterparts. Among normal-weight women, we observed that 60.5 and 14.0% of GDM(+) had prediabetes and T2D, respectively, compared to 26.7% and 0% in women with GDM(−). In obese women, 81.7%, and 30.0% of women with GDM(+) had prediabetes and T2D, respectively, compared to 26.7% and 0% in women with GDM(−).

Having shown that women with normal weight present glycemic and insulinogenic deteriorations according to GDM status, comparisons were conducted for GDM(−) with overweight or obesity (BMI \( \geq 25 \text{ kg m}^{-2} \)) [ow/ob/GDM(−)] compared with GDM(+) only (BMI < 25 kg m\(^{-2}\)), and both conditions [ow/ob/GDM(+)](Table 3). We observed differences between groups for all glycemic and insulinogenic markers. As expected, BMI was higher for ow/ob/
Obesity

Discussion

Results of the present study showed that women with prior GDM present abnormal glucose and insulin metabolism compared to women without prior GDM, even in women with a normal BMI. Furthermore, the proportion of women with prediabetes and T2D was higher in overweight/obese women with prior GDM than in women with GDM or overweight/obesity only.

We observed that a history of GDM combined with overweight or obesity was associated with glycemic and insulinemic alterations compared to women with GDM(+) or women with ow/ob/GDM(−). In addition, we observed that the proportion of women with prior GDM who progressed to prediabetes and T2D was higher in those with overweight/obesity. Lauenborg et al. reported that there was a sevenfold increase in the prevalence of the metabolic syndrome among obese women with a history of GDM compared with normal-weight women with prior GDM (10). Ryan et al. showed that, in premenopausal and postmenopausal women with prior GDM, total body fat mass and subcutaneous abdominal fat were associated with insulin resistance highlighting the importance of obesity to increase the risk for the development of T2D (28). In the present study, we observed a greater proportion of overweight and obese women with a GDM history (32.2% overweight and 28.5% obesity) compared to data obtained from a national survey of Canadian women aged 30-39 years (23.4% overweight and 15.8% obesity) (29). Combined with results observed in the present study, these data underscore the importance of obesity in T2D risk, particularly in a high risk population like women with a history of GDM.

In addition, results from the present study showed that a majority of women with GDM(+) developed IFG, IGT, prediabetes, and T2D after their pregnancy despite having a normal BMI. Moreover, women with GDM(+) were more likely to develop abnormal glucose tolerance status than women with ow/ob/GDM(−). Similarly, Bo et al. observed higher glycemia among a group of 21 normal-weight women with prior GDM compared to controls (30). These women did not present other metabolic abnormalities (30). Furthermore, compared to their counterparts without prior GDM, Mexican-American women with prior GDM had a faster deterioration in insulin sensitivity combined with beta-cell compensation which was not explained by adiposity differences (31). These results combined with the present study suggest that a history of GDM, even in the absence of obesity, is associated with decreased insulin sensitivity and with compensation in beta-cell activity. Pirkola et al. showed that concomitant prepregnancy overweight and prior GDM was associated with a higher risk for subsequent diabetes after a 20-year follow-up (32). They also observed an increased risk of diabetes in women with normal prepregnancy weight and GDM (32). These results combined with findings of the present study suggest that a history of GDM in women with a normal weight either prepregnancy or after delivery is associated with T2D-related metabolic deteriorations.

Among normal-weight women, those with GDM(+) showed higher percent fat, android mass, and lower lean body mass. These individuals, despite having a normal BMI, displayed differences in body composition and fat distribution which may explain the presence of an altered metabolic profile in women with prior GDM. Excess abdominal fat is a risk factor of impaired glucose tolerance, insulin resistance, and their metabolic consequences (33). Measures of body mass and fat distribution were commonly used as predictor variables to identify T2D (34). Carey et al. have demonstrated a negative relationship between central abdominal fat measured by DEXA and insulin sensitivity in normal-weight and overweight women (35). In addition, Pallardo et al. have shown that glucose metabolism deteriorations following pregnancies complicated by GDM were associated with abdominal obesity assessed by an increased waist circumference (36).

Strengths of this study include the use of a 2-h OGTT to provide a detailed characterization of glucose and insulin metabolism. In addition, our sample of women with GDM(+) covers a wide range of BMI, and body composition measures were available for a large proportion of these women. Some limitations should also be considered. Our sample includes a small number of obese women with GDM(−), limiting the interpretation of results for this group of women. In addition, other potential confounding factors related to pregnancy such as pre-pregnancy BMI and excessive weight gain during pregnancy could not be addressed in the present study. Moreover, data from DEXA measures were not available for the entire study sample. Further studies with similar detailed characterization.
of their metabolic and anthropometric profile but with larger sample size will be needed to confirm results obtained in the current study.

Women with prior GDM represent a unique population of young individuals who have an increased likelihood of developing chronic and lifelong illness. Results from the present study suggest that a combination of a history of GDM with overweight/obesity was associated with T2D-related metabolic deteriorations. Nevertheless, even within a normal BMI, women with a history of GDM had increased android fat mass and greater metabolic complications compared to women without prior GDM. This study supports the importance of adequate management of women with prior GDM early after delivery in any BMI category.

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References