Pre-pregnancy overweight overtakes gestational diabetes as a risk factor for subsequent metabolic syndrome

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Abstract

Objective: Gestational diabetes mellitus (GDM) is associated with an increased risk of subsequent diabetes and metabolic syndrome (MS). The independent significance of overweight, often associated with GDM, is controversial. This study was aimed to investigate the prevalence of MS and carotid intima-media thickness (CIMT) values in normal and overweight women with previous insulin-treated GDM and control without GDM 19 years after the index pregnancy.

Methods: The study group consisted of 61 women with prior GDM and 55 controls who gave birth in Oulu University Hospital between 1988 and 1993. These women were further divided into subgroups according to pre-pregnancy BMI (< 25 or ≥ 25 kg/m²). In 2008–2010, anthropometrics and blood pressure were measured, blood samples were taken, and an oral glucose tolerance test was performed to investigate the components of MS. CIMT was measured by Doppler ultrasound.

Results: Total prevalence of MS was 62% in the GDM group and 31% in the control group (P < 0.001); it was highest (86%) in GDM women with pre-pregnancy overweight. CIMT was significantly thicker (0.67 vs 0.56 mm, P = 0.007) and more often abnormal (71.7 vs 45.3%, P = 0.004) in the GDM group compared with the controls. In logistic regression analysis, the strongest factor predicting MS in the whole study population was pre-pregnancy overweight.

Conclusions: Pre-pregnancy overweight was the strongest predictive factor for later MS, whereas GDM indicated increased risk of subsequent diabetes and subclinical atherosclerosis. The risk of MS was highest when both of these factors were present.

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Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that is first recognized during pregnancy (1, 2). Its incidence varies from 3 to 10% in different populations and appears to be increasing worldwide (3). In Finland, the incidence of GDM was 12.5% in 2011 (4).

Women with a history of GDM have a sixfold risk of developing diabetes later in their life as compared with women with normal glucose tolerance during pregnancy (5). Several studies have indicated that history of GDM increases the risk of metabolic syndrome (MS) and cardiovascular diseases (CVD), especially when it is associated with obesity, increased fasting glucose concentration, and excessive weight gain during pregnancy (6, 7, 8, 9, 10).

Visceral obesity, insulin resistance and hyperglycemia, hypertension, and dyslipidemia are the most important features of MS, and this adverse metabolic profile predisposes to type 2 diabetes and cardiovascular events (11). Increased CVD risk associates closely with atherogenesis, and subclinical atherosclerosis can be demonstrated by increased carotid artery intima-media thickness (CIMT), which thus predicts the risk of cardiovascular events (12, 13). Women with previous GDM appear to have higher CIMT values compared with control women (14, 15). The development of atherogenesis is also affected considerably by systemic inflammation (16). A year after index pregnancy, women with previous GDM were demonstrated to have increased markers of systemic inflammation, such as higher values of high-sensitivity C-reactive protein (hsCRP), IL6, and plasminogen activator inhibitor 1 (PAI1) (17).

The aim of our study was to investigate the incidence of MS together with levels of CIMT values and serum inflammatory markers in women with a history of insulin-treated GDM compared with control women without GDM on an average of 19 years after the index...
pregnancy. We took the advantage of an homogenous population with well-defined criteria for the diagnosis of GDM and a long follow-up time.

### Subjects and methods

The women in the study population gave birth between the years 1988 and 1993 in the tertiary level Oulu University Hospital. The primary study group consisted of 127 women with insulin-treated GDM and a control group of 127 women without GDM. The control women were selected from the delivery log and were matched for age (±2 years), parity (nulliparous, 1–3, and ≥3 deliveries), and year of delivery. Two women in the control group were excluded because of GDM diagnosed in their subsequent pregnancy. Until 2008, there were six deaths in both groups and 19 women were not traceable (seven women in the study group and 12 women in the control group), leaving a total of 114 women in the study group and 107 women in the control group (Fig. 1). All participants were asked to complete a detailed postal questionnaire including obstetric history, smoking (yes/no), and data on current diseases (medically treated diabetes, hypertension, and dyslipidemia); the response rate was 81%. A total of 116 women (52.5%), with 61 women in the study group and 55 women in the control group, were willing to attend clinical examinations (Fig. 1). The study was approved by the Ethics Committee of Northern Ostrobothnia Hospital District, and all the participants gave written informed consent.

Between 1988 and 1993, GDM was diagnosed in Finnish women by a 2-h 75-g oral glucose tolerance test (OGTT) mainly at the 24th–28th weeks of gestation. During this period, a risk factor-based screening was performed using the following indications: prior GDM, glucosuria, overweight (BMI ≥ 25.0 kg/m²), previous macrosomic infant (>4500 g), suspected fetal macrosomy in the current pregnancy, or age over 40 years. The cut-off values for capillary blood glucose concentrations were 4.8, 10.0, and 8.7 mmol/l at fasting, at 1, and at 2 h after the glucose load respectively. The diagnosis of GDM was set after one or more abnormal values. After the diagnosis of GDM, the patients received dietary and lifestyle counseling and began self-monitoring of glucose concentrations. According to the treatment guidelines at the time, insulin therapy was begun if blood glucose concentrations exceeded the target levels (5.3 mmol/l at fasting and 6.7 mmol/l at 1.5 h postprandial) repeatedly.

The clinical examination including anthropometrics (measurement of weight, height, and waist and hip circumferences) and blood pressure measurements was performed by a trained nurse at the Oulu University Hospital between 2008 and 2010. Weight was measured to the nearest 0.1 kg and height to the nearest 0.5 cm in the standing position without shoes or heavy clothing, and BMI was calculated as the weight (kg) divided by the square of the height (m). Overweight was defined as BMI ≥ 25.0 kg/m². Waist circumference was measured in the standing position at the level midway between the lower rib margin and the iliac crest, and the hip circumference from the maximum circumference over the buttocks (18). The waist:hip ratio was calculated as the waist circumference divided by the hip circumference. Blood pressure was measured twice using an automatic device (AND UA-767) after 5 min rest in the sitting position. The average of the two measurements was used in the analysis.

CIMT was measured by an experienced radiologist (AKK) using a high-resolution B-mode ultrasound (iU22, Philips Ultrasound, Bothell, WA, USA) with a 3–9-MHz linear-array transducer. The right carotid common artery was scanned (1 cm proximal to the dilatation of the carotid bulb) and the image was focused on the posterior wall. A minimum of three measurements were taken over a 1 cm length in the plaque-free area. The far wall of the carotid IMT was analyzed using an offline automatic computerized analyzing system (Philips Qlab quantification software). The limits of normal and abnormal CIMT values were defined according to Simon et al.’s study, who demonstrated the distribution of normal values of CIMT according to age and gender. Abnormally increased CIMT was considered as a value above the 75th upper percentile in each age category (19).

A venous blood sample was drawn from the antecubital vein after an overnight fast of 10–12 h. The 2-h 75-g OGTT, with fasting and 2-h values of glucose and insulin, was performed on those without preexisting diabetes. In the cases of those with diabetes, only fasting glucose and insulin concentrations were measured. Lipid profile (total cholesterol, LDL-C, HDL-C, and triglycerides (TG)), hsCRP, PAI1, leptin, and adiponectin were measured.

The fasting glucose and insulin concentrations were analyzed immediately; the rest of the sample was frozen, and all of these samples were analyzed later.
simultaneously. Plasma glucose and insulin were determined by using an automatic chemical analyzer (Cobas Integra 700, Roche Diagnostics), Total cholesterol, LDL-C, HDL-C, and TG were analyzed using an automatic chemical analyzer (Advia 1800, Siemens Healthcare Diagnostics, Terrytown, NY, USA); hsCRP, by immunonephelometry (BN ProSpec, Siemens Healthcare Diagnostics, Marburg, Germany); PAI1, by enzyme immunoassay (Diagnostica Stago, Asnieres-sur-Seine, France); and adiponectin and leptin, by RIAs (Millipore Corporation, Billerica, MA, USA).

The criteria used in the diagnosis of diabetes, impaired glucose tolerance (IGT), hypertension, and dyslipidemia are listed in Figure 2. MS was defined according to the NCEP criteria (Fig. 3).

Statistical analyses

Statistical analyses were performed using SPSS for Windows (version 16.0; SPSS, Inc.). Comparisons between the groups were made using the Student’s t-test for continuous variables and the χ² test for categorical variables. The Mann–Whitney U test was used to analyze variables with non-normal distribution. One-way ANOVA was used for comparing the four groups. A P value < 0.05 was considered statistically significant. Logistic regression analysis was performed with MS as the dependent variable and the following predictive variables: pre-pregnancy BMI, GDM, preeclampsia, and essential hypertension during pregnancy.

Results

Index pregnancy

During the index pregnancy, the mean age of the women was 35.9 years in the study group and 33.7 years in the control group (P = 0.067). The pre-pregnancy BMI was significantly higher in GDM women than that in controls (27.1 vs 24.5 kg/m², P = 0.004, respectively, Table 1). Smoking was rare in both groups (6.6 vs 5.8%, P = 0.163, respectively). The diagnosis of GDM in the study group was set in the median of 26 (range: 6–39) gestational weeks.

Clinical examination

The mean age of the women was 52.2 years during the clinical examination that was performed on average 19 years (range: 16–21) after the index pregnancy (Fig. 1). The menopause status did not differ between the groups. Women with a history of GDM smoked more often than women in the control group. The self-reported incidences of diabetes, chronic hypertension, and medically treated dyslipidemia were significantly higher among the GDM women than that of the controls (Table 1).

After the index pregnancy, 67.2% of the GDM women and 92.3% of the control women had gained weight (relative risk (RR): 0.5, 95% CI 0.4–0.7) – every fourth woman in the GDM group and every second woman in the control group gained more than 10 kg. During the clinical examination, the mean BMI was similar in both groups, and 65.6 and 76.4% of the GDM and control women had gained weight respectively (Table 1).

We diagnosed six and two new cases of diabetes in the GDM group and the control group, which increased the diabetes prevalence to 65.6 and 5.5% in these groups respectively. In addition, we found seven and six cases of IGT in the GDM group and the control group respectively.

When women without medication for dyslipidemia were analyzed, eight women out of 31 (25.8%) in the GDM group and 22 out of 44 (50.0%) in the control group had abnormal LDL-C, HDL-C, and/or TG concentration (RR: 0.5, 95% CI 0.3–1.0). When the old and new cases were summarized, the total prevalence of dyslipidemia in the GDM and the control groups was 61 and 60% respectively. GDM women had significantly lower LDL-C concentration than control women (Table 1), and this difference remained significant after the exclusion of women with medication for dyslipidemia (2.6 vs 3.2 mmol/l, respectively, P = 0.03).
The incidence of MS was significantly higher in the GDM group than that in the study group (62.3 vs 30.9% respectively). There was no significant difference between the groups in terms of the concentrations of systemic inflammation markers.

GDM women had significantly greater mean value of CIMT than the control women. The CIMT values were more often abnormal among women with GDM (Table 1). After excluding smokers, the difference between the mean CIMT values remained significant (0.63 vs 0.56 mm, respectively, \( P = 0.003 \)).

**Subgroup analyses**

To assess the significance of pre-pregnancy overweight, both groups were divided into two subgroups (pre-pregnancy BMI < 25 or \( \geq 25 \) kg/m\(^2\), Table 2). Three women in the control group were excluded because of missing pre-pregnancy weight data. The prevalence of MS was 85.7% in GDM women with pre-pregnancy overweight, 66.7% in control women with pre-pregnancy overweight, 30.8% in normal-weight GDM women, and 11.8% in normal-weight control women (\( P < 0.001 \)). Other characteristics of these subgroups are reported in Table 2.

**Logistic regression**

A logistic regression analysis showed pre-pregnancy overweight to be the strongest factor predicting subsequent MS. One unit increase in the pre-pregnancy BMI caused a 1.5-fold increase in the estimated risk of MS. Previous insulin-treated GDM caused a 3.5-fold increase in the estimated risk of MS. When the
control women with normal pre-pregnancy BMI (<25 kg/m²) were considered as a reference group, the estimated risk of MS was threefold in normal-weight GDM women, 15-fold in overweight control women, and 45-fold in women with pre-pregnancy overweight and GDM (Table 3).

Discussion

In this study, 62% of the GDM women met the criteria of MS 19 years after the index pregnancy. Pre-pregnancy overweight was the strongest independent risk factor for subsequent MS when GDM alone seemed to indicate an increased risk for subsequent diabetes and subclinical atherosclerosis. Overweight GDM women were at the highest risk of MS.

After 19 years, follow-up, the estimated risk of MS was 3.5-fold in women with a history of insulin-treated GDM when compared with the control women. The MS prevalence was almost twice as much as in the previous studies, where the rates at 10–11 years after pregnancy were 27–38% in GDM women and 8–13% in controls (7, 8). The higher incidence of MS in our study after longer follow-up may represent a continuum of metabolic disease and it may also be affected by transition to the menopausal state (20, 21). Another plausible explanation for the high proportion of MS in our study is that we only included GDM women who required insulin treatment during pregnancy. In previous studies, the requirement of insulin to achieve normoglycemia in GDM has been associated with an increased rate of subsequent morbidity, especially diabetes (22). The high prevalence of single components of MS (diabetes, hypertension, or dyslipidemia) that do not yet meet the full criteria of this disturbance suggests a further increased prevalence of MS.

According to the logistic regression analysis, pre-pregnancy overweight was the strongest independent risk factor for subsequent MS in this study. This is in agreement with a previous register-based cohort study that found pre-pregnancy overweight to be an essential risk factor for subsequent diabetes and hypertension (23). Interestingly, 19 years after the index pregnancy, control women had gained weight more often than GDM women, which may reflect the success of the lifestyle counseling given to GDM women during pregnancy. Though the current weight of the women in both study groups was similar, the women in the control group had diabetes and hypertension less often, which might be partly explained by the shorter duration of overweight. GDM women who were able to maintain normal weight after pregnancy had lower prevalence of chronic hypertension, dyslipidemia, and MS than control women with pre-pregnancy overweight. Despite this, they could not avoid the higher prevalence of MS risk in prior GDM women and controls.

Table 2 Comparison between the pre-pregnancy BMI groups 19 years after index pregnancy. Data are mean±s.d. or n (%), P value between groups.

<table>
<thead>
<tr>
<th>Clinical examination</th>
<th>GDM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometrics</strong></td>
<td></td>
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<tr>
<td>Current weight (kg)</td>
<td>67.3±10.0</td>
<td>82.6±17.4</td>
</tr>
<tr>
<td>Current BMI (kg/m²)</td>
<td>25.0±3.1</td>
<td>31.8±6.1</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>85.5±7.7</td>
<td>101.5±15.6</td>
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<tr>
<td>Waist-hip ratio</td>
<td>0.88±0.04</td>
<td>0.95±0.08</td>
</tr>
<tr>
<td>SBP (mm/Hg)</td>
<td>129.9±12.8</td>
<td>138.8±19.4</td>
</tr>
<tr>
<td>DBP (mm/Hg)</td>
<td>77.1±8.0</td>
<td>78.1±10.0</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>8 (30.8)</td>
<td>30 (85.7)</td>
</tr>
<tr>
<td>CIMT (mm)</td>
<td>0.60±0.14</td>
<td>0.72±0.36</td>
</tr>
<tr>
<td>Abnormal CIMT</td>
<td>14 (53.8)</td>
<td>29 (85.3)</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td></td>
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</tr>
<tr>
<td>OGGT 0 h glucose (mmol/l)</td>
<td>7.1±3.1</td>
<td>5.3±0.5</td>
</tr>
<tr>
<td>OGGT 2 h glucose (mmol/l)</td>
<td>6.0±1.9</td>
<td>5.3±1.8</td>
</tr>
<tr>
<td>Insulin 0 h (mU/l)</td>
<td>9.7±7.3</td>
<td>7.8±3.6</td>
</tr>
<tr>
<td>Insulin 2 h (mU/l)</td>
<td>41.9±40.9</td>
<td>45.0±37.3</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.7±0.4</td>
<td>1.7±0.3</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>2.3±0.8</td>
<td>3.1±0.8</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>1.3±0.8</td>
<td>1.5±0.7</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; CIMT, carotid intima-media thickness; OGGT, oral glucose tolerance test; TG, triglycerides.

*Women without medically treated DM n=15/11/34/17.
of later diabetes and abnormal CIMT, which may be associated at least partly with genetic factors. The significant increase in smoking among women with GDM was a disappointing finding and reflects an important failure in the diabetes education program. Smoking may have had a beneficial influence on weight control but it drastically increases the metabolic risks of the GDM women.

Increased CIMT has been reported to reflect a higher risk of cardiovascular events in women with a history of GDM (14, 15, 24). In this study, the women with previous insulin-treated GDM exhibited a significantly thicker CIMT, and the proportion of abnormal CIMT-values was also significantly higher among them. This was seen in GDM women regardless of pre-pregnancy weight class and was also independent of smoking status. All these findings support the conception of increased CVD risk in women with a history of GDM.

The higher proportion of self-reported medically treated hypertension and dyslipidemia in the GDM women compared with the controls is in line with previous studies (6, 7, 8). In this study, the prevalence of abnormal lipid concentrations was remarkably high in both groups and unexpectedly, it tended to be higher in the control group. Women in the control group, especially those with pre-pregnancy overweight, had higher LDL-C concentration than GDM women. This is parallel to the findings of Fraser et al. (10), who found women with both pregestational and gestational diabetes to have lower LDL-C concentrations than control women 18 years after delivery. The reason of this finding remains unclear.

To the best of our knowledge, the follow-up time in this study is longer than in any previous clinical study investigating the risk of MS in GDM women. Another advantage of our study is that the women in the study group were well characterized and the follow-up was restricted to women with insulin-treated GDM. We also ensured that the women in the control group did not have GDM in their subsequent pregnancies. Finally, we had the opportunity to evaluate the significance of pre-pregnancy BMI in the current health of the women and compare the outcome in different BMI groups.

The limitation of this study was that only slightly more than half of the women attended the clinical examination. Of all the recruited women, 81% answered the questionnaire, but long geographical distances to the study center reduced the attendance. However, the women who only answered the questionnaire did not differ from those who attended the clinical study in terms of the self-reported health parameters.

In conclusion, we found that pre-pregnancy overweight was a stronger risk factor for MS than GDM. However, the risk of MS was highest when GDM and pre-pregnancy overweight were combined. On the other hand, GDM seems to indicate an increased risk of subsequent diabetes and subclinical atherosclerosis as defined by an increased CIMT. Our findings suggest that weight control and lifestyle counseling should be extended to all overweight women after pregnancy. However, the most important target is an overweight woman with GDM.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
H Ija¨s initiated and designed the study, collected the study population, interpreted the data, and wrote the manuscript. L Morin-Papunen, T Raudaskoski, and T Ebeling initiated and designed the study and methods section. A Ruokonen and K Puukka performed the laboratory analyses and participated in the writing of the manuscript. A K Keränen performed the statistical analyses and participated in the writing of the manuscript. R Bloigu and H Ija¨s performed the statistical analyses. M Va¨a¨ra¨sma¨ki initiated and designed the study, collected the study population, and interpreted the data; M Va¨a¨rismäki is also responsible for the final version of the manuscript.

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