Prepregnancy Overweight and Gestational Diabetes as Determinants of Subsequent Diabetes and Hypertension after 20-Year Follow-Up

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Context: Overweight is a strong risk factor for gestational diabetes (GDM), and both states indicate increased risk for subsequent metabolic syndrome. Data separating effects of overweight and GDM on risk for metabolic diseases are limited.

Objective: The aim of the study was to evaluate prepregnancy overweight and GDM as determinants of risk for subsequent diabetes and hypertension.

Design: Population-based data from the Northern Finland Birth Cohort 1986 were compounded with register-based data on diagnosis of diabetes and hypertension.

Setting: The study was conducted in Northern Finland.

Participants: We studied: 1) normal-weight women with GDM (n = 70); 2) overweight women with GDM (n = 54); 3) normal-weight (n = 768) and 4) overweight (n = 250) women with risk factors for GDM but normal oral glucose tolerance test results; and 5) women with no risk factors for GDM (n = 5341).

Main Outcome Measures: We measured cumulative incidence of diabetes and hypertension, hazard ratio (HR), and population-attributable fraction (PAF) for determinants of risk.

Results: The cumulative incidence of diagnosed diabetes and hypertension in the whole study population was 1.3 and 7.5%, respectively. Concomitant overweight and GDM indicated high risks for diabetes (HR, 47.24; PAF, 15.8%) and hypertension (HR, 9.16; PAF, 4.4%). Even when the OGTT in pregnancy was normal, prepregnancy overweight associated with risks for diabetes (HR, 12.63; PAF, 22.2%) and hypertension (HR, 2.86; PAF, 6.0%). In normal-weight women, GDM indicated risk for diabetes (HR, 10.61; PAF, 5.2%) but not for hypertension.

Conclusions: Prepregnancy overweight is an essential risk factor for subsequent diabetes and hypertension, especially when combined with GDM. (J Clin Endocrinol Metab 95: 772–778, 2010)
otherwise healthy women (3). Thus, GDM can be considered an early warning sign of the susceptibility to develop diabetes (4, 5), metabolic syndrome (6–10), and even cardiovascular disease (11, 12). The risk factors for GDM and type 2 diabetes overlap (4, 5), and results of candidate gene studies suggest a shared ground for these diseases (13, 14). However, data are scant on the later risk of diabetes and metabolic diseases in women with risk factors for GDM but normal glucose tolerance during pregnancy.

Maternal obesity is a strong risk factor for GDM (15, 16) and for the development of metabolic abnormalities after delivery in women with GDM (17–19). However, the risks of diabetes and hypertension associated with prepregnancy overweight and GDM have seldom been assessed separately. We evaluated prepregnancy overweight and GDM as determinants of risk for diabetes and hypertension, separately and in combination, 20 yr after pregnancy in the prospective, population-based Northern Finland Birth Cohort 1986 (NFBC 1986).

Subjects and Methods

Health care in pregnancy during the study period

In Finland, cost-free health care is offered to all pregnant women in maternity welfare clinics (MWCs). Practically all pregnant women attend these clinics. During the study period, GDM screening in the MWCs was based on assessment of risk factors, in accordance with national guidelines. Women were considered to be at risk if one or more of the following factors were present: age over 40 yr, BMI of 25 kg/m² or greater, prior GDM, previous delivery of a macrosomic (birth weight >4500 g) infant, glucosuria, and suspected fetal macrosomia in the current pregnancy. These women underwent diagnostic glucose tolerance testing, performed after an overnight fast, conducted by administering a 2-h, 75-g oral glucose tolerance test (OGTT). The upper ranges of normal capillary blood glucose concentrations in 1985–1986 were 5.5, 11.0, and 8.0 mmol/liter at fasting and 1 h and 2 h after the glucose load, respectively. Diagnosis of GDM was set after one abnormal value in the OGTT.

Data collection and study population

We used data based on participants of the NFBC 1986, who were recruited and longitudinally assessed as described previously (20, 21). All mothers resident in the two northernmost provinces of Finland, with an expected delivery date between July 1, 1985, and June 30, 1986, were eligible for the study; 99% (n = 9362) enrolled at the first antenatal visit in the MWCs. The present study includes mothers with singleton pregnancies and with data available on prepregnancy body mass index (BMI) and screening and diagnosis of GDM. Mothers with diabetes (n = 27) or chronic hypertension before pregnancy (n = 209) were excluded, as were mothers who had risk factors for GDM but had not undergone a diagnostic OGTT despite indications (n = 1876) (Fig. 1). The Ethics Committee of the University of Oulu approved the study. All mothers have received written and oral information and gave their written informed consent to use all data.

In the NFBC 1986, prospective data have been acquired since gestation wk 12. Trained nurses helped mothers fill in two questionnaires at MWCs. These questionnaires covered the early (since 12–16th gestational week) and late pregnancy (after 24 wk gestation) including the perinatal period. A third questionnaire was filled in at the hospital by the attending midwives. The course of pregnancy and delivery, including complications and diseases, was further confirmed from patient records in MWCs and hospitals. Prepregnancy education, smoking habits, and weight were recorded; height (to one decimal place in centimeters) and weight (to one decimal place in kilograms) were measured at the first antenatal visit; and weight was also measured at every subsequent visit in the MWCs. Dipstick testing to detect glucosuria and proteinuria (≥0.3 g/liter) was done at every visit. Blood pressure was measured in millimeters of mercury (mm Hg) at every visit using a sphygmomanometer. In 2000–2001, at offspring age 16, the women filled in detailed postal questionnaires, including data on family size and income and current weight.

BMI was calculated in prepregnancy and in 2000–2001 and classified as normal weight/overweight with a cutoff at 25 kg/m². The study population was sorted according to glucose metabolism in pregnancy and prepregnancy BMI as follows: 1) normal-weight women with GDM (n = 70); 2) overweight women with GDM (n = 54); 3) normal-weight (n = 768) and 4) overweight (n = 250) women with risk factors for GDM but normal oral glucose tolerance test results; and 5) women with no risk factors for GDM (n = 5341). To assess the effect of current overweight, the study population was sorted in a similar way, substituting prepregnancy overweight with overweight in 2000–2001, 16 yr after the index pregnancy.

Register-based data

Data from the Social Insurance Institution of Finland (SIIF), the National Research and Development Centre for Welfare and Health (NRDCWH), and the Central Statistical Office (CSO) were obtained for the period 1985–2006. The SIIF data contains information on reimbursements of medical expenses for drugs. The NRDCWH data contains hospital discharge data, i.e. diagnoses at discharge from hospital wards and outpatient clinics (data from outpatient clinics from the year 2000 onward). The CSO data contains information on deaths. In Finland, reimbursements for medication are defined by diagnoses, i.e. those receiving reimbursements had been diagnosed with a disease by a physician, and the reimbursement data are classified by those diagnosis codes (or groups of codes). In the SIIF and NRDCWH
data, diagnosis codes were based on the International Classification of Diseases and Health Related Problems, ICD 8, ICD 9, and ICD 10. The codes used for diabetes were 250 (ICD 8 and ICD 9) and E10, E11, and E14 (ICD 10); and codes for hypertension were 400–404 (ICD 8), 401–405 (ICD 9), and I10, I11, and I15 (ICD 10).

Outcomes

Women were considered to have developed diabetes and/or hypertension if they had received reimbursement for drugs to treat the disease(s) and/or had a discharge diagnosis of the disease. Time to event was calculated as time from delivery to date of receiving reimbursement or date of discharge diagnosis.

Definitions

Age was considered as a continuous variable and dichotomized as under/over 40 yr. Glucosuria during pregnancy was dichotomized as ever/never, and the number of abnormal values in the OGTT during pregnancy as one/several. Mean arterial pressure (MAP) after gestation wk 36 was calculated using the formula MAP = diastolic blood pressure + (systolic blood pressure – diastolic blood pressure)/3. Gestational hypertension was defined as systolic blood pressure exceeding 140 mm Hg or diastolic blood pressure exceeding 90 mm Hg, and preeclampsia was defined as proteinuria and blood pressure exceeding the aforementioned values after gestation wk 20.

Statistical analyses

Statistical analyses were performed using SPSS v. 14.0 (SPSS Inc., Chicago, IL), CIA v. 1.2 (22), and R (23). The distributions of variables for clinical characteristics were skewed and therefore were logarithmically transformed. These data are presented as geometric means and 95% confidence intervals (CIs). Categorical data are presented as percentage. ANOVA and Pearson’s $\chi^2$ test were used to evaluate differences between groups.

Kaplan-Meier time-to-event curves were created to graphically evaluate the proportional hazards assumption and to estimate cumulative incidence of diabetes and hypertension. The unadjusted proportional hazard ratio (HR) for the determinants of risk were estimated using Cox regression analyses. To avoid overparameterization, no further adjusted analyses were performed.

The population-attributable fraction (PAF) is the percentage of a disease in a population that is due to a specific risk factor (24). To estimate the fractions of risks for diabetes and hypertension attributable to GDM and prepregnancy overweight, PAFs were calculated using the formula $\text{PAF} = \frac{P \times (HR - 1)}{HR}$, where $P$ is the proportion of cases in each risk factor group and HR is the HR comparing each risk factor group with the reference category. Although the attributable fraction of risk can be time varying, we excluded time from the formula because the period of interest was the end of the follow-up period (25).

Because the focus of this study was to evaluate the risks of diabetes and hypertension associated with GDM (i.e. an abnormal OGTT in pregnancy), we excluded from the risk analyses the

### TABLE 1. Characteristics of the NFBC 1986 mothers, sorted according to prepregnancy weight and glucose metabolism in pregnancy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GDM</th>
<th>OGTT normal</th>
<th>No risk factors for GDM</th>
<th>$P^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal weight</td>
<td>Overweight</td>
<td>Normal weight</td>
<td>Overweight</td>
</tr>
<tr>
<td>n</td>
<td>70</td>
<td>54</td>
<td>768</td>
<td>250</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>27.0 (25.6, 28.5)</td>
<td>31.8 (30.0, 33.7)</td>
<td>27.0 (26.7, 27.4)</td>
<td>28.6 (27.9, 29.3)</td>
</tr>
<tr>
<td>Age &gt;40 yr (%)</td>
<td>1.4</td>
<td>9.3</td>
<td>1.0</td>
<td>3.1</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.63 (1.62, 1.65)</td>
<td>1.62 (1.61, 1.64)</td>
<td>1.64 (1.63, 1.64)</td>
<td>1.63 (1.62, 1.64)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.6 (55.0, 58.2)</td>
<td>79.5 (76.2, 82.9)</td>
<td>56.7 (56.3, 57.2)</td>
<td>76.7 (75.4, 78.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.2 (20.8, 21.7)</td>
<td>30.2 (29.0, 31.4)</td>
<td>21.2 (21.1, 21.3)</td>
<td>28.8 (28.4, 29.2)</td>
</tr>
<tr>
<td>Glucosuria on dipstick (%)</td>
<td>62.9</td>
<td>44.4</td>
<td>52.4</td>
<td>41.7</td>
</tr>
<tr>
<td>OGTT 0 h (mmol/liter)</td>
<td>4.9 (4.6, 5.1)</td>
<td>5.2 (4.9, 5.4)</td>
<td>4.2 (4.2, 4.2)</td>
<td>4.3 (4.3, 4.4)</td>
</tr>
<tr>
<td>OGTT 1 h (mmol/liter)</td>
<td>9.1 (8.7, 9.6)</td>
<td>9.9 (9.4, 10.4)</td>
<td>7.4 (7.3, 7.5)</td>
<td>7.7 (7.5, 7.9)</td>
</tr>
<tr>
<td>OGTT 2 h (mmol/liter)</td>
<td>8.5 (8.1, 8.8)</td>
<td>7.9 (7.5, 8.4)</td>
<td>5.6 (5.5, 5.7)</td>
<td>5.8 (5.7, 6.0)</td>
</tr>
<tr>
<td>% OAV</td>
<td>81.0</td>
<td>66.7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MAP after 36 wk gestation</td>
<td>91 (89, 94)</td>
<td>99 (96, 102)</td>
<td>93 (93, 95)</td>
<td>97 (96, 99)</td>
</tr>
<tr>
<td>% Gestational hypertension</td>
<td>1.4</td>
<td>5.9</td>
<td>4.1</td>
<td>5.4</td>
</tr>
<tr>
<td>% Preeclampsia</td>
<td>1.4</td>
<td>3.9</td>
<td>2.1</td>
<td>3.3</td>
</tr>
<tr>
<td>BMI in 2000–2001 (kg/m²)</td>
<td>23.6 (22.6, 24.6)</td>
<td>30.9 (29.5, 32.4)</td>
<td>24.3 (24.0, 24.5)</td>
<td>31.5 (30.7, 32.4)</td>
</tr>
<tr>
<td>% Overweight in 2000–2001</td>
<td>35.3</td>
<td>100.0</td>
<td>39.0</td>
<td>93.5</td>
</tr>
</tbody>
</table>

Data are expressed as geometric means (95% CI) for continuous variables and as percentage for categorical variables. NA, Not applicable; NS, non-significant; OAV, one abnormal value in the OGTT.

$a$ Differences between groups are assessed by ANOVA for continuous variables and by Pearson’s $\chi^2$ test for categorical variables.

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women who had not undergone a diagnostic OGTT despite indications. The most often overlooked GDM risk factor was overweight; 58.2% of these women were overweight and the geometric means of BMI in the whole group were 21.2 (95% CI, 21.1, 21.4) kg/m² for normal-weight women and 27.8 (95% CI, 27.6, 27.9) kg/m² for overweight women.

In data attrition analysis, no differences in demographic or clinical characteristics were found between those with missing data and the present study population (data not shown).

Results

Characteristics

In the whole study population, the prevalence of GDM was 1.9%, and risk factors for GDM but normal glucose tolerance in pregnancy were observed in 15.7%. Prepregnancy overweight was present in 43.5% of the women with GDM and in 24.6% of the women with a normal OGTT. Diagnosis of GDM was based on only one abnormal value in the OGTT in 81.0% of the normal-weight women with GDM and in 66.7% of the overweight women with GDM. The characteristics of the study population, assorted according to risk factors for GDM, OGTT results, and prepregnancy weight, are shown in Table 1.

Mortality

Overall mortality during the study period was 1.5% (n = 97). Of the deceased, four had treated diabetes and six had treated hypertension. No statistically significant differences in mortality between groups sorted according to risk factors for GDM, OGTT results, and prepregnancy weight were observed (P for difference between groups, 0.35).

Cumulative incidence of diabetes and hypertension

Kaplan-Meier time-to-event curves are shown in Fig. 2. Twenty years after delivery, the cumulative incidence of diagnosed diabetes and hypertension in the whole study population was 1.3 and 7.5%, respectively. The incidence was highest in women with GDM and prepregnancy overweight (diabetes, 23.9%; and hypertension, 44.4%). In normal-weight women with a normal OGTT in pregnancy, the incidence did not differ significantly from the incidence in those with no risk factors for GDM (diabetes, 1.3 vs. 0.7%; and hypertension, 6.4 vs. 6.8%, respectively) (Table 2). The results did not change when substituting prepregnancy overweight with overweight of the women in 2000–2001 (data not shown).

Estimates of risk

For individual women, GDM indicated strikingly increased risk for diabetes in both normal-weight (HR, 10.61) and overweight women (HR, 47.24), and for hypertension in women with prepregnancy overweight (HR, 9.16). In women with normal glucose metabolism during pregnancy, prepregnancy overweight associated with risk for diabetes (HR, 12.63) and hypertension (HR, 2.86). The estimates of risks were similar when substituting prepregnancy overweight of the women with overweight in 2000–2001 (data not shown). In women with a normal OGTT during pregnancy, the risk of diabetes or hypertension did not differ from the women with no risk factors for GDM, i.e. the control population (Table 2).

In this population, the greatest fraction of risk for diabetes was attributable to prepregnancy overweight (PAF, 22.2%). Because the prevalence of concomitant prepregnancy overweight and GDM was not very high, the population level risk estimate was lower for these risk factors (PAF, 15.8%). The greatest fraction of risk for hypertension was also attributable to prepregnancy overweight (PAF, 6.0%) (Table 2).

Discussion

In this prospective, population-based study, overweight emerged as an essential risk factor for subsequent diabetes and hypertension. In women with prepregnancy normal weight, GDM indicated increased risk of diabetes, but in women with prepregnancy overweight and GDM, the risks of both diabetes and hypertension were alarmingly high. Even in women with a normal OGTT in preg-
nancy, prepregnancy overweight associated with increased risk for diabetes and hypertension.

Originally, the diagnostic criteria for GDM were based on the risk of type 2 diabetes and set statistically (26). The lack of uniform screening and diagnosis criteria over 40 yr later makes it difficult to compare results of studies on GDM. Recent studies suggest that even mild glucose intolerance during pregnancy, i.e. one abnormal value in the 3-h, 100-g OGTT, indicates increased risk for later, aberrant glucose metabolism (27–30). During the study period, diagnosis of GDM was set according to prevailing national guidelines, and hence it was diagnosed after one or more abnormal values in the 2-h, 75-g OGTT. Thus, women with relatively mild glucose intolerance were also included in the GDM group. Despite that, GDM indicated increased risk of diabetes in women with both normal weight and overweight before pregnancy and increased risk of hypertension in overweight women.

Previous studies report hypertension after GDM mainly as a component of the metabolic syndrome (7–10) and suggest that GDM indicates increased later risk for hypertension. The present study adds to previous research by presenting data on the risks of diabetes and hypertension attributable to GDM and prepregnancy overweight separately. Based on our study, prepregnancy overweight associates with the risk of subsequent hypertension, but the risk is not increased in normal-weight women, not even in those with a history of GDM.

Overweight is a strong risk factor for GDM (15, 16), and it associates with diabetes and metabolic syndrome in women with a history of GDM (7, 17, 18). The prevalence of GDM is increasing—a recent study from the United States reported a 94% increase in prevalence from 1989–1990 to 2003–2004 (31). Overweight is increasing among women in the fertile age, too; in Finland, a recent study showed a substantial increase in the proportion of overweight (18.8 to 24.5%) and obese (7.5 to 11%) parturients from the year 1990 to 2004 (32). In the present study, prepregnancy overweight was retained 20 yr after pregnancy, and approximately one third of the women with normal weight before the index pregnancy became overweight during follow-up. The alarmingly high risks of diabetes and hypertension associated with prepregnancy overweight, especially in the women with concomitant GDM, observed in the present study warrant public health attention. Further preventive measures—i.e. interventions aimed at weight control—are urgently needed in the high-risk groups identified.

The NFBC 1986 provides comprehensive, prospective, long-term data on a general population-based cohort. All participants were of white, Caucasian ethnicity and living in the same area during the same time period. The near 100% coverage of cost-free antenatal care and deliveries in public hospitals enabled similar data collection and follow-up for the whole study population. Because overweight and aberrant glucose metabolism in pregnancy were assessed as determinants of risk independently, the number of GDM women in the NFBC 1986 was not sufficient to further adjust the estimates of risk by possible confounding factors. However, because the differences observed were statistically significant and clinically plausible, we consider the results highly relevant.

Finnish registers containing data on health care are demonstrably comprehensive and reliable (33). However, when evaluating the results, it must be remembered that the outcomes were based on register data on diagnosis of diabetes and/or hypertension. Although the combination of SIIF and NRDCWH registers to achieve catchment of all those women who can control their disease by lifestyle are not included in the present study. In addition, diabetes and hypertension may be present for years before being diagnosed; in a previous, population-based study of Finnish middle-aged subjects, only 37.2% of those with diabetic blood glucose values were aware of the condition (34). Thus, it is likely that the cumulative incidence of diabetes and hypertension are to some extent underestimated in the present study. However, the observed trends can be considered reliable and representative because the

### TABLE 2. Prevalence and estimates of risk for diabetes and hypertension 20 yr after delivery in the NFBC 1986 mothers

<table>
<thead>
<tr>
<th>Determinants of risk</th>
<th>Diabetes</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence (%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>GDM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight</td>
<td>7.1</td>
<td>10.61 (4.17, 27.00)¹</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.9</td>
<td>47.24 (25.53, 87.40)¹</td>
</tr>
<tr>
<td>OGGT normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight</td>
<td>1.3</td>
<td>1.87 (0.93, 3.76)</td>
</tr>
<tr>
<td>Overweight</td>
<td>8.4</td>
<td>12.63 (7.39, 21.57)²</td>
</tr>
<tr>
<td>Controls</td>
<td>0.7</td>
<td>1 (ref)</td>
</tr>
</tbody>
</table>

¹P < 0.001.
data were nonselected and population-based, the study population was well-characterized, and there is no reason to expect bias in diagnosis and treatment of diabetes and hypertension between the study groups.

In the present study, diabetes types could not be differentiated, but type 2 diabetes is assumed to be predominant. A recent study in our area in women with GDM found that the prevalence of type 1 diabetes and type 2 diabetes at 6 yr after delivery was equal (5.3 and 5.6%) (35). It is probable that type 1 diabetes is diagnosed relatively soon after delivery, and the later increase in cumulative incidence is due to type 2 diabetes.

In summary, prepregnancy overweight emerges as an essential risk factor for subsequent diabetes and hypertension. The risks of these diseases were alarmingly high when prepregnancy overweight was combined with even mild abnormal glucose metabolism during pregnancy, but in normal-weight women with a normal OGTT, the risks were low despite the presence of risk factors. Thus, prepregnancy overweight and the OGTT during pregnancy sort women according to their future risk for these metabolic diseases. As the women at risk are identified at a young age, the possible prevention and early detection of diabetes and hypertension could have major public health implications. Further studies are necessary to assess preventive interventions and the possible role of endocrinological markers, e.g. adipocytokines, in identifying those at highest risk.

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