Original Contribution

Adolescent Manifestations of Metabolic Syndrome Among Children Born to Women With Gestational Diabetes in a General-Population Birth Cohort

Marja Vääräsmäki, Anneli Pouta, Paul Elliot, Päivi Tapanainen, Ulla Sovio, Aimo Ruokonen, Anna-Liisa Hartikainen, Mark McCarthy, and Marjo-Riitta Järvelin

Initially submitted June 10, 2008; accepted for publication January 15, 2009.

The association between maternal gestational diabetes (GDM) and manifestations of metabolic syndrome among Caucasian adolescents was studied with data from the population-based Northern Finland 1986 Birth Cohort. This is a longitudinal cohort study from early pregnancy until offspring age 16 years and includes data from a risk group-based GDM screen of pregnant mothers by an oral glucose tolerance test. Metabolic outcomes were compared between the offspring of women with GDM (OGDM; n = 95) and reference group offspring (n = 3,909). The prevalence of overweight was significantly higher in the OGDM group (18.8 vs. 8.4%; P < 0.001) than in the reference group. The median body mass index (20.8 vs. 20.2 kg/m², 95% confidence interval (CI) for the percentage difference adjusted for sex: 3.5%, 9.5%), waist circumference (73.3 vs. 71.5 cm, 95% CI: 3.2%, 7.5%), and fasting insulin (10.20 vs. 9.30 milliunits/L, 95% CI: 5.9%, 26.0%) were higher, and homeostatic model assessment-insulin sensitivity (74.7 vs. 82.3, 95% CI: −20.6%, −5.4%) was lower in the OGDM group. These differences were similar after an additional adjustment for birth weight and gestational age. The differences in waist circumference, insulin, and homeostatic model assessment-insulin sensitivity were attenuated but remained statistically significant after additional adjustment for body mass index at 16 years. These findings highlight the importance of prevention strategies among children born to women with GDM.

adolescent; cohort studies; diabetes, gestational; metabolic syndrome X; phenotype; women

Abbreviations: CI, confidence interval; GDM, maternal gestational diabetes; OGDM, offspring of women with GDM.

Overt maternal diabetes of both types 1 and 2 has been found to be associated with subsequent morbidity of the offspring (1–5), but data are far fewer and more inconsistent concerning the role of transient deviant glucose metabolism, such as maternal gestational diabetes (GDM), for metabolic disorders among the offspring (6–11). The etiology of GDM is heterogeneous (12), one well-known predisposing factor for GDM being obesity. As the prevalence of overweight is rapidly increasing in the population, an increase in glucose metabolism disorders during pregnancy is also expected.

Most previous studies on maternal diabetes and health of the offspring have been carried out in high-risk ethnic populations such as Pima Indians (3), and rarely have the different types or timing of maternal diabetes been taken into account. Only 2 studies in a low-risk GDM population have been reported (6, 8). Malcolm et al. (8) suggested that there is an increased risk of impaired glucose tolerance and overweight in the offspring of women with GDM (OGDM), while Boney et al. (6) reported that especially large-for-gestational-age children of GDM mothers were at increased risk of so-called metabolic syndrome. However, these studies failed to compare risks with those of a control population (8) and had a high drop-out rate or restricted sample representation (6). The use of the term “metabolic syndrome” has been debated and, until recently, no internationally accepted definition has been available (13, 14). In the present study, we use the term metabolic syndrome as an overarching description of the condition of several adverse metabolic phenotypes clustering together (13).

Correspondence to Dr. Marjo-Riitta Järvelin, Department of Epidemiology and Public Health, Imperial College London, Norfolk Place, W2 1PG London, United Kingdom (e-mail: m.jarvelin@imperial.ac.uk).

1209 Am J Epidemiol 2009;169:1209–1215
The development of features of metabolic syndrome may start much earlier in life than previously supposed and may be affected by both pre- and postnatal environmental and genetic variations and their interactions. To delay or prevent the development of overt disease, it is essential to identify groups at risk of metabolic disorders before clinical manifestations of disease. We report here the associations between GDM and metabolic syndrome (15) and its individual phenotypes (both as binary and continuous outcomes) in adolescent offspring, and we evaluate whether these associations are mediated/modified by factors such as gestational age, birth weight, and current body size. The critical questions are whether any increased risk of metabolic disorders among the offspring can be explained by overweight per se and whether other factors—independent of body mass index—are involved.

MATERIALS AND METHODS

Data collection

The prospective Northern Finland 1986 Birth Cohort is a general population-based sample with expected birth between July 1, 1985, and June 30, 1986, comprising offspring from 9,247 singleton pregnancies followed since the 12th gestational week (99% coverage) (16, 17). A clinical examination of the offspring was conducted at age 16 years in 2001–2002 with 75% participation. The ethical committee of the University of Oulu approved this study.

Screening of GDM

In Finland, free-of-charge health care is offered to pregnant women in municipal maternity welfare clinics with nearly 100% attendance. Screening for GDM by oral glucose tolerance test was performed in the clinics, according to national guidelines, at between 26 and 28 gestational weeks. Indications for screening were glucosuria, prior GDM, suspected fetal macrosomia, suspected macrosomia in the current pregnancy, and previous macrosomic infant (weight >4,500 g). Mainly data of prepregnancy body mass index were missing. OGTT, oral glucose tolerance test; DM 1, type 1 diabetes mellitus.
guar gum. The reference mothers consisted of those without indications for the oral glucose tolerance test. We excluded mothers with prepregnancy diabetes, those with normal results of the oral glucose tolerance test, and mothers without an oral glucose tolerance test despite indications, as well as the offspring whose clinical/laboratory outcome data at age 16 years were not available (Figure 1). The final study population with informed written consent included 95 offspring of GDM mothers (OGDM group) and 3,909 offspring of mothers without indications for screening.

Clinical outcomes in offspring

Trained nurses performed the clinical examinations at a mean offspring age of 16.0 (standard deviation, 0.4) years. Body mass index was calculated (weight (kg)/height (m)²). Waist circumference, a reliable indicator of metabolic adversity in pediatric clinical settings (18), was measured at the level midway between the lowest rib margin and the iliac crest. Systolic and diastolic blood pressures were measured in the sitting position after 15 minutes’ rest with the cuff on the right upper arm, by trained nurses using a standardized procedure and ongoing quality control. An Omron 705CP oscillometric pressure meter (Omron Corporation, Shiojiri, Japan), or mercury sphygmomanometer if this failed, was used. Two readings were taken 2 minutes apart, and the average of the 2 measurements was used. Mean arterial pressure (MAP) was calculated by the formula, MAP = (SBP + (2 × DBP))/3, where SBP refers to systolic blood pressure and DBP refers to diastolic blood pressure.

Blood samples and laboratory methods

The blood samples were drawn after overnight fasting (8:00–11:00 AM). Samples for serum insulin were stored at −20°C until analyzed by radioimmunooassay with commercial reagents (Pharmacia Diagnostics, Uppsala, Sweden) within 7 days. The other samples were analyzed within 24 hours of sampling in the Oulu University Hospital laboratory by using ongoing internal/external quality control. Plasma glucose, serum total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides were analyzed by a Cobas Integra 700 automatic analyzer (Roche Diagnostics, Basel, Switzerland). Paired fasting glucose and insulin levels were used to generate measures of insulin sensitivity by using the homeostatic model assessment method (19), a valid approach for insulin sensitivity in normal weight prepubertal and pubertal nondiabetic children (20).

Definition of metabolic syndrome

We used the International Diabetes Federation adult definition for metabolic syndrome, because it is recommended for adolescents 16 years of age or older (21, 22), and it covers body mass index contrary to the pediatric definition. The adult definition gives, however, a slightly lower prevalence of metabolic syndrome than does the pediatric definition (23). According to the adult definition, the diagnosis of metabolic syndrome requires central obesity as assessed by waist circumference (≥94 cm in men; ≥80 cm in women) or body mass index (≥30 kg/m²) and 2 of the following 4 criteria to be fulfilled: 1) raised triglycerides (≥1.7 mmol/L or specific treatment for this lipid abnormality), 2) reduced high density lipoprotein cholesterol (<1.03 mmol/L in men; <1.29 mmol/L in women; or specific treatment for this lipid abnormality), 3) raised blood pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg or treatment of previously diagnosed hypertension), and 4) raised fasting plasma glucose (≥5.6 mmol/L or previously diagnosed type 2 diabetes).

Statistical methods

The continuous outcome variables are reported as medians with interquartile ranges, and comparisons between groups are reported as percentage differences (95% confidence intervals) because of logarithmic transformations of the outcomes. The analyses were conducted for all adolescents and stratified by sex. There were no significant interactions between GDM and sex; consequently, the main results are presented sex adjusted. We report the results from multiple linear regression adjusted for the following: 1) sex only; 2) sex, birth weight, and gestational age; 3) sex and body mass index at age 16 years; and 4) all of the above. Adjustments for gestational age and birth weight by sex are shown in Web Table 1. (This information is posted on the Journal’s website (http://aje.oxfordjournals.org/).) Birth weight and gestational age are in these analyses intervening variables and, by adjusting for them, we explored the extent of differences in metabolic factors that were not fully explained by them. Socioeconomic status did not modify the associations (data not shown). Student’s t or chi-squared tests were used as appropriate. For the analysis of metabolic syndrome and its binary components, we used logistic regression and report results as odds ratios with their 95% confidence intervals. These analyses were conducted for all adolescents and were adjusted for 1) sex only and 2) sex, birth weight, and gestational age. We used SAS/STAT, version 9.1, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Compared with the reference group, mothers with GDM were older, heavier, and more often multiparous, and their infants had a shorter gestational age and higher birth weight (Table 1). The prevalence of overweight (body mass index >25 kg/m²) was significantly higher in the OGDM than in the reference group (18.8% vs. 8.4%; P < 0.001), as were the median body mass index (20.8 kg/m² vs. 20.2 kg/m², 95% confidence interval [CI] for the percentage difference adjusted for sex: 3.5%, 9.5%) and waist circumference (73.3 cm vs. 71.5 cm, 95% CI: 3.2%, 7.5%) (Table 2). Moreover, in the OGDM group, fasting insulin was higher, and homeostatic model assessment-insulin sensitivity was lower than in the reference group; the differences were similar after
The OGDM group compared with 7.1% in the reference group (for assessment by body mass index: 6.4% vs. 1.9%). The corresponding adjusted odds ratios were 2.71 (95% CI: 1.52, 4.82) for waist assessment and 3.10 (95% CI: 1.28, 7.52) for body mass index assessment.

DISCUSSION

In our prospective general population study, offspring of mothers with GDM had markers of insulin resistance and metabolic syndrome by adolescence, independently of birth weight, preterm birth, or later overweight. Alarmingly, a significant proportion of the adolescents already fulfill the criteria for metabolic syndrome, especially those born to the mothers with GDM. This may lead to a rapid increase in metabolic diseases, especially type 2 diabetes, in adulthood.

Disturbances of metabolic parameters in offspring after exposure to maternal diabetes in utero have been found in some studies (1–4, 6), but not all (7). As far as we know, only 3 prospective cohort studies have evaluated the association between GDM and intermediate markers of metabolic disease in the offspring (6, 8, 24). However, there were large age differences between the offspring groups, as well as high drop-out rates, and they were mainly retrospective (7), based on self-reporting (11), or failed to distinguish between different types of diabetes (4, 24). In contrast, in our study, all the children were of the same age at the outcome survey, minimizing the effect of variation in puberty stage. All were European, born in the same area during the same time period, and similarly followed up. The high retention rate, 75%–99% through the years, makes this cohort the most comprehensive long-term follow-up of offspring exposed to GDM in a general population to date. Data collection was prospective with validated methods including scrutiny of hospital records to confirm diagnoses of GDM. We therefore believe that the subgroups in the study are reliably allocated. Detailed case assessment additionally showed that the oral glucose tolerance test was not conducted according to current guidelines among all women at risk for GDM, even in the well-respected Finnish maternity care system; overweight was the most often overlooked indication for the oral glucose tolerance test. To avoid misclassification, we excluded those women and their offspring from the analyses, which may have introduced some selection bias. The control group included the women who did not have any specific risk factors for GDM and, therefore, were not oral glucose tolerance test screened. Consequently, it is possible that some of them may have developed GDM, which can dilute the associations between the groups. In spite of that, the differences in metabolic outcomes between the exposed and the unexposed were quite striking.

The association between GDM and metabolic disturbance of offspring is likely to be multifactorial, including genetic and shared prenatal and postnatal environmental factors and their interactions. In spite of intensive research, we do not know exactly how genes and the environment contribute to the observed association over the life course. For example, recently, Shaat et al. (12) associated a variant in the transcription factor 7-like 2 gene (TCF7L2) with increased risk of GDM, while we showed that the same variant associated...
with birth weight in offspring but that this was predominantly an effect mediated by maternal genotype, resulting in deficient glycemic control during pregnancy and higher birth weight (25). We showed in the present study that associations between GDM and the metabolic outcomes were independent of birth weight and gestational age, suggesting that other mechanisms than excessive growth may be involved. Elevated insulin concentrations during critical periods of fetal development may also contribute via incompletely understood mechanisms to a malprogramming of neuroendocrine systems that regulate later weight gain and metabolism (26). Intrauterine predisposition to maternal diabetes may further lead to the lack of acute insulin response in the offspring irrespective of obesity or insulin resistance (5, 27). This illustrates how complex the relations are between maternal and fetal genotypes and intrauterine environment in influencing a child’s health. In a current study, a lack of genetic data and a low number of adolescents whose parents had so far developed type 2 diabetes precluded further distinguishing of the roles of genes and environment (28).

Because GDM was diagnosed after 1 abnormal oral glucose tolerance test value, the screen-positive group includes mothers with a mild metabolic disturbance.

### Table 2. Outcome Measures in the Offspring of Mothers With Gestational Diabetes and Reference Group at Age 16 Years, Northern Finland 1986 Birth Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>OGDM Group, Median (Interquartile Range)</th>
<th>Reference Group, Median (Interquartile Range)</th>
<th>Adjusted for Sex</th>
<th>Adjusted for Birth Weight, Gestational Age, and Sex</th>
<th>Adjusted for Current Body Mass Index and Sex</th>
<th>Adjusted for Current Body Mass Index, Sex, Birth Weight, and Gestational Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>117 (111–125)</td>
<td>115 (106–123)</td>
<td>1.8 —0.2, 3.8</td>
<td>0.0 —2.0, 2.1</td>
<td>1.5 —0.6, 3.7</td>
<td>0.5 —1.4, 2.5</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>68 (65–73)</td>
<td>67 (62–72)</td>
<td>1.2 —1.1, 3.5</td>
<td>0.9 —1.4, 3.2</td>
<td>0.1 —2.0, 2.3</td>
<td>0.0 —2.2, 2.2</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>85 (80–90)</td>
<td>83 (77–89)</td>
<td>1.4 —0.6, 3.5</td>
<td>1.1 —0.9, 3.1</td>
<td>0.4 —1.5, 2.3</td>
<td>0.2 —1.7, 2.2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>20.8 (19.4–23.8)</td>
<td>20.2 (18.8–22.1)</td>
<td>6.5 3.5, 9.5</td>
<td>5.3 2.3, 8.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist, cm</td>
<td>73.3 (69.5–81.5)</td>
<td>71.5 (68.0–76.0)</td>
<td>5.4 3.2, 7.5</td>
<td>4.4 2.2, 6.6</td>
<td>1.3 0.3, 2.2</td>
<td>1.0 0.03, 2.0</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol, mmol/L</td>
<td>2.20 (2.00–2.70)</td>
<td>2.20 (1.90–2.60)</td>
<td>5.1 0.2, 10.7</td>
<td>6.0 0.6, 11.6</td>
<td>2.8 2.3, 8.2</td>
<td>4.0 0.03, 2.0</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol, mmol/L</td>
<td>1.33 (1.17–1.56)</td>
<td>1.39 (1.20–1.60)</td>
<td>—2.1 6.1, 2.0</td>
<td>—1.9 5.9, 2.3</td>
<td>0.0 3.9, 4.2</td>
<td>—0.1 4.0, 4.1</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>4.20 (3.90–4.75)</td>
<td>4.20 (3.70–4.70)</td>
<td>2.4 1.2, 6.2</td>
<td>3.1 0.6, 6.9</td>
<td>1.6 2.0, 5.3</td>
<td>2.3 1.3, 6.1</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.79 (0.63–0.97)</td>
<td>0.72 (0.57–0.96)</td>
<td>6.3 2.5, 16.0</td>
<td>7.8 1.2, 17.7</td>
<td>2.0 6.3, 11.0</td>
<td>4.1 4.4, 13.4</td>
</tr>
<tr>
<td>Insulin, milliunits/L</td>
<td>10.20 (8.45–14.30)</td>
<td>9.30 (7.30–11.90)</td>
<td>15.5 5.9, 26.0</td>
<td>16.2 6.5, 26.8</td>
<td>8.7 0.1, 18.1</td>
<td>10.9 2.0, 20.4</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.30 (5.00–5.50)</td>
<td>5.10 (4.90–5.40)</td>
<td>1.3 0.6, 3.4</td>
<td>1.4 0.5, 3.4</td>
<td>1.3 0.7, 3.3</td>
<td>1.3 0.7, 3.3</td>
</tr>
<tr>
<td>Homeostatic model assessment-insulin sensitivity</td>
<td>74.7 (54.1–91.2)</td>
<td>82.3 (64.0–104.7)</td>
<td>—13.3 20.6, 5.4</td>
<td>—14.0 21.2, 6.1</td>
<td>—8.5 15.8, 0.5</td>
<td>—10.4 17.6, 2.5</td>
</tr>
</tbody>
</table>

Abbreviation: OGDM, offspring of women with gestational diabetes.

* Numbers in the OGDM and reference groups vary because of unfasted samples: OGDM group (n = 87–96); reference group (n = 3,525–3,709).
Table 3. Prevalence and Risk of Metabolic Syndrome and Its Binary Components in the Offspring of Mothers With Gestational Diabetes and Reference Group at Age 16 Years, Northern Finland 1986 Birth Cohorta

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Prevalence in OGDM Group</th>
<th>Prevalence in Reference Group</th>
<th>Adjusted for Sex</th>
<th>Adjusted for Birth Weight, Gestational Age, and Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>5</td>
<td>5.9</td>
<td>54</td>
<td>1.6</td>
</tr>
<tr>
<td>Central obesity (waist)</td>
<td>16</td>
<td>17.0</td>
<td>261</td>
<td>7.1</td>
</tr>
<tr>
<td>Central obesity (body mass index)</td>
<td>6</td>
<td>6.4</td>
<td>70</td>
<td>1.9</td>
</tr>
<tr>
<td>Raised triglycerides</td>
<td>2</td>
<td>2.2</td>
<td>119</td>
<td>3.4</td>
</tr>
<tr>
<td>Reduced high density lipoprotein cholesterol</td>
<td>13</td>
<td>14.4</td>
<td>627</td>
<td>17.9</td>
</tr>
<tr>
<td>Raised blood pressure</td>
<td>11</td>
<td>11.8</td>
<td>490</td>
<td>13.3</td>
</tr>
<tr>
<td>Raised fasting blood glucose</td>
<td>21</td>
<td>23.6</td>
<td>520</td>
<td>15.3</td>
</tr>
</tbody>
</table>

Abbreviation: OGDM, offspring of women with gestational diabetes.

a OGDM group (n = 87–96); reference group (n = 3,525–3,709).

Disturbances. The results support previous, mostly smaller scale reports, in which even impaired maternal glucose tolerance under the threshold for overt diabetes was associated with increased risk of metabolic disturbance in the offspring (29, 30). On the basis of our study and previous studies, we can speculate that the classic Pedersen hypothesis (31) might be extended into later life by hypothesizing that maternal hyperglycemia leads not only to fetal hyperinsulinemia and macrosomia but also to obesity and insulin resistance in adolescence.

Adolescence is a critical period for the development of adiposity (10), and increased body mass index at or around puberty increases the risk of adult obesity (32, 33). We used waist circumference, serum insulin levels, and homeostatic model assessment-insulin sensitivity as the main indicators of adiposity and insulin resistance. Waist circumference was significantly higher in OGDM after adjustment for current body mass index, indicating increased visceral adiposity. The limitation of the study was that we could not investigate the effect(s) of potential modifying factors, such as breastfeeding, diet of the offspring during the life course, or current weight of the parents, on the development of adiposity or other adverse metabolic outcomes. It is probable that offspring adapt dietary and physical activity behaviors similar to those of their obese parents, potentially leading to adverse metabolic traits. With modification of families’ lifestyle factors, it may be possible at least to delay the onset of type 2 diabetes in people at risk (34). Even slight differences in body mass index are associated with large differences in the prevalence of metabolic disorders (21). These findings underscore the importance of identifying at-risk groups early enough to initiate guidance on lifestyle factors in order to avoid future development of metabolic syndrome and related sequelae.

Previous studies suggest that disturbances in glucose metabolism may differ between genders (22, 35), but there are no studies related to offspring exposure to GDM. In our study, measures of insulin resistance were more pronounced among female than male OGDM, although formal interaction tests were nonsignificant.

As a conclusion, we demonstrated that the metabolic syndrome and adverse metabolic phenotypes are already apparent in the adolescent offspring of GDM mothers. The associations were not modified by birth weight or gestational age and existed even after adjustment for current body mass. The indisputable strength of our analysis is the emphasis on metabolic phenotypes rather than on only metabolic syndrome. Planning preventive and therapeutic strategies for this at-risk group should be considered before the development of clinical manifestations of metabolic syndrome. Unraveling the role of genetic factors, abnormal fetal metabolic milieu, and environmental factors in postnatal life in increasing risk of metabolic disturbance will require ongoing longitudinal research into young adulthood and beyond.

ACKNOWLEDGMENTS

Author affiliations: Department of Clinical Sciences/Obstetrics and Gynecology, Oulu University Hospital and University of Oulu, Oulu, Finland (Anna-Liisa Hartikainen, Anneli Pouta, Marja Väärmäki); Department of Child and Adolescent Health, National Public Health Institute, Oulu, Finland (Anneli Pouta, Marjo-Riitta Järvelin); Imperial College London, London, United Kingdom (Paul Elliot, Marjo-Riitta Järvelin, Ulla Sovio); Department of Clinical Sciences/Pediatrics, Oulu University Hospital and University of Oulu, Oulu, Finland (Päivi Tapamäen; Department of Clinical Sciences/Clinical Chemistry, Oulu University Hospital, Oulu, Finland (Aimo Ruokonen); Oxford Centre for Diabetes and Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom (Mark McCarthy); and Institute of Health Sciences and Biocenter, University of Oulu, Oulu, Finland (Marjo-Riitta Järvelin).
The work in this study was conducted in part by the support of the Academy of Finland and the European Commission (Framework 5 award QLG1-CT-2000-01643).

Conflict of interest: none declared.

REFERENCES


