Abstract

Aim. – The objective of the present study was to determine whether or not maternal metabolic syndrome in early pregnancy in women without previous diabetes is associated with the development of gestational diabetes mellitus (GDM).

Methods. – A total of 508 women from the Rhea study—involving a pregnant cohort in Crete, Greece (2007–2009)—with singleton pregnancies were included in the present analysis. Maternal fasting serum samples were collected and blood pressure measured before gestational week 15. The metabolic syndrome in early pregnancy was defined according to NHLBI/AHA criteria. Pregnant women were screened for GDM between weeks 24 and 28 of gestation, as defined by Carpenter and Coustan criteria. Multivariable log-binomial regression models were used to estimate the effect of the metabolic syndrome in early pregnancy on the risk of GDM, after adjusting for confounding factors.

Results. – Women with the metabolic syndrome were at high risk of GDM (RR = 3.17; 95% CI: 1.06–9.50). Among the components of the metabolic syndrome, the most significant risk factors were impaired fasting glucose (RR = 4.92; 95% CI: 1.41–17.23) and pre-pregnancy obesity (RR = 2.65; 95% CI: 1.23–5.70). A 10-mmHg rise in systolic and diastolic blood pressure increased the relative risk of GDM by 49% (RR = 1.49; 95% CI: 1.10–2.02) and 34% (RR = 1.34; 95% CI: 1.04–1.73), respectively, whereas a 1-unit increase in pre-pregnancy BMI increased the relative risk of GDM by 6% (RR = 1.06; 95% CI: 1.01–1.12).

Conclusion. – These findings suggest that women with the metabolic syndrome in early pregnancy have a greater risk of developing GDM. © 2009 Published by Elsevier Masson SAS.

Keywords: Gestational diabetes; The metabolic syndrome; Pregnancy

Résumé

Syndrome métabolique en début de grossesse et risque de diabète gestational.

Objectif. – Déterminer si la présence d’un syndrome métabolique en début de grossesse, chez des femmes sans antécédent de diabète, est associée à l’apparition d’un diabète gestational (DG).


Introduction

The metabolic syndrome (MetS) refers to a cluster of metabolic abnormalities that appear to promote the development of atherosclerotic cardiovascular disease and are associated with chronic low-grade systemic inflammation [1–3]. The main maternal effect of gestational diabetes is a higher long-term risk of developing MetS and type 2 diabetes [4]. Several studies have reported links between gestational diabetes mellitus (GDM) and the subsequent risk of type 2 diabetes and MetS [5–8], but the association between metabolic alterations in early pregnancy and the development of GDM has been little explored.

For this reason, the objective of the present study was to examine the association between the MetS characteristics before and during early pregnancy in women with no previous diabetes, and the risk of developing GDM.

Materials and methods

2.1. Mother–child cohort in Crete (the Rhea study)

The mother–child cohort study in Crete (the Rhea study) examined a sample population of women who became pregnant within one year, starting in February 2007, living in the prefecture of Heraklion. Over the study period, 1765 eligible women were approached, and 1610 (91%) agreed to participate; 1317 were followed up to delivery. A total of 730 participants with singleton pregnancies provided fasting blood samples during their early pregnancy. Women who experienced spontaneous or induced abortions (n = 87) because of relocation out of the area, delivery elsewhere and/or missing medical records. We also excluded 16 women who had GDM in a previous pregnancy, as this is associated with a greater probability of GDM recurrence, and 66 women who had diabetes before becoming pregnant. This means that a final cohort of 508 women was available for analysis.

2.2. Biochemical analyses

Maternal fasting serum samples were collected during the first major ultrasound visit at or before week 15 of gestation (mean: 11.96 weeks, SD 1.49). Plasma triglycerides, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and glucose concentrations were determined, using standard enzymatic procedures and an automatic analyzer (Olympus AU5400 high-volume chemistry analyzer). Insulin sensitivity was determined by homoeostasis model assessment (HOMA-R) [9].

2.3. Maternal anthropometry

Height, measured at the first prenatal visit, and pre-pregnancy weight, as reported at the time of the first major ultrasound visit, were used to calculate the pre-pregnant body mass index (BMI; weight [kg]/height[m]^2).

2.4. Maternal blood pressure

Systolic (SBP) and diastolic (DBP) blood pressure were also measured at the time of the first major ultrasound visit, using an electronic BP monitor, after 10 minutes of rest in a sitting position. All readings were taken three times in the right arm for each woman. The mean value, obtained from the second and third readings, was used in the analysis.

2.5. Definition of the metabolic syndrome in early pregnancy

All participants were classified as having the MetS or not according to the criteria proposed by the US National Heart, Lung and Blood Institute/American Heart Association (NHLBI/AHA) [1], but with adaptations appropriate for the present study population; for example, abdominal circumference was not considered a criterion of obesity, as our study population involved pregnant women. Obesity was defined as a BMI > 30 kg/m^2 before pregnancy.

In addition, the MetS was defined as the presence of three or more of the following risk factors: pre-pregnancy BMI > 30 kg/m^2; triglycerides ≥ 150 mg/dL; HDL-cholesterol < 50 mg/dL; BP ≥ 130/85 mmHg; and fasting blood glucose (FBG) ≥ 100 mg/dL.

2.6. Gestational diabetes mellitus

Women were screened for GDM at weeks 24–28 of gestation, and were classified as having GDM in the index pregnancy if two or more of the four plasma glucose values obtained during the 100-g 3-h oral glucose tolerance test (OGTT)
were abnormal, as per the criteria proposed by Carpenter and Coustan [10]: FBG ≥ 95 mg/dL; 1-h values ≥ 180 mg/dL; 2-h values ≥ 155 mg/dL; and 3-h values ≥ 140 mg/dL.

2.7. Statistical analysis

Data analyses were performed using STATA 10.0 statistical software. Multivariable log-binomial regression models were used to estimate risk ratios (RR) and 95% confidence intervals (95% CI), after adjusting for confounders. Potential confounders related to the outcome of interest in the bivariate models with a P value < 0.2 were included in the multivariable models. The following variables were considered to be potential confounders: maternal age at delivery; education (low level: less or equal to six years of school; medium level: less or equal to 12 years of school; high level: university or technical college degree); smoking during pregnancy (yes/no); marital status (single/married-engaged); family history of hypertension (yes/no); family history of diabetes (yes/no); Greek ethnic origin (yes/no); parity; and physical activity during pregnancy (yes/no). All hypothesis testing was conducted assuming P < 0.05 as the level of significance and a two-sided alternative hypothesis.

3. Results

Complete information was available for all main model variables for our 508 pregnant women. These data revealed that women with the MetS were more likely to be less educated and to smoke more during pregnancy, while women with GDM were more likely to have a family history of diabetes.

Table 1 shows the associations between the MetS in early pregnancy, and its components, and GDM. Women with the MetS were at high risk of GDM (RR = 3.17; 95% CI: 1.06–9.50) and, of the components of MetS, the most significant risk factors were impaired fasting glucose (RR = 4.92; 95% CI: 1.41–17.23) and pre-pregnancy obesity (RR = 2.65; 95% CI: 1.23–5.70). An increase of 10 mmHg in SBP and DBP raised the RR of GDM by 49% (RR = 1.49; 95% CI: 1.10–2.02) and 34% (RR = 1.34; 95% CI: 1.04–1.73) respectively, whereas a 1-unit increase in pre-pregnancy BMI increased the RR of GDM by 6% (RR = 1.06; 95% CI: 1.01–1.12).

In an alternative analysis, we excluded pre-pregnancy BMI from the definition of the MetS and treated it instead as a potentially confounding factor. We also developed a composite measure, the ‘metabolic score’, using the remaining four factors in the NHLBI/AHA criteria to define the MetS. Thus, the ‘metabolic score’ was determined by the presence of two or more of the following risk factors: triglycerides ≥ 150 mg/dL; HDL cholesterol < 50 mg/dL; BP ≥ 130/85 mmHg; and FBG ≥ 100 mg/dL. The results were essentially the same as in the original analysis, although the RRs were relatively lower, indicating that the metabolic score is a significant risk factor for the development of GDM (RR = 2.05; 95% CI: 1.05–4.44). Of the components of the MetS, the most significant risk factor was impaired fasting glucose (RR = 4.53; 95% CI: 1.27–16.11).

4. Discussion

The present study provides novel evidence that women with singleton pregnancies who develop GDM were more likely to have the MetS before week 15 of gestation compared with women without GDM. The MetS refers to a cluster of cardiovascular risk factors that are thought to constitute a complete phenotype rather than separate conditions [11,12]. This is supported by the present study results showing that the greater the number of MetS components, the greater the increase in risk

### Table 1

**Association of the metabolic syndrome (MetS)**

<table>
<thead>
<tr>
<th>Gestational diabetes</th>
<th>Gestational diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
</tr>
<tr>
<td><strong>Without (n = 476) n (%)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>With (n = 32) n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>MetS</td>
<td>16 (3.3)</td>
</tr>
<tr>
<td>BMI pre-pregnancy &gt; 30 kg/m²</td>
<td>56 (11.8)</td>
</tr>
<tr>
<td>Triglycerides ≥ 150 mg/dL</td>
<td>82 (17.2)</td>
</tr>
<tr>
<td>HDL cholesterol &lt; 50 mg/dL</td>
<td>110 (23.1)</td>
</tr>
<tr>
<td>Blood pressure ≥ 130/85 mmHg</td>
<td>31 (6.5)</td>
</tr>
<tr>
<td>Fasting glucose ≥ 100 mg/dL</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td></td>
</tr>
<tr>
<td>Number of MetS components</td>
<td>0.60</td>
</tr>
<tr>
<td>Maternal pre-pregnancy BMI</td>
<td>24.0</td>
</tr>
<tr>
<td>Triglycerides (per 50-mg/dL increase)</td>
<td>112.2 (44.1)</td>
</tr>
<tr>
<td>Ratio of LDL-to-HDL</td>
<td>2.03 (0.7)</td>
</tr>
<tr>
<td>SBP (per 10-mmHg increase)</td>
<td>106.1 (9.5)</td>
</tr>
<tr>
<td>DBP (per 10-mmHg increase)</td>
<td>69.9 (9.6)</td>
</tr>
<tr>
<td>HOMA (log-transformed)</td>
<td>75.4 (10.8)</td>
</tr>
<tr>
<td>Glucose (per 10-mg/dL increase)</td>
<td>2.05 (3.2)</td>
</tr>
<tr>
<td>Insulin (per 20-mU/mL increase)</td>
<td>10.4 (14.7)</td>
</tr>
</tbody>
</table>

*Defined according to NHLBI/AHA criteria, but adapted to the present study population of pregnant women; RR: risk ratio (adjusted for maternal age, education, smoking during pregnancy and family history of diabetes); 95% CI: 95% confidence interval; BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; HOMA: homoeostasis model assessment.*
of GDM. There are several pathogenic pathways shared by the MetS and GDM, including insulin resistance [6], glucose intolerance [6], hyperlipidaemia [13] and impaired endothelial function [14]. The present study findings are also consistent with those of the few other studies evaluating the effects of maternal hypertension in early pregnancy on GDM [15,16]. In addition, numerous studies have reported an increased risk of GDM in women who are overweight or obese compared with lean or normal-weight women [17]. Consistent with our present study results, a large population-based cohort study of around 97,000 singleton births showed that obese women have a threefold greater risk of developing GDM than do non-obese women [18].

This was the first time that the MetS was evaluated in relation to GDM in early pregnancy, which may raise the question of the appropriateness of such a study. Obesity during pregnancy cannot be assessed on the basis of maternal abdominal circumference as, at this time, an enlarged abdominal circumference is likely to have different implications (such as fetal macrosomia or increased amniotic fluid volume). For this reason, we decided to define obesity according to World Health Organization diagnostic criteria (BMI ≥ 30 kg/m²), which is also in accordance with the three other studies evaluating the MetS in pregnant women [19–22]. However, as a sensitivity analysis using BMI as a confounding variable rather than a risk factor gave essentially the same results as the original analysis, we decided not to use the BMI assessed in the first trimester of gestation, as it may be more related to changes due to pregnancy. Indeed, in the present study, women of normal weight before pregnancy put on more weight at week 12 of gestation (3.8% of the initial weight) compared with overweight (2.7%) or obese (2.0%) women.

The collection of blood early in pregnancy (mean gestational age: 12 weeks) enabled the detection of disordered plasma lipid, glucose and insulin concentrations before the pregnancy–related changes occurred in these parameters. However, it is still unclear as to whether or not the rise in lipids detected early in pregnancy was present prior to conception or was an early aberration associated, perhaps, with implantation.

The strengths of the present study include its population-based prospective design, and use of detailed and validated data for the MetS components. Unlike previous epidemiological studies, BP, and lipid, glucose and insulin concentrations in early pregnancy, were precisely measured and not self-reported. Moreover, fasting serum samples—a somewhat complicated measure in a cohort of pregnant women—were available. A clear definition of GDM was based on objective measurements of pregnancy glycaemia at weeks 24–28 of gestation.

Nevertheless, several limitations need to be mentioned. The study sample size was relatively small, and the RRs were calculated from a small number of events. However, the exclusion of women with a diagnosis of diabetes or GDM in a previous pregnancy, as well as adjustments for several sociodemographic variables, reduced the likelihood of confounding factors.

In conclusion, the findings of the present study suggest that women with the MetS in early pregnancy have a higher risk of developing GDM. However, clarification of the complex processes underlying these findings requires further study.

5. Conflicts of interest

The authors have not declared any conflicts of interest.

Acknowledgments

This study was supported in part by the EU NewGeneris integrated project, Sixth Framework Programme (contract no. FOOD-CT-2005-016320), and by the EU-funded project HiWATE, Sixth Framework Programme (contract no. Food-CT-2006-036224). The authors gratefully acknowledge Dr Eleni Fthenou for her handling of the biobank.

References


