Cardiovascular risk factors in Chinese women with a history of gestational diabetes mellitus

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Abstract: Background: Women with a history of gestational diabetes (GDM) are at increased risk of developing cardiovascular diseases compared with normal women. This study aimed to evaluate the cardiovascular risk factors in Chinese women with GDM. Methods: 453 women with GDM (cases) and 1,180 healthy women (controls) were included in this study. The post-partum examinations included 2 h 75 g oral glucose tolerance tests, lipid profiles, anthropometric measurements (blood pressure, height, weight) and documentation of medical history, diet, and lifestyle. Results: Compared with controls, the risks of abnormal glucose metabolism, obesity, hypertension, metabolic syndrome in women with a history of GDM were 4.61, 1.30, 1.57 and 3.52, respectively. Fasting blood glucose, progestational body mass index (pBMI) and antenatal insulin resistance at antenatal visit were predictors for abnormal glucose metabolism. pBMI and antenatal diastolic blood pressure were predictors for hypertension. pBMI and weight gain during pregnancy were predictors for obesity/overweight. pBMI, antenatal systolic blood pressure and antenatal triglyceride were predictors for metabolic syndrome. Conclusions: Women with a history of GDM have increased rates of cardiovascular disease risk factors including abnormal glucose metabolism, obesity, hypertension, metabolic syndrome. pBMI is the common independent predictors of cardiometabolic disease in the post-partum.

Keywords: Gestational diabetes mellitus, cardiovascular disease, obesity, hypertension, metabolic syndrome

Introduction

Gestational diabetes mellitus (GDM) is defined as varying degrees of carbohydrate intolerance with onset or first recognition during pregnancy [1, 2]. The prevalence of GDM varies between 9.3% and 125.5%, according to the Hyperglycemia and Adverse Pregnancy Outcome Study (HAPO) in 2012 [3]. It has long been known that women with a history of GDM are at increased risk of developing type 2 diabetes mellitus (type 2 DM) later in life [4]. Recent studies have shown that GDM also increases the risk of long-term development of hypertension, dyslipidaemia, atherosclerosis and coronary heart disease [5, 6]. The frequently recognized association between glucose intolerance, obesity, hypertension and dyslipidaemia has led to the recognition of what is now known as the metabolic syndrome (MS). The major adverse consequence of MS is cardiovascular disease (CVD), as several of its constituent metabolic abnormalities are in fact CVD risk factors.

Insulin resistance is considered a crucial pathophysiological process involved in both metabolic syndrome and GDM [6, 7]. Indeed, several studies have suggested that GDM may be one of the first metabolic abnormalities to be recognized in the development of the metabolic syndrome [7-9]. In this study, we aimed to analyze cardiovascular risk factors in Chinese pregnant women with GDM and identify the risk factors associated with post-partum impaired glucose tolerance, obesity, hypertension and metabolic syndrome.

Materials and methods

Patients

This study was a prospective cohort study to compare a population with history of GDM (cases) with control individuals with normal pregnancy history (controls), at least half a year after the delivery. The study was approved by Ethics Committee of Guangdong Women and Children Hospital. Written informed consent...
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Table 1. Clinical data of women with history of GDM (cases) and with normal pregnancy history (control)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases</th>
<th>Controls</th>
<th>X²</th>
<th>P</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus (n, %)</td>
<td>24 (5.3%)</td>
<td>0 (0%)</td>
<td>63.449</td>
<td>0.000</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prediabetes (n, %)</td>
<td>182 (40.18%)</td>
<td>275 (23.31%)</td>
<td>46.233</td>
<td>0.000</td>
<td>2.21</td>
<td>1.754-2.785</td>
</tr>
<tr>
<td>Abnormal glucose metabolism (n, %)</td>
<td>206 (45.48%)</td>
<td>275 (23.31%)</td>
<td>155.06</td>
<td>0.000</td>
<td>4.612</td>
<td>3.588-5.927</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>28 (6.18%)</td>
<td>19 (1.61%)</td>
<td>24.466</td>
<td>0.000</td>
<td>4.026</td>
<td>2.225-7.285</td>
</tr>
<tr>
<td>Overweight/obesity (n, %)</td>
<td>120 (26.49%)</td>
<td>256 (21.69%)</td>
<td>15.163</td>
<td>0.039</td>
<td>1.301</td>
<td>1.013-1.671</td>
</tr>
<tr>
<td>Obesity (n, %)</td>
<td>28 (6.18%)</td>
<td>18 (1.53%)</td>
<td>24.466</td>
<td>0.000</td>
<td>4.155</td>
<td>2.275-7.589</td>
</tr>
<tr>
<td>MS (n, %)</td>
<td>26 (5.74%)</td>
<td>20 (1.69%)</td>
<td>19.561</td>
<td>0.000</td>
<td>3.532</td>
<td>1.951-6.393</td>
</tr>
</tbody>
</table>

MS: metabolic syndrome; RR: relative risk.

Table 2. Relationships between metabolic indexes and abnormal glucose metabolism in women with a history of GDM

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>3.296</td>
<td>26.991</td>
<td>2.001-364.01</td>
<td>0.013</td>
</tr>
<tr>
<td>Progestational BMI</td>
<td>1.7</td>
<td>5.475</td>
<td>1.176-25.486</td>
<td>0.03</td>
</tr>
<tr>
<td>Antenatal IR</td>
<td>-0.009</td>
<td>0.991</td>
<td>0.985-0.998</td>
<td>0.012</td>
</tr>
</tbody>
</table>

FBG: fasting plasma glucose; BMI: body mass index; IR: insulin resistance; OR: odds ratio.

Table 3. Relationships between metabolic indexes and hypertension in women with a history of GDM

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestational BMI</td>
<td>0.305</td>
<td>1.356</td>
<td>1.099-1.823</td>
<td>0.044</td>
</tr>
<tr>
<td>Antenatal DBP</td>
<td>0.283</td>
<td>1.327</td>
<td>1.069-1.646</td>
<td>0.01</td>
</tr>
</tbody>
</table>

BMI: body mass index; DBR: diastolic blood pressure; OR: odds ratio.

was obtained from all participants. Total 453 cases and 1180 controls were recruited who visited Department of Obstetrics, Guangdong Women and Children Hospital from 2009 to 2013.

Inclusion criteria were as follows: history of GDM in the 2nd or 3rd trimester of gestation as defined by the criteria of the American Diabetes Association [10]; age range between 18 and 40 years; and body mass index (BMI) ≤ 40 kg/m². Exclusion criteria were as follows: pre-pregnancy diabetes or family history suggestive of monogenic diabetes, metabolic syndrome, hypertension, cardiovascular disease, thyroid disease, hemopathy or polycystic ovary syndrome; concomitant systemic disease (chronic or acute infections), multiple pregnancy or pregnancy-assisted reproductive technologies; had severe diseases such as pancreatitis, hyperthyroidism or nephritis after the delivery; after the delivery took medications that had effects on blood sugar and blood pressure. Control individuals were recruited from females with previous pregnancy, but with a history of normal glucose tolerance.

Data of all the participants were collected by a retrospective survey, including family and personal history of DM, the age and date of birth record. Type 2 diabetes mellitus (DM2) and central obesity were diagnosed based on the criteria of American Diabetes Association [11]. MetS was defined as three or more of five risk factors: (1) waist circumference ≥ 80 cm, (2) fasting plasma glucose (FPG) ≥ 5.6 mmol/L, (3) systolic blood pressure (BP) ≥ 130 mmHg or diastolic BP ≥ 85 mmHg, (4) fasting plasma triglyceride ≥ 1.7 mmol/L and (5) high density lipoprotein cholesterol (HDL-C) < 1.3 mmol/L.

Measurements

Plasma glucose and insulin 120’ post-75 g oral glucose tolerance test (OGTT) were performed. Plasma glucose (mmol/L) was analyzed using an enzymatic calorimetric method for completely hemolyzed anti-coagulated blood in a Cobas Integra 700 autoanalyzer (Roche Diagnostics). Insulin resistance (IR) was calculated by the formula: fasting insulin (mU/mL) × fasting glucose (mmol/L)/22.5. The lipid profiles including total cholesterol (Total-Chol, mmol/L), triglycerides (TG, mmol/L), LDL-cholesterol (LDL-Chol, mmol/L), HDL-cholesterol (HDL-Chol, mmol/L) were quantified by enzymatic calorimetry in a Modular DPD biochemical autoanalyzer.

All anthropometric measurements were taken by trained nurses and with subjects wearing
light clothes and no shoes. A portable scale was used to measure body weight to the nearest half-kilogram. Height was measured to the nearest 0.1 cm with a wall-mounted stadiometer. BMI (kg/m²) was calculated as weight in kilograms divided by the square of height in meters. Blood pressure (BP) measurements were performed by trained nurses. Sitting BP was measured 10 min after rest with a standard adult sphygmomanometer at the beginning and the end of the interview. The mean BP value was calculated. Hypertension was defined on the basis of the Joint National Committee-7 cut-off point of 140 mmHg and above for systolic blood pressure (SBP) and/or 90 mmHg and above for diastolic blood pressure (DBP).

**Statistical analysis**

Statistical analysis was performed using the SPSS 13.0 (SPSS Inc., Chicago, IL) program. All data are expressed as mean ± SD or percentage (%). Comparisons between groups were made using Chi-square test, Fisher’s exact test or Student’s t-test as appropriate. The difference of measurement data among the groups were analyzed by Levene’s test. The relations between different factors were analyzed by Multivariate logistic regression analysis. A p-value < 0.05 for two-tailed statistical tests was considered significance.

**Results**

The interval time from pregnancy to recruitment was 1.36±0.81 years in the case group, and 1.47±0.69 years in the control group. Table 1 showed that women in case group had higher prevalence of abnormal glucose metabolism (OR: 4.61 95% CI 3.59-5.93; P=0.000), obesity (OR: 4.16; 95% CI 2.28-7.59; P=0.000), hypertension (OR: 4.03; 95% CI 2.23-7.29; P=0.000), metabolic syndrome (OR: 3.53; 95% CI 1.95-6.39; P=0.003) than women in control group.

In the multivariate model, FPG, Progestational BMI and antenatal IR increased the odds of later developing abnormal glucose metabolism with ORs of 26.99 (95% CI 2.0-364.01), 5.48 (95% CI 1.18-25.49) and 0.99 (95% CI 0.985-0.998) respectively. Progestational BMI and antenatal DBP increased the odds of later developing hypertension with ORs of 1.36 (95% CI 1.009-1.823) and 1.33 (95% CI 1.069-1.65), respectively. Progestational BMI and weight gain during pregnancy increased the odds of later developing obesity/overweight with ORs of 2.57 (95% CI 1.89-3.48) and 1.22 (95% CI 1.06-1.4), respectively. Basel BMI, antenatal SBP and antenatal TG increased the odds of later developing MS with ORs of 2.93 (95% CI 1.19-7.19), 1.12 (95% CI 1.003-1.24) and 9.02 (95% CI 1.07-75.92), respectively (Tables 2-5).

**Discussion**

Several studies have examined the development of metabolic syndrome in parous women and suggested that a history of GDM during pregnancy was an important risk factor [12, 13]. It is even postulated that GDM might be considered as early sign of metabolic syndrome, due to the increased prevalence of obesity, diabetes, hypertension and other obesity related health risk factors in women with a history of GDM [14, 15].

In our study we showed that Chinese women with a history of GDM have increased rates of cardiovascular disease risk factors including abnormal glucose metabolism, obesity, hypertension, metabolic syndrome, and have a high risk of developing cardiovascular disease in later years. Progestational BMI is the common independent predictors of cardiometabolic dis-
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Obesity is a simple criterion recommended by the WHO for non-systematic screening of GDM and obesity is also associated with other obstetric complications. Obesity was significantly associated with hypertension, dyslipidaemia and increased insulin need during pregnancy, emphasizing the independence of these parameters [16]. The metabolic burden of pregnancy leads to a progression of insulin resistance and its clinical complications. Indeed, the additional role of placental hormones in the development and accentuation of insulin resistance, even in non-diabetic women, is well established [17]. These women also had most of the risk factors for post-partum abnormal glucose tolerance, and high glycaemic values at diagnosis and in the immediate post-partum days. These results suggest that these factors act synergistically to produce adverse metabolic outcomes.

In most women, insulin resistance decreases after delivery and the glucose intolerance disappears. These women can be considered to have more subtle metabolic disturbances than those presenting with constituents of metabolic syndrome before their pregnancy. However, all women with a history of GDM are at increased risk for the future development of IGT and type 2 DM [18, 19]. Thus, these women have a lower resilience to metabolic challenges of pregnancy because they eventually have a decreased pancreatic beta-cell function reserve [19]. Even in the absence of pre-pregnancy obesity, women with a history of GDM have an almost 4-fold additional independent risk of developing metabolic syndrome compared to controls without GDM [13]. Winzer et al. showed that women with prior GDM had reduced adiponectin concentrations independently of obesity and metabolic abnormalities and this was associated with subclinical inflammation and atherogenic parameters [20]. The important consequence of this relationship is increased risk of cardiovascular disease in patients with metabolic syndrome [21, 22].

In conclusion, women with a history of GDM had an increased risk of diabetes compared with control subjects. These women also exhibited increased rates of other cardiovascular risk factors including obesity, high blood pressure and dyslipidaemia. Because GDM screening is non-systematic in many centers, we suggest adding obesity, hypertension and dyslipidaemia to the traditional risk factors used for screening high-risk pregnant women. Moreover, all the components of metabolic syndrome should be examined in every post-partum visit. These measures would allow earlier identification of all risk factors of cardiovascular disease in pregnant women.

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Disclosure of conflict of interest

None.

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References

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