The Postpartum Metabolic Outcome of Women with Previous Gestational Diabetes Mellitus

Chia-Hung Lin, MD; Shih-Fen Wen, BSc; Ya-Hui Wu, BSc; Yu-Yao Huang, MD, PhD; Miau-Ju Huang, MD

**Background:** This study investigated postpartum metabolic abnormality in women with previous gestational diabetes mellitus (GDM) and predictive factors for postpartum glucose intolerance.

**Methods:** From March 2001 to February 2003, 127 prior-GDM women underwent a 75g oral glucose tolerance test (OGTT) and metabolic assessment at least six weeks after delivery. To identify the predictors, clinical variables obtained at the time of GDM were compared.

**Results:** The cumulative incidence rates of diabetes mellitus (DM) and abnormal glucose tolerance (AGT) i.e. impaired fasting glucose or impaired glucose tolerance, in women with previous GDM were 13.4% and 29.1%, respectively. Postpartum body mass index (BMI), total cholesterol, HDL cholesterol, triglycerides, blood pressure, waist-to-hip ratio and fasting C-peptide were not significantly different among DM, AGT and normal glucose tolerance (NGT) women. However, the C-peptide/glucose score was lower in DM than in AGT and NGT women ($p < 0.01$). DM or AGT women had higher prepregnancy BMI and fasting glucose level for 100g OGTT than NGT women ($p < 0.05$) at the time of GDM. The fasting glucose value was an independent risk factor. The cutoff point of three abnormal values in 100g OGTT provided 86% sensitivity and 43% specificity for the prediction of postpartum DM or AGT.

**Conclusions:** High prepregnancy BMI and increased glycemic deterioration at the time of GDM are found in women developing postpartum DM and AGT. The fasting glucose value for 100g OGTT is an independent risk factor and more than three abnormal glucose values offers good diagnostic efficacy in predicting postpartum glucose intolerance.


Key words: gestational diabetes mellitus, postpartum, insulin resistance, beta-cell function, metabolic syndrome.

Gestational diabetes mellitus (GDM) is any glucose intolerance with onset or first recognition during pregnancy. Women with GDM have been found to be at risk of diabetes mellitus (DM), impaired glucose tolerance (IGT) and even metabolic syndrome, at postpartum follow-up. The inci-
Incidence of DM among women with a history of GDM has been shown to range from 6% to 62%. The predominant sources of difference in reported incidence rates may be ethnic variation, length of follow-up, diversity in selection and diagnostic criteria for GDM. Numerous predictors for diabetes after a GDM pregnancy have been identified; prepregnancy obesity and GDM severity are the most important factors. The local GDM data is limited and the incidence of GDM in Taiwan is reported to be 1% to 3%. However, there is a lack of studies, especially from longitudinal investigations, identifying characteristics of prior-GDM women who are at risk of glucose intolerance postpartum in the Taiwanese population. This study attempts to determine the postpartum metabolic abnormalities and predictive factors for subsequent diabetes in prior-GDM women in Taiwan.

**METHODS**

**Study samples**

From March 2001 to February 2003, 235 women diagnosed with GDM at Taipei Chang-Gung Memorial Hospital were enrolled in this prospective study. No women had a history of DM before pregnancy. Subjects were screened at 24-28 weeks of gestation and diagnosis of GDM was based on a 50g glucose challenge test of one-hour plasma glucose level \( \geq 140 \) mg/dl, followed by at least two abnormal values in a 100g oral glucose tolerance test (OGTT). Women with documented GDM fulfilled the Carpenter and Coustan modification of the National Diabetes Data Group (NDDG) criteria (requiring at least two of the following: fasting glucose \( \geq 95, \) 1-hour \( \geq 180, \) 2-hour \( \geq 155, \) 3-hour \( \geq 140 \) mg/dl). All women were recalled for postpartum metabolic assessments. Among the 235 women, 127 prior-GDM women returned at follow-up between 6 weeks to 2 years postpartum. Informed consent was obtained from each subject.

**Measurements**

Age, diabetic family history, body mass index (BMI) before and after pregnancy and weight gain during pregnancy were prospectively examined. Following a 75g OGTT the 127 prior-GDM subjects were divided into three groups: normal glucose tolerance (NGT); abnormal glucose tolerance (AGT) i.e. impaired fasting glucose or impaired glucose tolerance; DM based on American Diabetes Association (ADA) criteria. Postpartum fasting plasma C-peptide and insulin levels were measured. Other metabolic assessments were as follows: fasting plasma triglyceride; total and high-density lipoprotein (HDL) cholesterol concentrations; waist-to-hip ratio; systolic and diastolic blood pressures. Metabolic syndrome is defined by 2001 Adult Treatment Panel (ATP) III guidelines.

Plasma glucose was determined by the glucose dehydrogenase method (Olympus AU-640, Japan). Plasma total cholesterol, HDL-cholesterol and triglyceride concentrations were determined by commercial enzymatic methods (Cholesterol kit, Wako, Japan; HDL-C kit, Daiichi, Japan; Triglyceride kit, Roche, USA) on an automated analyzer (Hitachi 7600-210, Japan). HbA\(_1c\) values were measured by high-performance liquid chromatography (Primus CLC385, USA). C-peptide (DSL-7000 RIA Kit, Diagnostic Systems Laboratories, Inc. USA) and insulin (125 Tubes, Linco Research, Inc. USA) levels were determined by radioimmunoassay. The within and between assay variations of insulin measurements are 3.1% and 6.0% at an insulin value of 8 \( \mu \)U/ml. The within and between assay variations of C-peptide measurements are 3.3% and 5.3% at a C-peptide value of 1.80 and 1.68 ng/mL, respectively.

The C-peptide/glucose score was calculated as the ratio of C-peptide (ng/ml) to glucose (mg/dl) \( \times 100.\) Based on the homeostatic model assessment (HOMA), the \( \beta \)-cell function (HOMA\(_{beta}\)) was calculated as \( 20 \times \) fasting plasma insulin (FPI, mU/l) / fasting plasma glucose (FPG, mmol/l) - 3.5; insulin resistance (HOMAir) was measured by FPI / 22.5 \( \times e^{-\ln FPG} \).

Statistical analysis was conducted by SPSS V12.0 software. Differences in continuous variables between groups were tested with either ANOVA or independent-samples Student’s \( t \)-test when appropriate. Multiple comparisons of least significant difference (LSD) were performed for significant ANOVA. Differences in proportions were evaluated by \( \chi^2 \) or Fisher’s exact test. Multiple logistic regression analysis was applied to discern the independent risk factors of subsequent DM or AGT. Results were expressed as means \( \pm \) SD or %. A \( p \)-value of 0.05 or less was considered statistically significant.
RESULTS

Of the 235 prior-GDM subjects, 127 (54%) returned to attend the postpartum metabolic assessment at 1.0 to 19.0 (mean 3.3) months after delivery. One woman, for her convenience, returned at 1 month postpartum. Table 1 presents the baseline clinical characteristics of these 235 women. Women with or without postpartum follow-up had similar demographic and biochemical profiles. However, women who attended the follow-up program had more common diabetic family history (69.3 vs. 38.9%, \( p < 0.001 \)) and lower prepregnancy BMI (22.4 ± 3.7 vs. 23.5 ± 4.2 kg/m², \( p = 0.04 \)) than women without follow-up.

Table 2 shows 17 patients (13.4%) were diagnosed with DM, 37 (29.1%) had AGT and 73 (57.5%) had NGT. Comparison of the following postpartum clinical variables showed no significant differences among DM, AGT and NGT women: age, postpartum BMI, total cholesterol, HDL-cholesterol, triglycerides, waist-to-hip ratio, systolic and diastolic blood pressure, metabolic syndrome, 2-hour OGTT, fasting plasma glucose, 2-hour plasma insulin (FPI), homeostatic model assessment; HOMA_β: \( 20 \times FPI / \text{fasting plasma glucose} \) (FPG, \text{mmol/l}) -3.5; HOMA_α: \( 20 \times \text{fasting plasma insulin} \) (FPI, \text{mU/l})/\text{fasting plasma glucose} (FPG, \text{mmol/l}) -3.5; C-peptide/glucose score*:

<table>
<thead>
<tr>
<th>Postpartum variables</th>
<th>Postpartum glucose tolerance</th>
<th>DM</th>
<th>AGT (IGT or IFG)</th>
<th>NGT</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>17 (13.4%)</td>
<td>37 (29.1%)</td>
<td>73 (57.5%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>34.0 ± 4.6</td>
<td>34.0 ± 4.2</td>
<td>33.8 ± 4.0</td>
<td>0.938</td>
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</tr>
<tr>
<td>Postpartum BMI (kg/m²)</td>
<td>24.2 ± 3.0</td>
<td>24.9 ± 4.0</td>
<td>23.3 ± 5.2</td>
<td>0.226</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>213.2 ± 44.5</td>
<td>211.7 ± 34.0</td>
<td>203.2 ± 34.4</td>
<td>0.422</td>
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<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>56.1 ± 13.3</td>
<td>52.1 ± 10.2</td>
<td>56.8 ± 12.6</td>
<td>0.194</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>174.4 ± 185.4</td>
<td>161.8 ± 123.0</td>
<td>121.1 ± 68.3</td>
<td>0.087</td>
<td></td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.81 ± 0.03</td>
<td>0.81 ± 0.04</td>
<td>0.80 ± 0.05</td>
<td>0.099</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>119.5 ± 21.2</td>
<td>114.2 ± 11.5</td>
<td>111.0 ± 10.7</td>
<td>0.057</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>71.5 ± 17.0</td>
<td>68.1 ± 11.4</td>
<td>68.1 ± 9.3</td>
<td>0.531</td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>23.5%</td>
<td>8.1%</td>
<td>2.7%</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>HbA_1c (%)*</td>
<td>6.6 ± 1.9</td>
<td>5.3 ± 0.4</td>
<td>5.2 ± 0.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Fasting C-peptide level (ng/ml)</td>
<td>2.77 ± 1.10</td>
<td>3.02 ± 1.39</td>
<td>2.99 ± 1.05</td>
<td>0.777</td>
<td></td>
</tr>
<tr>
<td>C-peptide/glucose score*</td>
<td>2.08 ± 0.87</td>
<td>3.06 ± 1.38</td>
<td>3.22 ± 1.12</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>HOMA_β</td>
<td>127.0 ± 42.20</td>
<td>112.40 ± 43.90</td>
<td>160.99 ± 74.04</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td>HOMA_α*</td>
<td>5.89 ± 4.17</td>
<td>2.80 ± 2.19</td>
<td>2.99 ± 1.56</td>
<td>0.021</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DM: diabetes mellitus; GDM: gestational diabetes mellitus; BMI: body mass index; OGTT: oral glucose tolerance test.

Table 2. Comparison of Postpartum Clinical Variables Among the 127 Prior-GDM Women According to the Glucose Tolerance by 75g OGTT
blood pressures, and fasting C-peptide level. However, the prevalence of metabolic syndrome (\(p = 0.01\), HbA\(_1c\) levels (\(p < 0.001\)) and the C-peptide/glucose score (\(p = 0.004\)) were significantly different among the three groups. Multiple comparisons of LSD showed that the C-peptide/glucose score was lower in DM than AGT and NGT women (\(p < 0.01\)). Of 127 prior-GDM women, 61 had measurements of fasting insulin levels. The calculated HOMA\(_{\beta}\) and HOMAI were also significantly different among the three groups (\(p = 0.024\) and 0.021, respectively). Multiple comparisons of LSD revealed that HOMA\(_{\beta}\) was lower in AGT women than in NGT women (112.40 \(\pm\) 43.90 vs. 160.99 \(\pm\) 74.04, \(p < 0.01\)) but not in DM women (\(p = 0.68\)). The DM women, although a relatively small sample (\(n = 4\)), had higher HOMAI levels than those of AGT and NGT women (3.89 \(\pm\) 4.17 vs. 2.80 \(\pm\) 2.19 and 2.99 \(\pm\) 1.56 respectively, \(p < 0.01\)). Multiple comparisons of LSD showed no difference between AGT and NGT women in HOMAI (\(p = 0.73\)). The estimates of HOMA\(_{\beta}\) and HOMAI suggested the existence of beta-cell dysfunction and insulin resistance in the women with postpartum glucose intolerance.

To identify risk factors for subsequent DM or AGT, the clinical variables during pregnancy were compared among three different glucose tolerance groups (Table 3). Prepregnancy BMI; fasting, 1-hour, 2-hour, and 3-hour glucose levels of 100g OGTT; the number of abnormal values in the 100g OGTT were significantly different among the three groups. Multiple comparisons of LSD showed that women with postpartum DM or AGT had significantly higher pregestational BMI (\(p < 0.05\)), a greater number of abnormal glucose values in 100g OGTT (\(p < 0.01\)) and higher 100g OGTT glucose values on fasting (\(p < 0.01\)) than NGT women. In addition, DM women had higher glucose values than NGT women at 1-hour (\(p < 0.001\)), 2-hours (\(p < 0.001\)) and 3-hours (\(p < 0.001\)) of the 100g OGTT. Multiple logistic regression analysis demonstrated that the fasting glucose values of 100g OGTT in pregnancy was an independent risk factor of subsequent DM or AGT (odds ratio 1.03, 95% CI 1.00-1.07, \(p = 0.03\)). DM and AGT women had on average more than three abnormal glucose values for 100g OGTT (3.73 \(\pm\) 0.70 and 3.11 \(\pm\) 0.63, respectively). Furthermore, setting the critical number of abnormal values at three showed that the percentage of abnormal numbers \(\geq 3\) was higher for DM and AGT than for NGT women (86.7% and 85.7% vs. 57.5% respectively, \(p = 0.004\)). The cutoff point of three abnormal values in the 100g OGTT achieved 86% sensitivity and 43% specificity in the prediction of postpartum DM or AGT. Four abnormal glucose values in the 100g OGTT as the cut-off point provided sensitivity of only 44% and specificity of 86% in the prediction of postpartum DM or AGT. It was not better than three abnormal glucose values as the cut-off point in the

<table>
<thead>
<tr>
<th>Variables during pregnancy</th>
<th>DM</th>
<th>AGT (IFG or IGT)</th>
<th>NGT</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>17</td>
<td>37</td>
<td>73</td>
<td>-</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>70.6%</td>
<td>67.6%</td>
<td>69.9%</td>
<td>0.963</td>
</tr>
<tr>
<td>Prepregnancy BMI (kg/m(^2))(^*)</td>
<td>23.7 (\pm) 2.9</td>
<td>23.5 (\pm) 4.7</td>
<td>21.6 (\pm) 3.2</td>
<td>0.011</td>
</tr>
<tr>
<td>Weight gain during pregnancy (kg)</td>
<td>11.2 (\pm) 3.1</td>
<td>11.7 (\pm) 4.2</td>
<td>13.0 (\pm) 4.8</td>
<td>0.160</td>
</tr>
<tr>
<td>100g OGTT fasting plasma glucose (mg/dl)(^*)</td>
<td>125.3 (\pm) 40.1</td>
<td>100.2 (\pm) 16.1</td>
<td>91.8 (\pm) 11.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1-hour(^*)</td>
<td>229.6 (\pm) 43.7</td>
<td>209.3 (\pm) 30.8</td>
<td>200.9 (\pm) 22.5</td>
<td>0.001</td>
</tr>
<tr>
<td>2-hour(^*)</td>
<td>244.9 (\pm) 60.5</td>
<td>190.3 (\pm) 27.0</td>
<td>180.9 (\pm) 27.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3-hour(^*)</td>
<td>199.6 (\pm) 60.0</td>
<td>151.7 (\pm) 25.0</td>
<td>142.4 (\pm) 33.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number of abnormal values in 100g OGTT (\geq 3)</td>
<td>3.73 (\pm) 0.70</td>
<td>3.11 (\pm) 0.63</td>
<td>2.71 (\pm) 0.70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Numbers of abnormal values in 100g OGTT (\geq 3)</td>
<td>86.0%</td>
<td>85.7%</td>
<td>57.5%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**Abbreviations:** IFG: impaired fasting glucose; AGT: abnormal glucose tolerance; NGT: normal glucose tolerance.

\(^*\) Significant differences in DM vs. NGT, AGT vs. NGT and DM vs. AGT in multiple comparisons of LSD (\(p < 0.01\)).

\(^\dagger\) Significant differences in DM vs. AGT (\(p < 0.05\)) and DM vs. NGT (\(p < 0.001\)).

\(\dagger\) DM vs. NGT and AGT vs. NGT (\(p < 0.05\)).
DISCUSSION

The women who attended the postpartum follow-up examinations comprised 54.0% of the total prior-GDM women in this prospectively two-year study. This response rate is similar to that obtained in previous studies in Spain (55.2%) and Singapore (62.9%). More common diabetic family history existed in women who participated in the postpartum assessment. Therefore, these women may be more prone to postpartum DM. However, the women without postpartum follow-up had high pregnancy BMI which is also a well-known risk factor for DM.

Albareda et al. reported cumulative incidence rates of DM and IGT (based on World Health Organization (WHO) criteria) as 13.8% and 28.6%, respectively, after 11 years postpartum. For short-term postpartum follow-up, in a Korean study, Jang et al. reported the rates of 15.1% and 23.2% for DM and IGT, respectively (based on WHO criteria) at six to eight weeks postpartum. In another early postpartum assessment at three to six months after a GDM pregnancy in Spain, Pallardo et al. reported rates of 5.4% and 20.0% for DM and AGT, respectively (based on ADA criteria). The different lengths of postpartum assessment and ethnic variation may contribute to the diversity of incidence rates. A systemic review by Kim et al. noted that prior-GDM women appeared to progress to diabetes at similar rates in different studies after adjustment for various lengths of follow-up and testing rates. In our population, the incidence rate by ADA criteria is also in agreement with previous reports. Current ADA guidelines recommend glycemic status assessment in GDM women at least six weeks postpartum and reassessment annually in AGT women and every three years in NGT women. More frequent testing may be required for prior-GDM women with high risk.

Although no significant difference existed in fasting C-peptide levels among DM, AGT and NGT women with prior-GDM, the C-peptide/glucose score was significantly lower in DM than in AGT and NGT women. These findings imply impaired β-cell function in these women. The significantly lower HOMAβ levels in AGT women compared to NGT women also supports this view. In addition, insulin resistance in DM women is noted by increased HOMAβ. However, there are some limitations to these results. Firstly, the DM subgroup with insulin measurements is too small for a firm conclusion. Secondly, the HOMA assessment is not as valid as euglycemic insulin clamp. Nevertheless, these analytical results demonstrate, at least in part, that postpartum glucose intolerance is composed of both insulin resistance and beta-cell dysfunction. It has been proposed that GDM represents the transient unmasking of a latent metabolic syndrome that manifests later in life as diabetes. In this present study, the prevalence of metabolic syndrome is significantly higher in postpartum DM women than AGT and NGT women. According to previous reports, these prior-GDM women may have a high risk of developing cardiovascular events apart from diabetes.

The central role of obesity has been shown to mediate a systemic inflammatory response with potential downstream insulin resistance and glucose dysregulation. Compatible with other reports, our study shows that prepregnancy rather than postpartum BMI plays a critical role in the subsequent development of diabetes.

Kim et al. noted that an elevated fasting glucose level during pregnancy is the risk factor most commonly associated with future risk of type 2 DM. Our study’s data indicate that the fasting glucose value of the 100g OGTT is the exclusive independent risk factor for DM or AGT. We also found that more than three abnormal values for 100g OGTT in pregnancy is a good predictor of postpartum DM or AGT and may help primary prevention of diabetes in high-risk women.

In conclusion, prior-GDM women in Taiwan have an increased risk of developing diabetes and abnormal glucose tolerance. The prevalence of metabolic syndrome is also high in postpartum glucose intolerant women. The predictive risk factors of postpartum glucose intolerance, high prepregnancy BMI and severity of GDM, are recognized. The fasting glucose value of 100g OGTT is identified as the independent risk factor and more than three abnormal glucose values in the 100g OGTT offers good diagnostic efficacy in predicting postpartum diabetes or abnormal glucose tolerance.
Acknowledgements
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REFERENCES

妊娠糖尿病史的婦女於產後新陳代謝之變化

林嘉鴻 溫世芬 吳雅慧 黃禹堯 黃妙珠

背 景：本篇是針對有妊娠糖尿病 (GDM) 的婦女，產後發生葡萄糖代謝異常及相關危險因子的探討研究。

方 法：從 2001 年 3 月到 2003 年 2 月，陸續共計 127 位有妊娠糖尿病的婦女，在產後至少 6 週，回來接受 75 公克葡萄糖耐受試驗及其他新陳代謝的評估，並從被診斷為妊娠糖尿病當時的臨床數據之比較，尋找產後代謝異常的預測因子。

結 果：有妊娠糖尿病的婦女，在產後發生糖尿病 (DM) 和葡萄糖耐受異常 (AGT, 包括空腹高血糖或葡萄糖耐受障礙) 比率分別為 13.4% 和 29.1%。產後的身體質量指數 (BMI)，總膽固醇，高密度脂蛋白膽固醇，三酸甘油酯，血壓，腰臀比，和 C- 胎動 (C-peptide) 的濃度，在 DM, AGT 和葡萄糖耐受正常 (NGT) 的婦女之間，沒有顯著的差異。然而在空腹 C-胎動 / 血糖的比率上，DM 婦女明顯低於 AGT 和 NGT 婦女 (p < 0.01)。在診斷為妊娠糖尿病的當下，DM 或 AGT 婦女的懷孕前 BMI 和 100 公克葡萄糖耐受試驗中空腹的血糖數值，都明顯比 NGT 的婦女為高 (p < 0.05)。其中，空腹的血糖數值是個獨立的危險預測因子。以 100 公克葡萄糖耐受試驗中，大於 3 個不正常數值做一個分界值，則可以提供一個用來預測產後發生 DM 或 AGT 的方法，其敏感度為 86%，特異度為 43%。

結 論：在產後發生 DM 或 AGT 的婦女，發現有較高的懷孕前 BMI 數值和妊娠糖尿病當時有較高血糖的婦女。空腹的血糖數值是個獨立的危險預測因子，而以 100 公克葡萄糖耐受試驗中，大於 3 個不正常數值作分界，可以有效預測產後發生 DM 或 AGT 的風險。

（長庚醫誌 2005;28:794-800）

關鍵詞：妊娠糖尿病，產後，胰島素抗性，beta 細胞功能，代謝症候群。