Gestational hypertension but not pre-eclampsia is associated with insulin resistance syndrome characteristics

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The aim of this study was to assess whether the metabolic characteristics of insulin resistance syndrome are present in pre-eclamptic (PE), gestational (GH) and chronic hypertensive (CH) pregnancies. Glucose and insulin serum concentrations, both fasting and after oral administration of a glucose tolerance test, were evaluated in 26 hypertensive pregnant women (10 PE, 10 GH and six CH patients) and in 10 healthy controls during the third trimester of gestation. Insulin sensitivity was assessed using the hyperinsulinaemic–euglycaemic clamp technique. The plasma concentrations of triglyceride (TG), high density (HDL), low density (LDL), and very low density (VLDL) lipoprotein cholesterol, apolipoproteins A1 and B, and non-esterified fatty acid (NEFA) were also measured. Women with GH exhibited ~40% lower steady-state insulin sensitivity index (ISI) compared to controls (3.75 versus 6.34, P < 0.03), as well as ~33% higher mean plasma TG (3.57 versus 2.68 mmol/l, P < 0.01), and ~69% higher mean NEFA (0.59 versus 0.35 mmol/l, P < 0.01). Women with PE showed similar ISI but reduced insulin and glucose areas under curve compared to controls (P < 0.006, P < 0.0005 respectively). Women with PE also had higher HDL-cholesterol and apo-AI than controls. Patients with CH had similar lipid and carbohydrate metabolism to control subjects. In conclusion, women with GH exhibit metabolic features similar to those of patients with insulin resistance syndrome, suggesting that similar abnormalities could be involved in the pathogenesis of these disorders. In contrast, our data do not support an association between insulin resistance syndrome and hypertension in pregnant women with PE and chronic hypertension.

Key words: hypertension/insulin sensitivity/metabolism/pre-eclampsia/pregnancy

Introduction

Insulin resistance and hyperinsulinaemia are common features in patients affected by essential hypertension (Ferrannini et al., 1987). It has been suggested that insulin resistant subjects are at risk to develop a cluster of abnormalities, including high plasma concentrations of triglyceride (TG), a decrease in plasma high density lipoprotein (HDL) cholesterol concentrations, and hypertension (Reaven, 1988). This cluster of cardiovascular risk factors has been referred to as insulin resistance syndrome or the metabolic syndrome, and leads to an increased risk of coronary heart disease (Sheu et al., 1992).

Recently, interesting analogies between insulin resistance syndrome and the hypertensive state in pregnancy have been found. Some authors have suggested that hypertension in pregnancy is characterized by hyperinsulinaemia (Bauman et al., 1988; Sowers et al., 1995; Abundis et al., 1996). Other investigators have found high plasma TG and low HDL-cholesterol concentrations in women with pre-eclampsia (PE) and gestational hypertension (GH) (Kaaja et al., 1995; Sattar et al., 1997). Given these findings, it has been postulated that carbohydrate and lipids abnormalities could play a role in the pathogenesis of pre-eclampsia, causing altered endothelial function and vascular damage (Sowers et al., 1995; Sattar et al., 1996). While it is well known that vascular dysfunction is associated with hypertension in pregnancy (Rodgers et al., 1988; Pinto et al., 1991; Roberts and Redman, 1993), the data suggesting that these women present a ‘metabolic syndrome’ have not been consistent (Schobel et al., 1997). Indeed, it has not been established whether hypertensive pregnancies are more insulin resistant than normal pregnancies, and it is not clear if the above metabolic features are similarly present in PE, GH and chronic hypertensive (CH) pregnancies.

To elucidate further the metabolic factors present in pregnancies complicated by hypertension, we evaluated insulin sensitivity, lipids, lipoproteins and body composition in pregnant women with PE, GH and CH.

Materials and methods

This study was conducted in the Department of Perinatal Medicine at Catholic University in Rome between 1993 and 1995. The study was approved by the Institutional Review Board, and informed consent was obtained from each patient before the study.

During the study period, ~400 patients were seen at our outpatient centre for routine examination during the third trimester of gestation (range 27–39 weeks). Thirty subjects were invited to participate in the study because of hypertension. Of these, 11 had PE, 11 had GH and eight had CH. One patients with PE, one with GH, and two with CH declined to be enrolled. Hence, the study population comprised 10 patients with CE, 10 with GH and six with CH (n = 6). Hypertension during pregnancy was defined as diastolic blood pressure ≥90 mmHg at two consecutive measurements 6 h apart with the patient resting in the semirecumbent position. Proteinuria was considered present if urinary protein concentration was either
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Table I. Demographic characteristics of control and hypertension groups

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Chronic</th>
<th>Gestational</th>
<th>Pre-eclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 10)</td>
<td>hypertension (n = 6)</td>
<td>hypertension (n = 10)</td>
<td>(n = 10)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.9 ± 1.5</td>
<td>34.7 ± 2.5</td>
<td>32.1 ± 1.1</td>
<td>33.3 ± 1.9</td>
</tr>
<tr>
<td>Parity (nulliparous/parous)</td>
<td>4/6</td>
<td>1/5</td>
<td>8/2</td>
<td>8/2</td>
</tr>
<tr>
<td>Week of pregnancy</td>
<td>33.5 ± 1.1</td>
<td>31.0 ± 1.5</td>
<td>36.1 ± 0.8</td>
<td>32.1 ± 1.4</td>
</tr>
<tr>
<td>BMI (weight/height²)</td>
<td>21.3 ± 0.8</td>
<td>25.7 ± 1.9⁹</td>
<td>24.6 ± 1.2⁹</td>
<td>23.2 ± 0.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.1 ± 2.7</td>
<td>79.2 ± 6.1¹</td>
<td>81.8 ± 4.3⁷</td>
<td>71.9 ± 3.4</td>
</tr>
<tr>
<td>Percentage body fat</td>
<td>33.9 ± 0.7</td>
<td>36.3 ± 5.2</td>
<td>36.1 ± 2.1</td>
<td>28.7 ± 2.0</td>
</tr>
<tr>
<td>Percentage total body water</td>
<td>49.2 ± 0.4</td>
<td>49.6 ± 3.4</td>
<td>49.3 ± 1.2</td>
<td>52.6 ± 1.2</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>123 ± 4.9</td>
<td>170 ± 6.6⁶</td>
<td>154 ± 3.7⁶</td>
<td>165 ± 5.0⁹</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79 ± 2.7</td>
<td>111 ± 4.4ᵃ</td>
<td>103 ± 4.0³</td>
<td>107 ± 4.1¹</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE. BMI = body mass index calculated from the pregravid weight; SBP = systolic blood pressure; DBP = diastolic blood pressure. ⁿ < 0.05, ⁿp < 0.01, ⁿP < 0.0005 versus controls.

>0.3 g/24h or >1 g/l (or ++ with dipstick) in a random sample, in the absence of urinary infection. Gestational hypertension was defined as hypertension developing after 20 weeks of gestation in a previously normotensive woman; PE was gestational hypertension plus proteinuria; CH was hypertension documented before pregnancy or before 20 weeks of gestation. Twenty normotensive pregnant women at a comparable week of gestation were invited to participate in the study as controls; 10 agreed to be enrolled.

The study groups details are shown in Table I. In the PE group there were two parous women, both of whom had had previous PE. All patients were Caucasian. None had a personal or family history of diabetes mellitus or dyslipidaemia. None smoked during pregnancy. None took any medication known to influence carbohydrate or lipid metabolism. Four CH patients who were receiving α-methyldopa discontinued the treatment 2 days before the study. Anti-hypertensive drugs were administered or restored at the end of the study protocol.

Before admission to the hospital, each patient followed a diet of standard composition (the Italian diet typically contains 45% carbohydrate, 40% fat, and 15% protein). Body mass index (BMI) was calculated as pregestational weight/height².

The study protocol was divided between 2 days: on day 1, patients underwent an oral glucose tolerance test (OGTT) and blood samples were obtained for the measurement of lipids, lipoproteins, and routine laboratory procedures; on day 2, patients underwent bioelectrical impedance and hyperinsulinaemic–euglycaemic clamp.

An OGTT with a 100 g oral glucose load was performed after 2 days on a standard diet containing at least 250 g of carbohydrate per day. Samples were collected at 0800 h (after an overnight fast) and at 60, 90, 120 and 180 min after glucose ingestion. Insulin and glucose plasma concentrations were measured in each blood sample. Plasma samples for measurement of glucose concentrations were collected in tubes containing an inhibitor of glycolysis (sodium fluoride) and were analysed within 5 h. Plasma samples for measurement of insulin concentrations were placed in tubes standing in ice, centrifuged for 10 min at 1000 g using a 4226 ALC Centrifuge (ALC, Milan, Italy) and stored at –20°C until assayed. Plasma glucose concentrations were measured using the glucose oxidase method (Beckman, Fullerton, CA, USA). Plasma insulin concentrations were measured using commercial radioimmunoassay kits (Radium, Rome, Italy); the intra- and interassay coefficients of variation were <8 and 15% respectively. The glucose and insulin concentrations after the OGTT were analysed as the area under the curve (AUC) calculated by trapezoidal rule and expressed as mmol/l×180 min and pmol/l×180 min respectively. All patients exhibited a normal response to the OGTT according to National Diabetes Data Group criteria (1979).

Circulating concentrations of TG were measured enzymatically (Olympus). HDL-cholesterol was determined after precipitation with polyethylene glycol (MW = 6000). The very low density lipoprotein (VLDL) cholesterol and low density lipoprotein (LDL) cholesterol were isolated by sequential flotation in a Beckman Model L7-65 ultracentrifuge (Palo Alto, CA) using a Type 70 rotor (Beckman). Apolipoprotein A1 (apo-A1) and apolipoprotein B (apo-B) were determined by immunonephelometry using a Behring Nephelometer Analyser (Behring, Marburg, Germany). Plasma non-esterified fatty acid (NEFA) concentrations were determined with a commercially available enzymatic assay (Wako Nefica C, Neuss, Germany). Serum uric acid was measured using an enzymatic colorimetric test (Boehringer).

Bioelectrical impedance was used to estimate the subject’s body composition and was measured with a tetrapolar impedance plethysmograph (Human-IM Scan, Dietosystem, Milan, Italy) according to Lukasky et al. (1994). Briefly, at 0700 h, each woman lay supine on a bed made of non-conductive materials. Detector electrodes (Red Dot, 3M Health Care, St Paul, MN, USA) were placed in the middle of the dorsal surface of hands and feet proximal to the metacarpal–phalangeal joints respectively, and also medially between the distal prominances of the radius and ulna and between the medial and lateral malleoli at the ankle. The stimulating electrodes were placed at a minimum distance of the diameter of the wrist or ankle beyond the paired detector electrodes. An excitation current of 800 mA, AC, at 1, 5, 10, 50, and 100 kHz was introduced at the distal electrodes of the hand and foot; the voltage drop across the patient was detected with the proximal electrodes. The percentage of body fat, fat free mass (FFM), and total body water were calculated using the appropriate software (Dietosystem, Milan, Italy).

Insulin sensitivity was determined by the hyperinsulinaemic–euglycaemic clamp technique as described by DeFronzo et al. (1979). At 0800 h, an i.v. catheter was placed in the antecubital vein for the infusion of glucose and insulin. Another catheter was placed in the dorsal vein of the contralateral hand for blood withdrawal and warmed to 65°C with a warming box. After a primed constant infusion, insulin (Actrapid HM, Novo Nordisk, Copenhagen, Denmark) was infused at 40 mIU/m² surface area per minute for 120 min. A variable infusion of 20% glucose was adjusted, on the basis of plasma glucose samples obtained every 5 min, to maintain plasma glucose at 5.5 to 6.5°C with a warming box. After a primed constant infusion, clamp (expressed as mg/kgFFM/min) were used to calculate glucose disposal.
under steady-state conditions. Because different insulin concentrations (I) were achieved during clamp in the four study groups (range 390–660 pM, across all subjects), the GDR/I ratio (Insulin Sensitivity Index, ISI) was used as a more accurate estimate of insulin sensitivity.

The analysis of variance (ANOVA) with Fisher’s protected least significant difference test was used to detect significances of the differences between means in different groups. Comparisons between frequencies were assessed by $\chi^2$ analysis. Linear regression analysis with partial correlation was used for analysis of relationships between ISI, lipids, insulin AUC, and percentage of body fat. $P$ values of $<0.05$ were considered significant. Data are given as mean ± SE.

**Results**

The groups were comparable with respect to age, parity, week of study, and percentage of total body water. Pre-eclamptic women had ~15% less body fat compared to controls, although as a group PE exhibited ~9% higher pregravid BMI than normal subjects (Table I).

Figure 1 shows the insulin sensitivity index. Women with GH exhibited ~40% lower steady-state ISI compared to controls (3.75 versus 6.34, $P < 0.03$); in contrast, no differences were seen between the control and the other hypertensive groups. Regarding insulin and glucose concentrations, fasting and after glucose challenge, there were no significant differences between control subjects and CH or between control and GH groups. However, in PE women insulin and glucose AUC were much lower than controls (85 748 versus 146 428 pmol/l, $P < 0.0005$ respectively) (Figure 2).

Gestational hypertensive patients showed ~33% higher mean plasma TG (3.57 versus 2.68 mmol/l, $P < 0.01$), and ~69% higher mean NEFA (0.59 versus 0.35 mmol/l, $P < 0.01$) compared to controls. No significant differences were seen between controls and GH groups regarding other serum lipids and apo-B, whereas apo-AI and uric acid were significantly higher in GH patients (Table II). Pre-eclamptic women exhibited higher HDL-cholesterol and apo-AI concentrations than normal subjects. As expected, uric acid was significantly higher in PE compared to control women. Patients with chronic hypertension were not different from controls regarding lipids, apolipoproteins and urate concentrations (Table II).

To evaluate the relationships among ISI, lipids, insulin AUC, and percentage of body fat, the data from the four study groups were pooled. The insulin sensitivity index was negatively correlated with the independent variables TG and insulin AUC ($r = -0.35, P < 0.04$; $r = -0.41, P < 0.02$ respectively). These relationships were still present after adjusting for percentage of body fat, LDL-cholesterol and insulin AUC were strongly positively related to the independent variable percentage of body fat ($r = 0.59, P < 0.0001$; $r = 0.52, P < 0.002$ respectively).

**Discussion**

The literature suggests that women who develop hypertension and/or PE have metabolic abnormalities similar to those present in patients with insulin resistance syndrome (Kaaja *et al.*, 1995; Sattar *et al.*, 1997). In a preliminary study, Gans *et al.* (1996) reported a low insulin sensitivity index in patients who subsequently developed PE compared to patients at risk of but without hypertensive disorders. Women with PE had higher BMI compared to controls (28.5 ± 3.4 versus 25.8 ± 5.2 kg/m$^2$), suggesting that the association between insulin resistance and PE was determined by the degree of obesity. However, the estimation of insulin sensitivity was not controlled for the degree of body fat mass, and no information was given regarding lipid profile. Recently, Kaaja *et al.* (1995) reported high HDL-cholesterol, triglyceride, uric acid and fasting insulin concentrations in both proteinuric and non-proteinuric hypertensive women. Nevertheless, this report did not define BMI, body composition, or week of study of each hypertensive group, despite the fact that all of these variables have well

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**Figure 1.** Insulin sensitivity index in pregnant women with chronic hypertension (CH), gestational hypertension (GH), pre-eclampsia (PE), and controls (CTR). *P* < 0.03 versus controls.

**Figure 2.** Insulin (A) and glucose (B) areas under the curve (AUC) after the oral glucose tolerance test in pregnant women with chronic hypertension (CH), gestational hypertension (GH), pre-eclampsia (PE), and controls (CTR). †*P* < 0.006, ¶*P* < 0.0005 versus controls.
known relationships with insulin sensitivity (Catalano et al., 1993). Thus, the issue of whether PE and other hypertensive states in pregnancy are associated with the presence of abnormalities observed in patients with the insulin resistance syndrome was not well established. In the present report, we found that women with GH were characterized by reduced insulin sensitivity, high concentrations of triglyceride, non-esterified fatty acid, and uric acid. In addition, these patients presented a relative, although not significant, increase in insulin concentrations. Thus, GH appears to resemble the classic insulin resistance syndrome. On the contrary, we did not observe the same abnormalities in either PE or CH groups, the only exception being an increase in urate concentrations in PE patients. Moreover, PE women had higher HDL-cholesterol concentrations and lower insulin secretion than controls.

The differences in carbohydrate metabolism between PE and GH are consistent with previous reports showing a significantly elevated frequency of glucose intolerance, and a higher insulin resistance, among women in whom transient hypertension developed during pregnancy but not among women in whom PE developed (Solomon et al., 1994). The observation of a ~15% lower body fat mass in our pregnant subjects, obesity alone does not account for the development of insulin resistance in pregnancy (Sivan et al., 1994). In conclusion, the results of this work suggest that alterations in carbohydrate and lipid metabolism are present in women with GH. These metabolic features are similar to those present in subjects with insulin resistance syndrome, and thus could play a role in the pathogenesis of vascular dysfunction in these patients. On the other hand, our data do not support an association between the metabolic syndrome and the hypertensive state associated with PE. Other abnormalities, such as an altered maternal immunological reaction to the fetus could be related to endothelial dysfunction and vascular damage in pre-eclamptic patients (Shuiling et al., 1997). Longitudinal metabolic studies are needed to confirm these findings and to better understand the pathogenesis of GH and PE.

Acknowledgements

This study was partially supported by grant 95.00784.PF41 from Targeted Project FATMA, National Research Council [ (CNR) – Targeted Project 'Prevention and Control Disease Factors'], Subproject 'Study of haemodynamic parameters and endocrine factors in placental–fetal development'.

References


Received on April 6, 1998; accepted on October 19, 1998