Essential hypertension is associated with insulin resistance and hyperinsulinemia. To assess whether hyperinsulinemia is also present in hypertensive disease induced by pregnancy, we studied the plasma glucose and insulin responses to 50 g of oral glucose in 10 women with definite, severe preeclampsia but normal glucose tolerance, and compared them with the responses observed in a well-matched control group of healthy pregnant women. Fasting plasma glucose concentrations were similar in healthy and preeclamptic pregnant mothers (4.1 ± 0.4 mmol/L v 4.5 ± 0.4 mmol/L, respectively, P = NS). Similar plasma glucose levels were also observed after glucose ingestion (5.5 ± 0.3 mmol/L v 6.2 ± 0.3 mmol/L in healthy and preeclamptic women, respectively P = NS). In contrast, fasting plasma insulin concentrations in the preeclamptic women were significantly higher than in normal pregnant mothers (175 ± 29 pmol/L v 101 ± 11 pmol/L, P < .05). Postload plasma insulin concentrations were nearly fourfold higher in the preeclamptic group as compared with the control group (1162 ± 70 pmol/L v 366 ± 39 pmol/L, P < .01).

We conclude that preeclampsia is associated with marked hyperinsulinemia both in the fasting state and after oral glucose ingestion, suggesting that insulin resistance may play a role in pregnancy-induced hypertension. Am J Hypertens 1996:9:610–614

KEY WORDS: Preeclampsia, insulin, insulin resistance, hyperinsulinemia, pregnancy, hypertension.
MATERIAL AND METHODS

Screening for gestational diabetes during the third trimester is a routine test in our outpatient clinic. During 8 months, we identified 10 patients with severe pre-eclampsia, diagnosed according to the following criteria: 1) High blood pressure defined as systolic blood pressure increases of 30 mm Hg or greater or diastolic blood pressure increases of 15 mm Hg or greater, above the average value during the first 20 weeks of gestation and; 2) Proteinuria. Severity of preeclampsia was judged when at least two of the following signs were present: 1) proteinuria of 2 g/24 h or more; 2) Increased serum creatinine values (>1.2 mg/dL unless known to be elevated previously); 3) elevated hepatic enzymes; 4) headaches or other cerebral or visual disturbances; 5) epigastric pain; 6) retinal hemorrhage, exudates, or papilledema; 7) platelet count >100,000/mm³; and 8) systolic blood pressure of 160 mm Hg or more or diastolic blood pressure 110 mm Hg or more.

For the control group, we selected 10 healthy pregnant women matched to the patients by age, pregestational body mass index (BMI), and gestational age. Every effort was made to match a preeclamptic woman with a healthy pregnant woman on a one-to-one basis (Table 1). In the patients with preeclampsia, the study was carried out before the prescription of any antihypertensive drugs. Patients with familial or personal antecedents of diabetes mellitus were excluded, as were patients with obesity (as indicated by a BMI before pregnancy of >26 kg/m²), ischemic heart disease, nephropathy, dyslipidemia, chronic hypertension plus preeclampsia, gestational diabetes mellitus or glucose intolerance, or drug treatment known to influence plasma insulin or glucose concentrations.

### TABLE 1. CLINICAL CHARACTERISTICS OF THE STUDY SUBJECTS*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Normal Pregnancy</th>
<th>Preeclampsia</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>25 ± 6</td>
<td>28 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Pregestational BMI (kg/m²)</td>
<td>24.8 ± 1.1</td>
<td>25.0 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td>3.0 ± 0.5</td>
<td>2.3 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>32 ± 4</td>
<td>33 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>114 ± 3</td>
<td>158 ± 4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>74 ± 7</td>
<td>110 ± 7</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* Values are mean ± SEM. P values refer to the comparison of group means by the unpaired Student's t test.

All patients were studied at 8 AM after an overnight (10 to 12 h) fast. A polyethylene 18-gauge catheter was inserted into an antecubital vein for blood sampling. Oral glucose tolerance was assessed by the ingestion of 50 g glucose load. Before the start of the study and again 60 min after glucose ingestion, blood samples were obtained for the measurement of plasma glucose (by the glucose oxidase method on a Beckman Glucose Analyzer [Beckman Instruments Inc., Fullerton, CA]) and insulin (by radioimmunoassay). Blood pressure was measured at baseline with the use of a standard mercury sphygmomanometer.

The protocol was reviewed and approved by the Institutional Review Board of the Centro Medico Nacional de Occidente, Instituto Mexicano del Seguro Social at Guadalajara, Jalisco, Mexico. Purpose, nature, and risks involved in the study were explained to all the patients before obtaining their oral consent to participate in the study.

Values are given as a mean ± SEM. Statistical analysis of differences between mean group values was carried out by the unpaired Student's t test.

RESULTS

The study groups had similar mean age, pregestational BMI, and gestational age, whereas systolic and diastolic blood pressure values were significantly higher in the preeclamptic group than in healthy pregnant women.

Fasting and postload plasma glucose and insulin concentrations are depicted in Figure 1. Fasting plasma glucose concentrations (4.1 ± 0.4 mmol/L vs 4.5 ± 0.4 mmol/L, control and preeclamptic mothers, respectively; P = NS) and glucose levels 1 h after glucose ingestion (5.5 ± 0.3 mmol/L vs 6.2 ± 0.3 mmol/L, P = NS) were similar in the two groups. In contrast, fasting plasma insulin concentrations in the preeclamptic women were significantly higher than in normal pregnant mothers (175 ± 29 pmol/L vs 101 ± 11 pmol/L, P < .05). Postload plasma insulin concentrations were nearly fourfold higher in the preeclamptic group as compared with the control group (1162 ± 70 pmol/L vs 366 ± 39 pmol/L, P < .01).

DISCUSSION

There is mention in the literature of high insulin levels in hypertensive and/or preeclamptic women. In their report, Bauman et al. also found hyperinsulinemia with normal glucose tolerance in a group of pregnant women with high blood pressure as compared with normotensive pregnant women. However, the comparison was not controlled for obesity nor was it specified whether the hypertensive women had chronic essential hypertension, gestational hypertension, or preeclampsia. Thus, the issue of whether pre-
Basal hyperinsulinemia per se is associated with hyperinsulinemia remained unresolved. In the current report, we demonstrate that women with clear-cut preeclampsia but normal glucose tolerance have higher insulin levels in comparison with matched healthy pregnant women.

Several reports have indicated that hyperinsulinemia is present in a substantial proportion of patients with essential hypertension. In our study, normal plasma glucose levels in the face of marked hyperinsulinemia strongly suggest that a state of resistance to insulin action on glucose metabolism is also present in preeclamptic women. Several hypotheses can be advanced to explain the presence of hyperinsulinemia/insulin resistance in this condition. Hyperinsulinemia might be a secondary event or a primary factor in preeclampsia. Preeclampsia appears to be a disorder of vasospasm with increased reactivity to vasopressors such as angiotensin II, catecholamines, and vasopressin. This vascular hyperresponsiveness is present as early as the 18th week of pregnancy, and precedes the onset of hypertension. In addition, endothelial cells of preeclamptic patients may abnormally release pressor substances, such as endothelin-1 (ET-1), which cause long-lasting vasoconstriction and stimulation of catecholamine release. Norepinephrine and ET-1 levels have been found to be higher in preeclamptic women than in healthy pregnant women or pregnant women with chronic hypertension. Sympathetic overactivity may lead to insulin resistance, as has been suggested by Julius et al. and others. Thus, a primary activation of sympathetic outflow could account for both high blood pressure and insulin resistance in preeclamptic women.

Alternatively, some evidence suggests that insulin can stimulate the release of vasopressor substances in humans. Insulin stimulates ET-1 production from endothelial cell cultures and, in rats, even physiologic amounts of insulin are associated with increased ET-1 gene expression. However, in healthy human volunteers, administration of insulin at physiologic doses does not increase serum ET-1 levels but similar studies are not available in hypertensive or preeclamptic patients.

There is evidence that in vivo insulin stimulates sympathetic nervous system activity. It has been recently demonstrated that insulin-resistant patients with essential hypertension have higher norepinephrine output in forearm tissues in response to insulin than normotensive insulin-sensitive individuals. If these effects of insulin are preserved or amplified in preeclamptic women, hyperinsulinemia might play a primary role in the increased vascular resistance and high cardiac output that are observed in preeclampsia.

In the preeclamptic patients studied by Zemei and co-workers, suppressed platelet Ca$^{2+}$-ATPase activity predicted the development of preeclampsia, and correlated with reduced intracellular Ca$^{2+}$ efflux in umbilical cord smooth muscle cells at delivery. Thus, in preeclamptic women, insulin resistance/hyperinsulinemia is associated with an increment in intracellular Ca$^{2+}$ at the smooth muscle level. In line with this, we have recently found that platelets from hypertensive insulin-resistant subjects exhibited a higher intracellular calcium concentration after in vivo exposure to physiologic doses of insulin as compared with platelets obtained from normotensive, insulin-sensitive subjects. Thus, in analogy with essential hypertension, altered intracellular calcium handling might represent the link between insulin resistance/hyper-
insulinemia and high blood pressure in the pathogenesis of preeclampsia.

In preeclampsia, an increase in cardiac output has been proposed as the primary hemodynamic event, which is associated with compensatory vasodilation to maintain normotension in the early stages of preeclampsia. Later, peripheral vascular resistance increases, leading to hypertension. Through its antinatriuretic action, hyperinsulinemia might favor the initial volume expansion that is observed in early pregnancy and later contributes to the increase in peripheral vascular resistance by activating or facilitating the action of vasopressors during the last months of pregnancy.

Hyperuricemia has been described as an early predictive finding in preeclamptic women. Some evidence suggests that hyperuricemia in preeclampsia is attributable to enhanced tubular reabsorption of uric acid. Recently, we have demonstrated that physiologic hyperinsulinemia is associated with a net decrease (~30%) in fractional uric acid excretion in healthy humans. Thus, hyperinsulinemia might precede or aggravate the hyperuricemia of preeclampsia.

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REFERENCES


