**Pregnancy**

# Determination of Insulin Resistance Using the Homeostatic Model Assessment (HOMA) and its Relation With the Risk of Developing Pregnancy-Induced Hypertension

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**Objective:** To assess whether increased insulin resistance determined by homeostatic model assessment (HOMA) early in pregnancy is associated with the subsequent development of pregnancy-induced hypertension (PIH) in Colombian women with known risk factors.

**Methods:** We conducted a nested case control study in a prospective cohort of 572 normotensive pregnant women, with gestational age ≤30 weeks, recruited in Bucaramanga and Floridablanca, Colombia. Fasting plasma glucose and insulin concentrations were determined at enrollment, and HOMA index was calculated. Log-transformed HOMA (log-HOMA) was used in the statistical analysis. Thirty nine PIH cases (18 preeclampsia [PE], 21 gestational hypertension [GH]) were compared to 78 controls, matched by body mass index, gestational and maternal age at enrollment.

**Results:** Women who subsequently developed PIH had higher levels of log-HOMA at enrollment ($-0.13 \pm 0.54$ *v* $0.21 \pm 0.60$; $P = .002$), which was significantly associated with the development of PIH (odds ratio 3.13, 95% confidence interval 1.41–6.94; $P = .005$). Higher log-HOMA was found in women who subsequently developed PE ($0.28 \pm 0.58$; $P = .003$), and in those who presented with GH ($0.15 \pm 0.62$; $P = .026$).

**Conclusions:** Women who subsequently develop PIH have a higher degree of insulin resistance determined by log-HOMA early in pregnancy, before the onset of clinical manifestations of the disease. The HOMA seems to be a useful method to evaluate women at risk of developing PIH. More studies are required to confirm its usefulness as a screening tool to identify pregnant women at risk of developing PIH. Am J Hypertens 2007;20:437–442


**Key Words:** Pregnancy-induced hypertension, insulin resistance, HOMA, metabolic syndrome.

Worldwide, pregnancy-induced hypertension (PIH) affects up to 8% of pregnant women with an important impact on morbidity and mortality in mothers and neonates.[1] In Colombia, PIH is the main cause of maternal mortality.[2] The etiology of PIH is not completely known, but some factors as insulin resistance (IR), malnutrition, subclinical infections, genetic and immunologic factors have been involved in the risk of developing this disorder.[3]

Insulin resistance is characterized by a cluster of cardiovascular risk factors that increase the probability of developing coronary artery disease (CAD), diabetes mellitus, and hypertension (HT).[4] Observational studies reported that women with a history of PIH have increased risk of future cardiovascular disease,[5] which suggests an association between IR and PIH.

During normal pregnancy, some degree of IR is observed. The major degree of IR is achieved in the third trimester and returns to prepregnancy levels after delivery.[6] Recent studies have demonstrated that women with established PIH are more insulin resistant than normal pregnant women.[7] Some characteristics associated with IR, such as obesity, dyslipidemia, systemic inflammation, and fibrinolytic alterations have also been associated with

Received June 27, 2006. First decision October 6, 2006. Accepted October 15, 2006.

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This study was supported by the Colombian Institute for Science and Technology Development "COLCIENCIAS" (Grant No 6566-04-13113).

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0895-7061/07/$32.00
doi:10.1016/j.amjhyper.2006.10.009

PIH.[8] However, studies that described this association lacked both an adequate design and consensus about the tests used to evaluate IR.[9–11] The homeostasis model assessment (HOMA) is a mathematical formula that permits clinical evaluation of IR and assesses $\beta$-cell function, calculated using fasting glycemia and insulin concentrations.[12] Log-transformed HOMA (log-HOMA) has been reported as a reliable test with high correlation coefficients with the hyperinsulinemic euglycemic clamp in nonpregnant women.[13] The purpose of this study was to assess whether increased IR determined by HOMA early in pregnancy was associated with the subsequent development of PIH in Colombian pregnant women at risk.

# Methods

## Participants

A cohort was built with normotensive pregnant women with at least one risk factor for the development of PIH to increase the probability of incident cases. All women were recruited before the 31st week of gestation in medical centers from Bucaramanga and Floridablanca, Colombia. Gestational age was determined by date of last menstrual period or ultrasound in the first trimester of pregnancy. Risk factors considered were: maternal age $<25$ years or $>35$ years, family history of PIH, and nuliparity or prepregnancy body mass index (BMI) $\geq 25$ kg/m$^2$. At enrollment, none of the patients had multiple pregnancy, hypertension, cardiovascular or renal disease, and none of them was taking any medications. Previous smoking was referred by 30.8% of the women, only one participant admitted to have smoked during pregnancy. Forty-nine percent of the women reported previous alcohol intake; none of the patients consumed alcohol during pregnancy. The study was approved by the local institutional review board and all subjects gave written informed consent before entering the study.

## Clinical Assessment

For each pregnant woman enrolled, a complete chart, including obstetric history, was recorded, and physical examination was performed. Systolic blood pressure (BP), diastolic BP, heart rate, and anthropometric measurements were taken, as well as weight and height, using standardized methods. Mean arterial blood pressure (MABP) was calculated using the formula: [(Systolic BP + 2 $\times$ Diastolic BP)/3]. The BMI was calculated as: weight (in kilograms)/height$^2$ (in meters squared).

## Biochemical Determinations

At enrollment, a blood sample was withdrawn from the antecubital vein, after a fasting period of 12 h. Plasma was separated by centrifugation at 3000 rpm for 15 min and then frozen at $-70$°C and stored until analysis. An aliquot of whole blood was taken to determine hematocrit, hemoglobin, leukocyte count, and glucose concentration in all subjects (Baker System 9120 AX, Biochem Immunosystem, Allentown, PA). The lowest detectable concentration of glucose was 0.0126 mmol/L. Within-assay coefficient of variation (CV) for glucose determination was 1.2%. Plasma of women selected for the nested case-control study was used for the determination of lipid profile and insulin by enzyme colorimetric test (Biosystems BTS-303 Photometric, Barcelona, Spain) and by high sensitivity chemiluminescent immunometric assay (IMMULITE 1000, DPC, Los Angeles, CA), respectively. Within-assay CV for insulin determination was 6.4%. The HOMA index was calculated as: [(Fasting plasma insulin (in $\mu$U/mL) $\times$ Fasting plasma glucose (in mmol/L)/22.5]. All assays were performed by personnel blinded to the case-control status.

## Follow-Up

Patients were followed-up by phone calls during the period of the study to establish the moment of delivery and if they had developed PIH. This approach was implemented to avoid interfering with the normal course of the prenatal care program established in the Colombian health system. Thereafter, each patient's medical record was reviewed to confirm the presence or absence of the disorder. We obtained information about the course of pregnancy, mode of delivery, infant weight at birth, and postpartum BP for all women. The PIH was defined by the presence of gestational hypertension (GH) or preeclampsia (PE). Preeclampsia was defined as normotension before 20 week's gestation with the subsequent development of hypertension ($\geq$140/90 mm Hg), and concomitant 24-h proteinuria ($\geq$0.3 g/L) in the absence of urinary tract infection. The GH was defined as de novo hypertension arising after the 20th week of gestation, without proteinuria.[14]

## Nested Case-Control Study

Thirty-nine pregnant women (6.82%) developed PIH (18 PE, 21 GH). Members of the cohort who remained normotensive until delivery were eligible as controls. Two controls were randomly selected for each case, matched by BMI, gestational and maternal age at study entry.

## Statistical Analysis

Descriptive data were expressed as mean $\pm$ SD. The Shapiro-Wilk test was used to assess the normality of the continuous data. Because reported validation of HOMA was made using its logarithm, analysis was made and results were reported in terms of log-HOMA. Using the logarithmic scale also gave the variable a normal distribution. We conducted a standard case-control analysis. Although individually matched controls were selected for each case, unpaired analyses were used, without taking advantage of the paired matching. Continuous variables were analyzed using two-sample $t$ tests or Mann-Whitney test; categorical variables, using $\chi^2$ test or Fisher's exact test. Statistical significance was defined as $P < .05$. When more than two groups were compared, either one-way variance analysis or Kruskall-Wallis analysis was used,