Assessment of Pregestational Insulin Resistance as a Risk Factor of Preeclampsia

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Key Words
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Abstract
Aim: To assess the impact that pregestational insulin resistance (PIR) has as a risk factor for preeclampsia (PE). Methods: Nested case-control study that included patients with PIR and a control group that was randomly selected from pregnancies admitted to the Fetal Medicine Unit between January 2005 and May 2011. Clinical and hemodynamic variables were analyzed by a multiple logistic regression analysis. Results: Of the 13,124 patients admitted during the study period, 119 had a diagnosis of PIR (0.9%). Patients with PIR were older and had a higher body mass index (BMI). PIR was also related to a significantly higher frequency of chronic hypertension (CrHT; 10.1 vs. 2.2%, p < 0.05) and hypothyroidism (5.0 vs. 1.6%, p < 0.05) than in the control group. Moreover, women with PIR were more likely to develop PE (8.4 vs. 4.2%, p < 0.05) and gestational diabetes mellitus (9.2 vs. 2.9%) than the control group. Multivariate analysis showed that maternal age, CrHT and altered uterine artery Doppler sonography during the first and second trimesters were good predictors of PE and that PIR was not. Conclusion: Although PIR correlates with PE, conditions related to the latter (CrHT, higher maternal age and increased BMI) may be predominant as risk factors for PE.

Introduction
Preeclampsia (PE) is a pathological condition constituent of the pregnancy-induced hypertensive syndrome. It is characterized by arterial hypertension and proteinuria affecting 4–7% of the pregnant population. Its etiology is only partially known, and it represents a high maternal-perinatal morbidity and mortality risk. Currently, although it is true that screening methods are available to identify the population at the highest risk, the implementation of such methods is difficult and the economic costs are high [1–8].

The metabolic syndrome is an association of health problems that may have a simultaneous or sequential onset in the individual. It is caused by a combination of genetic and environmental factors related to lifestyle, among which insulin resistance (IR) is considered as the main pathogenic component. In fact, the association between obesity, IR and risk for diabetes mellitus and cardiovascular diseases is well known [9, 10].
In Chile, the prevalence of metabolic syndrome among adults is 22.6%, with 23% among males and 22.3% among females. For the age range between 17 and 24 years, the prevalence is about 4.6%, between 25 and 44 years 17.9%, between 45 and 64 years 36.5% and among individuals older than 64 years the prevalence is 48% [10]. In view of the lack of representative data regarding IR prevalence and because of the close relationship between metabolic syndrome and polycystic ovary syndrome, the latter with a reported prevalence between 4 and 15%, the prevalence of IR among childbearing women is presumed to be close to 20% [11, 12].

On the other hand, progressive IR during pregnancy is known as a physiological effect needed to ensure energy requirements of the fetus. However, there is evidence suggesting that higher degrees of such a condition might have a negative impact on maternal health and perinatal outcome. Lately, studies have associated polycystic ovary syndrome, an entity closely related to IR, with an increased risk for developing not only gestational diabetes mellitus (GDM) but also abnormal placentation-related pathologies such as PE and fetal growth restriction [13–16]. To support the latter, it has been shown that the increased severity of IR during pregnancy, assessed by abnormal concentrations of biomarkers of such a condition throughout the different stages of gestation (sex hormone-binding globulin, adiponectin, leptin, resistin, etc.), would be closely related to the onset of stillbirths during the first trimester and of pathologies affecting the mother-child binomial. The etiopathogenesis of such conditions would involve endothelial dysfunction and/or predisposing metabolic conditions having an abnormal placentation, as that seen in PE and fetal growth restriction [17–22]. PE shares a series of pathophysiological findings with IR, among which are the following: endothelial dysfunction, atherosclerosis and inflammation. Therefore, pregestational IR (PIR) or higher degrees of IR during pregnancy might play a coadjuvant role in the development of PE. This hypothesis has been confirmed by a recent publication stating that a diagnosis of IR during pregnancy predisposes to the onset of PE. In that study, primigravid women with a diagnosis of IR determined by a homeostasis model assessment of IR and the quantitative insulin sensitivity check index between gestation weeks 22 and 26 had a higher incidence of PE than control patients (40.5 vs. 24.8%) [23].

The mechanisms involved that might explain the high blood pressure values found among insulin-resistant adults would be those mediated by sympathetic nervous system activation, sodium retention, increased cation transport and endothelial dysfunction.

On the other hand, the maternal morbid nutritional status, specifically given by the high pre- and postconception body mass index (BMI) and the exaggerated weight gain during gestation mainly due to fat deposits at the abdominal viscera, would be closely related to IR and would represent a common denominator for the genesis of PE [24–27].

Aiming at predicting PE in early gestational age, models have been proposed. However, such models have a low predictive value and their implementation has a high economic cost. Moreover, they do not supply a prophylactic intervention that might prevent or delay the onset of such pathologies [3, 8, 28].

The aim of the present study is to assess the impact that PIR has as a predictive factor for PE.

### Methods

#### Study Design

This nested case-control study included 13,124 pregnant women who attended the Fetal Medicine Unit of the University of Chile Hospital between January 2005 and May 2011 to undergo an ultrasound scan during the second trimester of pregnancy, which included the assessment of fetal anatomy and/or cervical length and uterine artery (UtA) Doppler measurement, as predictors of preterm delivery and PE, respectively.

All women were interviewed immediately before the ultrasound scan to obtain demographic data for computer database input. The demographic characteristics were maternal age, smoking habit during pregnancy, alcohol intake during pregnancy, history of drug abuse, medical history, medications, parity, obstetric history and the BMI calculated from maternal weight and height before pregnancy.

A transvaginal UtA Doppler sonogram was made at gestation age 20 weeks 0 days (20\(^0\)) to 24\(^6\) and/or 11\(^6\) to 13\(^6\). Briefly, transvaginal UtA Doppler measurements were performed using an Aloka 4000® ultrasound machine with a 5-MHz probe. Women were placed in the lithotomy position, and then the transducer was inserted into the vagina and placed in the anterior fornix. At the time of the cervical length measurement, the probe was gently tilted laterally at the level of the internal cervical os, and the UtAs were recognized using color Doppler sonography. After ensuring that the angle of insonation was less than 30°, pulsed wave Doppler sonography was used to obtain 3 consecutive waveforms. Both UtA pulsatility indices were recorded in the Fetal Medicine Unit database (Astraia®), and the presence or absence of early diastolic notches was noted.

The diagnosis of IR in women who self-reported this condition at the moment of the interview was based on an altered homeostasis model assessment of IR values and at least one of the following clinical conditions: polycystic ovary syndrome, acanthosis nigricans and acrochordons, suggested by the American Association of Clinical Endocrinologists and the American College of Endocrinologists [29, 30].
For this study, PE was defined as hypertension and proteinuria presenting after 20 weeks of gestation, meeting the following criteria: blood pressure of 140/90 mm Hg or higher on 2 occasions, at least 6 h apart, or a single measurement of 160/110 mm Hg or higher. Proteinuria is defined as the presence of ≥1+ protein on random dipstick or at least 300 mg of protein in a 24-hour urine collection, in the absence of urinary tract infection [31].

Patient Selection
Cases were selected retrospectively from all women who self-reported to have the diagnosis of PIR at the second trimester scan (n = 119), and the control group included pregnancies without PIR in a 1:5 proportion in the same study period (n = 595). Forty-six pregnancies were excluded because of incomplete demographic and outcome data. The UtA Doppler sonogram was made at week 20+0 to 24+6 in 93.3% (n = 623) and at week 11+0 to 13+6 in 55.5% (n = 371) of the study population.

Statistical Analysis
The Kolmogorov-Smirnov test was used to assess the normality of continuous data. Logistic regression analysis was used to determine whether significant maternal characteristics or first and second trimester UtA Doppler values made a significant contribution in predicting PE. Finally, the performance of screening was determined by receiver-operating characteristic curves.

Comparisons between groups were performed using the Student t or Mann-Whitney U test according to data distribution. Categorical variables were compared using the χ² test. A difference was considered statistically significant when p < 0.05.

Results
Of the 13,124 patients admitted across the study period, 119 pregnant women self-reported to have a diagnosis of PIR, accounting for 0.9% of the study sample. Patients with PIR were older and had a higher BMI (table 1). Pregnant women with PIR had a significantly higher rate of chronic arterial hypertension (CrHT; 10.1 vs. 2.2%, p < 0.05) and hypothyroidism (5.0 vs. 1.6%, p < 0.05) than those from the control group.

The UtA pulsatility index during the second and first trimesters did not significantly differ between the PIR group and the control group (fig. 1, 2).

With regard to perinatal outcomes, patients with PIR had a higher prevalence of PE (8.4 vs. 4.2%, p < 0.05), GDM (9.2 vs. 2.9%), stillbirths/newborn deaths (4.2 vs. 2.6%, p < 0.05) and cesarean sections than their controls. However, gestational age at delivery and birth weight percentile, including newborns with fetal growth restriction...
and large newborns for gestational age, were not significantly different from the control group (table 2).

On the other hand, when carrying out a univariate analysis of PE predictive factors, we found that maternal features, such as maternal age (OR = 1.08; 95% CI = 1.01–1.13), BMI (1.04; 1.01–1.07), GDM (3.7; 1.2–11.3) and a history of CrHT (7.6; 2.8–20.7), were significantly associated with this disease. The pulsatility index of UtAs at the first (3.6; 1.3–9.9) and second (3.2; 1.6–6.5) trimesters was also found to be significantly associated with the onset of PE (fig. 3). Nevertheless, upon the multivariate analysis, only maternal age, CrHT and increased UtA Doppler sonographic values, both during the first and the second trimesters of gestation, were significant and independent predictors of PE. Although IR did not prove being a predictive factor for such a condition, a post hoc power analysis showed that this study was underpowered (β = 0.26) to reveal differences between both groups.

Combined PE predictive models were assessed by the receiver-operating characteristic curve. With a false-positive rate of 5 and 10%, sensitivity for PE during the second trimester was 41.4 and 58.6%, whereas during the first trimester, sensitivity was 30 and 50%, respectively (fig. 3).

**Table 2.** Gestational pathology and perinatal outcome in patients with a history of PIR and their controls

<table>
<thead>
<tr>
<th>Feature</th>
<th>Control (n = 549)</th>
<th>PIR (n = 119)</th>
</tr>
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<tbody>
<tr>
<td>PE, n</td>
<td>23 (4.2)</td>
<td>10 (8.4)*</td>
</tr>
<tr>
<td>SB/ND, n</td>
<td>14 (2.6)</td>
<td>5 (4.2)*</td>
</tr>
<tr>
<td>GDM</td>
<td>16 (2.9)</td>
<td>11 (9.2)*</td>
</tr>
<tr>
<td>Cesarean section, n</td>
<td>239 (44.3)</td>
<td>76 (65.0)*</td>
</tr>
<tr>
<td>GA at delivery, weeks</td>
<td>38.1 ± 2.8</td>
<td>37.7 ± 3.0</td>
</tr>
<tr>
<td>Newborn weight, g</td>
<td>3,195.4 ± 847.8</td>
<td>3,203.0 ± 763.9</td>
</tr>
<tr>
<td>Fetal growth percentile</td>
<td>50.8 ± 27.5</td>
<td>51.9 ± 27.5</td>
</tr>
<tr>
<td>IUGR (&lt;p10), n</td>
<td>36 (6.6)</td>
<td>8 (6.8)</td>
</tr>
<tr>
<td>LGA &gt;p90, n</td>
<td>42 (7.8)</td>
<td>6 (5.1)</td>
</tr>
</tbody>
</table>

Results are expressed as numbers with percentages in parentheses or means ± SD. SB/ND = Stillbirth/newborn death; GA = gestational age; IUGR = intrauterine growth restriction; p10, p90 = 10th, 90th percentile; LGA = large for gestational age. * p < 0.05.

In spite of recent evidence proposing that IR diagnosed near pregnancy increases the risk of developing PE, our nested case-control study failed to demonstrate that, not only in the univariate but also in the multivariate analysis.

It is worth pointing out that in the univariate analysis, biodemographic factors that were associated with an increased risk for PE were the following: maternal age, BMI, CrHT, GDM and the increase in the pulsatility index of UtAs evaluated during the first and second trimesters.

The maternal morbid nutritional status defined by high pre- and postconception BMI and/or an exaggerated increase in body weight during gestation has been proposed as a risk factor for the development of PE [24–27, 32]. In fact, Barton and Sibai [32] concluded that obese pregnant women had a 10–15% higher risk of presenting PE. In our study, in accordance with literature reports, preconception weight correlated with the onset of subsequent PE. The latter variable is difficult to analyze upon evaluating its predictive role for PE, since an increase in BMI correlates significantly with IR, and therefore one might deduce that many of such overweight patients also presented relative hyperinsulinemia.

Additionally, this study supports the association between PIR and the onset of GDM. Both entities are etiopathogenetically related since GDM as well as type 2 dia-
betes mellitus share a common pathophysiology characterized by a peripheral IR and a relative hyperinsulinism [33]. The latter together with the 50–60% decrease in insulin sensitivity that can be seen in physiological pregnancy render patients with higher degrees of IR during pregnancy more prone to develop GDM [33, 34]. The well-known association of GDM with a higher PE risk was also found in our study. The latter might probably share the etiopathogenesis with IR.

In our study, the main variables associated with the subsequent development of PE were CrHT and maternal age. The latter is supported by published evidence stating that 20–25% of patients with CrHT will develop PE during pregnancy and reporting a relative risk of 1.68 (95% CI = 1.23–2.29) for nulliparous and of 1.96 (95% CI = 1.34–2.87) in multiparous women older than 40 [35].

Regarding the association found between CrHT and the subsequent onset of PE, it is important to consider that the etiopathogenesis of CrHT is multifactorial and among those factors is IR; thus, it might be inferred that such a metabolic condition might partially play a role, either directly or indirectly, in the genesis of PE. Such a deduction is supported by the observation that IR may generate a vascular damage mechanism characterized by chronic inflammatory levels, facilitation of atherogenic and prothrombotic processes that would affect the normal vascular tree and the normal placentation, well-known factors in the etiopathogenesis of PE [1, 11, 21, 33, 34]. However, the etiopathogenesis of CrHT is multifactorial.

As for the relationship found between PIR and hypothyroidism, it must be pointed out that this finding has been evidenced in recent studies, and therefore it has been demonstrated that carriers of clinical and subclinical hypothyroidism have lower baseline insulin concentrations and higher glucose-ingestion-induced insulinemias than control groups. Etiopathogenetically, this association would be based on the fact that in hypothyroid patients glucose uptake by muscle and adipose tissue is decreased after glucose ingestion, an effect that is not observed in fasting conditions [36]. It is important to bear in mind that within the vascular injury mechanism identified in those patients with IR statuses are an altered lipid profile (hypertriglyceridemia and decreased high-density lipoprotein cholesterol fraction) and a systemic chronic inflammatory factor (increased protein C). Such conditions would act in a complementary fashion to favor endothelial injury and thus result in atherosclerosis and prothrombotic statuses. In fact, in cross-sectional analyses the risk of cardiovascular disease and cardiovascular death has been shown to be higher in individuals with clinical and subclinical hypothyroidism than in euthyroid subjects [37]. These data suggest that hypothyroidism, even the subclinical variant, is an independent risk factor in the development of cardiovascular disease [36, 37]. All the above would explain the significant association between PIR, hypothyroidism and the subsequent development of PE. This relationship should be confirmed in further studies carried out in populations of pregnant women. Should this hypothesis be confirmed, it would represent another element justifying the need to screen for eventual hypothyroidism, even subclinical types, in early stages of pregnancy.

Finally, it is well known that the study of UtA resistance by Doppler flowmetry is a helpful tool to assess placental development, and thus an increase in the pulsatility index of these vessels would reflect an abnormal placentation, a phenomenon that has been described as an etiopathogenic factor for PE development. Therefore, increased pulsatility index values detected during the first and second trimesters of gestation have been demonstrated to be sensitive and predictive factors for a further development of PE [3, 28]. This conclusion is supported by our study, where the detection of an increased UtA resistance between gestation weeks 22 and 25 is a good PE predictor.

Although the size of this study was underpowered to demonstrate whether PIR was a predictor of PE, we may state based on our findings that maternal age and the history of CrHT are predominant clinical factors, and that together with a UtA Doppler study, they may detect more than half of the PEs during the first and second trimesters of gestation.

As a conclusion, PIR is associated with higher maternal age, higher BMI and other maternal medical pathologies (CrHT, hypothyroidism and GDM) that, regardless of IR, generate a higher risk of developing PE.

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