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Preeclampsia in Lean Normotensive Normotolerant Pregnant Women Can Be Predicted by Simple Insulin Sensitivity Indexes

Elena Parretti, Annunziata Lapolla, MariaGrazia Dalfrà, Giovanni Pacini, Andrea Mari, Riccardo Cioni, Chiara Marzari, Gianfranco Scarselli, Giorgio Mello

Abstract—Certain similarities between preeclampsia and insulin resistance syndrome suggest a possible link between the 2 diseases. The aim of our study was to evaluate 3 insulin sensitivity (IS) indexes (fasting homeostasis model assessment IS [IS_{HOMA}], quantitative insulin sensitivity check index [IS_{QUICKI}], and oral glucose IS [OGIS]) early and late in pregnancy in a large number of normotensive pregnant women with a normal glucose tolerance and to test the ability of these indexes to predict the risk of subsequent preeclampsia. In all, 829 pregnant women were tested with a 75-g, 2-hour oral glucose load in 2 periods of pregnancy: early (16 to 20 weeks) and late (26 to 30 weeks). In early and late pregnancy, respectively, IS_{HOMA} was 1.23 ± 0.05 and 1.44 ± 0.05 ($P < 0.01$), IS_{QUICKI} was 0.40 ± 0.002 and 0.38 ± 0.002 ($P < 0.01$), and OGIS was $457 \pm 2.4 \text{ mL min}^{-1} \text{ m}^{-2}$ and 445 ± 2.2 ($P < 0.001$), all confirming the reduction in insulin sensitivity during pregnancy. Preeclampsia developed in 6.4% of the pregnant women and correlated positively with the 75th centile of IS_{HOMA} ($P = 0.001$), with a sensitivity of 79% in the early and 83% in the late period and a specificity of 97% in both. $IS_{QUICKI} < 25$ th centile was also related with preeclampsia ($P = 0.001$), with a sensitivity of 85% in the early and 88% in the late period and a specificity of 97% in both. Judging from our findings, IS_{HOMA} and IS_{QUICKI} are simple tests that can pinpoint impaired insulin sensitivity early in the pregnancy. Given their high sensitivity and specificity, these indexes could be useful in predicting the development of preeclampsia in early pregnancy, before the disease become clinically evident. (*Hypertension*. 2006;47:449-453.)

Key Words: pregnancy ■ metabolism ■ insulin ■ insulin resistance ■ hypertension, pregnancy ■ preeclampsia

Normal pregnancy can be considered as a state of insulin resistance, and fasting insulin concentrations double during the course of gestation. Insulin resistance peaks in the 3rd trimester and rapidly returns to prepregnancy levels after delivery.¹ The reasons for this insulin resistance in normal pregnancy are not well known, although it has been suggested that placental hormones, such as lactogen, cortisol, progesterone, and estrogen,² and tumor necrosis factor α^3 may be responsible.

A number of standard clinical procedures are available for evaluating maternal insulin sensitivity during pregnancy, such as the euglycemic-hyperinsulinemic clamp, the oral and intravenous glucose tolerance tests (OGTT and IVGTT, respectively), and various derivations of fasting glucose and insulin levels,^{1,4} including the fasting homeostasis model assessment insulin sensitivity index (IS_{HOMA})⁵ and the quantitative insulin sensitivity check index [IS_{QUICKI}].⁶ The oral glucose insulin sensitivity index (OGIS), for instance, is a widely used index of dynamic insulin sensitivity by assessing glucose clearance during an OGTT.⁷

Preeclampsia is a complication of late pregnancy characterized mainly by hypertension and proteinuria.⁸ It is a major cause of perinatal and maternal morbidity and mortality worldwide, affecting 5% to 8% of all pregnancies.⁸ The etiology of this disease is still unknown, and there are multiple factors implicated in its pathogenesis, including genetic⁹ and immunological factors.⁹

Women with polycystic ovary syndrome or gestational diabetes mellitus (GDM), 2 disorders characterized by insulin resistance, are at greater risk of preeclampsia.^{10,11} In addition to hypertension,¹² several features of insulin resistance syndrome, such as obesity,¹³ dyslipidemia,¹⁴ cardiovascular disease,¹⁵ systemic inflammation,¹⁶ and impaired fibrinolysis,¹⁷ are also associated with preeclampsia. Collectively, these data suggest that insulin resistance may contribute to the pathogenesis of preeclampsia, with the added considerable risk of diabetes and severe cardiovascular diseases.

High plasma glucose levels have been observed after a glucose load in pregnant women who subsequently exhibit preeclampsia,¹⁸ and high post-OGTT basal insulin levels are

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characteristic of women with preeclampsia.^{19,20} Not all studies describe a positive relationship between insulin resistance and preeclampsia, however^{21,22}; this may be due to the fact that different methods have been used to assess insulin resistance and their outcome may not be consistent in pregnancy.

Thus, the aim of our study was to evaluate insulin sensitivity indexes in a large number of normotensive pregnant women with a normal glucose tolerance early and late in the pregnancy and to test the ability of these indexes to predict the risk of subsequent preeclampsia.

Patients and Methods

Between 1997 and 1999, among the unselected population of pregnant women tested for GDM using a 75-g, 2-hour glucose load in 2 periods of pregnancy (ie, early [16 to 20 weeks] and late [26 to 30 weeks]) at the Perinatal Medicine Unit of the University of Florence, subjects who met the following inclusion criteria were invited to take part in this prospective longitudinal study: white race, nulliparity, singleton pregnancy, absence of chronic hypertension, pregestational body mass index (BMI) between 19 and 25 kg/m², and absence of GDM according to the Carpenter and Coustan criteria²³ as recommended by the Fourth International Workshop Conference on Gestational Diabetes Mellitus Recommendations.²⁴ The women had not been prescreened by any other screening test. The study protocol, made according to the Helsinki Declaration, was approved by the local ethic committee, and written informed consent was obtained from each subject before they joined the study protocol. The clinical features of the women involved are shown in Table 1. Following a 10 to 12 h overnight fast, the 829 subjects recruited for the study ingested a solution containing 75 g of glucose; venous blood samples were drawn for glucose and insulin determination at 0, 60, and 120 minutes. Plasma glucose values lower than 95 mg/dL at 0, 180 mg/dL at 60, and 155 mg/dL at 120 minutes were considered normal.^{23,24} Preeclampsia was diagnosed if the blood pressure was $\geq 140/90$ mm Hg and proteinuria was ≥ 0.3 g in a 24-hour urine specimen taken after 20 weeks of gestation (American College of Obstetricians and Gynecologists criteria⁸). For the purposes of this study, only cases that developed preeclampsia in the interval between at least 2 weeks after the second glucose load and the first week after delivery were selected for the prediction of preeclampsia.

Plasma glucose levels were measured using the glucose oxidase method²⁵ and plasma insulin levels by using a double antibody radioimmunoassay.²⁶ HOMA was calculated according to Matthews⁵: $IS_{HOMA} = G_0 \times I_0 / 22.5$; QUICKI was calculated according to Katz⁶: $IS_{QUICKI} = 1 / [\log(I_0) + \log(G_0)]$, where G_0 and I_0 are fasting glucose and insulin concentrations. Both indexes describe fasting insulin sensitivity. Dynamic insulin sensitivity was evaluated by OGIS, a model-derived measurement of glucose clearance (mL/min per m²) during OGTT.⁷ Higher levels of IS_{HOMA} and lower values of IS_{QUICKI} and OGIS express insulin resistance. All these indexes have been validated against the glucose clamp.⁴

TABLE 1. Clinical Parameters (Mean \pm SD) of 829 Pregnant Women With Normal Glucose Tolerance

| Clinical Parameters | Values |
|--------------------------------------|------------------|
| Age, y | 31 \pm 4.5 |
| Pre-pregnancy BMI, kg/m ² | 22.5 \pm 3.0 |
| Early pregnancy | |
| SBP, mm Hg | 111.3 \pm 12.1 |
| DBP, mm Hg | 68.4 \pm 10.9 |
| Late pregnancy | |
| SBP, mm Hg | 109.4 \pm 13.8 |
| DBP, mm Hg | 67.5 \pm 11.6 |

*SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

Statistical analysis was carried out using the SAS system (SAS Institute, Inc). Data and results are expressed as mean \pm SE or SD, as appropriate. The percentile distribution curve was processed for the insulin sensitivity indexes early and late in the pregnancy. Data were analyzed by Student *t* test for paired comparisons and the correlation test. A logistic regression model was used to assess risk factors in early and late periods of gestation. Any association between the variables was expressed by χ^2 . The predictive power of the binary logistic regression was assessed by evaluating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios (LR) for an abnormal test corresponding to a cut-off of 0.5.²⁷ The receiver operating characteristic (ROC) curve was performed for the insulin sensitivity indexes (IS_{HOMA} , early and late, IS_{QUICKI} , early and late, and OGIS, early and late), to determine the index threshold value that yielded the highest combined sensitivity and specificity for the prediction of preeclampsia. The highest combinations of sensitivity and specificity correspond to $IS_{HOMA} > 75$ th percentile (early and late), $IS_{QUICKI} < 25$ th (early and late) and OGIS < 25 th (early and late) in the studied group. Statistical significance was set at $P < 0.05$.

Results

The insulin sensitivity parameters calculated in early and late pregnancy are shown in Table 2. Fasting plasma glucose and insulin did not differ significantly between early and late pregnancy, but there was a clear tendency for insulin to rise, reflected by a significant increase in IS_{HOMA} and decrease in IS_{QUICKI} (ie, fasting insulin sensitivity dropped later in the pregnancy). Dynamic insulin sensitivity (OGIS) also dropped significantly.

The curves and percentile distributions of the insulin sensitivity indexes calculated early and late in the pregnancy are shown in the Figure: the curves describe 2 near-parallel lines in both periods.

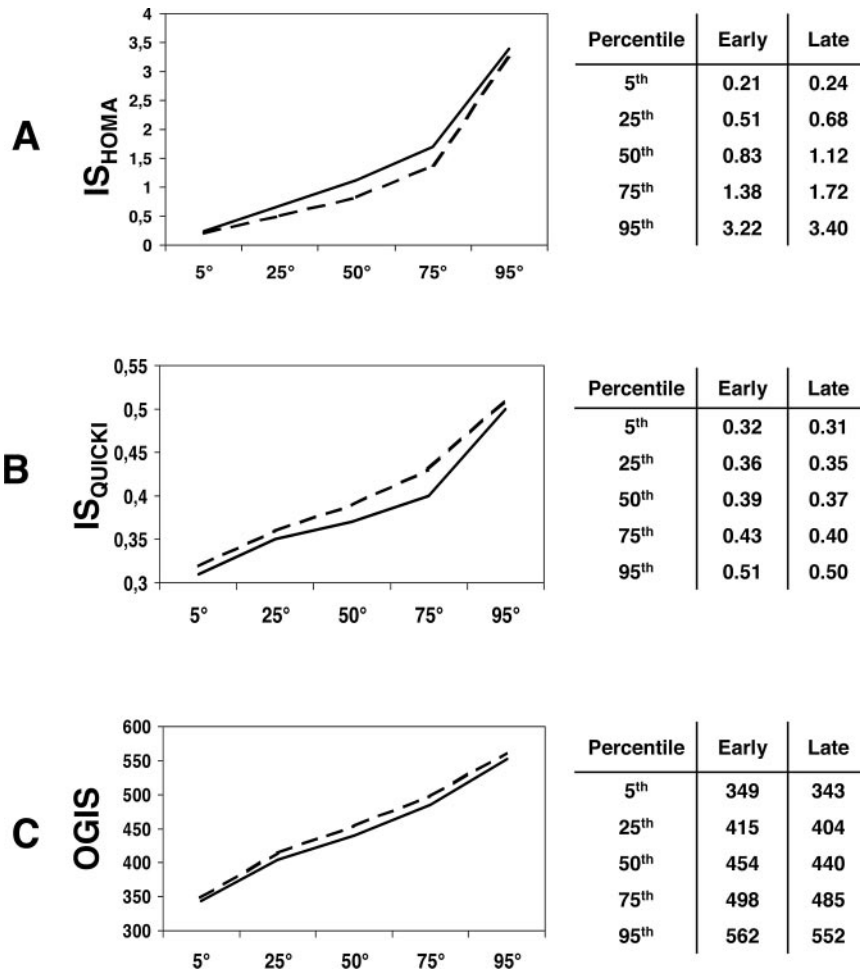
Preeclampsia developed in 53 women (6.4%) in the interval between at least 2 weeks after the second glucose load and the first week after delivery.

The fasting insulin sensitivity indexes were very capable of predicting in both periods of pregnancy the subsequent development of preeclampsia, with a better and significant association (Table 3) with an IS_{HOMA} value higher than the 75th percentile (1.38 in early and 1.72 in late pregnancy), an IS_{QUICKI} below the 25th percentile (0.36 in early and 0.35 in late pregnancy), and a value for OGIS below the 25th percentile (498 in early and 485 in late pregnancy) (Figure). These values are confirmed by ROC curves (data not shown).

The performance of the binary logistic regression to establish the insulin sensitivity index thresholds for predicting the subsequent onset of preeclampsia is shown in Table 4.

TABLE 2. Fasting Glucose, Insulin Levels, and Insulin Sensitivity Indexes (Mean Values \pm SE) in 829 Pregnant Women With a Normal Glucose Tolerance

| Metabolic Parameters | Early Pregnancy | Late Pregnancy | P |
|---------------------------------|------------------|------------------|------------|
| Fasting glucose, mmol/L | 3.59 \pm 0.16 | 3.41 \pm 0.18 | NS |
| Fasting insulin, μ U/mL | 6.5 \pm 0.9 | 8.1 \pm 0.8 | NS |
| IS_{HOMA} | 1.23 \pm 0.05 | 1.44 \pm 0.05 | < 0.01 |
| IS_{QUICKI} | 0.40 \pm 0.002 | 0.38 \pm 0.002 | < 0.01 |
| OGIS, mL/min per m ² | 457 \pm 2.4 | 445 \pm 2.2 | < 0.0001 |



Percentile distribution curves IS_{HOMA} (A), IS_{QUICKI} (B), and OGIS (C) in 829 pregnant women with a normal glucose tolerance.

Discussion

To date, most of the evidence on the association of insulin resistance and preeclampsia comes from cross-sectional and retrospective studies. In a case control study that excluded women with prior or gestational diabetes, plasma glucose levels after a 50-g glucose load were significantly higher among women who later developed preeclampsia.¹⁸ In the Toronto Tri-Hospital study, involving 3673 women without gestational diabetes, a direct link emerged between the degree of carbohydrate intolerance (based on glucose levels after OGTT) and the risk of preeclampsia.²⁸ In some cross-sectional studies, women with established preeclampsia had higher insulin levels after fasting and after oral or intravenous

glucose loading, and lower insulin sensitivity than controls.^{19,20,29,30} The point remains, however, that these studies examine insulin resistance when preeclampsia is already established, and it is not clear whether insulin resistance is a factor in the pathogenesis of preeclampsia or a consequence of the disease. The results of our study on a large sample of homogeneous, normotensive, nulliparous, pregnant women with a normal glucose tolerance and normal body weight support the hypothesis that insulin resistance, irrespective of any presence of obesity, may contribute to the pathogenesis of preeclampsia.

Three prospective studies have suggested an association between insulin resistance and subsequent preeclampsia. Among black women, Sowers et al showed that fasting insulin levels rose significantly at 20 weeks of gestation in the women who ultimately developed preeclampsia.³¹ In a large prospective study involving more than 3600 women, Joffe et al reported that the increase in deciles of glucose levels during the 50-g oral glucose challenge test was matched by an associated greater risk of subsequent preeclampsia.³² In the third study, Wolf et al found that lower sex hormone binding globulin in the first trimester correlated negatively with insulin resistance in women subsequently developing preeclampsia compared with those whose pregnancy was uncomplicated.³³

Preeclampsia is a common, hazardous complication of pregnancy, the mechanisms of which are still largely un-

TABLE 3. Association Between Insulin Sensitivity Indexes and Arbitrary Preeclampsia Thresholds in 829 Pregnant Women With a Normal Glucose Tolerance

| Index and Percentile | Early | Late | P |
|------------------------|-------|------|--------|
| $IS_{HOMA} >75^{th}$ | 1.38 | 1.70 | 0.0001 |
| | | | 0.0001 |
| $IS_{QUICKI} <25^{th}$ | 0.36 | 0.35 | 0.0001 |
| | | | 0.0001 |
| $OGIS <25^{th}$ | 415 | 404 | 0.03 |
| | | | 0.01 |

TABLE 4. Performance of Fasting Insulin Indexes in Predicting Preeclampsia in 829 Pregnant Women With a Normal Glucose Tolerance

| Statistical Evaluations | Early Period | | Late Period | |
|-------------------------|-------------------------------------|---------------------------------------|-------------------------------------|---------------------------------------|
| | IS _{HOMA} >75th Percentile | IS _{QUICKI} <25th Percentile | IS _{HOMA} >75th Percentile | IS _{QUICKI} <25th Percentile |
| True positive | 42 | 45 | 44 | 47 |
| False negative | 11 | 8 | 9 | 6 |
| False positive | 23 | 22 | 20 | 19 |
| True negative | 753 | 754 | 756 | 757 |
| Sensitivity (%) | 79.2 | 84.9 | 83.0 | 88.4 |
| Specificity (%) | 97.0 | 97.2 | 97.4 | 97.6 |
| PPV (%) | 64.6 | 67.2 | 68.8 | 71.2 |
| NPV (%) | 98.6 | 98.9 | 98.8 | 99.2 |
| LR (abnormal) | 26.3 | 30.3 | 31.9 | 36.9 |
| OR (CI 95th) | 2.57 (2.04–3.24) | 6.35 (3.37–11.95) | 2.63 (2.07–3.34) | 8.54 (4.62–15.80) |

known and, because of our limited understanding of the biology of this disease, no effective preventive strategies have been identified as yet. In addition, there are currently no early diagnostic tests capable of identifying women at higher risk. Here, we show that a few simple insulin sensitivity indexes, such as IS_{HOMA} and IS_{QUICKI}, that only use fasting insulin and glucose concentration, can predict in early and late periods of pregnancy the subsequent development of preeclampsia. Although the dynamic OGTT index OGIS also showed a significant association with preeclampsia, it was weaker (0.03 and 0.01 in early and late gestation, respectively). For this reason it was not considered in the prediction of preeclampsia.

To our knowledge, this is the first study to demonstrate that fasting insulin sensitivity indexes (IS_{HOMA} and IS_{QUICKI}) can predict in early and late pregnancy the subsequent development of preeclampsia in lean normotensive women with a normal glucose tolerance. These indexes had already been validated in pregnant women, but only in a small group.³⁴ In our experience, the performance of both indexes in early and late periods of pregnancy proved highly sensitive and specific, with a good PPV for the prediction of preeclampsia (Table 4). In particular, the high PPV of these indexes (especially considering the relatively low number of false-positives) already in the early gestational period suggests that they could be valuable in predicting preeclampsia, well before preeclampsia becomes clinically evident. One might argue that our study did not consider obese women, but we chose to exclude obese women to have a homogenous population and eliminate the recognized predisposing effect of obesity on the development of both preeclampsia and insulin resistance.^{8,10}

Because insulin sensitivity indexes are continuous variables, and there is no fixed threshold for insulin resistance, we considered the percentile distribution curves for IS_{HOMA}, IS_{QUICKI}, and OGIS (Figure). Given the large number of patients assessed, this distribution can be used as a reference in our white population.

Perspectives

The strength of this study is that we found evidence of a greater insulin resistance early in pregnancy (16 to 20 weeks),

before preeclampsia became clinically evident. This temporal relationship supports the hypothesis that insulin resistance is one of the causes of preeclampsia.³³ It would be tempting to assume that improving insulin sensitivity might reduce the risk of preeclampsia. The specificity of the tests is a relevant issue to consider in this context: using these tests might reliably identify a population at low risk of developing preeclampsia.

It should be noted that the indexes used in this study meet the requirements of the ideal predictive test: they are simple and easy to perform early in pregnancy (16 to 20 weeks), they are noninvasive, and they are highly sensitive and have a high PPV for detecting the subsequent risk of preeclampsia in lean, normotensive, pregnant women with a normal glucose tolerance. Moreover, the tests could be considered as a tool for secondary prevention, enabling the disease process to be interrupted before any clinically recognizable disease (preeclampsia) occurs, thus allowing for both early treatment and preventive measures.

Furthermore, the gestational period examined in this study is before the time when most of the physiological insulin resistance of pregnancy occurs,³⁵ so the insulin resistance that we detected may, in some cases, have already existed before the pregnancy. This has important future therapeutic implications. If preeclampsia is associated with a higher basal insulin resistance, then it is a potentially modifiable risk factor for the greater long-term cardiovascular risk observed in women with a history of preeclampsia.³⁶

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