Hypertension in Pregnancy
A Manifestation of the Insulin Resistance Syndrome?
Caren G. Solomon, Ellen W. Seely

Abstract—Pregnancy-induced hypertension (PIH), which includes both gestational hypertension and preeclampsia, is a common and morbid pregnancy complication for which the pathogenesis remains unclear. Emerging evidence suggests that insulin resistance, which has been linked to essential hypertension, may play a role in PIH. Conditions associated with increased insulin resistance, including gestational diabetes, polycystic ovary syndrome, and obesity, may predispose to hypertensive pregnancy. Furthermore, metabolic abnormalities linked to the insulin resistance syndrome are also observed in women with PIH to a greater degree than in normotensive pregnant women: These include glucose intolerance, hyperinsulinemia, hyperlipidemia, and high levels of plasminogen activator inhibitor-1, leptin, and tumor necrosis factor-α. These observations suggest the possibility that insulin resistance may be involved in the pathogenesis of PIH and that approaches that improve insulin sensitivity might have benefit in the prevention or treatment of this syndrome, although this requires further study. (Hypertension. 2001;37:232-239.)

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

Hypertension complicates 5% to 10% of pregnancies and includes several disorders: preeclampsia (proteinuric hypertension), gestational (nonproteinuric) hypertension, and chronic hypertension with or without superimposed preeclampsia. Despite the significant morbidity associated with new-onset hypertension in pregnancy, the pathogenesis remains unclear, which limits the ability to prevent and treat this disorder. Although it is likely that the cause of pregnancy-induced hypertension (PIH) is multifactorial and involves both genetic and other factors, insulin resistance may be an important contributor to the development of both preeclampsia and gestational hypertension.

The association of essential hypertension with insulin resistance and hyperinsulinemia has been well described. More than 40 years ago, a relationship between insulin resistance and PIH was postulated. However, it was not until recent years that more widespread interest developed in the possible role of insulin resistance in the pathogenesis of PIH. This report integrates the literature supporting a role of insulin resistance in hypertensive pregnancy and discusses clinical implications of these observations. The term PIH is used in this report to represent new-onset hypertension in pregnancy and includes both preeclampsia and gestational hypertension.

Terminology of Hypertension in Pregnancy
Determination of risk factors for and sequelae of PIH is complicated by the lack of uniformity of criteria used to classify hypertensive disorders of pregnancy. Definitions according to the National High Blood Pressure Education Program are listed in Table 1. Preeclampsia and gestational hypertension may represent different manifestations of one disease process, although there is some evidence that these conditions may be pathophysiologically distinct. Preeclampsia is a systemic disease characterized not only by hypertension but also by increased vascular resistance, diffuse endothelial dysfunction, proteinuria, and coagulopathy.

In the absence of severe disease manifestations, discrimination between preeclampsia and gestational hypertension may be difficult. This distinction is often made solely on the basis of urine protein determination, frequently by dipstick protein measurement, which is recognized to be an imperfect surrogate for 24-hour measurements. Also, essential hypertension may be erroneously diagnosed as PIH when a woman’s first blood pressure determination is in the second trimester of pregnancy, a time when blood pressure normally has fallen from prepregnancy values. As a result, the return to usual blood pressure in the third trimester may be mistaken for new-onset hypertension in pregnancy.

Insulin Resistance in Normal Pregnancy
Hyperinsulinemia and insulin resistance are hallmarks of normal pregnancy. Insulin resistance increases during pregnancy, peaks in the third trimester, and rapidly returns to prepregnancy levels after delivery. The basis of the insulin resistance seen in normal pregnancy is not well understood.
TABLE 1. Classification of Hypertension in Pregnancy

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Definition</th>
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<tr>
<td>Preeclampsia</td>
<td>Hypertension developing after 20 weeks’ gestation with proteinuria and/or edema</td>
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<tr>
<td>Gestational hypertension (also termed transient hypertension of pregnancy)</td>
<td>Hypertension developing after 20 weeks’ gestation without other signs of preeclampsia</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>Hypertension before 20 weeks’ gestation in the absence of neoplastic trophoblastic disease</td>
</tr>
<tr>
<td>Preeclampsia superimposed on chronic hypertension</td>
<td>Hypertension developing in a woman with preexisting hypertension</td>
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Hypertension is defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg; or systolic blood pressure increase of ≥30 mm Hg or diastolic blood pressure increase of ≥15 mm Hg over first trimester of prepregnancy values. Proteinuria refers to 24-hour urine protein ≥300 mg or dipstick protein ≥1 g/L.

Various hormonal changes of pregnancy have been implicated including human placental lactogen, cortisol, progesterone, and estrogen.

Review of Data Linking Insulin Resistance and PIH
Several lines of evidence suggest that both preeclampsia and gestational hypertension (together considered “PIH”) may be associated with greater degrees of insulin resistance than characteristic of normal pregnancy. The usual onset of PIH in late pregnancy, a time when the insulin resistance characteristic of pregnancy is maximal, supports a possible association. Postulated mechanisms through which insulin resistance might increase blood pressure in pregnancy, as in essential hypertensives, include sympathetic nervous system activation, renal sodium retention, increased cation transport, and associated endothelial dysfunction.

In addition, increased risks for preeclampsia and/or gestational hypertension have been reported with several conditions associated with insulin resistance. These include gestational diabetes, polycystic ovary syndrome, obesity, and increased weight gain (Table 2). In many studies assessing associations between these conditions and PIH risk, PIH subgroups of preeclampsia and gestational hypertension are combined because of limited power to analyze these subgroups separately.

Gestational Diabetes Mellitus
Gestational diabetes mellitus (GDM), diabetes first diagnosed during pregnancy, complicates 3% to 5% of all pregnancies.

TABLE 2. Correlates of Insulin Resistance Associated With Pregnancy-Induced Hypertension

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Biomarkers</th>
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<tr>
<td>Gestational diabetes mellitus</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Polycystic ovary syndrome</td>
<td>Hyperinsulinemia</td>
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<tr>
<td>Obesity/excessive weight gain</td>
<td>Hyperlipidemia</td>
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<td></td>
<td>Increased TNF-α</td>
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<tr>
<td></td>
<td>High PAI-1 Levels</td>
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<td></td>
<td>Hyperleptinemia</td>
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Women with GDM appear more insulin resistant during and after pregnancy than do normal women. Some data suggest an increased risk of PIH among women with GDM. Among 221 Swedish women with GDM, the incidence of preeclampsia and gestational hypertension combined was significantly higher than among women in a control group with uncomplicated pregnancy (14% versus 7%). In another study, the incidence of preeclampsia was slightly higher among women with GDM diagnosed in the third trimester (7.5%) and significantly higher among women with diabetes diagnosed at <24 weeks’ gestation (14.7%) than among women with normal glucose tolerance (5.4%). However, these findings remain controversial because other studies have not observed a higher frequency of PIH in gestational diabetic women.

Polycystic Ovary Syndrome
Polycystic ovary syndrome (PCOS), a condition characterized by anovulation, androgen excess, and frequently by obesity, is associated with insulin resistance and hyperinsulinemia, even independent of body weight. In one uncontrolled study, a higher rate of preeclampsia was observed among women with PCOS as compared with expected rates in the general population; however, stratification by weight suggested that the increase in risk was explained by obesity. In another study including 81 women with PCOS and matched control subjects, the rate of PIH overall but not of preeclampsia alone was significantly higher among women with PCOS than among women in a control group. An increased PIH risk was observed in this report even in the nonobese subgroup of women with PCOS (body mass index [BMI] <25 kg/m²).

Obesity
Recognized associations between prepregnancy BMI and pregnancy weight gain and risk for PIH further support a link between hyperinsulinemia and hypertensive pregnancy. We have observed higher prepregnancy BMI among women in whom PIH (both preeclampsia and gestational hypertension) later developed. Other investigators have similarly reported higher BMI before development of preeclampsia or combined preeclampsia and gestational hypertension. In a prospective study involving >15 000 women, of whom 216 had gestational hypertension and 86 had preeclampsia, women with prepregnancy BMI ≥30 kg/m² had an age-adjusted relative risk of 1.9 for development of preeclampsia and 2.2 for development of gestational hypertension, as compared with lean women.

We and others have observed that greater weight gain during pregnancy likewise increases PIH risk. Women with PIH had an average weight gain of 12.2 kg in the first two trimesters of pregnancy as compared with 10.1 kg in women who remained normotensive. Significantly greater weight gain was observed only among women who had preeclampsia and not among those who had gestational hypertension.

Biomarkers Associated With Insulin Resistance
Insulin resistance is associated with hyperglycemia, hyperinsulinemia, and dyslipidemia. More recently, it has been
### TABLE 3. Studies Linking Insulin Resistance to Pregnancy-Induced Hypertension

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Criteria for Cases</th>
<th>Measure of Insulin Resistance</th>
<th>Results</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td><strong>Cross-sectional (third-trimester) studies</strong></td>
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<tr>
<td>Burt⁵</td>
<td>13 PE, historic control subjects</td>
<td>BP ≥140/90, with proteinuria</td>
<td>Nonfasting intravenous GTT</td>
<td>Glucose levels during first hour higher in PE (P&lt;0.05)</td>
<td>1, 2 Level of proteinuria not specified</td>
</tr>
<tr>
<td>Madsen et al⁴⁴</td>
<td>15 mild PE, 12 nonpregnant, 12 normal pregnant</td>
<td>BP ≥140/90, (2) nonpedal edema (3) urinary protein &gt;0.1%</td>
<td>OGT Tdosed by body weight</td>
<td>AUC insulin greater for PE vs both control groups (P&lt;0.05); no difference in glucose AUCs</td>
<td>1, 2</td>
</tr>
<tr>
<td>Bauman et al⁴⁵</td>
<td>16 hypertensive pregnant, 27 normal pregnant</td>
<td>BP ≥140/90</td>
<td>100 g OGT T</td>
<td>Higher insulin level at 1, 2 h (P&lt;0.02); no difference in glucose level</td>
<td>1, 2 Population was high-risk for pregnancy complications</td>
</tr>
<tr>
<td>Abundis et al⁴⁶</td>
<td>10 severe PE, 10 normal pregnant, matched for BMI</td>
<td>SBP ≥30 and/or DBP ≥15 from before 20 wks, with proteinuria</td>
<td>50 g GLT</td>
<td>Glucose levels similar; fasting insulin (P&lt;0.05) and postload (P&lt;0.01) insulin levels higher in PE</td>
<td>1,2 Proteinuria criteria not specified for all patients</td>
</tr>
<tr>
<td>Kaaja et al⁴⁷</td>
<td>8 PE, 23 GH, 21 normal pregnant, weight-matched</td>
<td>BP ≥140/90 after 20 wk, resolving within 4 wk postpartum; proteinuria &gt;500 mg/24 h</td>
<td>Fasting insulin</td>
<td>Insulin level higher in PE and GH (P&lt;0.01)</td>
<td>Excluded essential hypertension; some in “nonproteinuric” group may have met criteria for PE</td>
</tr>
<tr>
<td>Lorentzen et al⁴⁸</td>
<td>10 PE, 8 normal pregnant</td>
<td>BP ≥140/90 after 20 wk</td>
<td>75 g OGT T</td>
<td>AUC glucose (P=0.001), insulin (P=0.02) higher in PE</td>
<td>1 Not adjusted for BMI; required normotension before 20 wks</td>
</tr>
<tr>
<td>Kaaja et al⁴⁹</td>
<td>22 PE, 16 normal pregnant, BMI-matched</td>
<td>BP ≥140/90 after 27 wks, with proteinuria &gt;300 mg/24 h</td>
<td>75 g OGT T, intravenous GTT</td>
<td>AUC insulin higher (P&lt;0.001); and insulin sensitivity lower (P&lt;0.009) in PE</td>
<td>1</td>
</tr>
<tr>
<td>Caruso et al⁵⁰</td>
<td>10 PE, 10 GH, 6 chronic hypertension, 10 normal pregnant</td>
<td>DBP ≥90 after 20 wks; PE required proteinuria &gt;300 mg/24 h or dipstick ≥1 g/L</td>
<td>Euglycemic clamp, 100 g OGT T</td>
<td>Lower insulin sensitivity index in GH vs control subjects (P&lt;0.03); PE comparable to normals</td>
<td>1 Not adjusted for BMI; required normotension before 20 wks</td>
</tr>
<tr>
<td><strong>Insulin resistance before PIH</strong></td>
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<tr>
<td>Solomon et al⁵¹</td>
<td>50 PE, 47 GH, 77 normal control subjects who had been screened for GDM ~28 wks</td>
<td>SBP ≥140 and/or DBP ≥90, and SBP ≥30 and/or DBP ≥15, vs first trimester or prepregnancy values; PE required proteinuria ≥300 mg/24 h or dipstick ≥2+</td>
<td>50 g GLT</td>
<td>Higher 1-h glucose levels in PIH overall (P&lt;0.01) and specifically GH (P&lt;0.025); nonsignificantly higher 1-h insulin levels in PE and GH</td>
<td>Nonfasting insulins measured only in a subset; no standardization of intake before GTL; excluded GDM</td>
</tr>
<tr>
<td>Sowers et al⁵²</td>
<td>164 women screened for GDM at 19 wks; 8 developed GH/3 PE</td>
<td>SBP ≥140 and/or DBP ≥90, or DBP ≥15 after 24 wks, PE required proteinuria ≥300 mg/24 h or dipstick ≥2+</td>
<td>50 g GLT</td>
<td>Higher 1-h insulin level (P&lt;0.005) and glucose level (P&lt;0.0001) before PIH</td>
<td>1 Predominantly black women; required normotension before 24 wks; excluded GDM; only glucose was significant predictor adjusting for BMI</td>
</tr>
<tr>
<td>Roberts et al⁵³</td>
<td>1321 women screened with HbA1c early pregnancy and 28 wks; 225 developed GH/51 PE</td>
<td>SBP ≥140 or DBP ≥90, without “preexisting hypertension”; PE required dipstick protein ≥0.3 g/L</td>
<td>HbA1c</td>
<td>28-wk HbA1c level higher in GH vs normal (P&lt;0.02); PE similar to normals</td>
<td>1, Preexisting hypertension was defined by use of antihypertensive medications; excluded DM; differences between GH and normals significant after adjusting for BMI</td>
</tr>
</tbody>
</table>
recognized that the insulin resistance syndrome also may involve other metabolic abnormalities, including increased concentrations of plasminogen activator inhibitor (PAI)-1, leptin, and tumor necrosis factor-α (TNF-α). Although these markers are surrogate measures of insulin sensitivity, observed associations between many of these markers and PIH risk further suggest a role for insulin resistance in the development of PIH (Table 2).

### Glucose and Insulin

The euglycemic clamp is considered by many to be the gold standard for determining insulin sensitivity. However, the difficulty in performing this procedure on large samples has led to the use of other simpler measures of insulin sensitivity. Investigators have often used fasting glucose and insulin levels or levels after glucose administration as indicators of insulin sensitivity.

Several reports have linked PIH and gestational glucose intolerance, even in the absence of GDM. In a case-control study that specifically excluded women with preexisting or gestational diabetes, we observed that plasma glucose concentrations after a 50-g glucose load were significantly higher among women in whom PIH later developed, an observation consistent with the work of others. In a subgroup analysis, we observed significantly higher postload glucose levels in women who developed gestational hypertension, whereas women who developed preclampsia had intermediate glucose levels not significantly different from those of women who remained normotensive. Consistent with these results, Roberts et al reported that early pregnancy levels of hemoglobin A1c were predictive of gestational hypertension but not preeclampsia. In addition, the Toronto Tri-Hospital study of 3637 women without gestational diabetes showed a direct relation between degree of carbohydrate intolerance as measured by glucose levels after oral glucose administration and risk for preeclampsia.

Several cross-sectional studies have reported increased insulin levels fasting and after oral or intravenous glucose load.
Data are lacking among women with gestational hypertension as compared with normal pregnancy. In a cross-sectional study, increasing severity of preeclampsia ranging from mild disease to eclampsia was associated with increased plasma levels of PAI-1. PAI-1 antigen and mRNA were likewise increased in placental tissue from women with severe preeclampsia as compared with normal pregnant women. It is possible that PAI-1 may be involved in the fibrin deposition and placental vascular lesions that are characteristic of preeclampsia.

**Leptin**

Elevated leptin levels are associated with insulin resistance, even independent of the recognized association with BMI. Insulin infusions raise plasma leptin levels in healthy men. During normal pregnancy, leptin levels increase as much as 2- to 3-fold and peak in the second trimester.

Higher leptin levels independent of obesity have been described in pregnant women with preeclampsia in case-control studies. One study showed the highest leptin levels were observed in women with the most severe preeclampsia. A report that leptin levels are increased among normotensive first-degree relatives of hypertensive subjects supports an association between this biomarker and elevated blood pressure. Furthermore, data that leptin levels are associated with increased PAI-1 levels in nonpregnant individuals, independent of age and BMI, suggest a potential relation between this marker and the coagulation disturbances characteristic of preeclampsia.

**Tumor Necrosis Factor**

TNF-α is another marker of the insulin resistance syndrome. TNF-α correlates negatively with insulin sensitivity as determined by intravenous glucose tolerance testing and hyperinsulinemic euglycemic clamp studies, and higher TNF-α levels are observed in type 2 diabetes mellitus. In normal pregnancy, TNF-α is low in the first trimester and subsequently increases with advancing gestational age. Some but not all studies report higher plasma TNF-α levels in women with established preeclampsia. In addition, increased levels of TNF-α antigen and mRNA have been described in placental tissue from preeclamptic women. Furthermore, in a study including 35 women in whom preeclampsia later developed and 222 women who remained normotensive, second-trimester TNF-α levels predicted development of preeclampsia, adjusting for maternal age and adiposity. Because TNF-α may impair insulin signaling, inhibit lipoprotein lipase, induce PAI-1, and directly contribute to endothelial dysfunction, this cytokine may be involved in the pathogenesis of PIH.

**Clinical Implications**

Although the causes of preeclampsia and gestational hypertension probably are multifactorial, the data reviewed support insulin resistance as a potential contributor to the pathogenesis of both these conditions. Because of clinical overlap between preeclampsia and gestational hypertension, more data are needed across the entire spectrum of PIH to better understand the possible role of insulin resistance in different conditions.
subgroups. Nonetheless, available data linking each of these conditions with greater insulin resistance during pregnancy and postpartum has implications for identification of women at risk of these and related disorders as well as for potential preventive or therapeutic strategies.

Implications During Pregnancy
Although the observed association between insulin resistance and PIH does not prove a causal relation, this observation nonetheless raises the possibility of potential preventive strategies before and during pregnancy. Among potential measures would be avoidance of obesity and excessive weight gain before pregnancy, which is likewise indicated to reduce the risk for other pregnancy complications (including GDM	extsuperscript{80} and macrosomia	extsuperscript{81}). Furthermore, a limitation of weight gain in women who start pregnancy already obese may be of value because greater weight gain during pregnancy is another predictor of preeclampsia.\textsuperscript{32} Increased physical activity level, an intervention known to improve insulin sensitivity, has been associated with reduced PIH risk\textsuperscript{82} and thus may be useful. Given data that diets lower in glycemic index or higher in fiber may improve insulin resistance in women,\textsuperscript{83} it is possible that such diets may reduce PIH risk. However, we are unaware of any data at present that directly assess these interventions in the prevention of PIH.

Implications in Later Life
The presence of hyperinsulinemia in nonpregnant women years after a diagnosis of preeclampsia\textsuperscript{84} indicates that these women may be at increased risk for later-life conditions associated with insulin resistance, which include type 2 diabetes, hypertension, dyslipidemia, and coronary heart disease.\textsuperscript{15} We are unaware of long-term studies of insulin resistance in women with a history of gestational hypertension, although observations of increased insulin resistance during pregnancy indicate the need for studies of these women later in life. At present, some\textsuperscript{84,85} but not all\textsuperscript{6} data link PIH to later hypertension and to later coronary heart disease.\textsuperscript{84,86,87} Further studies should better delineate whether long-term disease risks differ for preeclampsia and gestational hypertension.

To the extent that PIH may provide an early window into future disease risks,\textsuperscript{88} it is possible that interventions that improve insulin sensitivity might reduce later risk of cardiovascular disease in women with this history. Strategies similar to those now recommended in women with history of GDM may similarly have a role in the postpregnancy management of women with history of PIH; these would include avoidance of obesity, weight gain, and medications that impair insulin sensitivity.\textsuperscript{81} The efficacy of these interventions, as well as the possible use of insulin sensitizers, warrants formal study.

Conclusions
Recognized associations between correlates of insulin resistance and both preeclampsia and gestational hypertension suggest that PIH may be part of the spectrum of the insulin resistance syndrome. Insofar as the development of PIH may relate to the insulin resistance characteristic of advancing gestation, pregnancy may unmask an underlying tendency to insulin resistance and associated disorders that otherwise would not be manifest until later in life. Close monitoring of women with risk factors for insulin resistance during pregnancy and longer-term follow-up of women with a history of PIH may allow for more successful interventions, specifically with approaches that reduce insulin resistance. Whether links to insulin resistance for both conditions suggest a common pathophysiology still remains to be determined.

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